Association between incident falls and subsequent fractures in patients attending the fracture liaison service after an index fracture: a 3-year prospective observational cohort study

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ABSTRACT

Objectives To evaluate the risk of subsequent fractures in patients who attended the Fracture Liaison Service (FLS), with and without incident falls after the index fracture.

Design A 3-year prospective observational cohort study.

Setting An outpatient FLS in the Netherlands.

Participants Patients aged 50+ years with a recent clinical fracture.

Outcome measures Incident falls and subsequent fractures.

Results The study included 488 patients (71.9% women, mean age: 64.6±8.6 years). During the 3-year follow-up, 959 falls had been ascertained in 296 patients (60.7%) (ie, fallers), and 60 subsequent fractures were ascertained in 53 patients (10.9%). Of the fractures, 47 (78.3%) were fall related, of which 25 (53.2%) were sustained at the first fall incident at a median of 34 weeks. An incident fall was associated with an approximately 9-fold (HR: 8.6, 95% CI 3.1 to 23.8) increase in the risk of subsequent fractures.

Conclusion These data suggest that subsequent fractures among patients on treatment prescribed in an FLS setting are common, and that an incident fall is a strong predictor of subsequent fracture risk. Immediate attention for fall risk could be beneficial in an FLS model of care.

Trial registration number NL45707.072.13.

INTRODUCTION

Patients with a recent fracture have a high imminent risk of subsequent fractures as shown after most fractures, and a high risk of subsequent falls, as shown after a recent hip fracture. The Fracture Liaison Service (FLS) is considered the most effective organisational approach for secondary fracture prevention in patients after the age of 50 years with a recent fracture.

Most fractures are caused by a fall, but most falls do not result in a fracture. Falls are a major contributing factor to the occurrence of fractures, independent and additive to the risk attributable to age and bone mineral density (BMD). Guidelines on the FLS, therefore, recommend fall prevention and prescription of anti-osteoporosis medication (AOM) in patients at a high risk.

However, it is not well known to what extent the imminent risk of subsequent fractures after an index fracture can be attributed to incident falls. We hypothesised that the risk of subsequent fractures would be substantially higher in patients with falls after a recent fracture than in those without falls. The aim of this study was, therefore, to evaluate the incidence of falls and subsequent fractures, and the risk of subsequent fractures in those with and without falls after a recent index fracture in patients who attend the FLS.

METHODS

Study population and design
A 3-year prospective observational cohort study was conducted, including 500 consecutive patients aged between 50 years and
90 years, with a recent, radiologically confirmed clinical vertebral or non-vertebral low-trauma fracture, and who were willing and able to participate. Patients were recruited at the FLS in VieCuri Medical Center, Venlo, the Netherlands.

Low-trauma fractures were defined as fractures that resulted from a fall from standing height or less. Excluded were non-Caucasian patients, patients with bone metastasis, failure of prosthesis or osteomyelitis and patients with cognitive impairment.

According to standard care, a nurse specialised in osteoporosis invited all patients aged 50 years and older, who visited the emergency department because of a recent clinical vertebral or non-vertebral fracture, to the FLS. All patients who responded and agreed to be evaluated scheduled an appointment for fracture risk evaluation. Fracture risk evaluation included a detailed questionnaire for evaluation of risk factors for fractures and falls, including medical history and medication use. This questionnaire was based on the Dutch guidelines on osteoporosis and fracture prevention, and prevention of falls in the elderly. Also, height and weight were measured, a BMD measurement with dual-energy X-ray absorptiometry of the lumbar spine, total hip and femoral neck, with vertebral fracture assessment was performed, and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease. According to the Dutch osteoporosis guideline, AOM was started in patients with osteoporosis or having at least one moderate to severe prevalent vertebral fracture according to Genant et al. Bisphosphonates and denosumab were first-choice treatments. Teriparatide was restricted to patients already on another AOM with at least three fractures, of which two were vertebral fractures.

Falls and subsequent fractures
During the 3-year follow-up, patients were requested to record falls weekly in a fall diary. Fall registration started at the beginning of the study, mean 3.5±1.0 months after the index fracture. A fall was defined as an unintentional change in position resulting in coming to rest on the ground or other lower level. Patients were asked to return their fall diaries by mail at 3 months and 6 months, and during the study visit at 1 year, 2 years and 3 years of follow-up. They were contacted by telephone if the fall diary was not received or incomplete. Patients were categorised as those with at least one incident fall (ie, faller) or without an incident fall (ie, non-faller) during follow-up.

When patients recorded a fall in their diary, they were also asked to record whether or not they sustained a subsequent clinical fracture as a direct result of the fall. Additionally, at 1-year, 2-year and 3-year follow-ups, patients had to complete a detailed questionnaire, including a question on whether they sustained a fracture due to another trauma than a fall or without an overt trauma. All subsequent fractures were radiologically confirmed according to radiology reports in the electronic patient records. Since no imaging of the spine was performed at the end of the study, all reported vertebral fractures were symptomatic, clinical vertebral fractures. A distinction was made between subsequent fractures that were directly caused by a fall (ie, fall-related fractures) and those that occurred without an overt trauma or were the result of another trauma than a fall (ie, non-fall-related fractures).

Data analysis
Baseline characteristics were compared between fallers and non-fallers, and between patients with and without subsequent fractures using the Student’s t-test or Wilcoxon test for continuous variables, and Chi-squared or Fisher’s exact test for categorical variables where appropriate. The incidence rate of falls and subsequent fractures per 100 person-years was estimated at 3 and 6 months and 1, 2 and 3 year follow-up, assuming a Poisson distribution. Kaplan Meier curves were made for incident falls and subsequent fractures, in which patients were included once, and only the first incident fall or subsequent fracture was included. Cox proportional hazards regression was used to determine the association between incident falls and subsequent fractures, yielding HRs and 95% CIs. Proportional hazard assumptions were not violated. Follow-up time was determined by the first subsequent fracture, lost to follow-up or the end of the study, whatever occurred first. All analyses were adjusted for the predefined covariates, including age, gender, index fracture type (major or hip vs any other fracture), BMD (lowest measured at lumbar spine, total hip and femoral neck) and prevalent vertebral fractures (moderate or severe vs mild or no prevalent vertebral fractures). A p value of <0.05 was considered statistically significant.

Two sensitivity analyses were planned: (1) excluding patients with index and subsequent finger or toe fractures and (2) by classifying patients with a non-fall-related subsequent fracture as non-faller, even if they fell at another time during follow-up.

Patient and public involvement
Patients or members of the public were not involved in the design, or conduct, or reporting, or dissemination plans of the research.

RESULTS
Study population
Among 1220 patients who approached from the FLS, 1011 patients met the study criteria. Of the 1011 patients, 511 were not willing or able to participate in the study, and after excluding 12 patients with missing fall data, ultimately 488 patients were available for analysis (online supplemental figure 1) of whom 34 patients (7.0%) had incomplete follow-up data on incident falls (5 patients died, 8 withdrew consent and 21 had incomplete fall registration).

The mean time between the index fracture and FLS visit at which patients were included for this study was
3.9±1.1 months for patients with a hip fracture and 3.5±1.0 months for patients with other fractures. Baseline characteristics of the 488 study participants are presented in table 1. Mean age was 64.6±8.6 years and 71.9% of the patients were women. In 86.5% of patients, the index fracture was caused by a fall, and 28.5% of patients had at least one other fall in the year before the start of the study. At baseline, 21.9% of patients were diagnosed with osteoporosis, 51.1% with osteopenia and 27.1% had a normal BMD. Lowest BMD was measured at the femoral neck in 470 participants, at the total hip in 3 participants and at the lumbar spine in 15 participants. Moderate to severe (ie, grade 2–3) prevalent vertebral fractures were present in 14.3% of patients. AOM was prescribed in 34.2% of patients (8 (1.6%) were already using AOM and 159 (32.6%) started using AOM at baseline visit).

Compared with eligible FLS attenders, who were not willing or able to participate in our study, patients included in our study were younger, had fewer major or hip fractures and had a higher BMD, and a lower proportion had prevalent vertebral fractures (see online supplemental table 1).

### Table 1 Baseline characteristics of 488 participants stratified by incident fall and subsequent fracture status

<table>
<thead>
<tr>
<th></th>
<th>Total population (n=488)</th>
<th>Non-fallers (n=192)</th>
<th>Fallers (n=296)</th>
<th>P value</th>
<th>No subsequent fracture (n=435)</th>
<th>Subsequent fracture (n=53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.6±8.6</td>
<td>64.4±8.0</td>
<td>64.8±9.0</td>
<td>0.608</td>
<td>64.5±8.8</td>
<td>65.3±7.1</td>
<td>0.488</td>
</tr>
<tr>
<td>Female gender</td>
<td>351 (71.9)</td>
<td>130 (67.7)</td>
<td>221 (74.7)</td>
<td>0.095</td>
<td>308 (70.8)</td>
<td>43 (81.1)</td>
<td>0.114</td>
</tr>
<tr>
<td>Baseline fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger or toe</td>
<td>55 (11.3)</td>
<td>30 (15.6)</td>
<td>25 (8.4)</td>
<td>0.060</td>
<td>49 (11.3)</td>
<td>6 (11.3)</td>
<td>0.460</td>
</tr>
<tr>
<td>Minor</td>
<td>303 (62.1)</td>
<td>109 (56.8)</td>
<td>194 (65.5)</td>
<td></td>
<td>270 (62.1)</td>
<td>33 (62.3)</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>104 (21.3)</td>
<td>44 (22.9)</td>
<td>60 (20.3)</td>
<td></td>
<td>95 (21.8)</td>
<td>9 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>26 (5.3)</td>
<td>9 (4.7)</td>
<td>17 (5.7)</td>
<td></td>
<td>21 (4.8)</td>
<td>5 (9.4)</td>
<td></td>
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<tr>
<td>Fall related*</td>
<td>422 (86.5)</td>
<td>164 (85.4)</td>
<td>258 (87.2)</td>
<td>0.582</td>
<td>378 (86.9)</td>
<td>44 (83.0)</td>
<td>0.436</td>
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<td>Fall previous year†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>349 (71.5)</td>
<td>155 (80.7)</td>
<td>194 (65.5)</td>
<td>&lt;0.001</td>
<td>315 (72.4)</td>
<td>34 (64.2)</td>
<td>0.208</td>
</tr>
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<td>≥1</td>
<td>139 (28.5)</td>
<td>37 (19.3)</td>
<td>102 (34.5)</td>
<td></td>
<td>120 (27.6)</td>
<td>19 (35.8)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.7±4.4</td>
<td>27.7±4.4</td>
<td>27.7±4.4</td>
<td>0.961</td>
<td>27.8±4.4</td>
<td>26.9±4.8</td>
<td>0.154</td>
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<td>BMD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal BMD</td>
<td>132 (27.1)</td>
<td>54 (28.1)</td>
<td>78 (26.4)</td>
<td>0.906</td>
<td>123 (28.3)</td>
<td>9 (17.0)</td>
<td>0.081</td>
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<tr>
<td>Osteopenia</td>
<td>249 (51.0)</td>
<td>97 (50.5)</td>
<td>152 (51.4)</td>
<td></td>
<td>222 (51.0)</td>
<td>27 (50.9)</td>
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<td>Osteoporosis</td>
<td>107 (21.9)</td>
<td>41 (21.4)</td>
<td>66 (22.3)</td>
<td></td>
<td>90 (20.7)</td>
<td>17 (32.1)</td>
<td></td>
</tr>
<tr>
<td>Prevalent vertebral fracture‡§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>356 (73.0)</td>
<td>139 (72.4)</td>
<td>217 (73.3)</td>
<td>0.572</td>
<td>328 (75.4)</td>
<td>28 (52.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>62 (12.7)</td>
<td>22 (11.5)</td>
<td>40 (13.5)</td>
<td></td>
<td>54 (12.4)</td>
<td>8 (15.1)</td>
<td></td>
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<tr>
<td>Grade 2–3</td>
<td>70 (14.3)</td>
<td>31 (16.1)</td>
<td>39 (13.2)</td>
<td></td>
<td>53 (12.2)</td>
<td>17 (32.1)</td>
<td></td>
</tr>
<tr>
<td>Anti-osteoporosis treatment</td>
<td>167 (34.2)</td>
<td>70 (36.5)</td>
<td>97 (32.8)</td>
<td>0.402</td>
<td>142 (32.6)</td>
<td>25 (47.2)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Continuous variables are shown in mean±SD (SD) and categorical variables are shown as number of patients (%).
*Signifying that fracture was caused by a fall.
†Fall resulting in baseline fracture not included.
‡According to Genant et al.26
§According to most severe prevalent vertebral fracture.
BMD, bone mineral density; BMI, body mass index.

### Falls
During a median follow-up of 3 years (range: 0.1–3.0 years), 296 patients (60.7%) recorded 959 falls, corresponding to 68.6 falls per 100 person-years. The cumulative fall incidences and incidence rates per 100 person-years at 3 months and 6 months, and at 1-year, 2-year and 3-year follow-ups are presented in figure 1. Of the 296 patients with at least one fall, 115 (38.9%) had one fall and 181 (61.1%) had two or more falls (up to 39 falls in one patient).

A first fall was recorded by 189/488 patients (38.7%) during the 1st year of follow-up, by 56/299 (18.7%) during the 2nd, and by 51/243 (21.0%) during the 3rd year of follow-up. The median time to the first fall was 34 weeks (range: 1–156 weeks). Of the 959 falls, 47 (4.9%) resulted in a subsequent fall-related fracture.
There were no significant differences in baseline characteristics between patients with and without a fall during the 3-year follow-up, except for that a higher proportion of patients with incident falls reported at least one fall in the year before the start of the study (34.5% vs 19.3%, p<0.001) (see table 1). There were no significant differences in baseline characteristics between patients with one fall and those with multiple falls (data not shown).

Subsequent fractures
In total, 53 patients (10.9%) recorded 60 subsequent fractures, corresponding to 4.29 subsequent fractures per 100 person-years. The cumulative subsequent fracture incidences and incidence rates (per 100-person years) at 3 months and 6 months, and at 1-year, 2-year and 3-year follow-ups are presented in figure 2. Of all subsequent fractures, 47 (78.3%) were fall-related and 13 (21.7%) were non-fall-related. Fall-related subsequent fracture sites were: radius and ulna (n=9), tibia and fibula (n=8), proximal femur (n=4), metatarsal (n=4), hand phalanx (n=4), symptomatic vertebra (n=3), proximal humerus (n=3), clavicle (n=3), scapula (n=2), rib (n=2), pelvic bone (n=1), metacarpal (n=1), tarsal (n=1), patella (n=1) and foot phalanx (n=1), whereas subsequent non-fall-related fracture sites were symptomatic vertebral (n=5), metatarsal (n=2), foot phalanx (n=5) and hand phalanx (n=1). Half (53.2%) of all fall-related subsequent fractures were sustained at the first fall.

Baseline characteristics for patients with and without subsequent fractures are presented in table 1.

Of the 296 patients with at least one fall, 41 (13.9%) had 46 fall-related subsequent fractures, 7 (2.4%) had seven non-fall-related subsequent fractures and 1 (0.3%) had 1 fall-related and 1 non-fall-related subsequent fractures. Of the 192 patients without a fall, 4 (2.1%) had 5 non-fall-related subsequent fractures. Of note, the risk of subsequent fractures was higher in patients with at least one fall than in those without a fall (adjusted HR: 8.6; 95% CI 3.1 to 23.8; cumulative incidence: 16.6% vs 2.1%) (figure 3 and table 2). Results were similar when femoral neck BMD instead of the lowest BMD was used for adjustments (adjusted HR: 8.3; 95% CI 3.0 to 23.0). Additionally, subsequent fracture risk was higher in patients with moderate or severe prevalent vertebral fractures than in those with no or mild prevalent vertebral fractures (adjusted HR: 3.9; 95% CI 2.1 to 7.3; cumulative incidence: 24.3% vs 8.6%) (table 2).

The association between falls and subsequent fractures remained significant in sensitivity analyses (1) excluding...
patients with index and subsequent finger and toe fractures (adjusted HR: 8.2; 95% CI 2.5 to 26.6), and (2) by classifying patients with a non-fall-related subsequent fracture as non-faller (adjusted HR: 2.9; 95% CI 1.5 to 5.6).

DISCUSSION

In this 3-year prospective observational cohort study in patients aged 50+ years with a recent clinical fracture, treated according to current Dutch osteoporosis guidelines at an FLS, 60.7% of patients had at least one fall and 10.9% had at least one subsequent fracture. The majority (78.3%) of subsequent fractures was caused by a fall, and of all fall-related subsequent fractures, 53.2% occurred at the first fall. Subsequent fracture risk was ninefold higher in fallers than in non-fallers.

Literature reporting fall incidence in patients with a fracture is limited. Comparable to our results, van Helden et al reported a 3-month fall incidence of 15% in patients with a recent fracture at an FLS, and Matsumoto et al reported a 1-year fall incidence of 40% in ambulatory patients with a recent fracture. Various other studies included older, hip fracture patients and reported higher 1-year fall incidences up to 55%, except for the study from Yeh et al that reported a lower 1-year fall incidence (31%). Higher fall incidences in hip fracture studies can partially be explained by the older study population. Unfortunately, other fall risk factors cannot be compared.

An explanation for the lower fall incidence in the study by Yeh et al may be that information on the occurrence of falls was provided by patients and family caregivers, which may have resulted in under registration of falls.

A comparison between the fall incidence in our study and that in the general population is difficult to make, because population-based studies were conducted in a 65+ years old, community-dwelling population, whereas approximately 50% of our study population was <65 years old. The proportion of community-dwelling people aged 65+ years sustaining at least 1 fall over a 1-year period ranged from 28% to 35%, with an increasing incidence with increasing age. The 1-year fall incidence reported is our study is comparable to that in an older (65+ years aged) population, and, therefore, relatively high. However, in contrast to what has been reported in the literature, we found no higher 3-year fall incidence with increasing age. An explanation for this could be that, especially in the older age group, relatively more healthy patients participated in our study, resulting in a lower fall incidence in older age group. Another explanation could be that patients aged 50–65 years are more physically active, and, therefore, fall more often.

Compared with our results, previously published FLS studies reported lower, similar, and higher subsequent fracture rates. Differences can be explained by differences in patient selection. Studies that included

Figure 2  Cumulative incidence of subsequent fractures stratified by gender.

older patients and patients with more severe fractures reported higher subsequent fracture rates, whereas studies that excluded hand and foot index and subsequent fractures or frail patients reported lower rates. In 2010, the Dutch population consisted of approximately 6,000,000 people aged 50+ years, of whom 119,419 sustained a fracture that year, corresponding to a calculated annual fracture incidence of 2.0% in the general Dutch population of 50+ years. Compared with the general Dutch population of 50+ years, the fracture incidence was more than 2 times higher in our study, even in the 3rd year of follow-up. In our study, fracture incidence remained high despite treatment according to the current osteoporosis guideline, raising the question of what more can be done to prevent subsequent fractures. Even though conflicting results have been published about the effect of fall prevention strategies on subsequent fracture, we hypothesise that fall interventions could be effective in patients at highest risk, namely those with a recent fracture at risk of falling. Furthermore, according to literature, recurrent fallers have an almost fourfold increased odds of sustaining a fall-related fracture compared with individuals with a single fall. However, we found that the majority of subsequent fall-related fractures occur at the first fall after the index fracture, with a median time to the first fall of 34 weeks. Interestingly, fall incidence was higher in the first year of follow-up compared with the second and third years. This may indicate an imminent fall risk, which may attribute to the imminent subsequent fracture risk after an index fracture. This implies that the FLS patients with a high fall risk should be identified immediately, because there is a small window of opportunity to prevent falls and fall-related subsequent fractures.

Remarkably, in contrast to previous studies indicating that imminent fracture risk that was highest in the 1st year after an index fracture, there was a linear subsequent fracture incidence during a 3-year follow-up in this study. An explanation for the linear subsequent fracture incidence may be the relatively healthy patients who

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unit of comparison</th>
<th>HR and 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Women vs men</td>
<td>1.39 (0.68 to 2.83)</td>
<td>0.362</td>
</tr>
<tr>
<td>Age</td>
<td>+5 years</td>
<td>0.97 (0.82 to 1.13)</td>
<td>0.662</td>
</tr>
<tr>
<td>Index fracture</td>
<td>Major or hip vs all other</td>
<td>0.68 (0.35 to 1.33)</td>
<td>0.263</td>
</tr>
<tr>
<td>BMD</td>
<td>−0.12 g/cm²</td>
<td>1.30 (0.95 to 1.78)</td>
<td>0.101</td>
</tr>
<tr>
<td>Prevalent vertebral fracture</td>
<td>Yes vs no</td>
<td>3.88 (2.07 to 7.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fall</td>
<td>Yes vs no</td>
<td>8.58 (3.09 to 23.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMD, bone mineral density.
agreed to participate in our study. Compared with non-attenders, they were younger, and a lower proportion had a major baseline fracture, a prevalent vertebral fracture and osteoporosis, and if indicated, were more likely to receive AOM. Importantly, in addition to falls, moderate to severe prevalent vertebral fractures at baseline were associated with subsequent fractures, even though anti-osteoporosis medication had been prescribed to these patients according to the current Dutch osteoporosis guideline.

This study has several limitations. Although, this is one of the largest prospective studies in an FLS population focusing on the incidence of falls after an index fracture, the number of patients is modest and the number of subsequent fractures relatively low. Therefore, the association between falls and fall-related, and non-fall-related subsequent fractures could not be analysed separately. A fall ‘not resulting in a subsequent fracture’ might indicate frailty of patients, and might be different from those falls that directly resulted in a subsequent fracture. Future studies are needed to investigate this difference. Finally, because of small numbers, subgroup analyses should not be performed. Furthermore, data on falls were collected prospectively using fall diaries that had to be returned at 3 months and 6 months, and 1 year, 2 years and 3 years. However, no procedures were in place to validate self-reported falls, and it is possible that recall bias could have led to underregistration of falls. Moreover, no information was available on falls between the index fracture and enrolment in the study. Finally, relatively healthy patients participated in the study. Compared with non-attenders, they were younger, a lower proportion had a major baseline fracture, a prevalent vertebral fracture and osteoporosis. The proportion of patients with a fall and subsequent fractures could be expected to be even higher in the total FLS population.

In conclusion, in this 3-year prospective observational cohort study in FLS patients, subsequent fracture incidence was high despite being prescribed anti-osteoporosis medications according to the current Dutch osteoporosis guidelines. Subsequent fracture risk was 9-fold higher in fallers than in non-fallers, and the majority of fall-related subsequent fractures occurred at the first fall at a median time of 34 weeks. These findings emphasise that immediate attention for fall risk reduction could be beneficial in FLS care. Various risk factors, including comorbidities, medication use, polypharmacy and alcohol use among others, contribute to patient’s fall risk and further research is needed to determine predictors for falls to identify patients at highest risk of falling.

**REFERENCES**


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Contributors LV collected data, carried out data analysis and drafted the manuscript. CEW and JPvdB developed the study design, wrote the research protocol, collected data and critically reviewed the manuscript. PG developed the study design, wrote the research protocol and critically reviewed the manuscript. RYVdV collected data and critically reviewed the manuscript. TVN and TT assisted with data analysis and critically reviewed the manuscript. HMJJ, SK, JD, JE, JRC and DB critically reviewed the manuscript. JPvdB was responsible for the overall content as the guarantor. All authors approved the final version of the manuscript.

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