


# Incidence of Subsequent Hip Fracture and Mortality in Elderly Patients: A Multistate Population-Based Cohort Study in Eastern Spain

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## ABSTRACT

Osteoporotic hip fractures in older people may confer an increased risk of subsequent hip fractures and death. The aim of this study was to estimate the cumulative incidence of both recurrent hip fracture and death in the Valencia region. We followed a cohort of 34,491 patients aged  $\geq 65$  years who were discharged alive from Valencia Health System hospitals after an osteoporotic hip fracture between 2008 and 2015, until death or end of study (December 31, 2016). Two Bayesian illness-death models were applied to estimate the cumulative incidences of recurrent hip fracture and death by sex, age, and year of discharge. We estimated 1-year cumulative incidences of recurrent hip fracture at 2.5% in women and 2.3% in men, and 8.3% and 6.6%, respectively, at 5 years. Cumulative incidences of total death were 18.3% in women and 28.6% in men at 1 year, and 51.2% and 69.8% at 5 years. One-year probabilities of death after recurrent hip fracture were estimated at 26.8% and 43.8%, respectively, and at 57.3% and 79.2% at 5 years. Our analysis showed an increasing trend in the 1-year cumulative incidence of recurrent hip fracture from 2008 to 2015, but a decreasing trend in 1-year mortality. Male sex and age at discharge were associated with increased risk of death. Women showed higher incidence of subsequent hip fracture than men although they were at the same risk of recurrent hip fracture. Probabilities of death after recurrent hip fracture were higher than those observed in the general population. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

**KEY WORDS:** AGING; FRACTURE PREVENTION; FRACTURE RISK ASSESSMENT; HEALTH SERVICES RESEARCH; OSTEOPOROSIS

## Introduction

Hip fracture is one of the most frequent health consequences of osteoporosis among the elderly population. Osteoporosis is characterized by low bone mass and the deterioration of bone architecture, resulting in a higher risk of fragility fractures.<sup>(1)</sup> These disrupt patients' daily life and have a high economic impact on healthcare systems. A 2013 report estimated that the cost of osteoporosis in the EU reached €37 billion in 2010, with 66% of this sum employed for treating incident fractures.<sup>(2)</sup> In the case of Spain, data on resource use in the year following a first osteoporotic hip fracture have also shown high derived costs.<sup>(3)</sup>

Beyond its economic cost, subsequent hip fractures may happen with higher risk than the first hip fracture. Some studies

show that patients with a hip fracture are at twofold risk<sup>(4,5)</sup> and threefold risk<sup>(6)</sup> of posterior hip fractures, whereas other authors estimate the incidence of second hip fracture as four times the incidence of first in elderly women.<sup>(7)</sup> The cumulative incidence of a second hip fracture has been estimated according to population, country, age, comorbidities, and follow-up time, and it ranges from 1% to 9% at 1 year and from 4.42% to 20% at 5 years.<sup>(4,5,8-15)</sup> These recurrences frustrate the possibility of a recovery and cause chronic pain, disability, and social dependence.<sup>(16)</sup> In addition, hip fracture increases the risk of death by at least twofold in age-matched populations.<sup>(17)</sup> That excess of mortality has been estimated to be even higher after a second hip fracture, increasing hazard of death by 55%.<sup>(18)</sup>

Although hip fracture has been widely studied worldwide,<sup>(19-23)</sup> fewer reports deal with recurrent hip fracture and subsequent

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death, and those that do were mostly published many years ago. Thus, there is a lack of updated information about this recurrent health problem and its effect on mortality. Moreover, differences in the incidence of hip fracture between Spanish regions have been observed,<sup>(24)</sup> making it necessary to analyze them separately. The body of evidence about recurrent hip fracture for individual regions is even more limited.

Regarding post-hip fracture therapeutic management, osteoporosis medication is effective for preventing subsequent fractures and is recommended by every clinical guideline.<sup>(25)</sup> However, low prescription rates have been reported worldwide,<sup>(26)</sup> with evidence that these have even been decreasing over the years.<sup>(27)</sup> Given this management aggravation, studying incidence trends for recurrent fracture and death over time is of interest.

The overarching aim of the study is to provide information about recurrent hip fracture and associated mortality, from 2008 to 2015 in the Valencia region of Spain. Specific objectives are to assess the incidence of recurrent hip fracture, death, and death after recurrent hip fracture by sex and age and to compare incidence the year of discharge to detect trends in recurrent fracture management.

## Subjects and Methods

### Design

A population-based cohort of 34,491 patients aged  $\geq 65$  years who were discharged after a hip fracture from January 1, 2008, to December 31, 2015. These patients were followed for a minimum of 365 days and a maximum of 8 years, until the end of study (December 31, 2016).

### Setting

The study took place in the Valencia region of Spain, with a population of roughly 5 million people, or 10% of the Spanish population. The region provides universal healthcare services (with no out-of-pocket expenditure except for drug cost-sharing) to 97% of the population through the Valencia Health System (VHS), an extensive network of public hospitals, primary care centers, and other public resources managed by the regional government.

### Population

We included all patients aged  $\geq 65$  years discharged alive from VHS hospitals after suffering a hip fracture (International Classification of Diseases 9th revision Clinical Modification [ICD-9-CM] codes: 820.xx and 733.14) between January 1, 2008, and December 31, 2015. Exclusion criteria were as follows: being  $< 65$  years old at discharge, diagnosis of multiple fracture, road accident, or active bone cancer as well as nonresidents in the region and lack of pharmaceutical coverage (due to difficulties associated with follow-up).

### Data sources

Data were obtained from the VHS Integrated Database (VID). The VID represents a comprehensive set of information from different sources about the inhabitants in the region of Valencia such as sociodemographic and administrative data (sex, age, nationality, etc.), diagnoses, procedures, pharmaceutical prescription and dispensation, healthcare utilization data from hospital care, ambulatory care, and other public health services. Although

these databases were not initiated at the same time, the VID integrates their information since 2008. Linkage between them has become possible through a unique personal identification number.

### Study endpoints

The outcomes measures were hospitalization for a recurrent osteoporotic hip fracture (ICD-9-CM codes 820.xx and 733.14 for those recurrent hip fractures between 2008 and 2015; and ICD-10 codes S72.0, S72.1, and S72.2 in 2016) and death for any cause after the index date (index hip fracture). Patients were followed after a first hip fracture, only being censored because of death or end of study (December 31, 2016). Relevant outcomes were the time to a recurrent hip fracture, time to death, and time from recurrent hip fracture to death. Recurrent hip fracture was considered both a transient state between index hip fracture and death, and an endpoint as we were interested in the incidence of recurrent hip fracture. Patients who died before a recurrent hip fracture counted as censored observations for the calculation of the risks and incidences of recurrent hip fracture. Note that posterior admissions with a main diagnosis of hip fracture within 2 days after the index episode were considered the same episode, and not recurrent hip fractures.

### Covariates

We collected variables that were potentially related to the risk of hip fracture, in particular sociodemographic characteristics; comorbidities; and use of osteoporosis medication, other drugs, and emergency services in the 365 days before hospitalization. Nevertheless, only sex, age at the index discharge, and calendar year of the index discharge were included as baseline covariates in our statistical analysis. The first two were considered relevant for defining a basic patient profile, whereas the last could shed light on differences in clinical practice over time.

### Ethics

The study was observational and used population-based cohort data, which were anonymized before transferring to the research team. It was approved by the Ethics Committee for Clinical Research of the General Directorate of Public Health and the Centre for Public Health Research (session on October 26, 2012). All protocols were performed in accordance with Spanish laws on data protection for health research (Act 3/2018 transposing the 2015 European Data Protection Regulation).

### Analysis

A Bayesian statistical analysis was conducted using two multistate models. They are a class of stochastic processes which account for event history data, with individuals who may experience different events in time. Relevant data are the events and their subsequent survival times. Multistate models allow for different structures depending on the number and relationships between the states. These models result in a generalization of the widely used competing risks model with estimations for the mortality and time-to-event after a non-terminal event as additional information. On the other hand, Bayesian inference is a statistical methodology based on a conception of probability that allows probability distributions to be assigned to any element of uncertainty in a statistical study. In the particular case of survival models, Bayesian models allow us to estimate the

parameters naturally through a probability distribution without the need to use asymptotic resources to assess the behavior of their estimators.

We considered two illness-death models,<sup>(28)</sup> a class of multi-state models with three possible states: initial state (discharged), recurrent fracture, and death. Transitions between states were from the initial state to recurrent fracture, from the initial state to death, and from recurrent fracture to death (Supplemental Fig. 1).

The first model included sex and age as covariates, leading to general conclusions on hip fracture epidemiology. The second model also considered the year of discharge as a covariate to show differences between years. Age was included as a continuous predictor.

Transition times between states (discharge alive after index fracture, refracture, and death) were modeled using the subsequent hazard functions through Cox proportional hazards models with Weibull baseline hazard functions. This fully parametric approach with Weibull distributions was coherent with previous knowledge indicating higher risks of recurrent hip fracture and mortality during the first years. A semi-Markov assumption was made for the transition from recurrent hip fracture to death, defining its hazard as dependent on the time from discharge to recurrent hip fracture.

A non-informative prior independent scenario was considered for specifying the prior distribution of the model parameters. The posterior distribution contains all the current information of the problem, and it is usually the starting point of all relevant inferences. The subsequent posterior distribution was approximated using a Markov chain Monte Carlo (MCMC) algorithm. Convergence to the posterior distribution was assessed using three chains and 10,000 iterations per chain (with an adapt period and burn-in of 1000 iterations each). For the first model, posterior distributions of the cumulative incidence of recurrent hip fracture, total death, and death after recurrent hip fracture were computed. Predicted cumulative incidences were summarized with their posterior means by sex for average-aged patients (Table 2). Cumulative incidences were also presented for some specific ages (70, 80, and 90 years old) and depicted as predicted cumulative incidence curves. For the second model, 1-year cumulative incidences of recurrent hip fracture and total death were estimated by sex and year of discharge for average age patients and summarized using posterior means and 95% credible intervals (CIs). Posterior distributions for hazard ratios (HRs) were estimated to compare recurrent hip fracture and death risks among different covariate levels. Specific HRs were provided for each transition to death, without and after recurrent hip fracture, and summarized with the posterior mean and 95% CIs.

All analyses were performed using the R environment,<sup>(29)</sup> with the packages rjags<sup>(30)</sup> and snow<sup>(31)</sup> for a parallel estimation of the chains resulting from the MCMC method.

## Results

We included 34,491 patients  $\geq 65$  years old who were discharged alive after a hip fracture from January 1, 2008, to December 31, 2015. Baseline patient characteristics have been summarized in Table 1. Our cohort comprised a majority of women (74.8%) and the mean age at the first fracture was 83.4 years (IQR 79.0–88.3 years). The main comorbidities were hypertension (73.8%), diabetes (31.8%), and dementia (27.8%). Low rates of previous

**Table 1.** Baseline Patient Characteristics for the Complete Cohort and for Those With a Recurrent Fracture

Covariates	Total (n = 34,491)		Refractured (n = 2532)	
	n	%	n	%
<b>Sociodemographic</b>				
Sex				
Women	25,807	74.8	2016	79.6
Men	8684	25.2	516	20.4
Age (years)				
65–74	4282	12.4	249	9.8
75–84	15,040	43.6	1261	49.8
85–94	13,994	40.6	970	38.3
$\geq 95$	1175	3.4	52	2.1
<b>Comorbidities</b>				
Dementia	9582	27.8	644	25.4
Diabetes	10,966	31.8	786	31.0
Heart failure	4658	13.5	272	10.7
Hypertension	25,469	73.8	1852	73.1
Depression	6556	19.0	532	21.0
<b>Medication use</b>				
Osteoporosis	5631	16.3	476	18.8
Dementia	4959	14.4	395	15.6
Diabetes	8821	25.6	716	28.3
Opioids	5983	17.4	491	19.4
NSAID	10,319	29.9	883	34.9
Anxiolytics	13,827	40.1	1208	47.7
Antipsychotics	6527	18.9	481	19.0
<b>Emergencies</b>				
0	3846	11.2	267	10.6
1	17,680	51.3	1352	53.4
$\geq 2$	12,965	37.6	913	36.1
<b>Polypharmacy</b>				
0–5	17,601	51.0	1140	45.0
6–12	15,696	45.5	1301	51.4
$\geq 13$	1194	3.5	91	3.6

osteoporosis medication use were observed (16.3%); these were slightly higher among the refractured (18.8%). Anxiolytics (40.1%) and NSAIDs (29.9%) were the most commonly used medications in the year preceding hip-fracture hospitalization (47.7% and 34.9%, respectively, for refractured patients). Half the patients (45.5%) had six to 12 prescribed medications over the year prior to the index fracture (refractured: 51.4%). Patients were followed for a median time of 5.0 years (IQR 3.0–7.0 years).

### Multistate model by sex and age

Overall, women and men showed a similar risk of recurrent hip fracture (women versus men HR 1.03 [95% CI, 0.94–1.12]; Supplemental Table 1). One-year incidence was 2.5% in average-aged women and 2.3% in average-aged men, while mean cumulative incidence at 5 years from discharge was 8.3% and 6.6%, respectively (Table 2).

Regarding cumulative incidences of recurrent hip fracture up to 10 years after the discharge by sex and age (Fig. 1), faster increase was observed for older ages in both sexes, until the fourth for women and the second year for men, when few of those older patients were still alive and thus at risk of a recurrent hip fracture.

**Table 2.** Cumulative Incidences of Recurrent Hip Fracture, Total Death, and Death After Recurrent Hip Fracture, by Sex and Follow-Up Time

Time	Recurrent hip fracture (%)		Total death (%)		Death after recurrent hip fracture (%)	
	Women	Men	Women	Men	Women	Men
6 months	1.4	1.3	11.1	17.7	18.3	31.2
1 year	2.5	2.3	18.3	28.5	26.8	43.8
2 years	4.4	3.8	29.4	44.0	38.1	58.8
3 years	5.9	5.0	38.1	55.0	46.1	68.1
4 years	7.2	5.9	45.2	63.3	52.3	74.5
5 years	8.3	6.6	51.2	69.8	57.3	79.2
10 years	12.0	8.6	71.1	87.4	73.0	91.1

With respect to the estimated incidence of total death up to 10 years after discharge, by sex and age (Table 2, Fig. 2A), women were at lower risk of death than men of the same age, both for death without recurrent hip fracture (HR 0.60 [95% CI, 0.58–0.62]) and after recurrent hip fracture (HR 0.54 [95% CI, 0.48–0.61]). Mean 1-year cumulative incidence of total death was estimated at 18.3% in women and 28.5% in men, reaching 51.2% and 69.8%, respectively, 5 years after discharge. Mean probabilities of death after a recurrent hip fracture were estimated at 26.8% in women and 43.8% in men at 1 year and 57.3% and 79.2% at 5 years (Table 2, Fig. 2B).

#### Multistate model including year of discharge

Overall, 1-year incidence of recurrent hip fracture by year of discharge (Fig. 3) was stable for both, men and women, until the end of the study period, where a relevant growth was observed (2014 versus 2008 HR 1.36 [95% CI, 1.16–1.60]; 2015 versus 2008 HR 1.37 [95% CI, 1.14–1.64]) (Supplemental Table 2). For those who had a hip fracture in 2008, it was estimated that in the year after the initial fracture a 2.24% and a 2.01% women and men, respectively, would have experienced a hip refracture, whereas a 3.13% and a 2.87% for those women and men discharged in 2015, respectively.

One-year cumulative incidence of mortality by year of discharge (Fig. 4A, Supplemental Table 2), was lower in women, 20%, than in men, 31%, for average-aged patients (83.4 years) fractured in 2008. A decline in incidence was observed over the

study period, reaching a nadir in 2015 with means of 15.6% and 24.7%, in average-aged women and men, respectively.

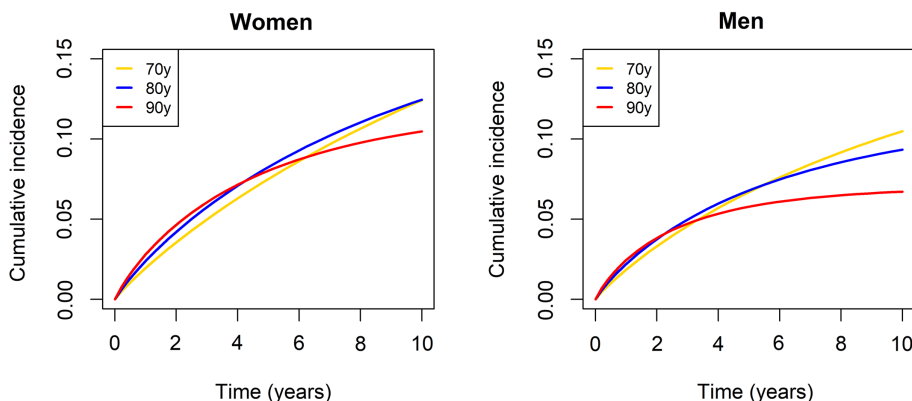
One-year cumulative incidence of death after recurrent hip fracture (Fig. 4B, Supplemental Table 2) was also lower in women than in men, at 28% and 46%, respectively, for average-aged patients fractured in 2008. Incidence was stable from 2008 to 2012, decreased to its nadir in 2014, and showed a slight increase in 2015, with means of 23% in women and 39% in men.

## Discussion

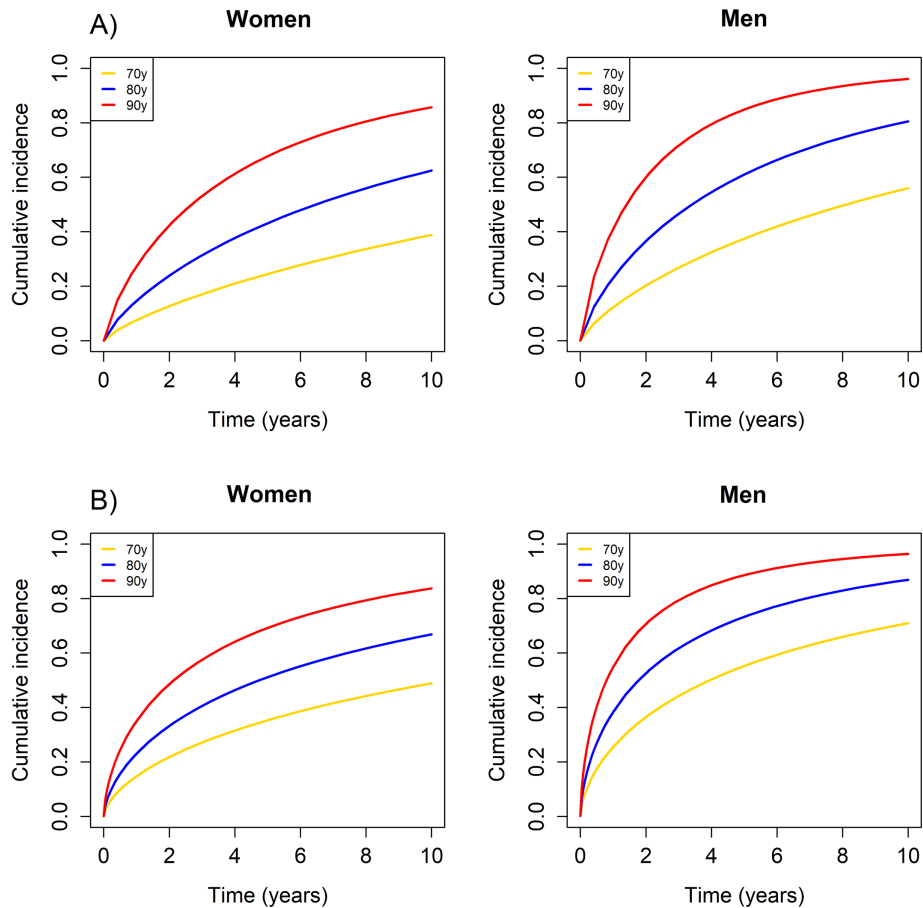
In our study population, we estimated similar cumulative incidences of recurrent hip fracture for women than for men. As expected, men were estimated to be more likely to die as compared to women both after the first and the second fracture. Indeed, mortality was estimated to be higher after that subsequent hip fracture. Regarding time trends, our analysis revealed a positive association between the incidence of recurrent hip fracture and the year of discharge after the index fracture, for the years 2008–2015. On the other hand, the incidence of death showed a decreasing trend.

#### Recurrent hip fracture

We estimated 1-year cumulative incidences of recurrent fracture 2.5% and 2.3% for women and men, which rose to 8.3% and 6.6% after 5 years, respectively. Initially, cumulative incidence of



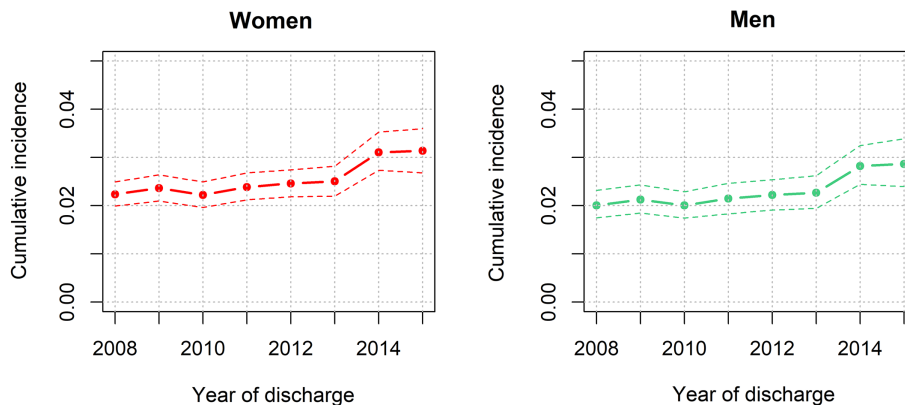
**Fig. 1.** Cumulative incidence of recurrent hip fracture, by sex and age. The legend shows colored lines as the mean of the posterior distribution of the cumulative incidence of recurrent hip fracture for patients aged 70, 80, and 90 years, respectively.



**Fig. 2.** Cumulative incidence of all-cause death by sex and age. (A) Cumulative incidence of total death (transition probability from discharge state to death). (B) Cumulative incidence of death after recurrent hip fracture (transition probability from recurrent hip fracture state, when the recurrent hip fracture occurs, to death). The legends show colored lines as the mean of the posterior distribution of the cumulative incidence of death for patients aged 70, 80, and 90 years, respectively.

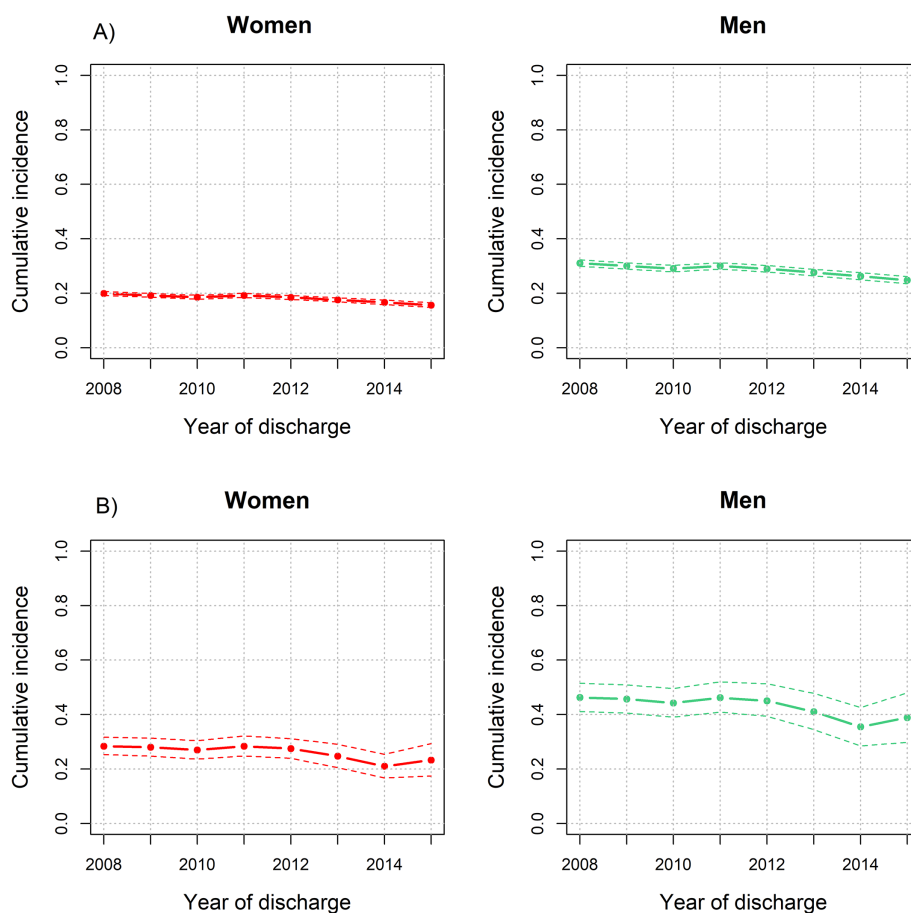
recurrent fracture was thus observed to be equal for women and men but became higher for women after some time (+0.9 after 3 years). Note that despite differences in the incidence, we have

estimated an HR which indicates no differences in the risk of recurrent hip fracture between women and men. Because there exist two possible causes of failure (refracture and death),



**Fig. 3.** One-year cumulative incidence of recurrent hip fracture (solid lines) and 95% credible intervals (dashed lines) by sex and year of discharge. Solid and dashed lines represent the mean, and the 2.5th and 97.5th percentiles, respectively, of the posterior distribution of the cumulative incidence of recurrent hip fracture 1 year after discharge.





**Fig. 4.** One-year cumulative incidence of death from any cause (solid lines) and 95% credible intervals (dashed lines) by sex and year of discharge. (A) One-year cumulative incidence of total death (transition probability from discharge state to death). (B) One-year cumulative incidence of death after recurrent hip fracture (transition probability from recurrent hip fracture state to death). Solid and dashed lines represent the mean, and the 2.5th and 97.5th percentiles, respectively, of the posterior distribution of the cumulative incidence of death 1 year after discharge.

incidence is calculated from a combination of two hazard functions. Our estimations point out that sex is not related with the risk of recurrent hip fracture. Therefore, considering that women showed fairly lower cumulative incidences of death than men, death must play a major role in explaining those differences. In addition, the knowledge that the risk of recurrent hip fracture does not differ between sexes has important implications in clinical practice. And, even more so when during the year before the index fracture, men in our study population showed significantly lower rates of treatment with antiosteoporosis medications than women (5.8% versus 19.9%, respectively). Considering that both sexes are at the same risk of recurrent hip fracture, there is no reasonable/evidence-based motivation to treat them differently (and maybe due to lack of knowledge or gender bias). To inform policymakers and clinicians on this finding should be prioritized because it may have a considerable impact in the prevention and care of hip fracture.

Regarding cumulative incidence of recurrent hip fracture in the literature, certain authors have reported similar results to ours in different populations. Lee et al.<sup>(4)</sup> estimated the cumulative incidence of second hip fracture in the Taiwanese population, for the years 2006–2011, at 2.2% for women and 1.8% for men 1 year after the first fracture (7.2% and 5.7% after 5 years).

Chen et al.<sup>(8)</sup> extended the population to Taiwanese patients with a first hip fracture between 2001 and 2011. They estimated the 1-year cumulative incidence of second hip fracture at 2.6% and 2.1% for women and men, respectively (8.1% and 5.9% after 5 years). Other studies reported lower cumulative incidences, such as Lee et al.<sup>(12)</sup> at 0.9% after 1 year, whereas Ryg et al.<sup>(5)</sup> estimated the highest, at 9% after 1 year (at 20% after 5 years). Table 3 includes results from several studies regarding cumulative incidence of second hip fracture for different follow-up times. Some estimates were stratified by sex, whereas other studies presented aggregated incidences.

#### Death after second hip fracture

On the other hand, we estimated the 1-year cumulative incidence of death after a second hip fracture at 26.8% in average-aged women and 43.8% in average-aged men, and 57.3% and 79.2%, respectively, after 5 years. These estimates were higher compared to the total population. However, note that a direct comparison is not right and is out of scope of this study. Our analysis considered age at discharge after the index fracture, but patients get older by the time of recurrent hip fracture. Additionally, it would be needed to adjust for some covariates such as

**Table 3.** Variation in the Estimations of the Cumulative Incidence of Second Hip Fracture Among Studies, By Country, Sex (When Stratified) and at 1, 2, 5, and 10 Years

Author	Country	Cumulative incidence of second hip fracture (%)				Mortality after second hip fracture (%)	
		1 year	2 years	5 years	10 years	1 year	5 years
Current study	Spain	2.5 W	4.4 W	8.3 W	12.0 W	26.8 W	57.3 W
		2.3 M	3.8 M	6.6 M	8.6 M	43.8 M	79.2 M
Lönnroos (Osteoporos Int) 2007 <sup>(14)</sup>	Finland	5.08	8.11	–	–	–	–
Berry (Arch Intern Med) 2007 <sup>(10)</sup>	EEUU	3.1 W	5.0 W	9.7 W	13.8 W	24.1	66.5
		0.0 M	1.1 M	2.2 M	5.7 M		
Ryg (JBMR) 2009 <sup>(5)</sup>	Denmark	9.0	–	20.0	–	21.0 W	58.0 W
						27.0 M	64.0 M
Kim (Bone) 2012 <sup>(11)</sup>	South Korea	1.9	–	–	5.5 <sup>a</sup>	–	–
Omsland (Bone) 2013 <sup>(15)</sup>	Norway	4.4 W	6.9 W	11.5 W	15.1 W	–	–
		3.2 M	5.0 M	8.3 M	11.0 M		
Lee (Osteoporos Int) 2013 <sup>(12)</sup>	South Korea	0.9	1.9	–	–	–	–
Lee (Osteoporos Int) 2013 <sup>(2,13)</sup>	South Korea	2.4	5.1	–	–	–	–
Lee (Acta Orthopaetica TT) 2016 <sup>(4)</sup>	Taiwan	2.2 W	3.9 W	7.2 W	–	12.1 W	41.2 W
		1.8 M	2.8 M	5.7 M		17.4 M	47.3 M
Chen (Osteoporos Int) 2017 <sup>(8)</sup>	Taiwan	2.6 W	4.4 W	8.1 W	11.2 W	–	–
		2.1 M	3.3 M	5.3 M	7.9 M		
Ho (Osteop & Sarcop) 2020 <sup>(9)</sup>	Hong Kong, China	1.24	–	4.42	6.79	12.8 W	46.7 W
						23.7 M	66.9 M

M = men, W = women.

<sup>a</sup>Overall cumulative incidence instead of 10-year.

comorbidities or medication use to do so. Only a few studies reported results of mortality after subsequent hip fracture<sup>(4,5,9,10)</sup>; all showed results compatible with ours with respect to the increased incidence of death after a recurrent fracture, although we estimated considerably higher mortality rates. In addition, several authors described an excess of mortality after a second hip fracture, demonstrating a higher risk compared to that after the first fracture.<sup>(18,28,29)</sup> Because recurrent fractures are supposed to increase the risk of death, even after adjusting for age, some fragility differences may exist. Some patient characteristics at baseline might differ from those after recurrent hip fracture, resulting in that increased risk of death. Further research into the relationship between these factors and the risk of death after second hip fracture, as well as the increase in frailty after a recurrent hip fracture, is needed to assess differences in risk and incidence.

### Trends in the incidences of refracture and death

Finally, our analysis showed an ascending trend in the 1-year cumulative incidence of recurrent hip fracture during the 2008–2015 enrolment period and a descending trend in 1-year mortality. Although lower mortality rates could result in an increased number of recurrent fractures, the relevant HRs for the years 2014 and 2015 show that, in fact, patients with a hip fracture during those years were at higher risk. Regarding mortality, HRs of death without recurrent hip fracture mostly indicated a relevant decrease among years in the associated risk, with 2014 and 2015 showing the largest differences with respect to 2008. However, regarding death after recurrent hip fracture, the year 2014, which showed the minimum 1-year cumulative incidence of death after recurrent hip fracture, was the only one with a relevant HR. Patients mostly died without a recurrent hip fracture because only 2532 of 34,491 had a second fracture.

As a result, we obtained wider 95% CIs for the HRs of death after recurrent hip fracture, which mostly include 1, indicating no strong enough evidence of differences among years. Several explanations of what causes these trends in the incidence and mortality may be possible. On the one hand, the increase in the number of recurrent hip fractures might be due to an aggravation in the clinical management of the hip fractures. In the region of Valencia, the proportion of patients treated with antio-osteoporosis medication experienced a decreasing trend during the period of interest.<sup>(27)</sup> Alternatively, many factors which could increase the number of falls might have changed during that period,<sup>(32)</sup> thus increasing the number of hip fractures. Another plausible reason would be a change in fracture classification or coding systems. However, no changes were observed in the standard classification of medical diagnoses; the ICD-9-CM system was used throughout the 2008–2015 period. Also note that the number of patients who suffer a hospitalization due to a hip fracture is quite stable. Thus, there is no change in the size of the population at risk of refracture, which explains the trend in the incidence of recurrent hip fracture. Although identifying the causes of the changing incidence of recurrent hip fracture would be of interest, our study did not provide any evidence to support a particular hypothesis. Further research is needed to shed light on the reasons behind the observed trends.

### Limitations

A common limitation in population-based cohort studies arises due to registry bias. The registered data might contain mistakes such as wrong diagnosis codes of fracture or wrong dates of death, introducing bias in the estimations of the incidence.

Not including a prefracture population also constitutes a limitation. The risk of recurrent hip fracture cannot be compared with the risk of a first hip fracture in the Valencian population,

and excess mortality in hip fracture patients cannot be compared with the background population of the Valencia region.

Another limitation is that our index hip fracture was not the first hip fracture in many cases. We defined it as a hip fracture after the age of 65 years, with some exclusion criteria. Thus, recurrent hip fractures are the second for some patients, but the third or more for others, which might hinder the comparison with other studies where only the first fracture is included.

The study considers only recurrent hip fracture, although the risk of other osteoporotic fractures might be of interest in our population. This is because, first, hip fracture is associated with the worst consequences in terms of morbidity and mortality, disability, functional loss and costs. Second, we used data from hospitalizations since these data have the highest reliability to identify acute events, whereas other major fractures, such as wrist or vertebral fractures, are very difficult to identify in this data source.

Last, patients comprising the cohort were all discharged alive after hospitalization due to a hip fracture, not having information about those who died in the hospital. On the other hand, we included patients who died at the hospital after recurrent hip fracture given that the cohort was defined by the index hip fracture. Thus, caution is warranted when comparing mortality after the index versus recurrent hip fracture, especially during the first years after discharge.

## Conclusions

Recurrent hip fracture represents an important outcome after being discharged due to a previous hip fracture. Its incidence suggests that is an unlikely event, but it needs to be studied, due to its potential to increase the risk of disability<sup>(16)</sup> and death.<sup>(4,5,9,10,11,18,28,29)</sup>

In summary, our study provides valuable information on the cumulative incidence of recurrent hip fracture as well as on the less studied cumulative incidence of death after recurrent hip fracture. We estimated women to be at the same risk of subsequent fracture as men, although there were considerable differences in the cumulative incidence of second hip fracture between them, due to the increased risk of death among men. This finding is particularly relevant for the appropriate postfracture management in the male population, for whom appropriate treatment is needed to prevent recurrent fractures. Furthermore, it should be appropriately studied in other populations, and if confirmed could have important clinical and public health implications. The cumulative incidence of death after the second hip fracture was estimated higher for men than for women. Furthermore, despite both risks of death with and without recurrent hip fracture are not directly compared in our analysis, mortality after a recurrent fracture was greater than that in the general population, which reinforces the importance of dealing with those recurrences appropriately. Regarding time-trends, a decline was observed in mortality, but the cumulative incidence of a recurrent hip fracture grew over time. Further research is needed to identify the reasons behind those trends as well as related risk factors.

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## AUTHOR CONTRIBUTIONS

**Fran Llopis-Cardona:** Conceptualization; data curation; formal analysis; investigation; methodology; software; visualization; writing – original draft; writing – review and editing. **Carmen Armero:** Methodology; resources; supervision; writing – review and editing. **Isabel Hurtado:** Conceptualization; data curation; investigation; methodology; resources; writing – review and editing. **Aníbal García-Sempere:** Conceptualization; data curation; investigation; methodology; resources; writing – review and editing. **Salvador Peiró:** Conceptualization; funding acquisition; investigation; methodology; resources; writing – review and editing. **Clara L Rodríguez-Bernal:** Conceptualization; data curation; investigation; methodology; resources; writing – review and editing. **Gabriel Sanfélix-Gimeno:** Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing.

## Conflicts of Interest

The authors declare that they have no competing interests.

## Peer Review

The peer review history for this article is available at <https://publons.com/publon/10.1002/jbmr.4562>.

## Data Availability Statement

The data that support the findings of this study are not publicly available due to legal restrictions on sharing the data set, regulated by the Valencia regional government by means of legal resolution by the Valencia Health Agency [2009/13312]. Data are however available from the authors upon reasonable request. Requests to access the datasets should be directed to Management Office of the Data Commission in the Valencia Health Agency (email: [solicitud\\_datos@gva.es](mailto:solicitud_datos@gva.es)).

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