Long-term refracture and mortality assessment in fractured elderly individuals: an evidence-based analysis based on T.A.R.Ge.T. data

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ABSTRACT

Purpose: The aim of this study was to estimate the incidence of fracture and refracture in the elderly, along with the risk of refracture and mortality among elderly fractured individuals.

Methods: An observational cohort study was carried out based on the healthcare administrative database of the Tuscany region (Italy). Individuals aged ≥65 years with a hospital discharge diagnosis of hip fracture identified between 1st January 2010 and 31st December 2016 were selected. Those presenting a diagnosis of neoplasia or Paget's disease were excluded from the analysis. Crude and age- and sex-standardized annual incidences of fracture (95% confidence intervals) were estimated. During the follow-up the cumulative incidence of refracture was assessed among fractured individuals. Lastly, the risks of refracture, death after fracture, and death after refracture were assessed in the study cohort by using a competing risk model.

Results: Overall, the standardized incidence of fracture remained stable, changing from 7.41 (95% CI: 7.21–7.61) in 2010 to 7.10 (95% CI: 6.93–7.27) in 2017. Higher incidence rates of fracture were observed among females and older individuals. The one-year cumulative incidence of refracture decreased slightly from 2010 (35 per 1,000 inhabitants) to 2016 (26.7 per 1,000 inhabitants). For those with a longer follow-up, a cumulative increased risk over time was observed. The competing risk analysis showed an increase in mortality risk in the study population, from 21% at the first to 49% at the fifth year. Similar patterns were observed for refracture (from 1% to 4%) and mortality risk after refracture (from 0.4% to 4%). Events in males, although less frequent than in females, were more likely to have a fatal outcome.

Conclusion: Our findings confirm previous epidemiological investigations reporting a higher risk of refracture and of mortality in elderly individuals. Future studies should be performed in order to assess the impact of demographic and clinical factors on the observed phenomena.

KEYWORDS

Epidemiology, fracture, refracture, mortality, elderly.

Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low mass and microarchitectural deterioration of bone tissue with consequent increases in bone fragility and susceptibility to fractures [1]. Recently, some studies have estimated that over 22 million women and 5.5 million men suffer from osteoporosis in Europe [1,2].

Hip fracture is the most serious type of osteoporotic fracture, as it results in higher rates of mortality, disability and need for long-term institutional care, and in increases of associated medical costs. It has been estimated that 1.6 million hip fractures occur worldwide each year, a number that is expected to increase to 6.3 million by 2050 [1,3]. This phenomenon might be driven by population ageing, and the consequent increased number of frail individuals.

The impact of fracture in elderly individuals has raised concern due to the high morbidity and economic burden associated with this phenomenon. This is particularly relevant in countries, like Italy, that have a higher percentage of elderly people [4]. In 2011, a new project entitled "Appropriate Treatment of Geriatric Refracture in Tuscany-T.A.R.Ge.T." was started in the Italian region of Tuscany. The primary objective of this ongoing project is to reduce fracture events in the elderly by improving the appropriateness of pharmacological and non-pharmacological interventions. In particular, the project aims to decrease the incidence rates of refracture and of death associated with first fracture among elderly patients.

Preliminary results from the project focused on fracture incidence and patterns of anti-osteoporotic drug use among el-

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derly individuals between 2006 and 2013 [5,6].

The present updated analysis was conducted to estimate annual incidence rates of fracture and refracture among elderly individuals over a longer follow-up period. The secondary aim of this study was to estimate the risk of refracture and of mortality among fractured elderly individuals, while accounting for competing risks.

Methods

Data source and study design

We conducted an observational retrospective cohort study based on the population of Tuscany, a central Italian region with a population of 3.7 million inhabitants. Italy has a tax-based, universal coverage national health system organized on three levels: national, regional and local.

The Tuscany regional healthcare administrative database collects pseudo-anonymized patient-level information on the utilization of healthcare services dispensed to all subjects who are resident and registered with a general practitioner in the catchment area. In this study, the following information was selected by using the demographic registry and the hospital discharge database: age, gender, start date and end date of enrollment in the database, date of birth, date of death, date of admission to and date of discharge from the hospital, and one main plus five secondary diagnoses codified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM).

Study population

All individuals aged 65 years or older with a hospital discharge diagnosis of hip fracture (ICD9-CM: 808.x, excl. 808.1x, 808.3x, 808.5x, 820.x, 821.0, 821.2, 805.x, 733.1, 813.0, 814.0) identified between 1st January 2010 and 31st December 2016 were selected. The date of the first observed event was considered the index date. Among the selected individuals, those with a lookback period shorter than 365 days or with a history of neoplasia (140-239) or Paget's disease (731) were excluded from the analysis.

Follow-up

Each subject accumulated person-time from the index date until the date of: 1) the end of the study period (31/12/2017); 2) the patient's exit from the database; or 3) death, whichever occurred first.

Outcome

During the study period, the following outcomes were assessed: refracture (using the hospital discharge database) and all-cause mortality following either the initial fracture or refracture (using the demographic registry).

Statistical analysis

The estimated number of residents on January 1st of each observed year was used to compute the annual crude and age- and sex-standardized rates of fracture. The results were expressed as incidence per 1,000 person-years with 95% confidence intervals (95%CI). The cohort was stratified by year of first observed event, and for each subgroup the annual incidence of refracture was assessed during follow-up. Results were expressed as incidence per 1,000 inhabitants.

A competing risk model was created to estimate the risk of occurrence of each selected outcome in the study cohort during the follow-up. Four possible outcomes were considered: death following refracture, refracture without death, death without refracture, and alive without refracture [7].

Results

We observed a stable standardized incidence rate over the study period: from 7.41 per 1,000 person-years (95%CI: 7.21–7.61) in 2010 to 7.10 (6.93–7.27) in 2017 (Table I). The incidence of fracture was differently distributed between the sexes and age groups. Higher rates were observed in females (from 9.89 in 2010 to 9.66 in 2017) compared with males (from 4.15 to 3.72), and among subjects aged 85+ years (from 26.7 to 26.9) compared with those aged 65–69 years (1.3 in 2010 and 2017; data not shown). Table II reports the cumulative incidence of refracture during the follow-up stratified by the year of the first

Table I Incidence of fracture in Tuscany between 1 January 2010 and 31 December 2017.

YEAR	POPULATION	N. EVENTS	CRUDE RATE (CI 95 %)		STD RATE (CI 95%) °	
2010	861250	6098	7.06	(6.88;7.24)	7.41	(7.21;7.61)
2011	865896	5756	6.61	(6.44;6.78)	6.86	(6.67;7.05)
2012	875208	5635	6.37	(6.21;6.54)	6.57	(6.39;6.75)
2013	892803	6178	6.83	(6.66;7.00)	7.03	(6.84;7.21)
2014	916640	6445	6.98	(6.81;7.15)	7.15	(6.97;7.32)
2015	929050	6610	7.10	(6.93;7.27)	7.22	(7.05;7.40)
2016	933022	6621	7.07	(6.90;7.24)	7.13	(6.96;7.31)
2017	939649	6682	7.10	(6.93;7.27)	7.10	(6.93;7.27)

^ Population at 1st January: Rates are x 1,000 person-years; °Age and sex standardized with 2017 Tuscany region population as standard

event. The one-year incidence of refracture was slightly higher in the 2010 cohort (35.5 cases per 1,000 individuals) compared with the 2016 cohort (26.7 per 1,000 inhabitants). Among individuals with 7 years of follow-up the cumulative incidence of refracture was estimated at 98.23 per 1,000 inhabitants in the 2010 cohort and 93.76 per 1,000 inhabitants in the 2011 cohort.

Figure 1 shows the competing risk model results of the four outcomes (refracture and alive, death following the first fracture, death following refracture, and alive without refracture). During the follow-up, mortality risk following the initial fracture was 21%, 38% and 49% at the first, third and fifth year from the index fracture, respectively. These values were higher among males compared with females: 33% *vs* 18% at the first year, 52% *vs* 34% at the third year, and 63% *vs* 46% at the fifth year (Figure 2). In the observed cohort, the estimated risk of refracture was 1% at the first and third year of follow-up, reaching 4% at the fifth year. Similarly, the mortality risk after refracture increased during follow-up as follows: 0.4%, 2% and 4% at the first, third and fifth year from the index fracture, respectively. The analysis stratified by sex showed a lower risk of refracture among males compared with females, in spite of a higher risk of death following refracture among males: 1% *vs* 0.3%, 2% *vs* 2% and 4% *vs* 3% at the first, third and fifth year of follow-up, respectively (Figure 2).

Discussion

The results of this study indicate a stable incidence of hip fractures across the entire study period, with higher incidence rates observed in females and older individuals compared with the rest of the population. Additionally, we analyzed the multiple relationships of fractures and refractures on mortality risk by

Table II Cumulative Incidence per 1,000 inhabitants of refracture in primary fractured individuals.

YEAR	N. PRIMARY FRACTURES	1YR	2YRS	3 YRS	4YRS	5YRS	6YRS	7 YRS
2010	5976	35.48	49.70	65.60	75.97	85.17	91.03	98.23
2011	5557	26.81	42.47	56.51	68.74	80.08	91.24	93.76
2012	5372	28.11	43.93	58.64	72.23	83.40	87.86	
2013	5815	28.72	48.84	62.77	73.77	77.39		
2014	6004	28.65	46.80	60.63	66.29			
2015	6107	32.59	47.00	51.91				
2016	6063	26.72	34.47					

Figure 1 Stacked cumulative incidence during follow-up.
The dark blue area showed the mortality risk following the initial fracture; the blue area represented mortality risk following a refracture; the light blue area represented the cumulative incidence of refracture without death at any time point; the upper curve of graph corresponds to the sum of all aforementioned events; the white area represents the proportion of individuals alive and without refracture during follow-up.

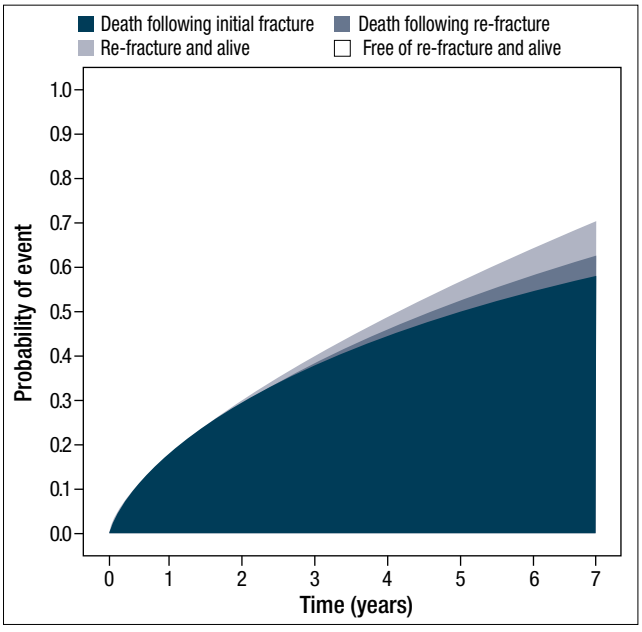
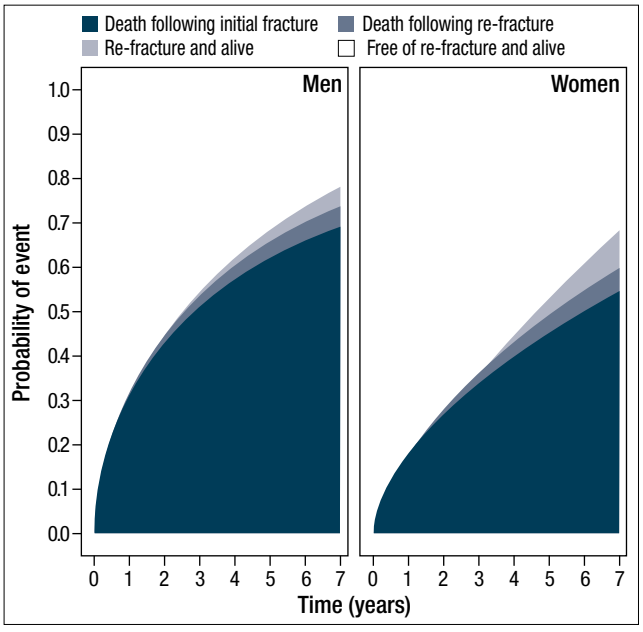


Figure 2 Stacked cumulative incidence during follow-up, stratified by sex.
The dark blue area showed the mortality risk following the initial fracture; the blue area represented mortality risk following a refracture; the light blue area represented the cumulative incidence of refracture without death at any time point; the upper curve of graph corresponds to the sum of all aforementioned events; the white area represents the proportion of individuals alive and without refracture during follow-up.



using a competing risk model. Although, several studies have already assessed the occurrence of refracture and mortality risk among fractured individuals [8-13], these studies focused on single events separately and did not consider the potential effect of each event on the occurrence of the second. To the best of our knowledge, this is the first European study attempting to investigate multiple outcomes following an initial fracture in the same model [14].

Overall, we observed a high incidence of mortality among fractured individuals after both first and subsequent fracture. At the end of follow-up, less than 30% of the initial cohort was alive and without any refracture, a pattern that seemed more marked in males than in females. Our results are in line with those of previous studies indicating a higher risk of refracture among females than males, but a higher rate of fatal outcomes among males [9-13]. Compared with a previous study [14] in which the same strategy of analysis was used, our findings indicated slightly higher mortality (67% males and 47% females) at 5 years from the index fracture. However, differences between the two studies should be acknowledged (i.e., setting, study period and potential immeasurable factors), as they make the comparison challenging.

Multiple factors might have been involved in the occurrence both of refracture and of death among our cohort: bone density modifications, genetic variants that affect bone mineral density, decreased muscle strength, comorbidities, and polypharmacy [15-17].

The present findings should be considered in the context of the potential limitations of the study. First, the analysis did not take into account the impact of health determinants (i.e., comorbidities, use of anti-fracture agents and concomitant medications). Second, the use of an administrative database does not allow retrieval of relevant information associated with the quality of care of fractured patients that might affect the risk of refracture and death, particularly among elderly individuals. In addition, as reported by Bliuc *et al*., the competing risk model does not allow for multiple adjustments [14].

In conclusion, our findings confirm high refracture and mortality rates among elderly people with an initial fracture. This phenomenon was particularly marked among males, in whom it more frequently resulted in a fatal outcome. This finding calls for future studies aiming to assess the role of other risk factors, such as comorbidities and anti-fracture treatments on the aforementioned outcomes. Considering the ageing of the population, particularly in high-income countries, our findings underline the need to implement strategies, like those proposed in the T.A.R.Ge.T project, aimed at preventing fracture, refracture and fatal events in elderly individuals. Additionally, the results of periodic monitoring of these events might be used by healthcare providers to reconsider the healthcare strategies adopted to manage these conditions.

References

1. Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013;8(1):136.
2. Häussler B, Gothe H, Göl D, Glaeske G, Pientka L, Felsenberg D. Epidemiology, treatment and costs of osteoporosis in Germany--the BoneEVA Study. Osteoporos Int. 2007;18(1):77-84.
3. Papadimitriou N, Tsilidis KK, Orfanos P, et al. Burden of hip fracture using disability-adjusted life-years: a pooled analysis of prospective cohorts in the CHANCES consortium. Lancet Public Health. 2017;2(5):e239-e246.
4. Eurostat statistics explained. Ageing Europe - statistics on population developments. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Ageing_Europe_-_statistics_on_population_developments#Older_people_.E2.80.94_population_overview. Accessed March 01, 2021.
5. Parri S, Cianferotti L, Marcucci G, et al. The T.A.R.Ge.T. project: a regional program to reduce hip fracture in elderly patients. Main results of retrospective phase. Clin Cases Miner Bone Metab. 2015;12(1):34-42.
6. Piscitelli P, Parri S, Brandi ML. Antifracture drugs consumption in Tuscany Region before the Target Project: a valuable model for the analysis of administrative database. Clin Cases Miner Bone Metab. 2012;9(2):76-9.
7. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res. 2007;13(2 Pt 1):559-65.
8. Ho-Le TP, Tran TS, Bliuc D, et al. Epidemiological transition to mortality and refracture following an initial fracture. Elife. 2021; 10:e61142.
9. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15(4):721-39.
10. Johnell O, Kanis JA, Odén A, et al. Fracture risk following an osteoporotic fracture. Osteoporos Int. 2004;15(3):175-9.
11. Trombetti A, Herrmann F, Hoffmeyer P, Schurch MA, Bonjour JP, Rizzoli R. Survival and potential years of life lost after hip fracture in men and age-matched women. Osteoporos Int. 2002;13(9):731-7.
12. Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. Age Ageing. 2010;39(2):203-9.
13. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA. 2007;297(4):387-94.
14. Bliuc D, Nguyen ND, Nguyen TV, Eisman JA, Center JR. Compound risk of high mortality following osteoporotic fracture and refracture in elderly women and men. J Bone Miner Res. 2013;28(11):2317-24.
15. Ho-Le TP, Center JR, Eisman JA, Nguyen HT, Nguyen TV. Prediction of bone mineral density and fragility fracture by genetic profiling. J Bone Miner Res. 2017;32(2):285-93.
16. Ho-Le TP, Tran HTT, Center JR, Eisman JA, Nguyen HT, Nguyen TV. Assessing the clinical utility of genetic profiling in fracture risk prediction: a decision curve analysis. Osteoporos Int. 2021;32(2):271-80.
17. Bliuc D, Center JR. Determinants of mortality risk following osteoporotic fractures. Curr Opin Rheumatol. 2016;28(4):413-9.

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Author contribution: *ICA, CF, LGM, GM and MLB made substantial contributions to the conception and design of the study. SP made a substantial contribution to the acquisition of the data. CF, EC and ICA made substantial contributions to the analysis and interpretation of the data. ICA was involved in drafting the manuscript. GM, CF, LGM and MLB made substantial contributions to revising the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.*