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Fractures in CKD Patients—Risk Analysis in RRT Lombardy Patients

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Abstract: The increase in the number of patients with CKD starting dialysis treatment has become a major health problem in recent years. Osteoporosis is a typical feature of advanced age, which, in the dialysis population, is almost always accompanied by uremic osteodystrophy (CKD-MBD). These two factors are involved in the pathogenesis of fractures, which represent an important risk factor for the outcome of patients. The real consistency of fractures in CKD patients on kidney replacement therapy (KRT) requiring hospitalization in the Lombardy region (over 9,000,000 inhabitants) was analyzed using data from the regional administrative databases in the years 2011–2012. Among 8109 prevalent patients, 251 (45.8% women), with fractures after 1 January 2011, entered the analysis. A follow-up of two years (2011–2012) was considered to evaluate the incidence of more frequent fractures (femur, pelvis, hip, and spine) using ICD-9-CM codes. The most frequent sites of fractures were the femur (68.5%), hip and pelvis (47.4%), and vertebrae (12%). The patients on hemodialysis (HD) had more events than PD (3.3% vs. 1.4%; $p = 0.03$), while patients undergoing kidney transplantation (KTx) had a significantly lower percentage of fractures (0.6% vs. 3.3%; $p < 0.001$). Observed mortality was very high: the estimated gross mortality rate for any cause was 25.9% at 90 days and 34.7% at 180 days. Diabetes, peripheral vasculopathy, and heart failure were associated with a numerical increase in fractures, although this was not significant. Proton pump inhibitor drugs (PPI), vitamin K antagonists, and diphosphonates were more frequently associated with fracture occurrence. The average total cost of fractured patients was 11.4% higher than that of non-fractured patients. On multivariate analysis, age >65 years, female gender, PPI therapy, and cerebrovascular disease were found to be strongly associated with fractures in dialysis patients, whereas undergoing renal transplantation presented a reduced risk.

Keywords: bone fractures; ESKD; dialysis; drugs; SHPT; PPI; CKD-MBD

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1. Introduction

Chronic kidney disease (CKD) has been an important health problem during the last few years. The number of patients affected by end-stage kidney disease (ESKD) has grown in the world, causing an economic impact on public health services. Until a few decades ago, people with CKD had a much lower life expectancy than the general population, and access to renal replacement treatment in many countries was conditioned by age and comorbid conditions. The liberalization of access to kidney replacement therapy (KRT) has led to an increase in the number of elderly dialysis patients with comorbidities associated with a substantial increase in costs [1,2]. These two factors are changing the pattern of subjects undergoing dialysis treatment and/or transplantation, with a new set of morbidities. With aging, there is a progressive loss of bone mass, which is generally accompanied by an increased risk of fractures. Skeletal fractures represent the main negative outcome of most bone diseases and, in the general population, are considered the landmark for judging

the efficacy of therapies for bone diseases [3]. All osteoporotic fractures increase patient morbidity, and the fractures of the hip and vertebrae are associated with significantly higher mortality. The incidence of hip fractures rises exponentially with age, and this incidence is greater in females. With a rising life expectancy throughout the globe, the number of elderly individuals is increasing in every geographical region; the incidence of hip fracture is estimated to rise from 1.66 million in 1990 to 6.26 million in 2050. There are geographic variations in the prevalence and incidence of fractures, with the highest rates being in the Northern regions (Scandinavian), and the lowest rates are in African countries [4]. The exact reasons for geographic differences in the prevalence of fractures are not well understood, but genetic factors, less bone mineral content, and environmental factors, such as dietary factors and vitamin D levels, may be important [5]. In an original article concerning the epidemiology of fragility fractures in Italy [6], the authors estimated a total of 88,647 hip fractures in the year 2006 among people aged 40 to 100 years old, with a 5.9% increase during the three examination years. Women aged > 75 years old accounted for 60% of total fractures observed in the population from 40 to 100 years of age. In males, the highest incidence was observed in people over 80. The ESOPO study estimated the prevalence of osteoporosis in Italy as about 23% among all women, and it was observed as almost 15% in men aged over 60, and these two statistics resulted in about four million Italian women and 800,000 men having osteoporosis [7]. According to the World Health Organization (WHO), osteoporosis is a critical health problem second only to cardiovascular disease. In Italy, as in other Western countries, the number of hospitalizations for hip fractures is comparable to that for acute myocardial infarction (MI) [8]. In the CKD population, the rate of fractures is enhanced owing to the high prevalence of uremic osteodystrophy (CKD-MBD), especially concerning dialysis patients, plus the presence of age-related osteoporosis. According to many studies, the rate of fractures in CKD patients has progressively increased over time, and it depends on the severity of the disease (stage 1–5) from 15.0 to 46.3 per 1000 person-years [1]. However, not all studies agree on defining the rate of incidence of fractures in patients on renal replacement therapy. In a DOPPS study [9] concerning over 34,000 patients from 12 countries on hemodialysis treatment, Tentori et al. found a 3% incidence of fractures, with an incidence rate that is highly variable among nations (from 12/1000 pts./year in Japan to 45/1000 pts./year in Belgium). The risk of fractures in KRT patients compared to the general population is between four and 14 times higher [4]. However, there are some differences among hemodialysis (HD), peritoneal dialysis (PD), and kidney transplant (KTx) patients. According to a USA report, the incidence rate of hip fractures was 20.6 per 1000 pts/year in HD patients, while in kidney transplanted patients, it was only 3.8 per 1000 pts./year [10]. On the contrary, other studies evaluated the incidence of hip fractures as 1.34 times higher in transplanted patients compared to those on hemodialysis [11]. Some differences in the incidence of hip fractures have also been found between patients with HD and PD, with a HD risk that is increased by 1.74 times [12]. To assess the real consistency of fractures in CKD patients on KRT requiring hospitalization in the Lombardy region (over 9,000,000 inhabitants), we examined the regional health databases in the years 2011–2012.

2. Material and Methods

This is a retrospective cohort study describing epidemiological features and risk of fractures in dialysis patients using data collected automatically by administrative databases of the Regional Health Service (RHS). Lombardy administrative database is an integrated system recording electronic information about all resident patients referred to RHS concerning hospitalizations, diagnostic/therapeutic procedures, and drug prescriptions performed in and out of the region. Prevalent patients, on 1 January 2011, without hospitalization for fractures before 2011, entered the analysis. A follow-up of two years (2011–2012) was performed to evaluate the incidence of more frequent fractures (femur, pelvis, hip, and spine) using ICD-9-CM codes (Table 1). Main demographic characteristics, dialysis treatments, secondary hyperparathyroidism (SHPT) status, presence of comorbidities (see Supplemen-

tary Materials for identification by ICD-9-CM codes), prescription of medications identified by the Anatomical Therapeutic Chemical Classification System (ATC), the incidence of fractures, and hospital admissions were investigated. SHPT patients identified from prescriptions of cinacalcet, paricalcitol, and/or on hospitalizations for parathyroidectomy (cod. ICD-9-CM 06.81, 06.89) and SHPT of renal origin (cod. ICD-9-CM 588.81) were submitted to a separate sub-analysis. The following analyses were performed to present the average total per-patient costs in charge to RHS, divided by cost category (including drugs supplied through territorial pharmacies, drugs directly delivered by the RHS structures, hospitalizations in and outside the region, and specialist and outpatient services). For the assessment of the costs, we used only the values in charge of the RHS reported in the administrative database. Considering the RHS point of view, no out-of-pocket and indirect costs were included. Anonymized tax codes were used to identify each patient and link the different datasets. In the evaluation of the costs, the expenses related to any rehabilitation measures after hospitalization have not been considered, nor have the social costs related to an increase in the disability degree of the subjects.

Table 1. ICD-9-CM codes identifying hospital admission for fractures.

ICD-9-CM Diagnosis		ICD-9-CM Procedures	
Codes	**Description**	**Codes**	**Description**
820	Fracture of neck of femur	78.55	Internal fixation of bone without fracture reduction femur
821	Fracture of other parts of femur	79.25	Open reduction of fracture without internal fixation femur
808	Fracture of pelvis	79.45	Closed reduction of separated epiphysis femur
805	Fracture of vertebral column	79.55	Open reduction of separated epiphysis femur
733.14	Pathological fracture of neck of femur	81.51	Total hip replacement
733.15	Pathological fracture of other parts of femur	81.52	Partial hip replacement
733.13	Pathological fracture of vertebra	81.53/81.40	Revision of hip replacement/ Repair of hip

3. Ethical Consideration

Retrospective observational studies performed by health system databases do not require a specific submission and approval by ethics committees. Data available from the regional database are in an anonymized format, such that specific individuals could not be identified, and there is no possibility of tracing back to the identification of each person. The selection criterion from the entire regional health service database was performed by choosing patients residing in the Lombardy region with a diagnosis of CKD (ICD-9-CM), excluding patients with acute kidney failure, taken in charge for a renal replacement treatment by the regional health service.

4. Statistical Analysis

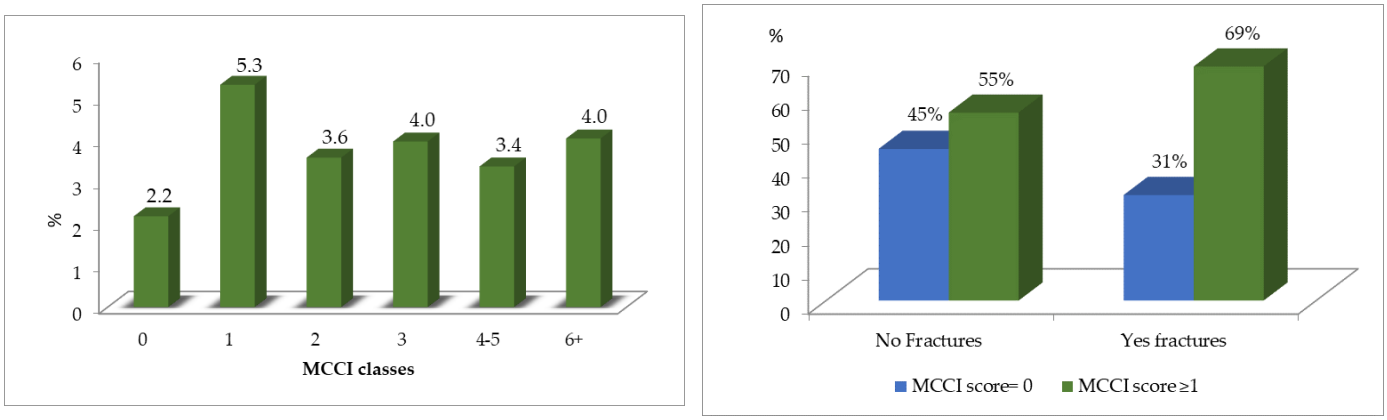
Proportions, as the descriptive statistic for categorical variables and mean $\pm$ standard deviation (SD) or the median for continuous variables, were used. Differences in the demographic and clinical characteristics were assessed through Pearson's Chi-squared or the Fisher exact test for categorical variables and the Kruskal-Wallis rank-sum test for continuous ones. A logistic regression model was used to assess variables independently associated with fractures. Regarding assumptions, we did not strongly detect influential outliers that could have distorted the outcome and accuracy of the model. Multicollinearity was checked

through the variance inflation factor (VIF) and rejected. The Hosmer and Lemeshow test was performed to verify the goodness of fit (X-squared = 5.8609, *p*-value = 0.4389). The R Project for Statistical Computing [13] (version 3.6.2) was used to perform data analysis.

5. Results

Out of 8109 prevalent patients (36.7% women), 251 (45.8% women) had 321 hospital admissions for fractures, with a rate of 3.1%, and an incidence of 18.3 per 1000 person/year (95% confidence interval (CI) 16.1–20.7). Women have a higher percentage of fractures than males (3.9% vs. 2.7%; $p = 0.0031$), with a ratio of 1.44 without any significant difference in the sites of fractures. The most frequent sites of fractures were the femur, at 68.5%, followed by the hip and pelvis at 47.4% and vertebrae at 12%. Fractures occurred in one site in 72.9% of cases, two sites in 25.9%, and three sites in 1.2%. Fractured patients were older (mean age: 73.7 $\pm$ 11.5 vs. 67.0 $\pm$ 14.6 years. $p < 0.001$), with the highest percentage of fractures in the age group >65 years vs. <65 years. (4.1% vs. 1.4%). The distribution of fractures in the age groups was: 0–45 years (0.7%), 46–65 years (1.6%), and >65 years (4.1%); 83.7% of the total fractures ($n = 210$) occurred in the over-65 years patients, while in the groups 0–44 and 45–64, the percentages of fractures were 2.0 and 14.3, respectively. Most of the patients (6860; 84.6%) who entered the study were undergoing replacement treatment by hemodialysis (HD). A minority (645; 8.0%) were undergoing replacement by peritoneal dialysis (PD). Additionally, a third group (604; 7.4%) underwent both treatments. When considering the number of admissions for fractures, 223 (88.8%) occurred in HD patients, 9 (3.6%) in PD patients, and 19 (7.6%) occurred in patients who underwent both treatments. As far as fracture rate, the patients on HD had more events than PD (3.3% vs. 1.4%; $p = 0.03$), while patients undergoing KTx during the observation period had a significantly lower percentage of fractures (0.6% vs. 3.3%; $p < 0.001$). Of the 251 patients who experienced fractures, 197 (78.5%) were hospitalized once, 44 (17.5%) were hospitalized twice, and 10 (4.0%) were hospitalized more than twice. The average length of hospitalization was 17.2 days $\pm$ 12.9, with a median value of 14 days. Patient outcome was analyzed regarding mortality during hospitalization, at 90 and 180 days after hospital admission. A total of 87 deaths occurred in this period: 27 deaths occurred during the first hospitalization, 38 occurred in the following three months, and 22 occurred in months three to six. The estimated gross mortality rate for any cause at 90 days was 25.9%, while the overall mortality at 180 days was 34.7%. To evaluate the impact of co-morbidities and drug use on fracture risk, the occurrence of fractures in association with drug exposure (Table 2) and the presence of comorbidity (Table 3) were analyzed. Patients with the prescription of renin-angiotensin inhibitors, lipid-lowering drugs, and calcimimetics (cinacalcet) were associated with a lower number of fractures. Although, for the last one, this reduction is not statistically significant. Patients receiving proton pump inhibitors (PPI), vitamin K antagonists, and diphosphonates were more frequently associated with fracture occurrence, and patients with prescriptions of aspirin, cardioactive glycosides, vitamin D and analogs, and steroids had no significant differences in fracture percentages. The presence of diabetes, peripheral vasculopathy, and heart failure were associated, although statistically non-significantly, with an increase in fractures, while the association with MI showed a non-statistically significant reduction in fracture occurrence. In contrast, a significant difference was shown when cerebral vascular disease and dementia status were present. Unfortunately, in the latter case, confirmed diagnoses of dementia in our database were too few to assign clinical consistency to this observation. The presence of comorbidities in each patient appears to be correlated with the risk of fractures more than the type of comorbidity (Figure 1a). The classification of patients into classes according to the Mary Charlson Comorbidity Index (MCCI), adjusted for ESKD [14], showed a significant increase in the percentage of fractures in patients with MCCI scores $\geq$1 (2.2% vs. 3.8%) (Figure 1b). Secondary hyperparathyroidism (SHPT) is well known to modify bone structure, mainly increasing bone turnover, with an enhancement of osteoclast activity and a reduction of cortical bone. The result would be increased bone frailty and fracture risk. A

sub-analysis of SHPT patients was performed to assess any difference in the occurrence of fractures in these patients. Patients with SHPT (30.8% of the analyzed sample), who were predominantly female, with lower mean age and higher KTx rate, had a non-statistically significant reduction in fracture percentage (Table 4). Total and per-patient costs are shown in Table 5: patients with fractures are associated with higher hospitalization-related costs (+68.4%) and lower drugs cost (territorial and directly distributed) (−24.3%). An analysis of the individual cost components is shown in Figure 2. The total per-patient mean cost in charge to RHS in the two years of observation was 76,830.5€ for patients with fractures vs. 68,946.9€ for patients without fractures (+11.4% fractures vs. no fractures patients). Most relevant variables analyzed in the univariate model (demographic information, co-morbidities, transplantations, drug used) were included in a multivariate logistic model to examine their role in influencing fracture risk. Not all variables analyzed entered the logistic model with a significant role: as highlighted in Table 6, age >65 years, female gender, prescription of PPI medications, and cerebrovascular disease were found to have a statistically significant role in increasing the risk of having one or more fractures. In contrast, being a kidney transplant recipient played a protective role against the risk of having any fracture, at least concerning the time window of our observation. Patients with a history of acute MI showed a reduced risk of fractures, although the statistical significance of this finding was very weak.



(**a**) (**b**)

Figure 1. Fractures' distribution (%) according to MCCI classes (**a**) and MCCI score (**b**).

Table 2. Drug prescriptions and fractures rate. CMH (Cochran-Mantel–Haenszel test).

Drugs Groups (ATC Classification Codes)	*n* (%) Patients Using Drugs	% Fractures in Users	% Fractures in Non-Users	*p* Value (CMH)
Active on bone structure and mineralization (M05B)	317 (3.9)	7.9	2.9	<0.001
Aspirin	4793 (59.1)	3.3	2.9	0.3517
Cardiac glycosides (C01AA05)	305 (3.8)	3.0	3.1	1.0000
Lipid-lowering drugs (C10A)	4447 (54.8)	2.7	3.5	0.0375
Steroid drugs (H02A, H02B)	2229 (27.5)	3.4	3.0	0.3502
Renin-angiotensin inhibitors (C09A, C09B, C09CA, C09D, C09X)	5479 (67.6)	2.7	3.9	0.0039
Vit D drugs (A11CB, A11CC)	6305 (77.8)	3.1	2.9	0.7183
Cinacalcet (H05BX01)	1728 (21.3)	2.5	3.2	0.1594
Proton pump inhibitors (A02BC)	7168 (88.4)	3.3	1.8	0.0199
Vit K antagonists (B01AA)	1681 (20.7)	3.8	2.9	0.0697

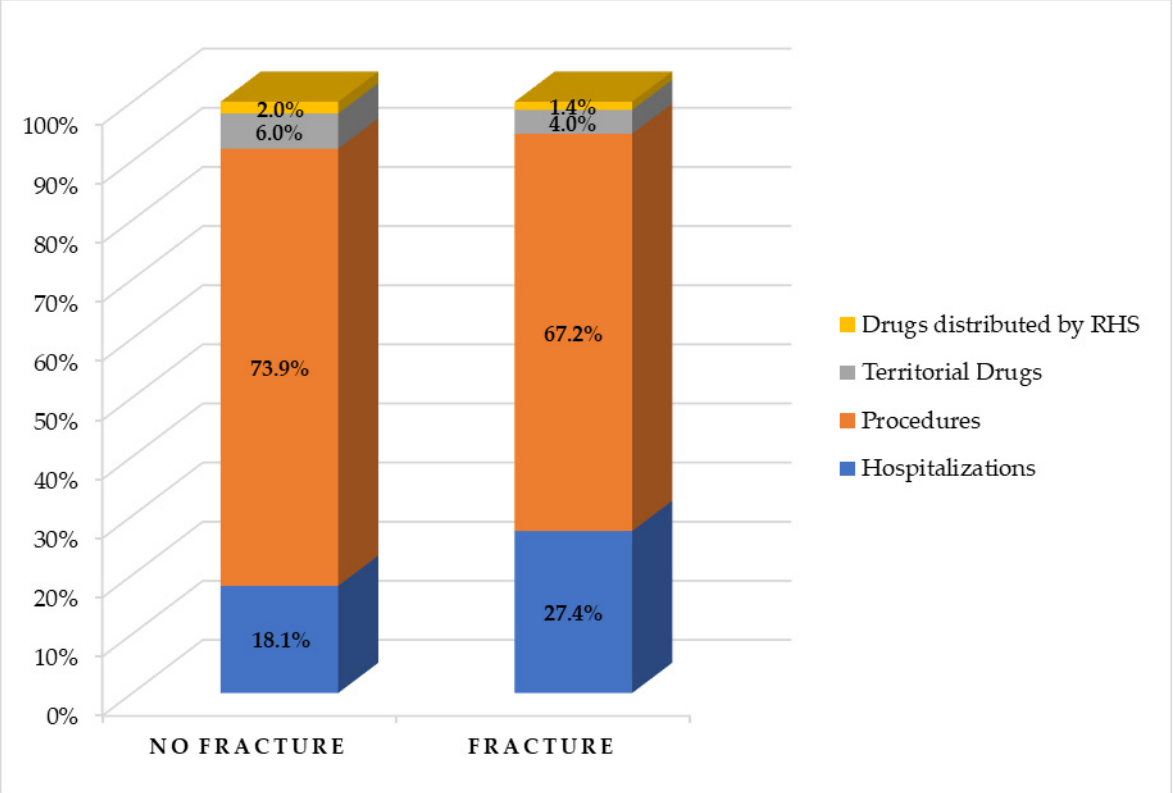


Figure 2. The percentage distribution shows an increase in hospitalization costs in patients with fractures. In contrast, the reduction in costs for procedures is attributable to their partial inclusion in the DRG hospitalization rate.

Table 3. Comorbidity presence and fracture risk in dialysis patients *MCCI = Mary Charlson Comorbidity Index—modified according to ESRD status [14].

Comorbidities	*n* (%) Patients Affected	% Fractures in Affected	% Fractures in Non-Affected	*p* Value (CMH)
Secondary hyperparathyroidism	2497 (30.8)	2.8	3.2	0.4213
Diabetes	2219 (27.4)	3.3	3.0	0.5833
Peripheral vascular disease	893 (11.0)	3.6	3.0	0.4293
Myocardial infarction	2024 (25.0)	2.9	3.2	0.5387
Congestive heart failure	1724 (21.3)	3.5	3.0	0.3362
Cerebral vascular disease	1195 (14.7)	5.4	2.7	<0.001
Dementia	100 (1.2)	7.0	3.0	0.03508
MCC*I (cat ≥1 vs. 0)	4521 (55.8)	3.8	2.2	<0.001

Table 4. Major differences in patients with secondary hyperparathyroidism (SHPT) versus non-SHPT.

	SHPT *n*(%)	NO_SHPT *n*(%)	*p* Value
Patients	2497 (30.8)	5612 (69.2)	———
Gender (females)	1028 (41.2)	1952 (34.8)	<0.001
Age (mean ± SD)	62.4 ± 15.0	69.3 ± 13.8	<0.001
Renal replacement therapy HD	2291 (91.8)	5173 (92.2)	0.5404
Kidney transplantation	228 (9.1)	310 (5.5)	<0.001
Fractures	71 (2.8)	180 (3.2)	0.4213

Table 5. Detail of costs concerning fractures (from 01/2011–to 12/2012)); RHS: Regional Health Service.

	Fractures	Number of Patients (*n*)	Total Costs for All Patients (€)	Mean Per-Patient Costs (€)
All drugs	No	7858	42,966,512.4	5467.9
	Yes	251	1,039,559.5	4141.7
Territorial Drugs	No	7858	32,261,086.1	4105.5
	Yes	251	773,330.6	3081.0
Drugs distributed directly by RHS	No	7858	10,705,426.3	1362.4
	Yes	251	266,228.9	1060.7
Diagnostic and therapeutic procedures	No	7858	400,579,033.0	50,977.2
	Yes	251	12,961,263.5	51,638.5
Hospitalizations (all)	No	7858	98,239,011.5	12,501.8
	Yes	251	5,283,639.7	21,050.4
Total costs	No	7858	541,784,556.9	68,946.9
	Yes	251	19,284,462.6	76,830.5

Table 6. Logistic regression (OR = odds ratio, Cl = Confidence limits, CVD = Cerebrovascular disease, PPI = proton pump inhibitors).

Variable	OR	95% Wald CI	*p* Value
Age > 65	2.608	1.846–3.685	$p < 0.01$
Gender (F, M)	1.403	1.086–1.811	$p < 0.01$
Kidney Transplant (Yes, No)	0.287	0.090–0.916	$p < 0.05$
PPI (Yes, No)	1.904	1.154–3.140	$p < 0.05$
CVD (/Yes, No)	1.766	1.316–2.370	$p < 0.05$
Myocardial Infarction (Yes, No)	0.771	0.568–1.045	$p < 0.1$
Observations: 8109; log–likelihood: −1074.519; Akaike inf. crit.: 2163.037			

6. Discussion

The study results obtained from the Lombardy RHS database [15] are enhanced by the real-time collection of information on the whole population without limitations usually required in randomized clinical trials [16]. Nevertheless, the main drawback of these databases is that the information is collected primarily for administrative purposes and is often lacking in important clinical details [17–19]. The rationale for the analysis of a regional administrative database was grounded in two key aspects: the reliability of the regional database of the health service and the exhaustiveness of the records. Moreover, to date, there are no specific and complete studies on fracture risks in dialysis patients in Italy, except for what was reported in the DOPPS 9 study on a selected number of dialysis centers and the prescription of PPI drugs [20].

6.1. Epidemiology

The results from our retrospective analysis of prevalent dialysis patients allowed us to find a fracture rate of 3.1 percent and an average incidence per 1000 patient-years of 18.3, which are comparable to the results of the DOPPS study relative to most European countries [9], except for Belgium and Sweden, which experienced higher rates. Our findings relative to a suitable number of patients are congruent with those obtained by Chang [21] and Wagner [22] from an analysis of data provided by administrative databases. An

estimate of the incidence of fractures in the general population of the region is not the purpose of the present study, since the database used contains information only on CKD patients in RRT in Lombardy. There are few studies in the literature concerning the incidence of fractures in the general population on a regional basis. In a 2019 study by P. Piscitelli et al. (Archives of Osteoporosis 14:81), the estimated incidence of hip fractures in the elderly population in Lombardy similar in time and age to that of this study was 6.82 occurrences by 1000 inhabitants, with a very high F/M ratio of 3/1. However, it is important to highlight that the two results cannot be compared because of the difference in the methods of event detection (number of hospitalizations versus the number of fractures). As expected, females had a greater propensity for fractures, with a ratio of almost 1.5 times that of males. This difference in the fracture rate in females is widely described also in the general population. In a recent report from the Swedish Registry, 64.5% of the fractures occurred in women. This ratio may vary at different ages of life, but, at over 55 years of age, the higher incidence of fractures in females holds steady [23]. Age is reported as the main risk factor for fractures in all studies and statistical reports in both individuals with CKD and/or KRT [24] and the general population [6,25]. Older age is an independent variable that could positively predict the occurrence of proximal femoral fracture type A (OR 95%CI: 1.03 [1.03–1.04], $p < 0.001$) and B (1.02 [1.01–1.02], $p < 0.001$) in the general population [26]. Our observations are fully consistent with the literature data, showing a clear increase in the rate of fracture hospitalizations after 65 years of age. Among the possible causes leading to an increased risk of fractures in the elderly, osteoporosis [27] is a disorder becoming more severe with aging. The elderly and very elderly in the general population are affected by several conditions that can promote osteoporosis, such as nutritional factors, namely, calcium and vitamin D deficiency, as well as sarcopenia associated with multi-morbidity.

6.2. CKD Treatment

Most of the patients in the surveyed cohort (84.6%) were on HD treatment, while only 8.0% were on PD, and, consequently, admissions for fracture occurred mostly in the HD group (88.8%), while only 3.6% of fracture hospitalizations occurred in the PD group. In terms of fracture occurrence, we found a statistically significant difference (3.3% vs. 1.4%; $p = 0.03$) between HD and PD, corresponding to the findings in the literature where the occurrence of a higher percentage of fractures in HD than in PD is reported by almost all authors, mainly by those who accounted for the overall population from administrative databases. In a retrospective database analysis of 2096 adult KRT subjects in Scotland from 2010 to 2011, the authors found an incidence of 99.2, 57.6, and 37.9 per 1000 patient-years in HD, PD, and KTx, respectively [24], as well as in a recent systematic review [10], of 47 studies, evaluating the risk of fracture in HD, PD, and KT populations. The incidence of hip fracture in HD (median 11.45 per 1000 person-years range: 9.3–13.6) was found to be higher than in KTx (median 2.6 per 1000; range 1.5–3.8) or in PD (median 5.2 per 1000; range 4.1–6.3). In a meta-analysis [28] of observational studies on fracture risk, the authors found that, in 1,276,677 patients enrolled in the study, a pooled OR of hip fracture of 1.57 (95%CI 1.43–1.72), after adjustment for confounding factors, was observed in HD compared with PD. The reasons for this difference are not univocally established; the most probable explanation may consist in a higher number of elderly patients in HD, a longer duration of stay in HD treatment, the prevalence of patients with major complications, potentially inducing falls, the prolonged exposure to unfractionated heparin [29], a greater reduction in cortical bone mineral density [30], a greater presence of SHPT, resulting in increased bone turnover, and reduced cortical bone component [31]. Concerning the low number of fractures found in KTx patients during the observation period, no definitive conclusions can be drawn from our data due to the lack of long-term follow-up linked to the therapeutic prescription. Undergoing kidney transplantation, however, is an important protective factor in reducing fracture risk. This result may be due to several reasons, such as the lower mean age in KTx patients of 50.144 years (1st Qu 41.537–3rd Qu 60.899) compared with no transplant recipients of 68.397 years (1st Qu 61.156–3rd Qu 78.292) and a lower prevalence

of comorbidity factors. Kidney transplantation, however, maintains the protective action against fractures in our patients independently of age. In fact, in multivariate analysis, even treating age as a continuous variable (every year), the protective effect remains significant. This finding would deserve further specific investigation with a larger number of cases and longer follow-ups. From the literature data, different considerations and values can be found concerning fracture risk in KTx patients. In a study on a cohort of more than 100,000 patients on the waiting list for KT in the U.S. in the years 90–99, the authors found a relative risk (RR) for hip fractures associated with transplantation 1.34 higher than in dialysis. The risk progressively decreased to equal the dialysis after 1.5–2 years. The interpretation of this high risk of fractures, especially in the first six months post-transplant, was related to the bone loss due to the use of high steroid doses and to the inactivity related to the first phases after KTx, which was followed by an increase in physical activity for the recovery of the general condition of the patients [11]. Other authors, [10,27,32], demonstrated that the risk of fracture in ESKD patients treated with HD, PD, and KTx, was the highest in HD and the lowest in KTx. It has been suggested by many authors that the progressive use of therapeutic protocols involving the early discontinuation of steroids in favor of immunosuppressive drugs, such as sirolimus with inhibitory activity on osteoclasts, may counterbalance the effects of steroids and calcineurin inhibitors [32–34].

6.3. Hospitalization

Length of stay (LOS) for fracture in dialysis patients may differ for several reasons, including age and health conditions, the type of fracture, and the need for surgery, but most of all, the effectiveness of the structural organization and the health service characteristics can be responsible in determining the length of hospitalization. In the survey of DOPPS data [9], the authors showed, in almost all countries, a significant difference in LOS, ranging from a median of 37 days in Japan to seven days in the USA. The results from our patient cohort showed an average LOS quite similar to that of several European countries, such as Spain, Germany, and Sweden. The median value of 14.0 days and the mean value of 17.2 ± 12.9 are in line with those reported in countries with public health systems. In a more recent paper [35], the median LOS in a cohort of 377 U.S. dialysis patients matched with 1508 non-dialysis patients was seven versus five days, respectively. Additionally, in our findings, the average LOS (17.2 days) was longer than that observed in the general Italian population in the same years for a similar type of fracture (12.9 days) [36]. However, the LOS for fractures is difficult to compare across countries due to differences in NHS. In some NHSs, the hospital stay is limited to the acute phase of surgery, thus generally being shorter. Whereas, in others, hospitalization for fractures also includes the rehabilitation period, thus lengthening the duration.

6.4. Mortality

Mortality in dialysis patients admitted for fractures is significantly higher compared with that reported in dialysis patients without fractures. The observed values are high and are widely higher than those reported in some clinical research in the literature. Original research [37] in the U.S. on a numerically smaller number of selected dialysis patients, focusing on surgical problems of fractures, showed in-hospital mortality of 7.7%, lower than that observed in our patients which, however, refers to the entire population on dialysis treatment. Other studies with different numbers of dialysis patients examined for fractures generally localized to the hip have shown different mortality rates. A Korean study on 1614 dialysis patients evaluating specific mortality at 30 days after hip fracture surgery found a mortality rate of 6.32%, and, after six years of observation, it was found to be 69.39%, with a RR of 1.97 (95 CI 1.83–2.1) compared with matched non-dialysis patients [38]. Meanwhile, a population-based study in Taiwan on a cohort of dialysis patients > 65 years old, evaluating mortality at different intervals after hospitalization for hip fracture, showed a death rate of 6.9% at 30 days, 17.3% at 90 days, and 26.0% at 180 days [39]. Concerning an explanatory hypothesis for the high mortality in our patient cohort, we are not able to

provide an evidence-based interpretation because of the lack of detailed clinical information from the database. We can only hypothesize that the subjects who suffered fractures had a higher prevalence of frailty. As evidenced by many studies, one interpretation of the high risk of death in dialysis patients is ascribed to the frailty syndrome, defined as a lack of physiological reserve observed in multiple organ systems [40]. Although we do not have solid evidence to define the prevalence of a frailty syndrome in our patients, some clues may suggest its presence, such as advanced age (median 76.3 years) [26] and the higher prevalence of comorbidities according to the MCCI [41] (Figure 1b). Hospital admission/discharge forms in our database do not include causes of death, but only the main diagnosis at discharge. It was, therefore, not possible to establish the specific death causes of our fractured patients.

6.5. Comorbidities

The role of comorbidities may be of great importance in determining the risk of falls and fragility fractures in dialysis patients. Based on the information in the database, we were able to find associations between major comorbidities and the occurrence of fractures by using the MCCI, obtaining a severity score. As illustrated in Table 3, diabetic disease, PVD, and CHF were present with a higher frequency, although they were not statistically significant in patients with fractures. However, CVD, dementia, and a MCCI score ≥ 1 were statistically significant. SHPT and MI seem to have a reverse trend, although they are not statistically significant. Patients with dementia need special consideration; although there are many papers in the literature associating this disease with an increased risk of fractures, the low number of cases in our database does not allow definitive conclusions to be drawn. In an analysis of 88,962 patients from the French National Hospital Database with hip fractures, including 362 on dialysis [42], the authors identified dementia status as the major fracture risk factor in dialysis patients. In a more recent study [43] in a population of 38,126 women who suffered a hip fracture compared with a similar cohort in the general population, dementia was the most prevalent disease (18,4%), followed by pulmonary, cardiovascular, and cerebrovascular diseases (13%). However, the additional interaction of co-morbidities on one-year mortality was positive only for solid tumors, CHF, kidney disease, and CVD, and not for dementia, which maintained a negative interaction on mortality at the six-year follow-up. Analyzing risk factors for fractures in a cohort of more than 90,000 dialysis patients from the Swedish Renal Registry [44] over five years, K. Iseri et al. found that, in patients with fractures (4%), the statistically most significant risk factors compared with patients without fractures did not include dementia or SHPT. It is well established that the widespread presence of comorbidities in dialysis patients is strongly associated with the occurrence of fractures. Because of structural limitations of the recording system, it was not possible to define the level of clinical severity of concomitant diseases in our patients, but only their association with fractures. However, to indicate the clinical severity of the patients, it seemed important to assess the occurrence of the number of comorbidities using the MCCI severity core. To this aim, applying the MCCI severity score from the model by Brenda R. Hemmelgarn [14] allowed us to cluster subjects into six classes of increasing severity, from zero to more than six comorbidities (Figure 1a), with the result that patients with a MCCI score $\geq$1 were more likely to be in the fractured group (69% vs. 55%) (Figure 1b). As a result, the rate of fractures in the group of patients with comorbidity class $\geq$1 was 3.8%, compared to 2.2% of patients in the zero class (Table 3). This finding, which is highly significant in our group of patients, is present in several other papers in the literature for both dialysis patients [42,45] and the general population [43].

6.6. Drugs Prescription

It is well known that dialysis patients are prescribed multiple medications and that these treatment schedules are often complex, owing to the number of comorbid factors affecting these patients [46]. Using the ATC classification system, we searched for the most commonly used drug classes in an attempt to assess a possible interaction with the observed

fractures (Table 2). For selected medications, the information provided by the database refers only to the dialysis center's prescription and cannot provide additional information about the patient's therapeutic compliance. No statistically valid association emerged from the use of aspirin, cardiac glycosides, steroids, vitamin D, and calcimimetics. However, concerning hypolipidemic drugs and RAAS inhibitors, the associative effect with the risk of fracture seems to be favorable to users. On the contrary, PPI, vitamin K antagonists, and diphosphonates are associated with a significant increase in fractures. Univocal results on the role of these drugs on fracture risk in both the dialysis and general population are not always reported in the literature. Concerning the use of PPIs, which are prescribed in more than 80% of our patients, almost all studies have highlighted the increased risk of fractures in dialysis and in the general population, although a mechanism of action explaining this effect has not yet been demonstrated. The DOPPS study [20] showed an increased risk for all fractures by 22% and for hip fractures by 35% in PPI users, which was also confirmed by a study carried out with USRDS data [47] on patients undergoing HD, which showed maintenance of the association with fractures regardless of the dose (low, moderate, and high) prescribed. Since the association of PPIs and fractures is also present in the general population, likely, this may represent not just a simple association, but an effect of the pharmacological activity of PPIs on bone. The increased gastrin production and hypochlorhydria may be two of the main mechanisms affecting bone remodeling, mineral absorption, and muscle strength, contributing to increased fracture risk among PPI users [48]. Vitamin K antagonists are used to prevent stroke in patients with an increased risk due to atrial fibrillation (AF). The guidelines for the treatment of AF by the European and American cardiology societies [49,50] suggest the prescription of vitamin K antagonists in subjects at high risk of stroke. However, in the general population, the ratio of the risk of bleeding to benefit of stroke reduction has been demonstrated by clinical trials, but, in the dialysis population, this is unknown [51,52]. The beneficial effects of vitamin K antagonists have been debated in recent years due to the lack of a direct relationship between AF and stroke in dialysis patients, as well as the absence of convincing studies that vitamin K antagonists can reduce the thromboembolic risk in these patients. However, recent studies have shown a higher level of safety of new oral anticoagulants compared to vitamin K antagonists, mainly because they can improve the status of vitamin K, which is often in a functional deficit condition in dialysis patients [53]. However, in the cohort of our patients, more than 20% had prescriptions for vitamin K antagonists. Additionally, the use of new oral anticoagulants had not yet entered prescribing for patients with ESKD during the reference period. In our patients treated with vitamin K antagonists, the percentage of fracture was significantly higher than in patients who did not have a prescription. The association between vitamin K and risk of fractures in HD has long been known [54] and, more recently, an observational study of HD patients identified vitamin K1 deficiency as the strongest predictor for the presence of fractures [55]. The same authors found that patients treated with warfarin had significantly more vertebral fractures than subjects not taking warfarin [56]. This finding was associated with a reduced level of bone Gla protein (BGP) and matrix Gla protein (MGP), confirming the role of vitamin K as an essential cofactor for site-specific carboxylation of osteocalcin and other bone matrix proteins. The group of drugs active on the bone structure was prescribed to a very small percentage of our patients (3.9%). The most prescribed drugs were bisphosphonates. Their low use is likely affected by initial approval guidelines contraindicating their prescription in patients with CKD. From the findings of the survey, these drugs were prescribed to patients who had a significantly higher rate of fractures than non-users. This observation can be considered significant only for an association and not as a causal factor; in addition, the low number of users and events further limit its clinical significance. Although recommendations for the use of these drugs concern patients with a high degree of osteoporosis or fracture episodes and only modest levels of kidney function, it has been unanimously concluded in several studies [57] and the recent European Consensus Statement on the Diagnosis and Treatment of Osteoporosis in Advanced Chronic Kidney Disease that " at present, there is

no clear reason to assume that the overall risk-benefit ratio of bisphosphonate therapy is less favorable in patients with G4-G5D CKD than in the general population" [58].

6.7. Secondary Hyperparathyroidism

SHPT is one of the most frequent complications in patients with CKD, stages G4 and G5D. The estimated prevalence of SHPT from the literature data is between 20% and 80%, according to the severity of CKD [59]. Based on the previously mentioned criteria, the prevalence of SHPT in our cohort of patients was 30.8%. Analyzing the patients with SHPT, it was possible to highlight a cohort with some significant differences compared to non-SHPT subjects (Table 4) with a specific reference to younger age, a higher number of transplants, and a larger female gender presence. Concerning the number of fractures in SHPT subjects, a lower percentage (2.8% vs. 3.2%), although not statistically significant, could be detected. Several studies have associated the presence of SHPT and increased risk of fractures, although there is no complete agreement on this. The physio-pathological rationale for this is based on the increase by PTH of osteoclastic bone resorption, resulting in abnormal bone morphology and turnover, so a persistent condition of SHPT has been associated with a higher probability of fractures in populations undergoing chronic dialysis [60]. Most (69.2%) of our SHPT patients have been prescribed cinacalcet, a calcimimetic agent specifically designed to counteract the consequences of CKD-MBD. Although statistically non-significant, the rate of fractures (2.5%) in patients taking cinacalcet was lower than in non-users (3.2%). From the analysis of four double-blind randomized clinical trials, the administration of cinacalcet, together with standard therapy for SHPT with phosphorus binders and vitamin D, led to a significant reduction in the risk of fractures. The rate of fractures fell significantly in patients receiving cinacalcet (from 6.9 per 100 patient-years to 3.2 per 100 patient-years; RR = 0.46) compared with standard care [61]. In the Evolve study, which tested the hypothesis that cinacalcet administration could reduce the incidence of fractures in HD patients, from the unadjusted intention-to-treat analysis, cinacalcet was unable to reduce the incidence of fractures, but from an analysis that took into account the difference in baseline characteristics, multiple fractures, and events conditioning the continuation of the drug, there was a reduction in fractures in a range of 16% to 29%. In addition, the rate of fractures was more elevated in older ($\geq$65 years.) than in younger patients, and the effect of cinacalcet was greater in the elderly [62]. Cinacalcet is effective in RCTs in reducing circulating PTH levels and counteracting their action in bone by suppressing their production and release by the parathyroid glands when the prescribed dose is taken regularly, despite side effects [63,64]. In a recent analysis of adherence to cinacalcet therapy and its consequences in dialysis patients [27], dividing patients into tertiles, patients in the third tertile experienced fewer hospitalizations for all causes, fractures, cardiovascular disease, and sepsis than the first tertile by 19.2%, 37.1%, 23.8%, and 32.3%, respectively. As we do not have clinical and biochemical data concerning the severity of SHPT in patients, it is not possible to provide any interpretation of the unreached significance of fracture poor compliance.

6.8. Costs Analysis

From the information of the database of Lombardy RHS, it was possible to calculate, for each patient, the costs related to the main expenditure areas, such as hospitalizations, drugs, and diagnostic and therapeutic procedures [65]. Only direct costs reimbursed by RHS and included in the database were considered. Therefore, all costs for post-fracture rehabilitation, social costs related to the loss of patient autonomy, caregivers' costs, and all direct or indirect costs charged to the patient or his/her family were not taken into account. In Table 5, the main expense chapters and the relative amounts expressed as total costs in charge to RHS and average per-patient costs for the two years of observation are reported. The average total cost for fractured patients was 11.4% higher than that of non-fractured patients. This difference is not spread equally across all cost items, but it is asymmetrically distributed. While in the fractured population, the expenditures for hospital

admissions increased as expected, by 68.4% vs. non-fractured patients, and the costs for drugs, especially those distributed through territorial pharmacies, decreased by 24.2%. Two factors could account for the difference in drug expenditures: the extended period of hospitalization with direct drug administration during the inpatient stay, which is not separately reimbursed by the RHS (hospitalizations are reimbursed as fixed regional rates for "Diagnosis Related Groups" (DRGs) attributed at discharge and include all interventions and drugs provided during the hospitalization), as well as any time spent in a post-fracture rehabilitation facility with direct drug administration. As regards diagnostic and therapeutic procedures, the differences found may be regarded as negligible. As is well known, the greatest burden of expenditure for patients undergoing dialysis treatment is the treatment itself [65], which is not greatly influenced by the occurrence of fractures.

6.9. Weakness and Strength

As pointed out earlier, the analysis of administrative databases does not allow the evaluation of qualitative components that may influence fragility fractures through various parameters, such as osteoporosis, indicators of bone metabolism, and so on, as well as the possibility of associating other biometric indicators and specific personal medical history with each patient. This problem, inherent to the structure of the information collected primarily for administrative purposes, as in the case of the databases analyzed, is certainly the study's main weakness, making it impossible to conduct a qualitative assessment of the variables being examined. On the contrary, the main strength of the study lies precisely in the use of an administrative database, which records for non-clinical purposes every event, accompanying a patient afferent to the regional universalist health care system, which thus allows for the precise identification of each case. The completeness of the database makes it possible to confidently express the results about the epidemiology of fractures in dialysis patients, providing an accurate finding on a specific population, which would not be possible to obtain with a clinical study.

6.10. Conclusions

The results of the study allowed us to measure, with reasonable accuracy, the incidence of skeletal fractures in CKD patients on RRT in a large Italian region of 9 million inhabitants. Female gender and older age were confirmed to be highly significant risk factors for fracture risk, as is also known in the general population. Other factors of significant importance emerged, such as proton pump inhibitor drugs and vitamin K antagonists. These risk factors could be reduced or even eliminated by using alternative drugs and/or by intervening early to antagonize their role in bone fragility. Limited to the study, it was confirmed that kidney transplantation, by normalizing bone metabolism, was found to be the best protective factor against fracture risk. Other factors that emerged, such as dementia and calcimimetic use, play roles, for different reasons, in increasing or reducing fracture risk, respectively, but they did not reach statistical significance in the study population, probably due to sample inadequacy. They could be the subject of ad hoc investigations.

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