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493. [10.1007/s12020-020-02553-5]

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Abstract

Purpose To evaluate clinical features, treatments, and outcomes of osteoporotic patients admitted to internal medicine and geriatric wards compared with non-osteoporotic patients (REPOSI registry).

Methods We studied 4714 patients hospitalized between 2010 and 2016. We reported age, sex, educational level, living status, comorbidities and drugs taken, Cumulative Illness Rating Scale (CIRS), Barthel Index, Short-Blessed Test, 4-item Geriatric Depression Scale, serum hemoglobin, creatinine, and clinical outcomes. Osteoporosis was defined based on the diagnoses recorded at admission, according to the following ICD9: 733, 805–813, 820–823.

Results Twelve percent of the patients had a preadmission diagnosis of osteoporosis. Only 20% of these had been prescribed oral bisphosphonates; 34% were taking vitamin D supplements. Osteoporotic patients were significantly older, with lower BMI, higher CIRS, and taking more drugs. They were significantly more depressed, less independent, with a higher severity of cognitive impairment compared with non-osteoporotic patients. At discharge, the number of patients receiving treatment for osteoporosis did not change. Length of stay and inhospital mortality did not differ between groups. Osteoporotic patients were more frequently nonhome discharged compared with those without osteoporosis (14.8 vs. 7.9%, $p = 0.0007$), mostly discharged to physical therapy or rehabilitation (8.8 vs. 2.5% of patients, $p < 0.0001$). Among osteoporotic patients deceased 3 months after discharge, the number of those treated with vitamin

D, with or without calcium supplements, was significantly lower compared with survivors (12 vs. 32%, p = 0.0168).

Conclusions The diagnosis of osteoporosis is poorly considered both during hospital stay and at discharge; osteoporotic patients are frailer compared to non-osteoporotic patients.

Keywords:

Osteoporosis

Fractures

Bisphosphonates

Vitamin D

Introduction

In Europe, the prevalence of osteoporosis is estimated to be between 5.9 and 7.2% in men and between 19.1 and 23.5% in women, respectively; this percentage significantly increases in older people [1]. However, osteoporosis is often not diagnosed until a fragility fracture occurs, and many patients remain untreated, even after osteoporotic fractures arise [2]. Less than one-third of postmenopausal women and fewer men are prescribed bone-active drugs to reduce fracture risk [3, 4]. In particular, the oldest old may be undertreated for osteoporosis, as shown by a nationwide population study based on a registry of drug prescriptions which comprised all of the Sweden population [5]. The probability of use of bisphosphonates declined with increasing age, and indeed for osteoporotic patients age ≥90 years versus those of 75–79 years, the OR for prescription of bisphosphonates was 0.36 (95% CI 0.34–0.38) for women and OR 0.46 (95% CI 0.37–0.56) for men. However, studies have shown that it is cost-effective to treat osteoporosis at higher ages [6]. This is an important issue facing demographic changes in western countries where elderly people represent a large part of the entire population. It should be noted that more than 95% of the adults with osteoporosis have at least one coexisting disease [7]. In a cohort of 1467 subjects, considering several diseases, such as osteoporosis, hypertension, and type 2 diabetes mellitus, with a mean follow-up time of 4 years, according to the multivariate analysis, osteoporosis was the most important risk factor for allcause mortality, followed by diabetes and hypertension [8]. Some studies have indicated that the excess mortality, after hip fracture, may be linked to complications following the fracture and to pre-fracture comorbid conditions [9]. However, other studies attempting to adjust for these factors have found an unexplained excess mortality [10]. There is evidence that drugs usually prescribed for osteoporosis, such as bisphosphonates, reduce not only hip fracture incidence but also mortality [11], as shown in different settings including outpatient clinics [12, 13] and intensive care units [14]. However, a recent meta-analysis failed to demonstrate such an effect of bisphosphonates on mortality [15]. Data showing characteristics of osteoporotic patients have been conducted only in out-patients or in long-term care facilities. Previous studies have shown that in longterm facilities osteoporotic patients reported a fracture rate 8–9 fold higher than those observed among less impaired seniors [16], the vast majority being undertreated [17, 18]. However, there are no data on sociodemographic and clinical features and outcomes of osteoporotic patients hospitalized in internal medicine wards. Therefore, this study was carried out to evaluate clinical features, treatments, and outcomes of osteoporotic patients, regardless of the reason for admission to internal medicine and geriatric wards, compared with non-osteoporotic patients.

Methods

Data collection

The REPOSI register (Registro Politerapie SIMI) is a collaborative and independent initiative of the Italian Society of Internal Medicine (SIMI), the IRCCS Istituto di Ricerche Farmacologiche Mario Negri and the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation. The registry was set up in 2008 with the voluntary participation of doctors working in internal medicine and geriatric wards; all patients investigated and included in the registry were required to sign an informed consent. Physicians contributing to the REPOSI Register fill out a standardized web-based case report form which includes: sociodemographic variables, treatments at hospital admission, in hospital and at discharge, laboratory parameters, comorbidities, clinical events occurring during hospital stay, and outcomes [19]. Comorbidity burden was defined according to the Cumulative Illness Rating Scale (CIRS), Comorbidity Index (CI), and Severity Index (SI) [20, 21]. Polypharmacy was defined as five or more medications [19]. To better characterize the population studied, we utilized the same clinical score previously utilized in the other REPOSI papers [19]. The Barthel Index (BI) was used for measuring functional dependence in the basic activities of daily living, partitioning dependence into five levels: total (scores 0–24), severe (scores 25–49), moderate (scores 50–

74), mild (scores 75–90), and minimal (scores 91–100) [22]. As a measure of cognitive impairment, the shortblessed test (SBT) was used, with the following standard cut-off points: normal cognition (score 0–4), possible cognitive deficit (score 5–9), probable cognitive deficit (score ≥ 10) [23]. For mood evaluation, we utilized the 4-item Geriatric Depression Scale (GDS-4), rating patient mood as probable absence of depression (0), minor (1), and probable depression (≥2) [24]. Biochemical evaluation included serum hemoglobin and creatinine; creatinine clearance (CrCl) was estimated by using the CKD-EPI equation. Osteoporosis was ascertained, using the diagnoses recorded at admission as reported by the patients, according to the following ICD9 codes corresponding to the diagnosis of osteoporosis and atraumatic fractures: 733, 805–813, 820–823. Those that reported fracture of skull, fingers and toes were not considered osteoporotic [25]. Patients were followed up for 3 months after discharge by a telephone interview in order to collect information.

Statistical analysis

Categorical variables were described using numbers and percentages. Continuous variables were expressed as mean values ± standard deviations (SDs). At uni-variable level the differences in proportions and medians were evaluated with chi-square or Fisher (where appropriate) and Mann–Whitney tests, respectively. The relation between osteoporosis and the outcomes was also adjusted for age, sex and CIRS CI by logistic regression or linear regression (where appropriate) in multivariable models. Statistical analyses were carried out using JMP Pro 14 (SAS Institute Inc. Cary. NC. USA). P values < 0.05 were considered statistically significant. Missing data were reported in the tables.

Results

Demographic and clinical characteristics of patients

We included all the patients (4714) enrolled in the REPOSI Registry between 2010 and 2016 in Italy. For 561 out of the 4714 (12%) patients, a diagnosis of osteoporosis was recorded as a comorbidity at admission (Table 1A). Patients with osteoporosis were significantly older, mainly females and with a lower BMI compared with non-osteoporotic patients. A higher proportion of osteoporotic patients lived alone, had a caregiver and reported a previous hospitalization (Table 1A). Osteoporotic patients showed a statistically significant mean higher CIRS SI and CIRS CI; however, only mean CIRS SI values persisted significantly higher when osteoarticular diseases were excluded. Moreover, they were taking more drugs with respect to those without a diagnosis of osteoporosis (Table 1A). Concerning the biochemical profile, osteoporotic patients had statistically significant mean lower serum hemoglobin and creatinine levels; however, creatinine may be related to different BMI, indeed, no significant difference in the proportion of patients in each K-DOQI classes was found compared to non-osteoporotic patients (Table 1B). Patients with osteoporosis were significantly more depressed; furthermore, we found that there was a statistically significant higher proportion of patients with cognitive impairment and that osteoporotic patients were significantly more dependent compared with non-osteoporotic patients (Table 1B).

Drug therapies for osteoporosis

Before admission, 20% of osteoporotic patients took bisphosphonates, only two patients (0.4%) denosumab and two patients (0.4%) teriparatide. Vitamin D supplementation was prescribed in 34% of osteoporotic patients, of whom 14.5% in combination with calcium supplements; only 6% of patients took calcium supplementation alone (Table 2). Interestingly, the number of patients treated for osteoporosis, during hospitalization and at discharge, remained largely unchanged (Table 2).

In-hospital and 3-month clinical outcomes

Length of stay in medicine wards was not different for osteoporotic compared to non-osteoporotic patients (Table 3); however, the discharge of osteoporotic patients to nursing homes or rehabilitation units was significantly more prevalent ($p < 0.0001$). Among the 3 months outcomes, a higher functional decline was observed in osteoporotic patients, with a trend near to significance (Table 3). Considering osteoporotic patients, we found a statistically significant higher rate of inhospital mortality in the following subgroups: males ($p = 0.007$), those who lived with a caregiver ($p = 0.02$), previous hospitalization ($p = 0.03$) or admitted from institution ($p = 0.04$), severely dependent ($p = 0.008$) and in those with kidney failure (0.004) (Supplementary Table 1). Osteoporotic patients who died after 3 months follow-up, compared to osteoporotic patients who survived, were significantly older (84.5 ± 7.9 vs. 79.8 ± 7.8 $p = 0.0017$), with a higher proportion of patients with a BMI lower than 25 kg/m2 (70.4 vs. 50.2%, $p = 0.0445$), and with lower mean serum hemoglobin levels (10.9 ± 1.8 vs. 11.7 ± 2.1, $p = 0.0187$). Furthermore, a higher proportion of osteoporotic patients, admitted from nursing homes, died after 3 months (11.4 vs. 3.7%, $p = 0.0565$).

Osteoporosis drugs and in-hospital and 3-month clinical outcomes

Inhospital mortality, among osteoporotic patients treated with bisphosphonates, did not differ from that of patients without treatment (2.7 vs. 4.1% $p = 0.63$). Among osteoporotic patients, those who had undergone preadmission treatment with bisphosphonates had a statistically significant lower comorbidity burden, a better renal function, were less dependent, and had a lower rate of previous hospitalization (Table 4). Among osteoporotic patients deceased 3 months after discharge, the number of those treated with vitamin D, with or without calcium supplements, was significantly lower compared with survivors (12 vs. 32%, $p = 0.0168$).

Discussion

In our study, we found that 12% of patients admitted to internal medicine wards had a concomitant diagnosis of osteoporosis, of whom only 20% had undergone a preadmission treatment with bone-active agents. The key message from our findings is that, in Italy, osteoporosis is underdiagnosed and undertreated in patients admitted and discharged from internal medicine wards. Indeed, based on osteoporosis prevalence in Europe and more specifically in Italy (ranging from 25 to 50% in the elderly), we would have expected a higher percentage of diagnosis of this common metabolic bone disease in the elderly [26, 27]. However, it can be correctly stated that, here in Italy, the problem resides outside the hospital, where the diagnosis of osteoporosis was first made, thus confirming what is already known in the literature [2, 3]. Moreover, the proportion of osteoporotic patients treated does not change following discharge resulting in a continuing persistence of undertreatment. This is of ominous prognostic significance since profound consequences regarding morbidity, mortality and especially social costs can be expected by such a behavior. Therefore, it seems that the issue of metabolic bone disease, in general and specifically of osteoporosis, does not capture the attention of doctors at hospital admission and during hospitalization. As a result, hospital physicians are not inclined to prescribe drugs against osteoporosis during hospital stay. This could be due to a number of reasons such as the low awareness of the disease even among skilled doctors [27], or its lower hierarchy in respect to concomitant diseases which have more of an influence on the patient short-term outcomes, as has been previously demonstrated [28]. In our cohort, osteoporotic patients were older, had a mean lower BMI, a higher burden of diseases, and were treated with more drugs compared to non-osteoporotic patients. Moreover, they were more depressed,

less independent and with cognitive impairment, all features which rendered them frailer. As regarding the outcomes, we found that osteoporotic patients showed a higher prevalence of discharge in rehabilitation settings. This may be explained considering their condition of frailty, as mentioned above. Therefore, in the frame of a comprehensive geriatric assessment, it is important to carefully look for a condition of osteoporosis in older hospitalized patients in order to identify those more vulnerable, requiring person-centered approaches (e.g., early inhospital mobilization or selection of the appropriate care setting). Interestingly, osteoporotic patients seem to be also more vulnerable to the hospitalization-associated disability, showing a higher functional decline, defined in terms of reduction of BI between admission and 3 months after discharge. We also found that among osteoporotic patients who died during hospital stay, males represented 50% of patients, a percentage significantly higher than the percentage of men among survivors (21.7%, $p = 0.007$). Moreover, those who died had a significantly higher rate of a previous hospitalization or were admitted from nursing facilities and were less dependent, further emphasizing the concept of frailty. Interestingly, several variables may affect physicians' choice in osteoporosis treatment. Bisphosphonates were more prescribed to subjects with a lower comorbidity burden and more independent. We found, that among patients who died after 3 months' follow-up, vitamin D supplements were significantly less prescribed, as well as bisphosphonates, although for bisphosphonates this difference was not statistically significant. A recent paper points to the role of serum vitamin D levels and mortality in subjects at least 80 years old [29]. This prospective multicenter, community-based cohort study of 2185 Chinese older adults, with a median age of 93 years, showed that in this population, after adjusting for multiple confounders, the risk of all-cause mortality decreased as the plasma 25(OH)D concentration increased [29]. Even though there is an ongoing debate about the role of vitamin D (and bisphosphonates) and survival, we believe that our findings should be interpreted with caution also considering the small number of patients enrolled. In this context, for example, it has been reported that compliance to treatment can be simply considered a surrogate of well-being in respect to those non adherent [27, 30] Our study has limitations and strengths. The REPOSI Study was not designed to collect osteoporosis-related variables. Therefore, no information on morphometric vertebral fractures are available in the REPOSI dataset; as a consequence, the number of osteoporotic patients may be further underestimated. Furthermore, we do not have information regarding densitometric parameters, as well as on some relevant biochemical measurements, i.e., serum vitamin D levels. As a result, analysis on the appropriateness of osteoporosis-related drugs, according to the validated scores, are not possible. Missing data for some patients is one of the limits, even though this does not change the final conclusions of our study. Despite these limits, we have characterized, for the first time, a cohort of patients admitted to internal medicine and geriatric wards with a concomitant diagnosis of osteoporosis. In conclusion, we report that in internal medicine wards, the diagnosis of osteoporosis is neglected both during hospital stay and at discharge, therefore substantially contributing to the economic and social burden of the disease. A cultural change is urgently required for the way hospital specialists view and treat metabolic bone diseases and, in particular, osteoporosis.

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