ORIGINAL ARTICLE

No association of anti-osteoporosis drugs with COVID-19-related outcomes in women: a nationwide cohort study

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Abstract

Summary This study was performed to evaluate whether the use of drugs in the treatment of osteoporosis in women is associated with COVID-19 outcomes. The results showed that the risk of hospitalization, intensive care unit admission, and mortality was not altered in individuals taking anti-osteoporosis drugs, suggesting no safety issues during a COVID-19 infection.

Introduction Whether patients with COVID-19 receiving anti-osteoporosis drugs have lower risk of worse outcomes has not been reported yet. The aim of this study was to evaluate the association of anti-osteoporosis drug use with COVID-19 outcomes in women.

Methods Data obtained from a nationwide, multicenter, retrospective cohort of patients diagnosed with COVID-19 from March 11th to May 30th, 2020 was retrieved from the Turkish Ministry of Health Database. Women 50 years or older with confirmed COVID-19 who were receiving anti-osteoporosis drugs were compared with a 1:1 propensity score-matched COVID-19 positive women who were not receiving these drugs. The primary outcomes were hospitalization, ICU (intensive care unit) admission, and mortality.

Results A total of 1997 women on anti-osteoporosis drugs and 1997 control patients were analyzed. In the treatment group, 1787 (89.5%) women were receiving bisphosphonates, 197 (9.9%) denosumab, and 17 (0.9%) teriparatide for the last 12 months. Hospitalization and mortality rates were similar between the treatment and control groups. ICU admission rate was lower in the treatment group (23.0% vs 27.0%, $p = 0.013$). However, multivariate analysis showed that anti-osteoporosis drug use was not an independent associate of any outcome. Hospitalization, ICU admission, and mortality rates were similar among bisphosphonate, denosumab, or teriparatide users.

Conclusion Results of this nationwide study showed that preexisting use of anti-osteoporosis drugs in women did not alter the COVID-19-related risk of hospitalization, ICU admission, and mortality. These results do not suggest discontinuation of these drugs during a COVID-19 infection.

Keywords Bisphosphonates · COVID-19 · Denosumab · Mortality · Osteoporosis · Teriparatide

Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a novel coronavirus that emerged in China in late 2019 [1, 2]. The disease that it causes, COVID-19, was announced as a global pandemic on March 11th, 2020 by World Health Organization (WHO) [3]. By June 13th, 2021, COVID-19 had infected 175,306,598 people and caused 3,792,777 deaths worldwide [4]. COVID-19 represents a

clinical spectrum ranging from asymptomatic or mild/moderate illness which resembles upper respiratory tract infection to severe disease evolving to pneumonia, acute respiratory distress syndrome, and death [1, 5, 6].

Both inborn and acquired immunological responses play important roles in the severity and progression of COVID-19. Replication of SARS-CoV-2 followed by destruction of cells triggers recruitment of monocytes and macrophages and release of cytokines [7, 8]. The immune system is dysregulated in severe forms of COVID-19 with exaggerated release of cytokines and inflammatory markers making them appropriate biomarkers for monitoring disease progression [8, 9]. In this context, some immune-modulating

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drugs used in chronic inflammatory diseases which reduce immune response may provide protection against COVID-19 by decreasing its incidence, severity, and mortality [10, 11].

Osteoporosis is a systemic skeletal disease characterized by low bone mass and deterioration of bone microarchitecture with a consequent increase in bone fragility and susceptibility to fractures [12]. It is a chronic disease resulting in increased morbidity, mortality, and treatment costs [13]. Currently, most organizations do not recommend discontinuation of drugs used in the treatment of osteoporosis during the management of COVID-19, assuming that these drugs do not have an impact on prognosis [14–17]. However, the effects of osteoporosis and drugs used in its treatment on the incidence or prognosis of COVID-19 are largely unknown. In one study, osteoporosis was among the factors that increased the risk of COVID-19 [18]. In another study, zoledronate, denosumab, and supplemental calcium users had a tendency for a lower incidence of COVID-19 [19]. Denosumab and zoledronate may exert their protective effects by immune-modulating actions [10, 11, 19]. The aim of the present study was to evaluate whether the use of anti-osteoporosis drugs was associated with the risk of worse COVID-19 outcomes in women.

Materials and methods

Study design and participants

In this nationwide, multicenter, retrospective cohort study, we used the data retrieved from the Turkish Ministry of Health National Electronic Database. This database includes information of all COVID-19 patients across the country who were confirmed with a positive polymerase chain reaction (PCR) test between March 11th, 2020 (diagnosis of the first COVID-19 patient in Turkey) and May 30th, 2020. This was the period in which nearly total lockdown was enforced in Turkey. The study was conducted in accordance with 1964 Helsinki Declaration, as revised in 2013 and approved by the COVID-19 Investigation Review Board (IRB) designated by the Ministry of Health, which waived the requirement of informed consent due to the retrospective study design and anonymity of the database (IRB number: 95741342–020:1 86,404/28.10.2020).

Of the 203,456 COVID-19 cases 53,785 (26.4%) were excluded since they were younger than 18 years. The remaining 149,671 adult cases who were followed ambulatory or in an inpatient setting were eligible for inclusion. Among this population, 2754 patients were identified with anti-osteoporosis drug (bisphosphonates, denosumab, and teriparatide) prescription in the last 12 months. Patients receiving these drugs for cancer treatment ($n = 438$) were excluded. Men ($n = 256$) and women younger than 50 years of age

($n = 63$) were also excluded. Women 50 years or older who were receiving anti-osteoporosis drugs (treatment group, $n = 1997$) were matched for age by 1:1 propensity score matching (PSM) with women who were not receiving these drugs (control group, $n = 1997$) (Fig. 1).

Data collection

Gender, age, attained level of education, smoking, comorbidities, body mass index (BMI), chest computerized tomography (CT) on admission, laboratory tests, and medications were obtained from the dataset.

Type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, obesity, asthma, chronic obstructive pulmonary disease (COPD), cardiovascular disease, rheumatic diseases, and chronic kidney disease (CKD) were noted as comorbidities.
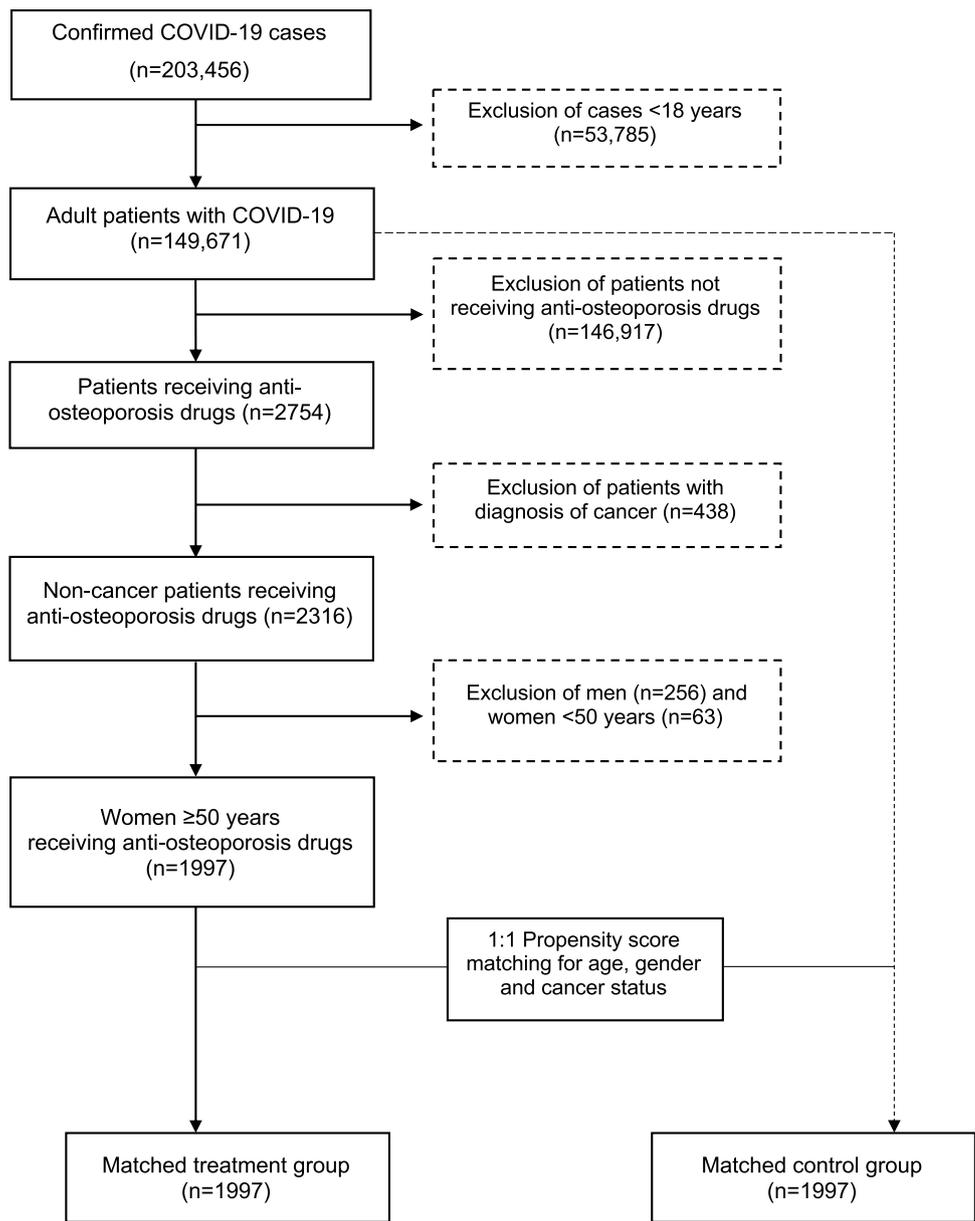
Serum calcium, albumin, phosphorus, alkaline phosphatase (ALP), magnesium, 25-hydroxyvitamin D (25(OH) D), estimated glomerular filtration rate (eGFR), liver function tests (AST and ALT), D-dimer, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), ferritin, fibrinogen, and lymphocyte count were recorded. All blood tests were performed in hospital laboratories certificated by the Turkish Ministry of Health. Test results that were available within the last 10 days before the diagnosis of COVID-19 and 25(OH)D results available in the last 3 months were included.

Information about the use of anti-osteoporosis drugs (bisphosphonates, denosumab, and teriparatide), drugs for neuropathic pain, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs), antidiabetic and antihypertensive medications, statins and acetylsalicylic acid was obtained from the Ministry of Health database. Anatomical Therapeutic Chemical (ATC) classification system was used for listing the drugs [20] (Supplementary Table 1).

Definitions

The term "treatment group" refers to women 50 years or older, receiving anti-osteoporosis drugs without diagnosis of cancer. Since menopausal status was not available in the database, the selection of this age as cutoff was based on the average menopause age of Turkish women in different cohorts [21, 22]. The term "control group" refers to age-matched women not receiving any osteoporosis treatment and not registered with diagnosis of osteoporosis and cancer. Higher education was defined as receiving formal education for 9 or more years. Smoking was defined as currently smoking at the time of diagnosis. BMI was calculated as the ratio of weight to the square of height (kg/ m^2). Calcium, albumin, phosphorus, ALP, magnesium, and 25(OH)D were expressed in units. eGFR was calculated based on the CKD-EPI equation [23]. Lymphopenia

Fig. 1 Flowchart of the study population selection

Confirmed COVID-19 cases
(n=203,456)

Exclusion of cases <18 years
(n=53,785)

Adult patients with COVID-19
(n=149,671)

Exclusion of patients not
receiving anti-osteoporosis drugs
(n=146,917)

Patients receiving anti-
osteoporosis drugs (n=2754)

Exclusion of patients with
diagnosis of cancer (n=438)

Non-cancer patients receiving
anti-osteoporosis drugs (n=2316)

Exclusion of men (n=256) and
women <50 years (n=63)

Women ≥50 years
receiving anti-osteoporosis drugs
(n=1997)

1:1 Propensity score
matching for age, gender
and cancer status

Matched treatment group
(n=1997)

Matched control group
(n=1997)

was defined as lymphocyte count less than 1000/μL, and percentage of patients with lymphopenia was used in the analyses. Other laboratory results were analyzed using the percentage of patients who exceed the upper limit of normal (ULN). T2DM, hypertension, dyslipidemia, obesity, asthma, COPD, cardiovascular disease, rheumatic diseases, and CKD were defined based on the International Classification of Diseases System-10 (ICD-10) codes.

Study outcomes

The study outcomes were COVID-19-related hospitalization, ICU admission, and mortality. Hospitalization and ICU admission were defined according to COVID-19 Guidelines prepared by the Turkish Ministry of Health Scientific Board [23]. Patients with moderate to severe Covid-19 and those who had underlying diseases such as cardiovascular disease, diabetes mellitus, hypertension, cancer, chronic lung, and other immunosuppressive diseases were hospitalized in hospitals reserved for the pandemic (Ministry of Health hospitals, State and Foundation University hospitals, and private hospitals). Patients with severe disease like pneumonia with respiratory failure, acute respiratory distress syndrome, sepsis, septic shock, myocarditis, arrhythmia, cardiogenic shock, metabolic acidosis, coagulation dysfunction, and multiple organ failure were followed in ICU [23].

Statistical analyses

All data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows 25.0 (SPSS Inc. 111 Chicago, IL). Numerical variables were expressed as mean ± standard deviation (SD) or medians and interquartile range (IQR) and categorical variables as counts (*n*) and percentages (%). Normality of distribution was assessed using Kolmogorov–Smirnov test. Differences between the groups were assessed using Chi-square test for categorical variables and Student's *t* test or Mann–Whitney *U* test for numerical variables. Multivariate logistic regression analysis was performed to study the independent predictors of hospitalization, ICU admission, and mortality. Statistical significance was defined as a two-sided *p* value of ≤ 0.05.

Results

Basic and demographic characteristics of the treatment and control groups are shown in Table 1. Both groups were 1:1 matched for age (median 59 years, IQR 13). BMI (26.6 vs 31.2 kg/m^2, *p* < 0.001) was lower and 25(OH)D level (22.64 vs 19.65 ng/mL, *p* = 0.043) was higher in the treatment group. Education, smoking, chest CT findings on admission, and other laboratory findings including markers of COVID-19 severity were similar in the two groups.

Asthma/COPD (47.8% vs 41.5%, *p* < 0.001) and rheumatic diseases (2.3% vs 0.7%, *p* < 0.001) were more common, and T2DM (48.2% vs 52.8%, *p* = 0.004), obesity (42.4% vs 60.4%, *p* < 0.001), and CKD (28.7% vs 35.4%, *p* = 0.012) were less common in the treatment group. The prevalence of hypertension, dyslipidemia, and cardiovascular diseases were not different between the groups (Table 1).

Among the treatment groups, 1787 (89.5%) women received bisphosphonates, 197 (9.9%) received denosumab, and 17 (0.9%) received teriparatide. A few patients were identified to receive both drugs at different times. Neuropathic pain medications (53.0% vs 34.7%, *p* < 0.001), antidepressants (51.9% vs 42.6%, *p* < 0.001), NSAIDs (97.3% vs 89.3%, *p* < 0.001), and acetylsalicylic acid (44.4% vs 39.7%, *p* = 0.002) were more commonly; and antidiabetic drugs (32.0% vs 40.1%, *p* < 0.001) were less commonly used in the treatment group. No significant difference was found regarding the use of antihypertensive drugs and statins between the groups (Table 1).

As shown in Table 1, hospitalization and mortality rates were similar between the treatment and control groups (70.7% vs 72.7%, *p* = 0.16 for hospitalization and 11.9% vs 12.8%, *p* = 0.386 for mortality). However, ICU admission rate was lower in the treatment group (23.0% vs 27.0%, *p* = 0.013). There were no significant differences in hospitalization, ICU admission, and mortality rates of women according to the type of anti-osteoporosis drug (Fig. 2).

The results of the multivariate logistic regression analysis are shown in Table 2. When age, T2DM, hypertension, dyslipidemia, obesity, asthma/COPD, cardiovascular disease, CKD, and anti-osteoporosis drug use were entered as independent variables into the regression model, hypertension (OR: 3.92, 95% CI: 1.05–14.56, *p* = 0.042) was significantly associated with hospitalization, and age (OR: 1.07, 95% CI: 1.02–1.13, *p* = 0.01) was significantly associated with ICU admission. None of the variables was associated with mortality. Multivariate analysis showed that anti-osteoporosis drug use was not significantly associated with hospitalization, ICU admission, or mortality in adjusted analyses (Table 2 and Fig. 3).

Discussion

This is one of the few studies focusing on COVID-19 outcomes in women who were receiving anti-osteoporosis drugs. The results revealed that hospitalization and mortality rates were similar between the treatment and control groups except for the ICU admission rate that was lower in the treatment group. In multivariate analysis, however, anti-osteoporosis drug use was not significantly associated with any of the three study outcomes. Also, women receiving bisphosphonates, denosumab, and teriparatide had similar rates for COVID-19 outcomes.

Most organizations do not recommend discontinuing anti-osteoporosis drugs during the COVID-19 era [14–17]. However, disruption of osteoporosis treatment may occur during the adoption of strict measures such as social distancing and lockdowns during any pandemic. In such a case, delay of intravenous bisphosphonates even for several months may not be harmful [15]. On the other hand, when denosumab treatment is not ensured within 7 months of the last injection, and the delay in treatment with teriparatide exceeds 2 to 3 months, temporarily transitioning to an oral bisphosphonate is suggested [15].

To date, there are no published studies on the potential effects of drugs used in the treatment of osteoporosis on significant outcomes such as hospitalization, ICU admission, and mortality in patients with COVID-19. In a study that evaluated the comorbidity burden among COVID-19 patients, osteoporosis was associated with an increased incidence of COVID-19, and it was identified as an independent risk factor in adjusted analysis [18]. On the other hand, a previous diagnosis of osteoporosis was not associated with disease severity in COVID-19 patients. The relation of anti-osteoporosis drugs with outcomes of COVID-19 was not evaluated in that study. Another study showed that

Table. 1 Clinical characteristics and outcomes of women 50 years or older diagnosed with COVID-19 who were receiving and not receiving anti-osteoporosis drugs

	Treatment group[a] (n=1997)	Control group[b] (n=1997)	Available data (n/n, treatment group/control group)	p[d]
Age, years, median (IQR)	59 (13)	59 (13)	1997/1997	1.000
Follow-up center, n (%)				
Public hospitals	1575 (78.9)	1512 (78.9)	1997/1997	0.055
University hospitals	138 (6.9)	153 (7.7)		
Private centers	284 (14.2)	332 (16.6)		
Education, 9 years and over, n (%)	12 (4.5)	12 (4.2)	265/284	0.862
Smoking, current smoker, n (%)	91 (7.4)	95 (7.5)	1237/1260	0.862
BMI, kg/m², median (IQR)	26.6 (6.8)	31.2 (6.9)	224/235	**< 0.001**
Chest CT on admission consistent with COVID-19, n (%)	805 (41.7)	849 (43.7)	1929/1945	0.227
Comorbid conditions				
T2DM, n (%)	949 (48.2)	1038 (52.8)	1969/1966	**0.004**
Hypertension, n (%)	1747 (87.5)	1752 (87.2)	1997/1997	0.810
Dyslipidemia, n (%)	859 (43.0)	835 (41.8)	1997/1997	0.442
Obesity, n (%)	95 (42.4)	142 (60.4)	224/235	**< 0.001**
Asthma/COPD, n (%)	955 (47.8)	829 (41.5)	1997/1997	**< 0.001**
Cardiovascular disease, n (%)	1047 (52.4)	990 (49.6)	1997/1997	0.071
Rheumatic diseases, n (%)	46 (2.3)	13 (0.7)	1997/1997	**< 0.001**
CKD, n (%)	236 (28.7)	272 (35.4)	823/768	**0.012**
Laboratory values				
Calcium, mg/dL, median (IQR)	8.90 (1.05)	8.80 (1.02)	253/258	0.202
Albumin, g/dL, median (IQR)	3.63 (0.78)	3.70 (1.00)	154/159	0.687
Phophorus, mg/dL, median (IQR)	3.20 (0.92)	3.33 (1.44)	65/80	0.358
ALP, IU/L, median (IQR)	72.50 (43.75)	72.50 (32.25)	118/138	0.398
Magnesium, mg/dL, median (IQR)	1.97 (0.45)	1.92 (0.38)	76/99	0.556
25(OH)D, ng/mL, median (IQR)	22.64 (21.96)	19.65 (16.27)	15/116	**0.043**
eGFR (mL/kg/min/1.73 m²), median (IQR)	88.95 (54.20)	85.47 (54.77)	568/631	0.085
AST, > ULN, n (%)	61 (17.9)	58 (16.6)	340/350	0.634
ALT, > ULN, n (%)	31 (9.0)	35 (10.1)	343/348	0.648
D-dimer > ULN, n (%)	128 (69.9)	139 (69.8)	183/199	0.984
CRP, > ULN, n (%)	492 (74.0)	462 (74.4)	665/621	0.866
Procalcitonin, > ULN, n (%)	5 (4.9)	14 (11.1)	102/126	0.147
LDH, > ULN, n (%)	222 (56.3)	197 (50.9)	394/387	0.127
Ferritin, > 100 ng/mL, n (%)	208 (62.3)	256 (67.2)	334/381	0.169
Fibrinogen, > ULN, n (%)	44 (75.9)	38 (67.9)	58/56	0.342
Lymphopenia, Lym# < 1000, n (%)	337 (26.8)	316 (25.1)	1258/1260	0.328
Treatments				
Bisphophonates, n (%)[c]	1787 (89.5)	NA	1997/—	—–
Denosumab, n (%)[c]	197 (9.9)	NA	1997/—	—–
Teriparatide, n (%)[c]	17 (0.9)	NA	1997/—	—–
Neuropathic pain medications, n (%)	1058 (53.0)	693 (34.7)	1997/1997	**< 0.001**
Antidepressant drugs, n (%)	1037 (51.9)	850 (42.6)	1997/1997	**< 0.001**
NSAIDs, n (%)	1943 (97.3)	1784 (89.3)	1997/1997	**< 0.001**
Antidiabetic drugs, n (%)	640 (32.0)	800 (40.1)	1997/1997	**< 0.001**
Antihypertensive drugs, n (%)	1561 (78.2)	1551 (77.7)	1997/1997	0.703
Statins, n (%)	525 (26.3)	554 (27.7)	1997/1997	0.301
Acetylsalicylic acid, n (%)	887 (44.4)	792 (39.7)	1997/1997	**0.002**
Hospitalization, n (%)	1411 (70.7)	1451 (72.7)	1997/1997	0.160

Table. 1 (continued)

	Treatment group[a] (n = 1997)	Control group[b] (n = 1997)	Available data (n/n, treatment group/control group)	p[d]
ICU admission, n (%)	324 (23.0)	391 (27.0)	1407/1446	**0.013**
Mortality, n (%)	237 (11.9)	255 (12.8)	1997/1997	0.386

[a]Women 50 years or older who were receiving anti-osteoporosis drugs, [b]Age-matched women who were not receiving anti-osteoporosis drugs, [c]Some patients received two anti-osteoporosis drugs at different times, [d]p values in bold show statistically significant results

25(OH)D, 25-hydroxy vitamin D; *ALP*, alkaline phosphatase; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CRP*, C-reactive protein; *CT*, computerized tomography; *eGFR*, estimated glomerular filtration rate; *ICU*, intensive care unit; *IQR*, interquartile range; *LDH*, lactate dehydrogenase; *Lym#*, Lymphocyte count per mililiter; *NA*, non available; *NSAIDs*, nonsteroid anti-inflammatory drugs; *T2DM*, type 2 diabetes mellitus; *ULN*, upper limit of normal

Fig. 2 Comparison of COVID-19 outcomes among the three anti-osteoporosis drug users and relative risks of outcomes compared to control group (ICU, intensive care unit)
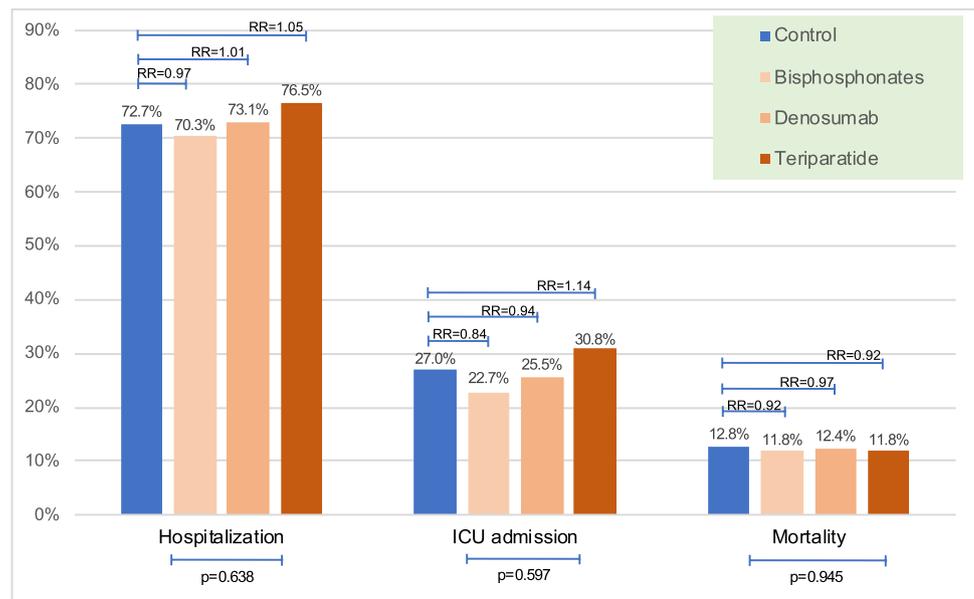
Table. 2 Multivariate logistic regression analysis of treatment (women 50 years or older who were receiving anti-osteoporosis drugs) and control (age-matched women who were not receiving anti-osteoporosis drugs) groups (dependent variable: hospitalization, ICU admission, mortality)

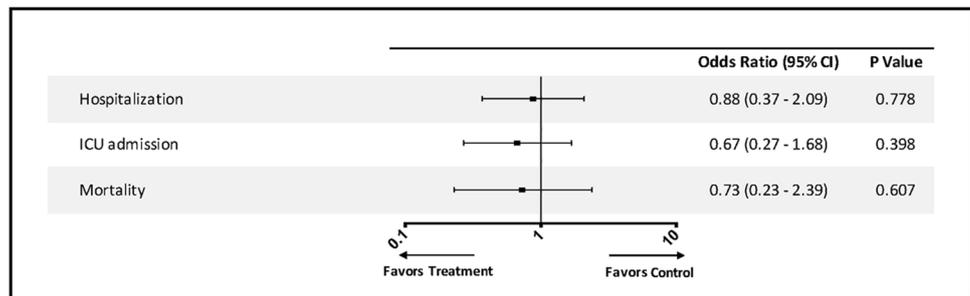|	Hospitalization		ICU admission		Mortality	
	OR, CI (95%)	[a]	OR, CI (95%)	[a]	OR, CI (95%)	p
Age	0.98 (0.94–1.04)	0.633	1.07 (1.02–1.13)	**0.010**	1.06 (0.99–1.14)	0.104
T2DM	1.06 (0.43–2.67)	0.894	2.62 (0.95–7.19)	0.062	2.82 (0.65–12.23)	0.167
Hypertension	3.92 (1.05–14.56)	**0.042**	0.28 (0.04–1.95)	0.200	0.47 (0.04–5.46)	0.545
Dyslipidemia	1.42 (0.59–3.42)	0.428	1.84 (0.72–4.70)	0.202	1.23 (0.37–4.05)	0.736
Obesity	0.55 (0.23–1.31)	0.177	0.85 (0.35–2.04)	0.709	1.36 (0.43–4.31)	0.603
Asthma/COPD	0.94 (0.41–2.20)	0.894	0.83 (0.35–1.93)	0.658	0.46 (0.15–1.47)	0.192
Cardiovascular disease	1.42 (0.58–3.48)	0.432	1.34 (0.52–3.46)	0.548	2.22 (0.60–8.17)	0.232
CKD	0.73 (0.30–1.77)	0.484	1.35 (0.56–3.26)	0.509	2.84 (0.92–8.81)	0.071
Anti-osteoporosis drug use	0.88 (0.37–2.08)	0.778	0.67 (0.27–1.68)	0.398	0.73 (0.23–2.39)	0.607

[a]p values in bold show stattistically significant result

CI, confidence interval; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *ICU*, intensive care unit; *OR*, odds ratio; *T2DM*, type 2 diabetes mellitus

preexisting use of denosumab and zoledronate was associated with a trend towards reduced incidence of COVID-19, although not statistically significant [19]. The authors proposed several mechanisms of action for zoledronate and denosumab, including their favorable role in the regulation of immune responses. The results of these two studies

Fig. 3 Multivariate adjusted odds ratio of outcomes. The term "Treatment" refers to women 50 years or older who were receiving anti-osteoporosis drugs; "Control" refers to age-matched women who were not receiving anti-osteoporosis drugs (ICU, intensive care unit)

	Odds Ratio (95% CI)	P Value
Hospitalization	0.88 (0.37 - 2.09)	0.778
ICU admission	0.67 (0.27 - 1.68)	0.398
Mortality	0.73 (0.23 - 2.39)	0.607

Favors Treatment — Favors Control

suggest that osteoporosis as a comorbidity may increase the incidence but anti-osteoporosis drugs may decrease the risk of COVID-19.

The studies mentioned above included both women and men, and the only outcome of interest was the incidence of COVID-19 [18, 19]. In the current study, only women 50 years or older who were receiving anti-osteoporosis drugs were included as a more homogenous group, and they were compared with age-matched women with COVID-19 who were not on anti-osteoporosis drugs. Therefore, the confounding effect of gender on study outcomes was eliminated. Women receiving anti-osteoporosis drugs had similar hospitalization and mortality but lower ICU admission rate than those who were not on an anti-osteoporosis drug. Thus, taken together with the results of the previous study [19], it is likely that the preexisting use of anti-osteoporosis drugs did not worsen the clinical course of COVID-19.

Obesity, T2DM, and CKD were less common whereas rheumatic diseases and asthma/COPD were more common in the treatment group in the sample of the current study. When these comorbidities were analyzed in multivariate analysis, none of them was found to be independent associates of the outcomes. Hypertension and age were significantly associated with hospitalization and ICU admission, respectively. However, mean age and frequency of hypertension did not differ between the groups. Therefore, we assume that our findings were not confounded by the chronic comorbidities. In accordance with disease states, more women in the treatment group received neuropathic pain medications, antidepressants, and NSAIDs, and fewer women received antidiabetic drugs. Although vitamin D status was available only in 3.3% of the total study population, women in the treatment group had higher 25(OH)D levels. They might be receiving vitamin D supplements as part of their osteoporosis management. We were unable to analyze if the differences in 25(OH)D levels and vitamin D replacement status had a confounding effect on our study outcomes. It is also likely that the preexisting use of several drugs such as analgesics and antidepressants may have some effects opposite to those of anti-osteoporosis drugs on the immune system [19]. However, the design of this study did not allow us to further investigate all medications of the patients.

Bisphosphonates are antiresorptive agents which bind to hydroxyapatite and inhibit farnesyl-pyrophosphate synthase, an enzyme in the mevalonate pathway [19, 24, 25]. They inhibit prenylation of intracellular signaling proteins which are essential for osteoclast function and survival and thereby they induce apoptosis of osteoclasts [24, 25]. Intravenous zoledronate was shown to decrease mortality by 28% after hip fracture but only 8% of this reduction was due to reductions in recurrent fractures [26, 27]. Zoledronate-treated patients were less likely to die from pneumonia and cardiac arrhythmias [27]. In SARS-CoV-2 infection, T cells are depleted, and the dendritic cells are abundant in the lungs [28]. The dendritic cells internalize inhaled SARS-CoV-2 particles. Virion release from the dendritic cells depends on the prenylation signal from the mevalonate pathway. Aminobisphosphonates were shown to increase T cells and disrupt dendritic cells by inhibiting the mevalonate pathway [28].

Denosumab, another antiresorptive agent, has a different mechanism of action [24]. It prevents RANKL from binding its receptor RANK on osteoclasts and eventually inhibits osteoclastogenesis. RANK/RANKL system is also involved in immune responses. Apart from its effects on bone, denosumab acts as an immune-modulating agent and decreases inflammatory cytokines [19, 24, 29]. There are many studies evaluating the protective and therapeutic effects of denosumab on microbial diseases, especially viral infections [30, 31]. Recently, the role of innate immune system and T cell activation in host responses against SARS-CoV-2 was demonstrated in rhesus macaques [32]. RANKL is expressed in the immune cells of humans and plays an important role in T cell activation [33]. These findings imply that denosumab may have an effect on the course of COVID-19. A recent meta-analysis showed an increased risk of the ear, nose, and throat, and gastrointestinal infections with denosumab [34]. However, the overall risks of any infections and mortality were not increased [34]. In a survey study, women older than 50 years receiving treatment for postmenopausal osteoporosis were not at high risk for severe COVID-19, and denosumab was not a risk factor for COVID-19 [35].

Teriparatide is a parathormone analogue and an anabolic agent which increases bone formation. In vitro and in vivo studies evaluating the effects of parathormone on

the immune system have shown inconsistent results mostly due to differences in the methodology of the studies [36, 37]. Most studies were performed in patients with CKD who had secondary hyperparathyroidism. In vitro and in vivo studies on the effects of high parathormone levels on T and B lymphocytes were summarized in a review article [36]. It appears that there are controversial reports about the effects of parathormone on the proliferation of T lymphocytes and the immunoglobulin production of the B lymphocytes [36]. Another study reported that parathormone had no effect on interleukin-6 and interleukin-8 production in activated leukocytes in healthy donors [37]. The clinical relevance of these findings is not clear, and laboratory studies are not perfect models to show the effects of chronic exposure to parathormone on the immune system. Besides, we cannot extrapolate these findings to patients receiving parathormone analogs for osteoporosis.

In this study, ICU admission rate was lower in the treatment group. This result may imply a less severe clinical course of COVID-19 infection in patients receiving anti-osteoporosis medications. The immune-modulating effects of anti-osteoporosis drugs, mainly bisphosphonates, may explain the lower rate. Since most of the patients in the treatment group received bisphosphonates (89.5%) and few of them received denosumab (9.9%) and teriparatide (0.9%), the effects of bisphosphonates on the immune system and hence COVID-19 course reflected by the ICU admission rate may be more prominent than the other drugs. However, hospitalization, ICU admission, and mortality rates were similar among women on three different drugs, and multivariate analysis showed that anti-osteoporosis drug use was not independently associated with any outcome.

This study has several limitations. Due to its retrospective design, the effects of missing data and confounding factors such as the use of drugs like steroids, calcium, and vitamin D supplements cannot be interpreted. Some patients in the control group may have osteoporosis although they were not receiving anti-osteoporosis drugs. In this regard, we relied on ICD-10 codes and included women without registered diagnosis of osteoporosis. Also, we were not able to separately analyze oral and intravenous bisphosphonate users, although some distinct immunologic properties of bisphosphonate class of drugs may cause differences in COVID-19 outcomes. Strengths of the study include a nationwide representation covering all seven geographical regions, involvement of all types of care hospitals in charge of government or private bodies, and the large number of patients. Besides, data of patients diagnosed in the first 3 months of the COVID-19 pandemic were collected. This is the period in which nearly total lockdown was enforced and the same treatment guideline prepared by the Ministry of Health was implemented for all patients diagnosed with COVID-19. Finally, the control group was selected by using 1:1 PSM

approach to exclude the possible confounding effects of age, gender, and cancer status.

In conclusion, this is the first study evaluating the association of anti-osteoporosis drugs and COVID-19 outcomes in women. The results showed that the preexisting use of anti-osteoporosis drugs was not associated with a worse clinical course of COVID-19. Therefore, it appears that the use of anti-osteoporosis drugs during the COVID-19 era is safe, and we do not recommend discontinuation of osteoporosis treatment in this period.

Declarations

Ethics approval and consent to participate The study was approved by the COVID-19 Investigation Review Board (IRB) designated by the Ministry of Health, which waived the requirement of informed consent due to the retrospective study design and anonymity of the database (IRB number: 95741342–020:186404/28.10.2020).

Informed consent was not required due to the retrospective design of the study.

Consent for publication All authors approved the final version and publication of the manuscript.

Conflict of interest The authors declare no competing interests.

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