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Research Paper

Chronic kidney disease and denosumab in metastatic bone disease: A multicenter Turkish cohort study on severe hypocalcemia, skeletal events, and survival

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HIGHLIGHTS

- CKD markedly increases risk of denosumab-related severe hypocalcemia.
- Grade ≥3 toxicity occurred in 31% with CKD versus 4% without CKD.
- CKD patients had more pathological fractures and skeletal surgeries.
- Severe toxicity and CKD status were associated with worse survival.
- Close calcium and renal monitoring is crucial in CKD on denosumab.

Abbreviations: CAD, coronary arterial disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DAH, denosumab-associated hypocalcemia; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HT, hypertension; IQR, interquartile range; SRE, skeletal-related events.

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ABSTRACT

Background: Denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), is widely used to prevent skeletal-related events (SREs) in patients with bone metastases from solid tumours. However, its safety in individuals with advanced chronic kidney disease (CKD), particularly regarding severe hypocalcaemia and skeletal complications, is not well defined.

Methods: We conducted a retrospective, multicentre study within the Turkish Oncology Group including patients with breast, prostate, or lung cancer who received denosumab between January 2011 and December 2022. Demographic and clinical data, CKD stage, prior fractures, serum calcium levels, episodes of hypocalcaemia, concomitant medications, and adverse events were recorded. Primary endpoints were the incidences of grade ≥ 3 hypocalcaemia and other grade ≥ 3 toxicities; secondary endpoints included skeletal-related events and overall survival.

Results: We analysed 264 patients from 17 oncology centres. Overall, 18 patients (6.8 %) experienced grade ≥ 3 toxicity, including 16 cases of severe hypocalcaemia and two of renal function decline. Among 42 patients with baseline estimated glomerular filtration rate (eGFR) < 60 mL/min, 13 (31.0 %) developed grade ≥ 3 toxicity (11 hypocalcaemia, two renal decline), representing a significantly higher risk than in patients with eGFR ≥ 60 mL/min ($p < 0.01$). Pathological fractures occurred in 21 patients, six with eGFR < 60 mL/min ($p = 0.035$). Eight patients required surgery for skeletal-related events, four with eGFR < 60 mL/min ($p = 0.012$).

Conclusion: Cancer patients with CKD receiving denosumab have an increased risk of severe hypocalcaemia and skeletal complications. Close monitoring of calcium and renal function is essential, and clinicians should carefully balance the benefits of denosumab against these risks in this vulnerable population.

1. Background

Bone metastases are a frequent complication in advanced-stage malignancies, with the skeleton being one of the most common sites of distant spread. The incidence varies by cancer type, affecting nearly 90 %–100 % of patients with multiple myeloma, 65 %–80 % with metastatic breast or prostate cancer, and 30–40 % with advanced lung cancer [1,2]. Although numerous malignancies can metastasize to bone, breast, lung, and prostate cancers demonstrate a particularly high predilection for skeletal involvement [3]. The mechanisms underlying this tropism remain incompletely understood.

Skeletal metastases are associated with significant morbidity, primarily through skeletal-related events (SREs) such as pathological fractures which is a bone fracture caused by weakness of the bone structure that leads to decrease mechanical resistance, spinal cord compression with resultant paralysis, hypercalcemia, and the need for orthopedic surgery or palliative radiotherapy. To reduce SRE risk, antiresorptive agents—most notably bisphosphonates and denosumab—are routinely used in clinical practice.

Denosumab, a fully human monoclonal antibody targeting the receptor activator of nuclear factor-κB ligand, inhibits osteoclast-mediated bone resorption, thereby limiting skeletal destruction, tumor-induced bone destruction, and skeletal-related events (SREs) [4]. Denosumab also disrupts the vicious cycle of growth factors and cytokine signaling between tumor cells and bone cells.Unlike bisphosphonates, denosumab is cleared via the reticuloendothelial system, allowing its use in patients with chronic kidney disease (CKD). However, its administration in individuals with moderate-to-severe CKD (estimated glomerular filtration rate [eGFR] < 30 mL/min) presents unique challenges. These patients often have concurrent CKD–mineral and bone disorder, which may exacerbate bone fragility and fracture risk. Furthermore, clinical trial data on denosumab in this population are scarce.

Denosumab-associated hypocalcemia (DAH) has been documented in several studies involving osteoporotic patients with CKD [5,6]. Notably, cancer patients typically receive higher and more frequent dosing—120 mg every 4 weeks for bone metastases versus 60 mg every 6 months for osteoporosis—potentially amplifying adverse effects. Despite this, real-world evidence on denosumab safety in cancer patients with CKD remains limited.

The present multicenter study aimed to evaluate whether CKD influences the incidence of denosumab-related adverse effects and SREs in patients with the three most common cancers associated with bone metastases—breast, prostate, and lung cancer.

2. Methods

This retrospective, multicenter observational study was conducted within the scope of the Turkish Oncology Group project. Patients aged $>$ 18 yr with breast, prostate, or lung cancer who received denosumab between January 2011 and December 2022 were included from 17 centers across Turkey. Patient data were retrospectively extracted from electronic medical records. Patients who had switched from zoledronic acid to denosumab were excluded. Those with bone metastases from other solid organ tumors or with hematological malignancies were also excluded, as denosumab is not indicated for these conditions in Turkey. Additionally, patients with incomplete data, follow-up of < 3 months, or who did not provide consent were excluded.

Subcutaneous denosumab (120 mg) was administered every 4 weeks following the diagnosis of breast, prostate, or lung cancer with bone metastases. Prostate cancer patients used denosumab during the castration-resistant disease stage.The dosing interval could be modified at the physician's discretion. The risk window for denosumab-associated toxicity was defined as the period from the first denosumab dose (baseline) to 12 months thereafter. Grade $\geq$ 3 toxicities occurring beyond this window were described descriptively but were not included in the primary logistic regression analyses.

The baseline timepoint (time zero) was defined as the date of the first denosumab 120 mg administration for bone metastases. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 documented for at least 3 months prior to or at baseline, or a chart-confirmed diagnosis of CKD by a nephrologist. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) ($186 \times$ [serum creatinine (mg/dL)] $^{-1.154} \times$ [age] $^{-0.203} \times$ [0.742 if the patient is female] $\times$ [1.21 if the patient is African American]) equation implemented in the participating centers' laboratory information systems. SREs were defined as pathological fractures, spinal cord compression, or the requirement for radiation therapy to bone (for pain control or high fracture risk) or bone surgery [7]. Data on SREs and surgical interventions were collected. Adverse events related to denosumab—including hypocalcemia, hypomagnesemia, and hypophosphatemia—were also assessed. Laboratory results at baseline, 3 months, and 6 months after diagnosis were recorded. Hypomagnesemia and hypophosphatemia were defined based on laboratory results obtained after treatment initiation. Baseline laboratory values are presented as median and interquartile range (IQR), reported as median [25th–75th percentile] according to CKD status. Hypocalcemia was defined as post-treatment serum calcium levels below the institution's

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standard albumin-adjusted reference range. Routine practice is to co-prescribe Ca/VitD; adherence could not be systematically assessed. Treatment changes following hypocalcemia were not recorded due to missing information in patient files regarding supplemental Ca/vitamin D replacement. The exact timing of hypocalcaemia events and any denosumab dose or schedule modifications were not consistently documented in the charts and were therefore not analysed.The severity of all adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 5.0 and according to these criteria, grade 3 and above toxicities − grade 3 and above toxicities are considered severe toxicities − were recorded. Overall survival (OS) was calculated from the date of initial diagnosis to death or last follow-up. To minimize immortal time bias, we performed a 12-month landmark analysis. Patients who died or were lost to follow-up before 12 months were excluded from this analysis. Overall survival was then compared between those who had experienced grade ≥ 3 toxicity within the first 12 months and those who had not, using Cox proportional hazards models.

2.1. Statistical analysis

Descriptive statistics are presented as mean ± standard deviation or median and interquartile range (IQR) for continuous variables and as counts and percentages for categorical variables. Baseline characteristics were compared between patients with CKD (eGFR < 60 mL/min/1.73 m2) and those without CKD (eGFR ≥ 60 mL/min/1.73 m2) using standardized mean differences (SMDs) and, where appropriate, the $\chi 2$ test or Fisher's exact test for categorical variables and the Student's *t* test or Mann–Whitney *U* test for continuous variables.

The primary endpoint was the occurrence of grade ≥ 3 denosumab-related toxicity (hypocalcemia, renal function decline, or other electrolyte abnormalities) within the predefined risk window (first 12 months after baseline). Grade ≥ 3 hypocalcaemia events were identified from all available serum calcium measurements in the electronic laboratory information systems after treatment initiation. Events occurring within the first 6 months after baseline were included in the primary endpoint analysis; hypocalcaemia episodes beyond 6 months were recorded descriptively but not used in the primary logistic regression models. To evaluate predictors of grade ≥ 3 toxicity, we fitted univariable and multivariable logistic regression models including CKD status and clinically relevant covariates (age, sex, body mass index, cancer type, comorbidities, dialysis, visceral metastases, denosumab dosing frequency, and duration of denosumab exposure). Results are reported as odds ratios (ORs) with 95 % confidence intervals (CIs).

Secondary endpoints included skeletal-related events (SREs) and overall survival (OS). OS was defined as the time from baseline to death from any cause or last follow-up. To account for immortal time bias in the analysis of grade ≥ 3 toxicity and survival, we performed a 6-month landmark analysis restricted to patients alive at 12 months after baseline. In this analysis, OS was compared between patients who had experienced grade ≥ 3 toxicity within the first 6 months and those who had not, using Kaplan–Meier estimates and Cox proportional hazards models. Hazard ratios (HRs) with 95 % CIs are reported. The proportional hazards assumption was assessed using Schoenfeld residuals.

All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 29 (BM Corp., Armonk, NY, USA).

3. Results

Data were obtained from a total of 285 patients. A total of 5 patients were excluded from the study due to missing data, and a total of 4 patients with a follow-up period shorter than 3 months were also excluded. To avoid immortal-time bias in the survival analysis, 12 patients with overall survival shorter than 12 months were excluded from the study. A total of 264 patients from 17 centers were included in the study. A total of 42 patients with CKD and 222 patients with no CKD were divided into two groups. The median age was 60 yr (interquartile range [IQR], 49–71 yr). Of the 264 patients, 164 had one or more comorbidities. Breast cancer was present in 148 patients (56.1 %), prostate cancer in 60 (22.7 %), and lung cancer in 54 (20.5 %). Median duration of denosumab use was 22.35 months (95 % CI; 10.12–30.24 months). All patient characteristics were examined between patients with CKD and those without CKD. There was an imbalanced distribution of age, gender, diagnoses, HT, and CAD in two groups.

Grade ≥ 3 toxicity occurred in 18 patients, of whom 16 experienced hypocalcemia and two had a decline in eGFR. No cases of hypomagnesemia, hypophosphatemia were observed. Only 1 patient was observed to develop osteonecrosis of jaw. The sociodemographic and clinicopathologic characteristics of the patients are summarized in Table 1.

In 42 patients, eGFR was < 60 mL/min. Grade ≥ 3 toxicity—comprising eGFR decline in two patients and hypocalcemia in 11—was detected in 13 of these patients, representing a statistically significant association ($p < 0.01$). Among nine patients with malignant hypercalcemia, two had eGFR < 60 mL/min; however, this was not statistically significant ($p = 0.640$). In 30 patients with pathological fractures, 11 had eGFR < 60 mL/min, which was statistically significant ($p = 0.032$). Similarly, of nine patients who underwent bone surgery for SREs, four had eGFR < 60 mL/min, a significant finding ($p = 0.012$). The characteristics of denosumab-related toxicities and SREs are summarized in Table 2.

In our cohort, the incidence of grade 3 toxicity was 31.0 % (13/42) in patients with CKD, compared with 4.1 % (5/222) in those without CKD. The absolute risk increase associated with CKD was 26.9 %, and the relative risk was 7.56, indicating that patients with CKD had approximately a seven-fold higher risk of developing grade 3 toxicity. Based on this difference, the number needed to harm (NNH) was 3.84 (≈4), meaning that for every four patients with CKD, one additional grade 3 toxicity event would be expected compared with patients without CKD. The relationship of other variables with grade 3 is summarized in Table 3. "In multivariable logistic regression, CKD was independently associated with grade ≥ 3 toxicity within 6 months (OR 7.70, 95 % CI 2.71–21.83, p < 0.01). There was no statistically significant difference in the other covariates.

We performed a 12-month landmark analysis for grade ≥ 3 toxicity to minimize immortal time bias. Median follow-up time was 28 months (95 % Confidence Interval [CI]: 28.95–30.22). OS did not reach the median duration. OS of all patients at 12 months, 24 months, 36 months, 48 months and 60 months were 95.3 %, 90.6 %, 88.7 %, 85.4 % and 83.8 %, respectively. The median OS was 13.5 months (95 % CI; 10.27–16.72) in patients with grade ≥ 3 toxicity, while in patients without grade 3 toxicity, the median OS was not reached, and this was statistically significant (Hazard Ratio (HR):0.290 (%95 CI;0.14–0.58) (p < 0.001) (Fig. 1). OS rates at 12 months, 24 months, 36 months, 48 months and 60 months were 94.5 %, 90 %, 87.1 %, 85.6 % and 85.1 %, respectively, in the non-CKD arm, while OS at 12 months, 24 months, were 72.5 %, and 54.5 %, in the CKD arm, and this was statistically significant (HR:0.59 (%95 CI;0.31–1.13) (p = 0.012) (Fig. 2).

4. Discussion

We evaluated adherence to denosumab treatment, changes in renal function, and all-cause mortality using data from a Turkish multicenter medical study. In our cohort, the pathological fracture rate was 11.4 % among patients receiving denosumab for metastatic bone disease. Rates of other SREs were 3.4 % for malignant hypercalcemia and only 1 patients for osteonecrosis of the jaw. Previous studies have reported SRE rates between 10.5 % and 14.4 % [8,9], which is consistent with our findings. Furthermore, grade ≥ 3 toxicity was significantly more common in patients with eGFR < 60 mL/min, with 89 % of these toxicities attributable to hypocalcemia.

DAH in patients with CKD has been reported previously in the

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Table 1
Sociodemographic,clinical-pathological characteristics and baseline laboratuary values of CKD (+), CKD (−), and overall patients.

Variables	CKD (+) (n = 42)	No CKD (n = 222)	Total (n = 264)	SMD	Odds Ratio (%95 CI)	P value
Age, median (percentiles, 25–75), year	63(55–70)	58(52–66)	60 (49–71)	0.779		
Age groups, n (%)						
<70	17 (40.5 %)	189 (85.2 %)	206(%44)	0.545	2.25	0.012
≥70	25 (59.5 %)	31 (14.8 %)	56(%22)			
Gender, n (%)						
Male	28 (66.7 %)	79 (35.6 %)	107(40.5 %)	0.791	5.184 (2.383–11.279)	<0.001
Female	14 (33.3 %)	143(64.4 %)	157(59.5 %)			
Body-mass Index, n (%)						
>18.0	2 (4.8 %)	–	2(0.8 %)	0.064		
18.0–24.9	20 (47.6 %)	54 (24.3 %)	74(28.0 %)			
25.0–30.0	12 (28.6 %)	122 (54.9 %)	134(50.8 %)			
>30.0	8 (19 %)	45 (20.2 %)	53(20.1 %)			
Missing	–	1 (0.6 %)	1(0.4 %)			
Comorbidity, n (%)						
CAD	16 (38.1 %)	16 (7.2 %)	32(12.2 %)	1.305	13.46 (5.64–32.11)	<0.01
COPD	5 (11.9 %)	14 (6.3 %)	19(7.3 %)	0.430	3.46(1.12–0.74)	0.040
DM	10 (23.8 %)	20 (9 %)	30(11.5 %)	0.589	3.85 (1.57–9.45)	0.05
HT	28 (66.7 %)	54 (24.3 %)	82(31.3 %)	1.207	13.08 (5.1–33.4)	<0.01
Hemodialysis	1 (2.4 %)	–	1(0.4 %)			
Primary diagnosis, n (%)						
Breast	10 (23.8 %)	138 (62.2 %)	148 (56.1 %)	−0.836	4.42(3.33–12.53)	<0.01
Prostate	22 (52.4 %)	38 (17.1 %)	60 (22.7 %)	1.011	3.54(2.25–9.56)	<0.01
Lung	10 (23.8 %)	44 (20.7 %)	54 (20.5 %)	−0.029	1.26 (0.90–1.45)	0.95
Metastasis site, n (%)						
Lung	14 (33.3 %)	72 (32.4 %)	86(32.6 %)	0.01	1.02(0.46–2.24)	0.94
Liver	6 (14.3 %)	54 (24.3 %)	60(22.7 %)	−0.23	0.55(0.2–1.5)	0.24
Peritoneum	2 (4.8 %)	5 (2.2 %)	7(2.3 %)	0.08	–	–
Brain	3 (7.1 %)	30 (13.5 %)	30(11.4 %)	−0.10	0.72(0.2–2.5)	0.77
Adrenal gland	4 (9.5 %)	16 (7.2 %)	20(7.6 %)	−0.05	–	–
Frequency of denosumab use, n (%)						
Monthly	38 (90.5 %)	216 (97.3 %)	245(92.8 %)	0.12	0.82 (0.51–1.54)	0.89
Quarterly	4 (9.5 %)	6 (2.7 %)	10(7.2 %)			
Toxicity (≥grade 3), n (%)						
Yes	13 (30.9 %)	5 (2.3 %)	18(6.8 %)	0.62	7.7 (2.71–21.83	<0.01
No	29 (69.1 %)	208 (93.7 %)	237 (89.8 %)			
Missing	–	9 (4 %)	9(3.4 %)			
Toxicity type, n (%)						
Hypocalcemia	11 (26.2 %)	5 (2.3 %)	16 (6.7 %)	0.75	–	–
eGFR decrease	2 (4.8 %)	–	2 (0.8 %)			
Serum magnesium, mg/dL,median (IQR)	1.96 (1.24–2.16)	2.00 (1.76–2.14)	1.98 (1.70–2.14)	–	–	–
Serum albumin, g/dL, median (IQR)	3.91(3.70–4.51)	4.20 (3.90–4.60)	4.20 (3.80–4.60)	–	–	–
Serum calcium, mg/dL, median (IQR)	9.47 (9.10–10.05)	9.40 (9.03–9.84)	9.40 (9.04–9.86)	–	–	–
Serum creatinine, mg/dL, median (IQR)	1.25 (0.98–1.81)	0.70 (0.60–0.88)	0.70 (0.60–0.92)	–	–	–

Note. CAD, coronary arterial disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension; SMD, standartized mean difference;

osteoporosis setting. In one study, a single 60-mg dose of denosumab reduced serum bone turnover markers in patients with eGFR < 60 mL/min, and this reduction was associated with hypocalcemia [10]. Another population-based study reported that hypocalcemia occurred in up to 42 % of patients with end-stage renal disease treated with denosumab for osteoporosis, with those in CKD stage 3b–5 at the highest risk (odds ratio, 2.92; 95 % CI, 1.38–6.20) [11].

Patients with bone metastases are inherently at high risk for skeletal complications, with reported incidences of first and multiple SREs reaching 0.63 and 3.9, respectively [12–14]. Both zoledronic acid and denosumab, although differing in their mechanisms of action, help reduce the risk of SREs, including pathological fractures. However, in CKD, reduced bone turnover can lead to adynamic bone disease. Studies in patients with osteoporosis and eGFR < 60 mL/min have shown higher rates of pathological fractures compared with patients with normal renal function, though still lower than in those who have never received denosumab [15–17]. In our study, pathological fractures were more common in patients with eGFR < 60 mL/min, suggesting that while denosumab has a protective effect, it cannot fully mitigate CKD-related bone damage [18].

Both grade ≥ 3 hypocalcemia and pathological fractures significantly affected OS in our study. However, the small sample size and heterogeneity of these patient subgroups limit the robustness of this observation. Previous research linking toxicity and pathological fractures to CKD has largely focused on osteoporosis populations [17,19]. Studies involving cancer patients are generally limited to single-center, non-comparative case series [20,21]. Despite the small number of patients in our study who developed toxicity or SREs, the observed associations with survival warrant further investigation in larger, more homogeneous cohorts.

Denosumab-associated hypocalcemia occurs in approximately 8–18 % of patients [22]. Denosumab severely suppresses osteoclast activity and causes serum calcium levels reducition. Denosumab-associated hypocalcemia is more common in conditions such as male gender, prostate cancer, small cell lung cancer, advanced age, and decreased creatinine clearance [23]. In our study, only the presence of CKD was found to affect the development of grade 3 ≤ toxicity. The reason for the lack of effect of other factors may be the low number of patients with CKD, the relatively low number of elderly patients (22 %), and the underrepresentation of patients with prostate cancer in our population.

Another problem with denosumab use in patients with CKD may be the increased risk of SRE due to low bone turnover in the long term[24]. Denosumab significantly reduces the risk of SREs for bone metastases; although there is no data on SREs that may occur in long-term use, denosumab can be used more cautiously, especially in patients with CKD aged 70 years and older.

Our findings are limited by the retrospective study design. The multicenter nature of the study introduced variability in patient records

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Table 2
Comparison of malignant hypercalcemia, skeletal-related events, and palliative radiotherapy between patients with and without chronic kidney disease (CKD).

Variables	CKD (+) (n = 42)	No CKD (n = 222)	Total (n = 264)	SMD	Odds Ratio (%95CI)	P value
Malignant hypercalcemia, n (%)						
Yes	2 (4.8 %)	7 (3.2 %)	9(3.4 %)	0.13	2.01 (0.39–10.40)	0.327
No	40 (95.2 %)	213 (96 %)	254(96.2 %)			
Missing	–	1 (0.8 %)	1(0.4 %)			
Pathological fracture, n (%)						
Yes	19 (45.2 %)	11 (5 %)	30(11.4 %)	0.37	3.232 (1.149–9.089)	0.032
No	22 (52.4 %)	211 (95 %)	233(88.3 %)			
Missing	1 (2.4 %)		1(0.3 %)			
Fracture site, n (%)						
Lower extremity	6 (14 %)	4 (2 %)	10(3.8 %)	0.25	–	–
Vertebra	11 (26 %)	6 (3 %)	17(6.4 %)			
Upper extremity	1 (2 %)	–	1(0.4 %)			
Other	1 (2 %)	1 (0.5 %)	2(0.8 %)			
Bone surgery, n (%)						
Yes	4 (9.5 %)	5 (2.3 %)	9(3.4 %)	0.44	7.5 (1.768–31.816)	0.012
No	24 (57.1 %)	202 (91 %)	226(85.6 %)			
Missing	14 (33.4 %)	15 (6.7 %)	29(11.0 %)			
Surgery site, n (%)						
Lower extremity	2 (4.8 %)	2 (0.9 %)	2(0.8 %)	0.14	–	–
Vertebra	1 (2.4 %)	3 (1.3 %)	5(1.9 %)			
Upper extremity	1 (2.4 %)	–	1(0.4 %)			
Other	–	–	1(0.4 %)			
Palliative radiotherapy, n (%)						
Yes	18 (42.9 %)	81 (36.5 %)	99(37.5 %)	0.19	1.471 (0.697–3.104)	0.310
No	22 (52.4 %)	133 (59.9 %)	155(58.7 %)			
Missing	2 (4.8 %)	8 (3.6 %)	10 (3.8 %)			

SMD: standardized mean difference; OR: odds ratio; CI: confidence interval; CKD: chronic kidney disease.

Table 3
Absolute risk difference, relative risk, and number needed to harm (NNH) for grade 3 toxicity according to baseline characteristics.

Predictor (exposure = "Yes")	Risk of grade 3 toxicity in unexposed (%)	Risk of grade 3 toxicity in exposed (%)	Absolute risk difference (%)[a]	Relative risk (RR)	Number needed to harm (NNH)[2]
CKD	4.1	31.0	26.9	7.56	4
COPD	6.4	12.5	6.1	1.94	16
CAD	6.4	9.7	3.3	1.51	31
Male sex	5.2	9.4	4.1	1.79	24
Diabetes mellitus	6.8	6.9	0.1	1.01	1276
Hypertension	4.1	12.5	8.4	3.02	12
Once-monthly denosumab use	1.2	7.1	5.9	5.91	17

Note. CAD, coronary arterial disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension.

[a] Absolute risk difference (ARD) = risk in exposed − risk in unexposed (i.e. absolute risk increase).[2] NNH = 1 / ARD, rounded to the nearest whole number.

and potential biases. Additionally, denosumab efficacy may vary by cancer type; while we observed no difference in efficacy or toxicity rates by cancer type, the small CKD subgroup precludes definitive conclusions. Although denosumab was generally initiated as a monthly regimen, continuation schedules were at the discretion of the treating physician, and our dataset lacks detailed information on dose adjustments in response to adverse events. Moreover, data on parathyroid hormone levels, vitamin D status, and other potential contributors to hypocalcemia were unavailable. Due to the multi-center nature of the study and the varying laboratory standards across different centers—particularly regarding eGFR changes—the percentage changes in the laboratory data could not be included in the data due to concerns that the data would be unreliable. Due to the short follow-up period, jaw osteonecrosis was detected in only one patient. We were unable to analyse in detail when hypocalcaemia occurred or how denosumab dosing was modified, because these data were not systematically recorded.The effects of this condition may be observed in more patients with longer follow-up periods. Prospective, large-scale studies with long-term follow-up are needed to address these gaps.

Despite these limitations, our results indicate that adverse events are more frequent in patients with CKD receiving denosumab, and this should be carefully considered during patient follow-up.

5. Conclusions

To the best of our knowledge, this is the first retrospective, observational, cross-sectional study to evaluate the use of denosumab 120 mg in patients with severe renal insufficiency. We observed a higher incidence of grade $\geq$ 3 hypocalcemia in patients with severe renal impairment (14 %) compared with the incidence reported in patients with normal renal function (3.1 %–9%) [25]. This finding may impact not only survival but also patients' quality of life. Further studies focusing specifically on cancer patients are warranted to expand our understanding of this issue.

CRediT authorship contribution statement

Halil İbrahim Ellez: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Hüseyin Salih Semiz:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Ferhat Ekinci:** Resources, Investigation, Data curation. **Atike Pınar Erdoğan:** Resources, Methodology, Data curation. **Fatih Kuş:** Resources, Investigation, Data curation. **Fatih Karataş:** Resources, Investigation, Data curation. **Ertuğrul Bayram:** Resources, Investigation, Data curation. **Kubilay Karaboyun:** Resources, Investigation, Formal analysis, Data curation. **Havva Yeşil Çınkır:** Resources, Investigation, Formal analysis, Data curation. **Nilgün Yıldırım:** Resources, Investigation, Formal analysis, Data curation. **Melek Karakurt Eryılmaz:** Resources, Methodology, Investigation, Data curation. **Esma Türkmen Bekmez:** Resources, Investigation, Formal analysis, Data curation. **Özkan Alan:** Methodology, Investigation, Data curation, Conceptualization. **Melike Özçelik:** Methodology, Investigation, Data curation. **Yakup Düzköprü:** Resources, Investigation, Data curation.

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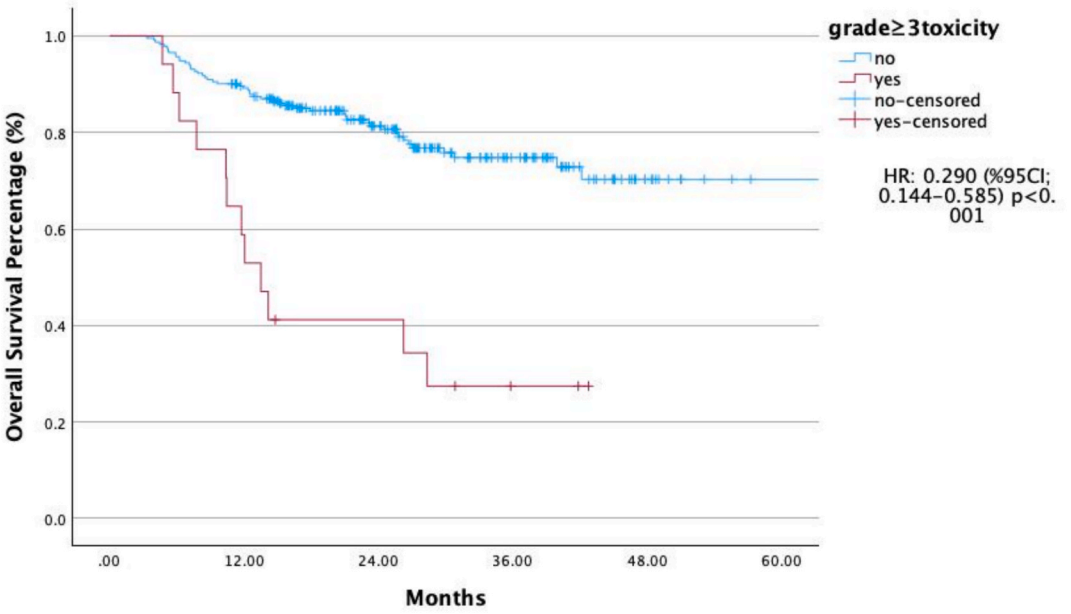


Fig. 1. Association between denosumab related toxicity and median overall survival.

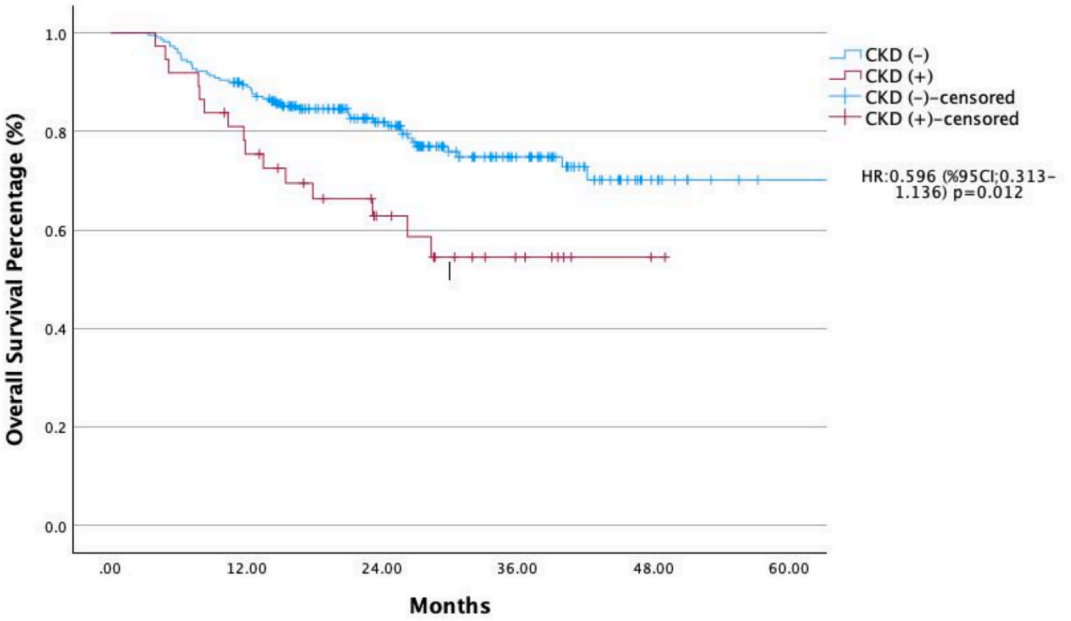


Fig. 2. Association between eGFR and median overall survival.

Teoman Şakalar: Resources, Investigation, Data curation. **Naziye Ak:** Resources, Investigation, Data curation. **Yusuf İlhan:** Resources, Investigation, Data curation. **Tuğba Yavuzşen:** Writing – review & editing, Validation, Project administration, Conceptualization. **Nazım Serdar Turhal:** Supervision, Project administration, Methodology, Data curation, Conceptualization.

Ethics approval and consent to participate

The study adhered to the principles of the Declaration of Helsinki (1964) and its later amendments as well as to relevant institutional and national research committee standards. Ethical approval was obtained from the Beykoz University Ethics Committee, Istanbul, Turkey (decision date: August 14, 2020; decision no. 2020/1). Patient data were obtained retrospectively from medical records after written informed consent was obtained from patients or their legal representatives.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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