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Research Paper

Progression of vertebral fractures in metastatic melanoma and non-small cell lung cancer patients given immune checkpoint inhibitors

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HIGHLIGHTS

- The immune system mediates important effects on bone metabolism, but little has been done tounderstand immunotherapy's role in this interaction.
- Among 135 patients with melanoma and NSCLC treated with immune-checkpoint inhibitors, 10(7.1%) experienced vertebral fracture progression.
- Of the 10 patients with vertebral fracture progression, 7 started steroid therapy while on immune checkpoint inhibitors.
- Steroid therapy resulted the sole factor significantly associated to vertebral fracture.
- Our single-center study suggests cancer patients on immune checkpoint inhibitors and steroids may face a higher risk of vertebral fractures.

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ABSTRACT

Introduction: The immune system mediates important effects on bone metabolism, but little has been done to understand immunotherapy's role in this interaction. This study aims to describe and identify risk factors for the occurrence and/or exacerbation of vertebral fractures (vertebral fracture progression) during immune checkpoint inhibitors (ICIs).

Methods: We conducted an observational, retrospective, monocentric study. We collected data on melanoma and NSCLC patients, treated with first-line ICIs at the Medical Oncology Department ASST Spedali Civili of Brescia, between January 2015 and November 2021, and with a median follow-up of 20.1 (6–36) months. We collected data on patients, diseases, immune-related adverse events, and cortico-steroid therapy initiated on concomitant ICIs.

Results: We identified 135 patients, 65 (48.2 %) with locally advanced/metastatic melanoma and 70 (51.8 %) with locally advanced/metastatic non-small cell lung cancer (NSCLC). Twenty-one (15.6 %) patients already had an asymptomatic vertebral fracture at baseline before starting ICIs in monotherapy. A total of ten patients, or 7.4 %, had a vertebra fracture progression defined as a new vertebral fracture or a worsening of a previous fracture. There was a strong relation between the steroid therapy and irAEs with vertebra fracture progression [OR (95 % CI) 8.1 (3.7–17.8) p-value < 0.001] in univariable analysis. However, only steroid therapy resulted to be an independent risk factor [8.260 (95 % CI 0.909–75.095); p-value 0.061] at the multivariable analysis.

Conclusion: Concurrent steroid therapy in patients receiving immunotherapy exposes them to a high risk of fractures due to skeletal fragility. The use of bone resorption inhibitors should be considered in these patients to prevent these adverse events.

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1. Introduction

The immune system mediates powerful effects on bone turnover. Osteoclast precursors derive from the monocyte-macrophage lineage [1–3]. B cells are physiologically involved in the secretion of Osteoprotegerin (OPG), a potent anti-osteoclastogenic factor that maintains bone mass. Activated T-cells and B-cells secrete pro-osteoclastogenic factors including the receptor activator of NF-kB ligand (RANKL), IL-17A, and TNF-alpha (TNF), which promote bone loss. The term *osteoimmunology* was coined in 2000 by Aaron J.R. and Choi Y. to underline the centralization of cell and cytokine effectors shared between skeletal and immune systems, the so-called *immune-skeletal interface* (ISI) [4]. Bone loss, which is a natural consequence of aging, it is exacerbated by many inflammatory diseases such as rheumatoid arthritis, periodontal infection and inflammatory bowel diseases including Crohn disease [5,6]. Immunotherapy, using modern checkpoint inhibitors, is currently widely used in the treatment of an increasing number of neoplasms. Given the growing evidence of the complex molecular interplay between the immune system and the skeletal system, it is rational to investigate how immunotherapy can affect or interact with bone metabolism [7]. If the hyperactivation of the immune system in autoimmune inflammatory pathologies appears to be related to bone loss, it is reasonable that immunotherapy, whose goal consists in hyperstimulation of the immune system, could itself lead to a weakening of bone strength. The interaction between immunotherapy and bone metabolism has been scarcely investigated [8,9]. Bozec A. et al. demonstrated that a greater number of osteoclast precursors were present in patients treated with ipilimumab compared to controls. Furthermore, comparing individual patients before and after ipilimumab therapy showed a significant increase in osteoclastogenesis after treatment, suggesting that CTLA-4 blockade increases osteoclastogenic potential *in vivo* [10]. A few case reports have only reported adverse ICIs on the skeletal system. Moseley K.F. et al. described 6 cases of adverse effects on bone tissue caused by ICIs: in 3 cases new osteoporotic fractures were documented and in 3 cases localized bone resorption phenomena were identified. The finding of a pro-inflammatory state in these patients could confirm the potential influence of immune hyperactivation on bone metabolism [8]. More recently, Ye C. et al. studied a sample of 1600 patients treated with ICIs, observing an increased bone fracture rate after ICIs, raising the evidence of a new potential immune-related adverse event [11].

To our knowledge, the impact of immunotherapy on bone health in cancer patients has not been evaluated in any case series studies. This study aimed to examine the prevalence of new vertebral fractures (VFs) or the worsening of existing ones in patients with advanced melanoma or NSCLC undergoing ICIs. Secondary aim of the study was to identify risk factors associated with ICIs-induced skeletal fragility.

2. Methods

2.1. Study design and selection of patients

This is an observational, retrospective, monocentric study. By the institutional archive of the Medical Oncology department ASST Spedali Civili of Brescia, Italy, we identified patients with melanoma or NSCLC who underwent ICIs in monotherapy as a first-line treatment, between January 2015 and November 2021, with a median follow-up of 20.1 (6–36) months.

This study was approved on June 23, 2022, Protocol Number 5429, by the Ethics Committee of ASST Spedali Civili of Brescia.

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [12]. Inclusion criteria were the following: histologically confirmed diagnosis of metastatic NSCLC or metastatic melanoma, clinical practice indication for first-line ICIs in monotherapy, age $\geq$18 years, ECOG PS = 0–1, availability of CT scan and/or PET-FDG imaging performed at the Spedali Civili di Brescia. We excluded patients treated with ICIs beyond the first line, patients treated with combinations of ICIs and other drugs (like chemo-immunotherapy), patients with known diagnosis of osteoporosis (defined by bone mineral density with a T-score equal to or less than −2.5), patients receiving anti-resorptive agents, patients already on chronic steroid therapy or other immunosuppressive therapies before starting ICIs, or with any bone metastasis (either axial or appendicular) present at baseline or that appeared during ongoing ICI treatment as assessed by CT-scan and/or PET-FDG.

We collected data on patients and disease characteristics, immunotherapy, and adverse events. At baseline, we calculated the FRAX score (a predictive parameter of a 10-years risk of major osteoporotic fracture based on age, sex, ethnicity, height, weight, history of low-energy fractures, family history of hip fractures, rheumatoid arthritis, use of oral glucocorticoids, smoking, alcohol intake $\geq$3 units per day, and known causes of secondary osteoporosis, excluding bone mineral density because not available). CT scans were used to detect baseline VFs and fractures that appeared during ICI treatment or subsequent follow-up. The CT-scans were assessed by two radiologists (blinded to each other), and the vertebral fracture was considered confirmed only if identified by both radiologists. A quantitative morphometric examination was conducted based on the measurement of the height of the dorsal (T4–T12) and lumbar vertebrae (L1-L4). VFs were classified, according to the Genant classification system, as follows: mild (G1): height reduction between 20 and 25 %; moderate (G2): height reduction between 26 and 40 %; severe (G3): height reduction >40 %; and according to the spinal deformity index (SDI) – a semi-quantitative method to assess spinal deformity using X-rays. It is calculated by assigning a score of 0 to 3 to each of the thoracic (T4-T12) and lumbar (L1-L4) vertebrae based on the severity of their vertebral compression [13]. For each patient at baseline and every radiological assessment of ongoing ICIs, the SDI was assessed and the most severe result was included in the analysis.

Vertebral fracture progression was defined as either new fracture (from no VF to any grade of VF) or worsening of pre-existing VF (from mild to moderate or severe; from moderate to severe) between baseline and follow-up.

2.2. Statistical analysis

We conducted the statistical analysis on the entire study population and on the two distinct NSCLC and melanoma sub-populations. We employed descriptive statistical analyses, including frequency distributions, medians, and ranges, for data analysis. We compared characteristics in the two distinct NSCLC populations using the chi-square test for categorical variables and the Wilcoxon-Mann-Whitney test for continuous variables. To test the association between the independent variables and the outcome of interest, we used a binary and multiple logistic regression model. Statistical significance was established with a type I error rate of less than 5 %. All statistical analyses were performed using IBM SPSS Statistics software, version 23.0 (IBM Corp., Armonk, NY, 2015).

3. Results

3.1. Characteristics of disease and immunotherapy

After screening more than 300 patients with advanced/metastatic melanoma or NSCLC at diagnosis from January 2015 to November 2021, we identified 135 patients, 65 (48.2 %) melanoma patients, and 70 (51.8 %) NCSLC patients according to the inclusion/exclusion criteria mentioned above. Fig. 1 depicts consort diagram flow-charts for selection of patients of the study.

Table 1 shows patients and disease characteristics. In melanoma group, the primary tumors were cutaneous in 47 (72.3 %) patients, uveal in 8 (12.3 %), mucosal in 7 (10.8 %) and unknown in 3 (4.6 %). BRAF gene mutation was found in 5 (7.7 %) patients. Forty-five (69.2 %)

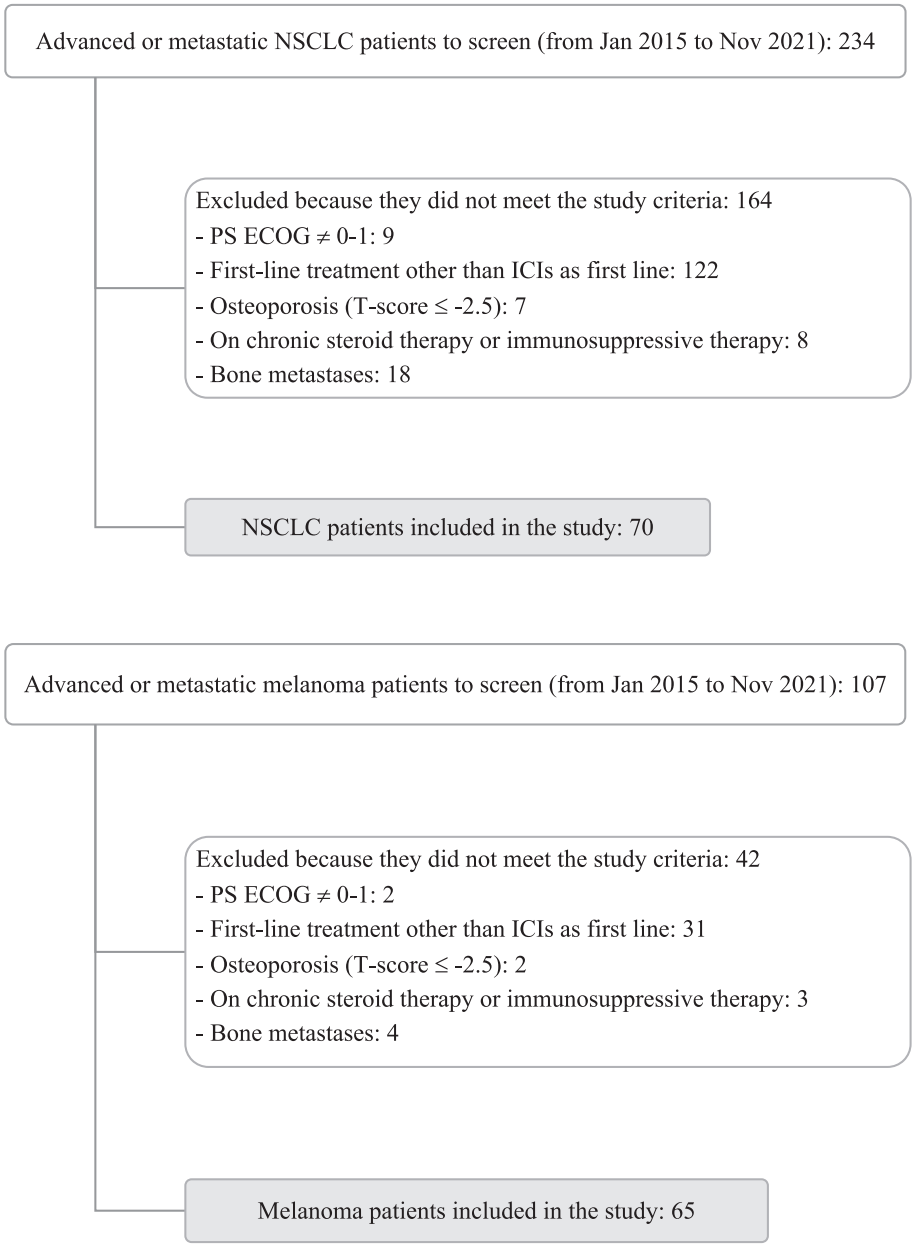

Fig. 1. Consort diagram flow-charts for selection of NSCLC and melanoma patients for the study.

patients were treated with Pembrolizumab and 20 (30.8 %) with Nivolumab. In NSCLC group, the primary tumour was adenocarcinoma in 54 (77.1 %) patients, squamous cell carcinoma in 10 (14.3 %), undifferentiated carcinoma in 5 (7.1 %) patients. Twenty-eight (40.0 %) patients had locally advanced disease while 42 (60.0 %) had metastatic disease. All lung cancer patients were treated with pembrolizumab.

Globally, the median exposure to ICIs in the whole population was of 10.6 (interquartile range 6–23.5) months.

3.2. Vertebral fractures

Among the entire population, 21 patients (15.6 %) had baseline VFs. The median FRAX score for major osteoporotic fractures in patients with VFs was 6.4 (interquartile range 5.7–8.6), while it was 7.1 (interquartile range 5.2–9.6) in the population without baseline VFs. Ten (7.1 %) patients experienced VF progression, of these 3 experienced a worsening of their fractures during treatment, while 7 others developed new VFs. The median exposure to ICIs in patients with VF progression was 5.5 months (interquartile range 4.1–110.1). Fig. 2 summarizes the distribution of VFs according to the Genant criteria, before and after treatment with ICIs. In the whole population two patients experienced a change of SDI from 0 to 1 during ICIs, three patients from 0 to 2, one patient from 0 to 4, one patient from 0 to 5, one patient from 1 to 2, one patient from 2 to 3 and one patient from 3 to 6. Fig. 3 summarizes the distribution of SDI before and after treatment with ICIs in melanoma, NSCLC and total population respectively.

Dividing patients according to tumor histology, 12 (18.5 %) melanoma patients had asymptomatic baseline VFs (10 fractures G1 and 2 fractures G2 according to the Genant criteria) and the median FRAX score was 6.4 (interquartile range 5.3–8.7). Three patients experienced VF progression: two 12 months after starting ICIs (both with new fractures, G1 and G2 respectively), and one patient after 36 months (worsening of the previous fracture from G1 to G2). The temporal variation of SDI in melanoma patients experiencing VF progression is shown in Table 2.

In the NSCLC group, 9 (12.9 %) patients had VFs at baseline (6

Table 1
Patients and disease characteristics.

		Melanoma = 65	NSCLC = 70	Total = 135	P value
Age at diagnosis of advanced disease (median, range)		61 (29–82)	71 (55–84)	68 (29–84)	0<.0001
Sex	Male	35 (53.8 %)	49 (70 %)	84 (62.2 %)	0.053
	Female	30 (46.2 %)	21 (30 %)	51 (27.8 %)	
Smoking habit current/ former (≥ 10 pack-year)	Smokers	34 (52.3 %)	64 (91.4 %)	98 (72.6 %)	0<.0001
	Non-smokers	31 (47.7 %)	4 (5.7 %)	35 (25.9 %)	
	Not known	0 (0 %)	2 (2.9 %)	2 (1.5 %)	
	Smoking pack-years (median, range)	20 (2–120)	40 (1–150)	39 (1–150)	0<.0001
Alcohol consumption (≥20 g/day in women and ≥40 g/ day in men	Yes	12 (34.3 %)	27 (38.6 %)	39 (28.9 %)	0.016
	No	50 (76.9 %)	43 (61.4 %)	93 (68.9 %)	
	Not know	3 (4.6 %)	0 (0 %)	3 (2.2 %)	
BMI	BMI before starting ICIs (median, range)	24 (17–44)	24 (17–38)	24 (17–44)	0.093
	Patients with BMI loss on ICIs.	2 (5.7 %)	5 (7.1 %)	7 (5.1 %)	0.287
Menopausal status at diagnosis of advanced disease (females)		21 (70.0 %)	21 (100.0 %)	42 (31.1 %)	0.014
irAEs		33 (50.8 %)	24 (34.3 %)	57 (42.2 %)	0.053
Steroid therapy	Steroid therapy started on ICIs	35 (53.8 %)	32 (45.7 %)	67 (49.7 %)	0.345
	Steroid therapy equivalent to <10 prednisone mg/day	8 (12.3 %)	2 (2.9 %)	10 (7.4 %)	0.057
	Steroid therapy equivalent to ≥10 prednisone mg/day	27 (41.5 %)	30 (42.9 %)	57 (42.2 %)	

fractures G1, 3 fractures G2), the median FRAX score was 6.7 (interquartile range 5.8–8.9). Seven patients experienced VF progression: three patients 6 months after ICI start, two patients after 12 months and two patients after 24 months. Two patients experienced an increase in fracture severity, one from G1 to G2, and the other one from G2 to G3. Five patients developed new VFs during treatment: two fractures G1, two G2, and one G3. SDI was 1 in 4 (5.7 %) cases, 2 in 3 (4.3 %) cases, and 3 in 2 (2.9 %) cases. The temporal variation of SDI in NSCLC patients experiencing VF progression is shown in Table 2.

All the melanoma patients who experienced VF progression started steroid therapy [in two of them in order to manage immune-related adverse events (irAEs)]). Among the 7 NSCLC patients who experienced VF progression, six patients started steroid therapy on ongoing ICIs, five of them to manage irAEs. In all these 6 patients the fracture event was detected after the start of steroid therapy. The distribution of VF progression in melanoma and NSCLC patients, stratified according to steroid therapy it's depicted in Fig. 4.

Considering the entire population, of the 10 patients who experienced VF progression, 9 (90 %) had previously undergone steroid therapy. Eight of these patients had received a dose equivalent to prednisone ≥10 mg/day, while only one had been treated with a dose <10 mg/day. The median duration of steroid therapy was 2.5 months (range: 1–14 months). Notably, 7 out of the 9 patients had received steroids to manage irAEs, such as diarrhea, interstitial pneumonia, hepatitis, and skin rash. As for the remaining two patients, one had been treated with steroids for brain metastases, while the other for dyspnea related to respiratory failure.

Three patients experienced VF progression 6 months after starting ICIs, 4 patients after 12 months, 2 patients after 24 months, and 1 patient after 36 months. Due to the very low number of events, it was not possible to study the temporal relationship between VF progression and the initiation of ICI therapy.

3.3. Risk factors for VF progression

As depicted in Table 3, several predictive factors of vertebral progression were evaluated according to univariable logistic regression analyses. Steroid therapy was the only factor significantly associated to VF progression in univariable analysis [OR: 10.397 (95 % CI 1.279–84.534); p-value 0.029], while the occurrence of irAEs approached statistically significance [OR 3.500 (95 % CI 0.864–14.180); p-value 0.079] but did not reach it. Therefore, in multivariable analysis, only these two variables (steroid therapy and irAEs) were considered as potential predictors of VF progression. In this model, steroid therapy remained the sole independent predictor of VF progression, although it was marginally statistically significant (OR: 8.260 (95 % CI: 0.909–75.095), p = 0.061).

4. Discussion

In this study, which enrolled metastatic patients with lung cancer and melanoma, it was found that 7.4 % (10/135) experienced VFs that are notoriously expression of skeletal fragility [9]. This proportion of patients is not negligible however this study clearly highlights the crucial role of steroid therapy in favoring these adverse events. The proportion of VF progression in fact was 8/67 (11.4 %) in patients who received steroid treatment and 1/68 (1.5 %) in those who did not. In this population, none of the common risk factors for osteoporosis like the FRAX score, resulted associated with VF progression. The lack of association between FRAX score and other factors with VF progression suggests that these factors may not be useful for identifying the subgroup at higher risk.

Steroid therapy represents a very well-known cause of bone fragility and it's the most common form of iatrogenic or secondary osteroporosis [14–18]. Numerous studies have shown that this risk increases after 3 consecutive months of therapy with a dosage ≥5 mg of prednisolone [19], suggesting the need for bone resorption inhibitor therapy. Steroids directly affect bone remodeling by suppressing osteoblast activity and stimulating osteoclast activity. This disrupts the normal coupling between bone resorption and formation, a key prerequisite for altered bone quality. Current guidelines on glucocorticoid-induced osteoporosis recommend the prescription of bone resorption inhibitors to all patients who receive steroid therapy for more than 3 months [19–22]. Patients during treatment with ICIs also frequently receive intercurrent steroid therapy. In our study, 67 patients (49.6 %) received steroids and about 40 % with a dose equivalent of prednisone >10 mg. These findings are consistent with percentages reported in the literature [23–25].

However, our study cannot determine whether immunotherapy has an additional or synergistic effect with steroids on fracture risk.

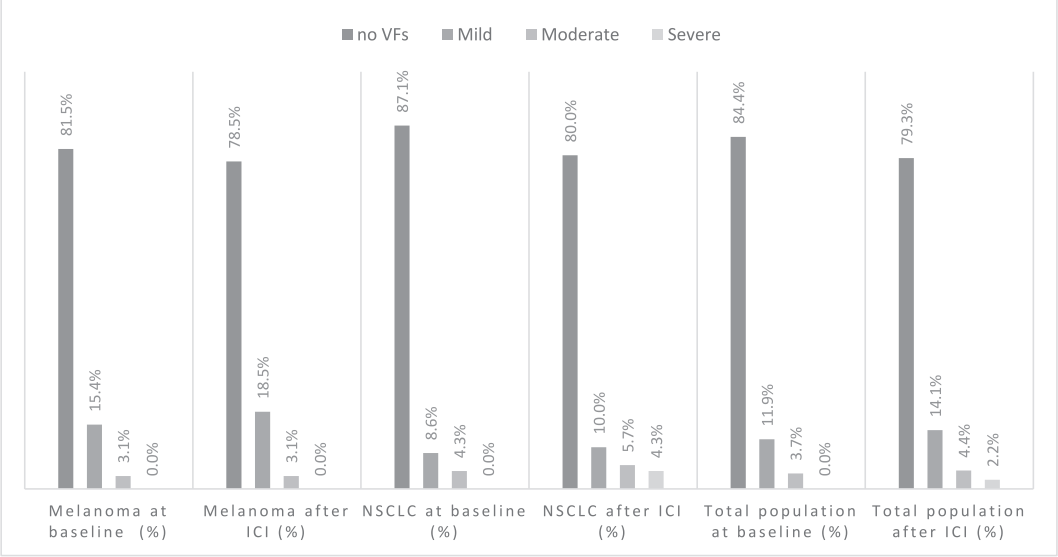

Fig. 2. Distribution of vertebral fractures before and after treatment with ICIs in melanoma, NSCLC and total population respectively, divided on the basis of the Genant criteria (mild, moderate, severe); VFs = vertebral fractures.

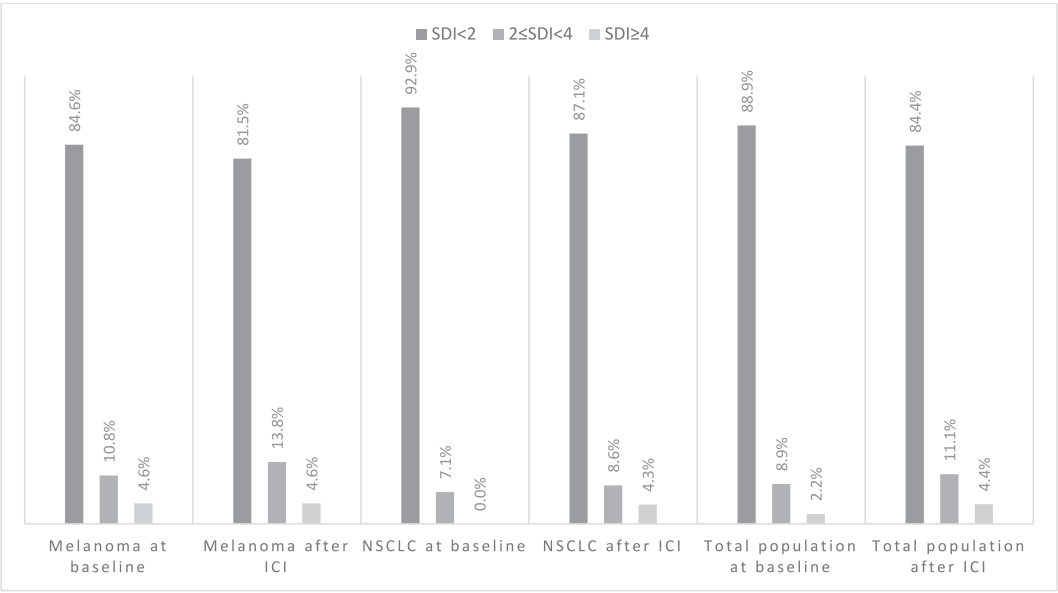

Fig. 3. Distribution of SDI before and after treatment with ICIs.

Table 2
SDI variation in patients experiencing VF progression, from start of treatment with ICIs.

Tumor	Baseline SDI	SDI at 6 months	SDI at 12 months	SDI at 24 months	SDI at 36 months
Melanoma (=3)	0		**2**		
	2				**3**
	0		**2**		
NSCLC (=7)	0	**1**			
	1		**2**		
	0		**5**		
	0	**4**			
	3			**6**	
	0	**2**			
	0			**1**	

Regardless of this matter, this study suggests that special attention should be paid to fracture risk in patients who need to take steroids during immunotherapy. It is recommended by international guidelines to consider these patients for initiating bone resorption inhibitor therapy. This recommendation is especially pertinent for patients who are receiving immunotherapy for adjuvant purposes since they have the potential to be cured.

For patients not receiving steroids, our study showed a low risk of developing new fractures after immunotherapy. However, the relevant percentage (15.6 %) of melanoma and NSCLC patients with advanced/metastatic disease with asymptomatic VFs at baseline underscores the importance of bone fragility in this patient population. Therefore, interventions aimed at preserving bone health should be implemented in those who are at greater risk of skeletal fragility. This study's strength lies in its monocentric design, where all VFs were evaluated by the same team of radiologists, which reduced variability in the assessment. Major drawbacks of the study include its retrospective design and small sample

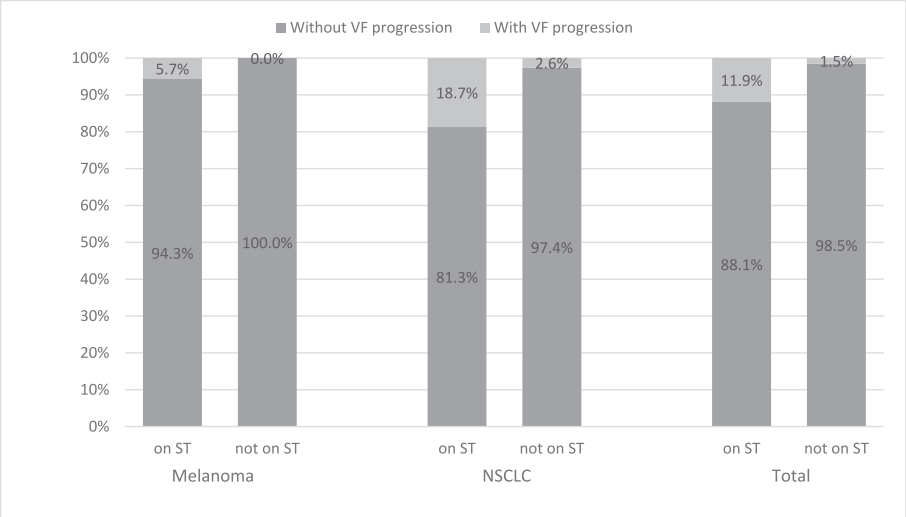

Fig. 4. Distribution of vertebral fracture (VF) progression according to steroid therapy. ST = steroid therapy.

Table 3
Univariate and multivariate analysis with *vertebral fracture progression* as dependent variable in the whole population.

Whole sample of the study = 135 patients (NSCLC, melanoma)				
	Univariate analysis		Multivariate analysis	
Characteristics	OR (95 % CI)	p-value		
Sex	0.388 (0.079–1.903)	0.243		
Age	1.033 (0.963–1.109)	0.365		
Smoking habit current/former (≥10 pack-year)	1.467 (0.296–7.264)	0.639		
Alcohol consumption (≥20 g/day in women and ≥40 g/day in men)	1.966 (0.498–7.753)	0.334		
Steroid therapy on ICIs (equivalent to prednisone either <or ≥10 mg/day)	10.397 (1.279–94.534)	**0.029**	8.260 (0.909–75.095)	**0.061**
irAEs	3.500 (0.731–1.110)	**0.079**	1.641 (0.366–7.359)	0.518
BMI loss	0.532 (0.112–3.978)	0.432		
Menopause	0.531 (0.108–2.617)	0.437		
Fractures at baseline	2.548 (0.603–10.771)	0.204		
FRAX score	0.901 (0.731–1.110)	0.327		

size.

4.1. Limitations of the study

The present study has some limitations. First, its retrospective nature lacks a control group of patients who did not undergo immunotherapy, which would allow for a comparison of the incidence of VF progression events. Second, the sample size is relatively small (135 patients), and the number of VF progression events observed is limited (10 events). Third, the follow-up period is short, which is a notable limitation, given that VF progression requires long-term observation. Additionally, the study on bone fragility did not account for important risk factors, such as a history of bone fragility fractures, family history of hip fractures, early menopausal status and history of falls.

5. Conclusion

Concurrent steroid therapy to manage irAEs on treatment with ICIs is a common scenario in cancer patients, our single-center design study suggests that cancer patients treated with ICIs and exposed to steroids may be at a higher risk of developing VFs. Our study raises awareness about the importance of bone health preservation by introducing bone resorption inhibitors appropriately in patients treated with ICIs who need to initiate concomitant steroid therapy.

CRediT authorship contribution statement

Marco Meazza Prina: Writing – review & editing, Supervision, Resources. **Andrea Alberti:** Writing – review & editing, Validation, Supervision. **Valeria Tovazzi:** Writing – review & editing. **Marco Ravanelli:** Writing – review & editing, Supervision, Resources. **Greta Schivardi:** Writing – review & editing. **Alice Baggi:** Writing – review & editing. **Luca Ammoni:** Writing – review & editing. **Lucilla Guarneri:** Data curation. **Francesca Salvotti:** Data curation. **Manuel Zamparini:** Formal analysis. **Davide Farina:** Writing – review & editing, Supervision, Resources. **Margherita Parolise:** Supervision, Data curation. **Salvatore Grisanti:** Writing – review & editing. **Alfredo Berruti:** Writing – original draft, Supervision, Methodology, Conceptualization.

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.

References

[1] D.G. Walker, Bone resorption restored in osteopetrotic mice by transplants of normal bone marrow and spleen cells, Science 190 (4216) (1975) 784–785, https://doi.org/10.1126/SCIENCE.1105786.
[2] D.G. Walker, Congenital osteopetrosis in mice cured by parabiotic union with normal siblings, Endocrinology 91 (4) (1972) 916–920, https://doi.org/10.1210/ENDO-91-4-916.
[3] K. Buring, On the origin of cells in heterotopic bone formation, Clin. Orthop. Relat. Res. 110 (110) (1975) 293–302, https://doi.org/10.1097/00003086-197507000-00040.
[4] J.R. Arron, Y. Choi, Bone versus immune system, Nature 408 (6812) (2000) 535–536, https://doi.org/10.1038/35046196.

[5] M.N. Weitzmann, R. Pacifici, Estrogen deficiency and bone loss: an inflammatory tale, J. Clin. Invest. 116 (5) (2006) 1186–1194, https://doi.org/10.1172/JCI28550.
[6] M.N. Weitzmann, I. Ofotokun, Physiological and pathophysiological bone turnover - role of the immune system, Nat. Rev. Endocrinol. 12 (9) (2016) 518–532, https://doi.org/10.1038/NRENDO.2016.91.
[7] G.J. Joseph, D.B. Johnson, R.W. Johnson, Immune checkpoint inhibitors in bone metastasis: clinical challenges, toxicities, and mechanisms, J. Bone Oncol. 43 (2023) 100505, https://doi.org/10.1016/J.JBO.2023.100505.
[8] K.F. Moseley, J. Naidoo, C.O. Bingham, et al., Immune-related adverse events with immune checkpoint inhibitors affecting the skeleton: a seminal case series, J. Immunother. Cancer 6 (1) (2018), https://doi.org/10.1186/S40425-018-0417-8.
[9] D.M. Filippini, M. Gatti, V. Di Martino, et al., Bone fracture as a novel immune-related adverse event with immune checkpoint inhibitors: case series and large-scale pharmacovigilance analysis, Int. J. Cancer 149 (3) (2021) 675–683, https://doi.org/10.1002/IJC.33592.
[10] A. Bozec, M.M. Zaiss, R. Kagwiria, et al., T cell costimulation molecules CD80/86 inhibit osteoclast differentiation by inducing the IDO/tryptophan pathway, Sci. Transl. Med. 6 (235) (2014), https://doi.org/10.1126/SCITRANSLMED.3007764.
[11] C. Ye, K. Lee, W.D. Leslie, M. Lin, J. Walker, M. Kolinsky, Fracture rate increases after immune checkpoint inhibitor treatment: a potential new immune related adverse event, Osteoporos Int. 34 (4) (2023) 735–740, https://doi.org/10.1007/S00198-023-06690-1.
[12] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J. P. Vandenbroucke, The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, J. Clin. Epidemiol. 61 (4) (2008) 344–349, https://doi.org/10.1016/J.JCLINEPI.2007.11.008.
[13] G.G. Crans, H.K. Genant, J.H. Krege, Prognostic utility of a semiquantitative spinal deformity index, Bone 37 (2) (2005) 175–179, https://doi.org/10.1016/J.BONE.2005.04.003.
[14] B.C. Lupsa, K. Insogna, Bone health and osteoporosis, Endocrinol. Metab. Clin. North Am. 44 (3) (2015) 517–530, https://doi.org/10.1016/J.ECL.2015.05.002.
[15] E. Canalis, G. Mazziotti, A. Giustina, J.P. Bilezikian, Glucocorticoid-induced osteoporosis: pathophysiology and therapy, Osteoporos. Int. 18 (10) (2007) 1319–1328, https://doi.org/10.1007/S00198-007-0394-0.
[16] L.M. Cruse, J. Valeriano, F.B. Vasey, J.D. Carter, Prevalence of evaluation and treatment of glucocorticoid-induced osteoporosis in men, J. Clin. Rheumatol. 12 (5) (2006) 221–225, https://doi.org/10.1097/01.RHU.0000242778.65766.22.
[17] D. Jia, C.A. O'Brien, S.A. Stewart, S.C. Manolagas, R.S. Weinstein, Glucocorticoids act directly on osteoclasts to increase their life span and reduce bone density, Endocrinology 147 (12) (2006) 5592–5599, https://doi.org/10.1210/EN.2006-0459.
[18] T.P. Van Staa, The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis, Calcif. Tissue Int. 79 (3) (2006) 129–137, https://doi.org/10.1007/S00223-006-0019-1.
[19] Y. Tanaka, S. Soen, S. Hirata, et al., The 2023 Guidelines for the management and treatment of glucocorticoid-induced osteoporosis, J. Bone Miner. Metab. 42 (2) (2024) 143–154, https://doi.org/10.1007/S00774-024-01502-W.
[20] K.F. Axelsson, A.G. Nilsson, H. Wedel, D. Lundh, M. Lorentzon, Association between alendronate use and hip fracture risk in older patients using oral prednisolone, J. Am. Med. Assoc. 318 (2) (2017) 146–155, https://doi.org/10.1001/JAMA.2017.8040.
[21] K. Panday, A. Gona, M.B. Humphrey, Medication-induced osteoporosis: screening and treatment strategies, Ther. Adv. Musculoskelet. Dis. 6 (5) (2014) 185–202, https://doi.org/10.1177/1759720X14546350.
[22] F. Manelli, R. Carpinteri, S. Bossoni, et al., Growth hormone in glucocorticoid-induced osteoporosis, Front. Horm. Res. 30 (2002) 174–183, https://doi.org/10.1159/000061083.
[23] A. De Giglio, M. Aprile, A. Di Federico, et al., Impact of baseline versus intercurrent steroids administration on upfront chemo-immunotherapy for advanced non-small cell lung cancer (NSCLC), Int. J. Mol. Sci. 23 (18) (2022), https://doi.org/10.3390/IJMS231810292.
[24] S.C. Scott, N.A. Pennell, Early use of systemic corticosteroids in patients with advanced NSCLC treated with nivolumab, J. Thorac. Oncol. 13 (11) (2018) 1771–1775, https://doi.org/10.1016/J.JTHO.2018.06.004.
[25] N. Bar-Hai, G. Ben-Betzalel, R. Stoff, et al., Better late than never: the impact of steroidal treatment on the outcome of melanoma patients treated with immunotherapy, Cancers (basel) 15 (11) (2023), https://doi.org/10.3390/CANCERS15113041.