

# Bone Damage After Chemotherapy for Lymphoma: A Real-World Experience

**Mancuso S**

University of Palermo

**Scaturro D** (✉ [dalila.scaturro@unipa.it](mailto:dalila.scaturro@unipa.it))

University of Palermo

**Santoro M**

University of Palermo

**Di Gaetano G**

University of Palermo

**Vitagliani F**

University of Catania

**Siragusa S**

University of Palermo

**Gonnelli S**

Siena University Hospital

**Letizia Mauro G**

University of Palermo

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## Research Article

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# Abstract

**Background:** Despite recent improvements in survival due to advances in treatment, the quality of life of patients with lymphoma may be compromised by the long-term complications of chemotherapy and steroid therapy. Among these, a potentially relevant problem is bone loss and the development of fragility fractures.

**Aim:** To provide further evidence of clinical or subclinical skeletal complications in correlation with biological variables and markers of bone disease in patients with complete response to therapy.

**Method:** A cross-sectional observational study was conducted on subjects diagnosed with lymphoma with subsequent antineoplastic treatment, disease status after therapy defined as complete response disease for at least a year now. We performed: blood chemistry tests, imaging techniques (DEXA) and screening tools for the assessment of functional status and quality of life (SARC-F and mini-OQLQ).

**Results:** Approximately 50% of the patients had osteoporosis. We found hypovitaminosis D and high PTH levels in most of the patients. We also found a high prevalence of vertebral fractures in 65.5% of cases. In the majority of patients, we found hypovitaminosis D and high levels of PTH. Furthermore, a statistically significant association between high PTH levels and previous lymphoma treatment. Finally, the Mini Osteoporosis Quality of Life questionnaire demonstrated a loss of quality of life as a consequence of the change in bone status.

**Conclusions:** Patient treatment design for personalized chemotherapy would be desirable to reduce late effects on bone. Also, early prevention programs need to be applied before starting treatment. The most benefited subpopulations could be not only elderly but also young patients.

## Introduction

Despite recent improvements in survival because of advances in treatment, quality of life of patients with lymphoma may be compromised by long-term complications of chemo and steroid therapy [1]. A potentially relevant issue for lymphoma survivors is bone loss - osteopenia and osteoporosis- as consequence of the treatment. Osteoporosis can lead to development of fragility fractures, a major cause of morbidity associated with considerable mortality [2].

Some studies have evaluated the occurrence and the impact of bone loss in adult patients with hematological neoplasms including lymphomas [3]. Baseline testing of BMD reveals osteopenia or osteoporosis in the majority of NHL patients [4]. Patients with lymphoma have significant bone loss compared to the normal general population [5].

It is known that the therapy of lymphoma with high-dose glucocorticoids and alkylating agents may result in premature bone loss, increasing the risk of vertebral and hip fractures. Glucocorticoids increased bone resorption and decreased bone formation, calcium retention, muscle mass, and endocrine gonadal

function. Alkylating agent–induced endocrine gonadal damage is a common complication and affects both men and women.

It is observed that low BMD seen at diagnosis may worsen after lymphoma therapy [6-7].

The effect of the individual drugs and combined therapy regimens on bone resorption are complex and molecular pathways and regulatory events are still not elucidated [8].

To date, very few studies have described functional status of bone with comprehensive analysis of clinical features, biochemical parameters and imaging studies in previously treated patients for lymphoma. The present real-world study was carried out to provide additional evidence of clinical or subclinical skeletal complications in correlation with biological variables and markers of bone disease in patients with complete response.

## Patients And Methods

### *Study design and population*

This is an observational, cross-sectional study conducted at Policlinico “Paolo Giaccone” of Palermo. within an interdisciplinary setting involving Hematology Unit and Physiatriic Unit. The patients were recruited from March 2018 to July 2020.

Inclusion criteria comprised: age between 16 and 85 years, previous diagnosis of lymphoma with subsequent antineoplastic treatment, disease status after therapy defined as complete response for at least a year [9]. Exclusion criteria were as follows: patients with progressive disease following first-line chemotherapy; patients treated with more than 1 line of chemotherapy; any previous or current treatment for osteoporosis; other concomitant malignancies both with and without metastasis; concurrent systemic inflammatory rheumatic disease; history of metabolic bone disease; any medical comorbidity that may cause osteoporosis and/or other variables alterations; physical disabilities that may prevent the patient to fully understand and adhere to study procedures; patients with previous known vertebral fractures for non-osteoporotic reasons; patients not able to understand and give informed consent.

### *Assessments*

Baseline data regarding demographic and clinical information was collected from clinical charts. Variables collected from this source were: age, gender, type of lymphoma, treatment protocol, response to therapy, comorbidities. Thereafter all patients were divided in age groups. At the time of physiatriic consultation other variables were evaluated, spread across three data sets: blood chemistry, imaging techniques, screening tools assessing functional status and quality of life. Laboratory parameters included individual measures of parathyroid hormone (PTH) and 25(OH)-Vitamin D (Vitamin D) concentrations. Dual-energy x-ray absorptiometry (DEXA) scans of the femoral neck and lumbar spine were performed to detected bone mineral density (BMD). According to the World Health Organization criteria, osteopenia is defined as a T score between -1 >-2.5, and osteoporosis is defined as a T score >

-2.5 or less [10]. Thoracolumbar radiography scans were performed to see fragility vertebral fractures by Genant criteria [11].

A screening test for sarcopenia, SARC-F (five item questionnaire) was used [12-13]. SARC-F includes five components: strength, assistance walking, rise from a chair, climb stairs, and falls. Scale scores range from 0 to 10 (i.e. 0–2 points for each component; 0 = *best* to 10 = *worst*). All patients were also questioned using the Mini-Osteoporosis Quality of Life Questionnaire (mini-OQLQ) [14]. The mini-OQLQ includes two items in each of five domains (symptoms, physical function, activities of daily living, emotional function, leisure activities). For each of the 10 questions a mark between 1 and 7 is assigned: score 1 corresponds to the worst possible function (extreme difficulty, permanent fear and extreme anxiety), instead score 7 is associated with the better function possible (absence of difficulty, of fear and anxiety). The total score of the questionnaire can vary from minimum of 10 to maximum of 70. The data collected were analyzed by calculating medium and median values of total score.

Correlation between PTH and Vitamin D concentrations was analyzed. In addition, correlation between PTH and Vitamin D and BMD, Vertebral fractures, and mini-OQLQ was evaluated.

The study was conducted in accordance with the Declaration of Helsinki and with the approval from the Ethical Committee, n. 02/2018. All participants provided written informed consent before study entry.

### *Statistical analysis*

All the information collected from patients enrolled were entered into an electronic database created by Excel 16.0 software.

All quantitative values were expressed as mean  $\pm$  SD or median with interquartiles. The Kolmogorov–Smirnov test was used to verify the normality of the distribution of the study variables. Absolute and relative frequencies were obtained to the data collected: age, sex, BMI, Vit D, PTH, femoral BMD and vertebral BMD, type of lymphoma, comorbidity, number of vertebral fractures, DEXA femoral, SARC-F and Mini-OQoL.

The sample was stratified and analysed through a univariate analysis by Vitamin D and Parathormone levels. Vitamin D levels were divided for the univariate analysis in reference  $\geq 31$  and insufficiency/deficiency  $\leq 30$  ng/mL. Parathormone levels were divided for the univariate analysis in reference  $\leq 70$  pg/mL and high  $>70$  pg/mL (hyperparathyroidism).

The differences in the categorical variables for levels of Vitamin D and Parathormone were analysed using chi-squared tests (Mantel–Haenszel) and the Student test for the means. The level of significance chosen for the univariate analysis was 0.05 (two tailed).

Pearson's correlation between VIT D, SARC-F and Mini-OQoL was also studied.

All the data were analysed using the statistical software package Stata/MP 12.1 (StataCorp LP, College Station, TX, USA).

## Results

A total of 29 patients previously treated with lymphotoxic therapy (chemotherapy, radiotherapy, steroid) for lymphoma were evaluated. Overall demographic and clinical features are shown in Table 1.

The patient group included 18 males (62.1%) and 11 females (37.9%). The mean age of the entire study group was 61.4 years (SD 16,7). The average BMI was 27.1 4.3. Overall, 12 patients (41.4%) reported 3 or more comorbidities and 10 patients (34.5%) one or two. 4 subjects (13.8%) had a diagnosis of Hodgkin Lymphoma (HL), and 25 (86.2%) of Non-Hodgkin Lymphoma (NHL).

The average vitamin D levels in the sample were 21.6 ng/ml (SD 8.8): in 5 patients they were normal (17.2%), while insufficient and deficient respectively in 22 (75.9%) and 2 (6.9%) cases. PTH values were high in 6 patients (20.7%), in the normal range in 20 cases (69%) and low in 3 cases (10.3%) with an average of 43.5 pg/ml (SD 26.8).

Femoral DEXA was determined in 27 patients, while the other 2 patients had bilateral hip prostheses, with these results of T-score: normal in 15 cases (55.6%), osteopenia in 10 (37%), osteoporosis in 2 (7.4%). The calculated average T-score was -0.8 (DS 1.2) and the average Z-score -0.1 (DS 1.1). Vertebral lumbar DEXA was performed in 28 patients, because one had had vertebral stabilization: 14 of them (50%) had normal findings, 7 (25%) had osteopenia and 7 (25%) osteoporosis. The average calculated T-score was -1.8 (DS 1.5) and the average Z-score was -0.2 (DS 1.4).

As for vertebral fractures, 10 (34.5%) patients had no fractures, but 10 (34.5%) had 1 or 2 fractures and 9 (31%) had 3 or more than one fracture. The average value was 2.1 (DS 1.8).

The average SARC-F values were 3.8 (DS 1.9). In Figure 1 shows the distribution of patients with a SARC-F of less than 4 points (38%) compared to those with a score of 4 or more (62%).

Mini-Osteoporosis quality of life questionnaire (MINI-OQoL) detected a mean total score of  $54.4 \pm 11.1$  and a median total score of 55 (range 32-70). In Figure 2, patients were classified by scores obtained at the questionnaire: the 37.9% of the patients was classified with a mild OQoL score (>60 points), the 55.2% had a moderate score (36-60 points), while the 6.9% had a severe score (<36 points).

Table 2 shows that older patients carry significantly higher levels of PTH ( $p=0.03$ ). In case of previous treatment with a multi-agent chemotherapy regimen including high dose corticosteroids, significant high levels of PTH have been observed ( $p=0.03$ ). Moreover, a significant association was found between higher levels of PTH and vertebral fractures ( $p=0.05$ ).

Table 2 shows that the SARC-F values higher than or equal to 4 points correlate with insufficiency/deficiency Vitamin D values ( $p=0.05$ ) and this was demonstrated also with a regression

model that reveals a moderate negative relation between the two variables with a Pearson's index of -0.29. This also shows the presence of a weak positive relation between the Mini-OQoL score and the Vitamin D values, with a Pearson's index of 0.13.

## Discussion

Our study exploring bone damage after treatment for lymphoma, adds information for late effects of antineoplastic therapy in adult patient survivors. In this experience, we identified cHL e NHL subjects who achieved complete remission for at least a year and then underwent a screening program for the detection of bone deficiencies. Previous studies conducted on this issue generally focused on patients prior to receive front-line therapy or on pediatric survivors, the latter examined, however, before peak bone mass achievement [15].

To assess the relative contribution of predictive markers of osteopathy, the presence of bone loss (osteopenia, osteoporosis), the burden of fractures and the effects on physical fitness and health-related quality of life, we designed an interdisciplinary study to provide further evidences. We found hypovitaminosis D in 82.8% of the patients, a condition known to be associated with low bone mass [16]. High levels of PTH (a bone mass reducing hormone) was also documented in 20.7% of the cases. Unknown osteopenia and osteoporosis were evidenced by DEXA in about a half of the patients, that is of note, particularly considering the presence of many young adults in the study group and the Z score values within the expected age range.

We also found a high prevalence of unknown vertebral fractures, accounting for 65.5% of the cases. This high rate is significant about its implications for morbidity and mortality following lymphoma treatment [17-18-19]. In order to find an association with predictive markers, we observed that serum PTH levels were increasing with age. Increased levels of PTH have been associated to bone loss rates in the elderly and to frailty indexes, that, in turn, is known to be an independent predictor of fractures [20-21]. Furthermore, we demonstrated a statistically significant association between high levels of PTH and previous treatment including chemotherapy and steroids [22]. We believe that these results reflect the combined activity of steroid and antineoplastic drugs on deterioration of bone.

These findings are consistent with what has been shown in previous studies, that is, systemic exposure to high dose steroids can increase osteoporosis and fracture risk [23-24].

Another statistically significant association was observed between high level of PTH and vertebral fractures. This confirms the contribution of PTH to predict bone damage in the studied population. However, these observations do not definitively establish the functional importance of high levels of PTH in subjects with lymphoma, but knowledge about the healthy population could be translated into lymphoma patients.

Another goal of our study was to explore muscle health impairment in this population, since sarcopenia combined with osteopenia increases fracture probabilities [25-26-27]. The relationship between

sarcopenia and chemotherapy is complex by forming a vicious circle [28]. Despite this is yet to be proven, our results support the hypothesis that antineoplastic drugs in patients with lymphoma may target muscle cells and worsen muscle function, in fact more than half of the sample had a SARC-F score at risk of sarcopenia.

Finally, Mini-osteoporosis Quality of Life questionnaire demonstrated loss of quality of life as a consequence of bone status change, with a moderate/severe impact on more than half of the population examined. Worse mini-OQoL scores related with low vitamin D levels, and this may support the real life observation that patients treated with vitamin D supplements often refer improvements in ordinary tasks. Similarly, SARC-F values consistent with sarcopenia (less than 5 points) have a relationship with insufficiency vitamin D values in our patients' study group, hinting that routine plain vitamin D dosage may help identifying patients not only at risk of developing fractures, but also already affected with bone metabolic alterations that may worsen the *quoad valetudinem* prognosis of lymphoma patients. To date, this is the first approach to assess osteoporosis-related health status in patients with lymphoma [29-30-31].

Limitations of our study include the sample size and selection bias inherent to different lymphoma subtypes with different chemotherapy protocols. Together, these data suggest that simple clinical check in asymptomatic patients is not yet sufficiently sensitive to screen bone loss or fractures after chemotherapy, it is necessary to supplement with humoral assays and imaging techniques.

Thus, upcoming prospective studies with larger case numbers are needed to further validate the best approach for monitoring bone damage in lymphoma patients, before and after chemotherapy.

## Conclusions

Despite generally favourable outcome, lymphoma patients experience an assortment of late complications. Only recently the term "lymphoma survivorship" was coined and researchers have begun to assess long-term side effects of antineoplastic therapy. In addition to cardiac concerns, infertility and secondary cancers, the musculoskeletal effects have been recognized as one of the most common potential risks [32-33-34]. Prevention and treatment of the bone damage in lymphoma patients often plays a minor role in clinical practice.

According to the results of our study, PTH elevations in elderly lymphoma-survivor patients, undergoing antineoplastic therapy could be considered a risk factor for fragility fractures. In addition, low Vit-D levels influence the quality of life related to the musculoskeletal apparatus.

Our approach using a set of methods to investigate potential bone damage and related impairment of health condition, has improved the detection of bone issues useful for primary and secondary prevention. Imaging screening with conventional radiography and DEXA associated a dosage of Vit D and PTH is the most effective method to detect early alterations or more serious lesions in oligosymptomatic subjects.

Despite bone damage can vary considerably, depending on particular chemotherapy regimen and age, our current investigation supports a rationale for the hypothesis that lymphoproliferative diseases and chemotherapy are items that have to be taken into consideration for fracture risk stratification.

The findings of this study, despite the little size of the sample, surely suggest to design a personalized lymphoma therapy and to build up an accurate follow-up plan, including bone health surveillance in lymphoma long-survivors, with the goal of reducing late bone adverse events or, at least, to timely diagnose them.

Furthermore, it is necessary to apply early prevention programs before starting treatment, despite the age of the patient, being the young people a potentially unconsidered, but still affected, subpopulation.

## Declarations

**Funding:** No funding was received for conducting this study.

**Conflicts of interest:** All authors declare no conflict of interest.

**Availability of data and material:** Data used to support the findings of this study is available from the corresponding author upon request.

**Authors' contributions:** all authors contributed to the conception, design, and drafting of the study. all authors have read and approved the final manuscript.

**Ethic approval:** Data were obtained and analysed according to the Helsinki declaration. Approval was granted by the Ethics Committee of the University Hospital of Palermo, Italy (n° 2/2018).

**Consent to participate:** Informed consent was obtained from all individual participants included in the study.

**Code availability:** Not applicable.

**Consent for publication:** Not applicable.

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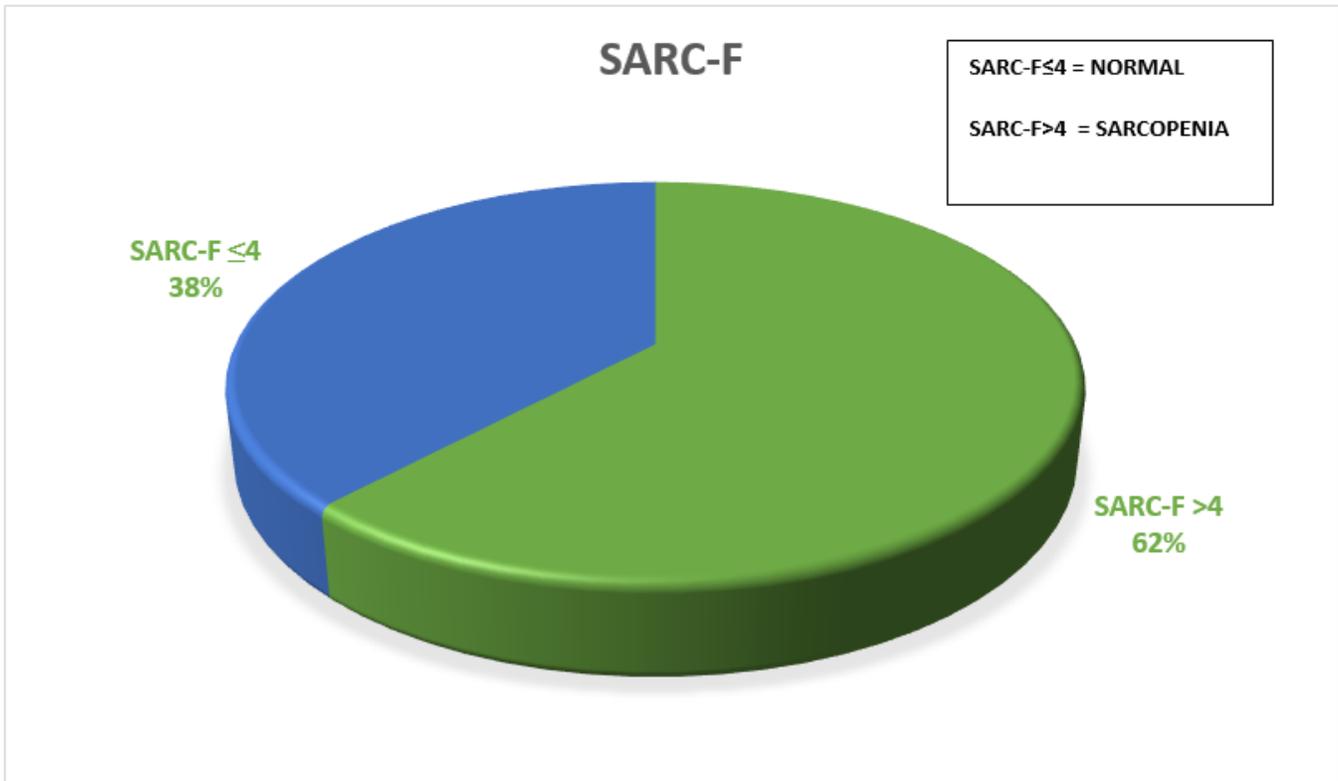
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## Tables

Due to technical limitations, table 1-2 is only available as a download in the Supplemental Files section.

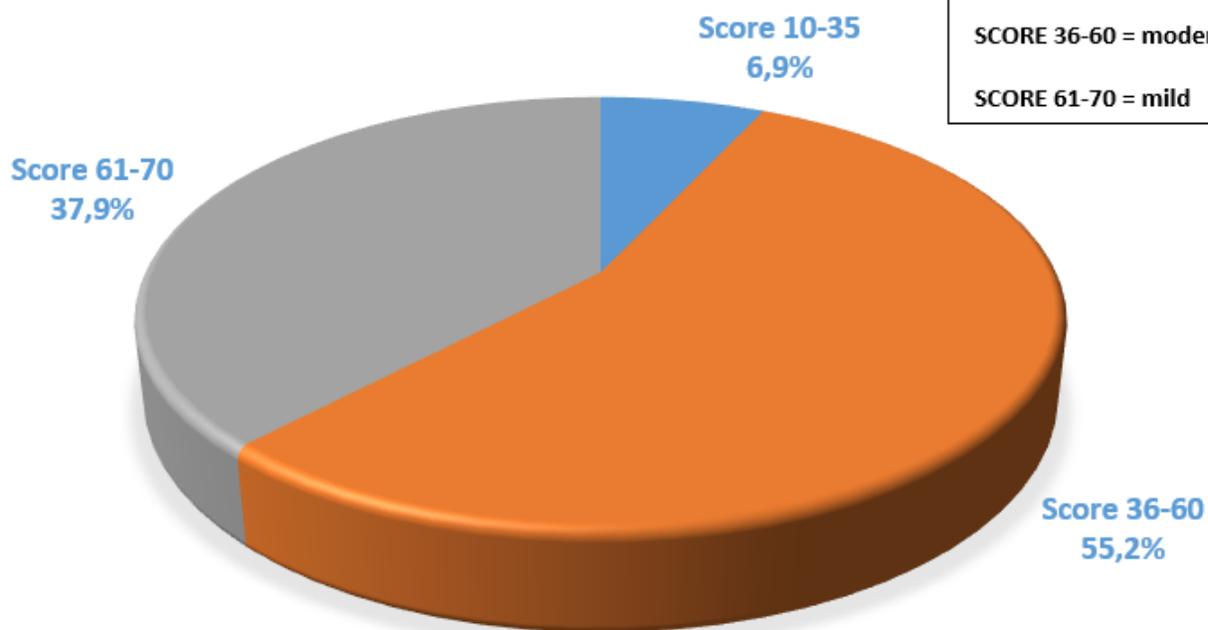
## Figures



**Figure 1**

Percentage of patients with SARC-F values  $>$  4 and  $\leq$  4

## MINI QOL



**Figure 2**

Mini QoL score

## Supplementary Files

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- [TableBone.pdf](#)