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Opportunistic bone density assessment using pre-treatment [^{18}F]FDG-PET/CT identifies fracture risk in lymphoma patients undergoing corticosteroid-containing chemotherapy

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Running title: Bone density on baseline PET/CT in lymphoma

Key words: Lymphoma, Osteoporosis, Corticosteroid, Bone mineral density

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Author contributions

GD, STL, KLH, CC, EAH designed the study and oversaw the conduct, analysis, and manuscript preparation. KMN, EP and STL performed L1HU on staging PET/CT. NW and GD collected clinical data. GD, ZL and AP performed statistical analysis. GC assisted with manuscript preparation. All authors approved the final manuscript.

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Dear Editor,

Osteoporosis (OP) and fragility fracture surpass general population rates following lymphoma therapy, contributing to increased morbidity, mortality, and health-care costs (1-6). Excess fracture incidence relates to corticosteroid exposure alongside other contributors such as gonadal toxicity and advancing age (4). As aggressive lymphoma is cured by first-line chemotherapy (including high-dose corticosteroid) in >50% of cases, and 5-year survival exceeds 70%, maintaining bone health during lymphoma survivorship should be prioritized. OP screening is challenging to incorporate into lymphoma work-up due to testing complexity and prioritisation of cancer control. Computed tomography (CT)-derived bone density using Hounsfield units measured at the L1 vertebra (L1HU) is an emerging strategy to opportunistically identify at-risk patients, correlating with Bone Mineral Density scan (BMD)-defined OP and fracture risk (7-9). We aimed to evaluate whether L1HU, quantified on routine pre-treatment [^{18}F]FDG-PET/CT, can detect those at increased risk of post-treatment fracture in a lymphoma-specific population. We demonstrate that in treatment-naïve lymphoma patients undergoing first-line corticosteroid-containing chemotherapy, pre-treatment L1HU is independently associated with increased fracture.

This single-centre, observational study identified 313 consecutive adults from our institutional database with treatment-naïve lymphoma undergoing first-line therapy with corticosteroid-containing regimens, from January 2012–May 2022 (Figure 1A). Eligible patients had staging [^{18}F]FDG-PET/CT within 2 months prior to therapy commencement and received $\geq$1 cycle of chemotherapy. Clinical data were extracted from electronic records and included diagnosis, treatment, OP, fracture, and pre-existing OP risk factors (osteopenia, smoking, $\geq$3 standard alcohol units daily, body-mass index <18, rheumatoid arthritis, prior corticosteroid exposure ($\geq$7.5mg daily prednisolone for $\geq$3 months), hypogonadism, hormone-deprivation therapies, prior malignancies, malabsorption syndromes), detailed in Tables 1/S1. Protective factors including receipt of vitamin D and/or calcium, antiresorptive therapy, hormone replacement therapy (HRT) and selective oestrogen receptor modulators (SERM) were collected (10). Parental hip fracture, early menopause, sedentary lifestyle, active thyroid/parathyroid disorder were not routinely recorded. Details of new fracture

during follow-up (from treatment commencement until death/last clinical review), and new diagnoses of OP/osteopenia were documented, noting that BMD scans were not routinely performed.

L1HU was measured manually on the CT component of pre-treatment [^{18}F]FDG-PET/CT and again following treatment completion, on an Ingenuity TF 128 PET/CT scanner (Philips Healthcare, Cleveland, OH, USA) with iterative reconstruction. Mean L1HU of three consecutive mid-vertebral axial slices (2-3 mm reformats) was calculated on the low-dose (60 mA and 120kVp on average with automatic exposure control) non-contrast CT component by manually drawing 2cm^2 circular regions of interest within the trabecular bone of L1. Measurements were performed and checked by a qualified radiologist using PACS (Enterprise Imaging 8, Agfa-Gervaert N.V., Mortsel, Belgium).

Demographics and baseline characteristics were summarized using frequencies and proportions for discrete data, and median with ranges for continuous data. Follow-up was calculated using the reverse Kaplan-Meier method. Receiver Operator Characteristic (ROC) analysis was performed to determine L1HU discriminatory power and propose a cutoff to predict post-treatment fracture. Cox regression was performed to analyse effects of fracture risk/protective factors on post-treatment fracture. To account for differences in timing of post-treatment [^{18}F]FDG-PET/CT, post-treatment L1HU was analysed as an absolute, and a derived annualised change. Statistical significance was accepted at $p<0.05$. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were reported. Cumulative incidence (censored at death/last follow-up) was determined using Kaplan-Meier method. The Log-Rank test compared fracture incidence in patients with pre-treatment L1HU<130 versus L1HU$\geq$130. Competing risk analysis (death a competing risk) was performed utilizing the methods of Fine and Grey. Statistical analysis was performed using SPSS version 29 (IBM, 2023) and R version 4.2.2 (2022). This study was approved by the local institutional review board (LNR17/Austin/186).

Median follow-up was 42 months (range 1-122). Patient characteristics, fracture risk and protective factors are summarised in Tables 1/S1. BMD scans were not routine, but 32(10.2%) had pre-treatment diagnoses of OP, and 17(5.4%) of osteopenia. In patients with

pre-treatment OP, 4(12.5%) experienced new fractures, and 10(31.3%) were receiving antiresorptive therapy. In patients without established OP, 20/281(7.1%) experienced ≥1 fracture and 31(11%) experienced any bone event (fracture and/or new OP and/or new osteopenia). Fractures occurred at a median of 21 months (range 1-99) following lymphoma therapy commencement. New fractures/bone events are detailed in Tables S2/S3.

Of 255 patients without known pre-treatment OP, and with [^{18}F]FDG-PET/CT available for L1HU analysis, mean pre-treatment L1HU was 145.5 (SD +/-46.9). Mean L1HU repeated on post-treatment [^{18}F]FDG-PET/CT was 117.5 HU (SD+/-44.9). Post-treatment [^{18}F]FDG-PET/CT timing varied; median time between assessments was 186 days (IQR 117-255). Estimated annualised mean L1HU reduction was -53.7 (SD +/-56.5) over 12 months compared to baseline. ROC identified that pre-treatment L1HU (Figure 1A) had reasonable predictability (AUC 0.742, p<0.001, 95%CI 0.616-0.868) for fracture events with 73.7% sensitivity and 62.4% specificity, using a cut-off of 130 HU. Univariable Cox regression (Table 2) identified that pre-treatment L1HU <130 was associated with higher fracture rates (HR 5.9, p<0.001, 95%CI 2.1-16.5), as was age ≥70 (HR 3.2, p=0.022, CI 1.2-8.5). A potential association between BMI<18 and fracture was identified (HR11.6, p=0.023, 95%CI 1.4-94.8), although patient numbers were low (n=4 with BMI ≤18). However, no significant association was identified between new fracture and other established risk factors, protective factors, or magnitude of reduction in L1HU following lymphoma treatment. Multivariable Cox regression identified that pre-treatment L1HU<130 remained an independent risk factor for fracture when controlling for age (HR 4.8, p=0.005, 95%CI 1.6-14.6). The Log-Rank test confirmed a significant difference in fracture events (p<0.001) between those with pre-treatment L1HU<130 versus L1HU≥130. Fractures in patients with L1HU<130 occurred in 14/102 (13.7%), versus 5/153 (3.3%) for those with L1HU≥130. Cumulative fracture incidence in those with baseline L1HU <130 versus L1HU ≥130 are detailed in Figure 1B. Competing risk regression (death as competing risk), continued to demonstrate a significantly higher fracture risk in those with L1HU<130 (HR 5.14, P<0.01, 95%CI 2.04-13.0).

Despite lack of routine BMD, we demonstrated that pre-existing OP(10.2%), fracture(11.8%), and osteopenia(5.4%) are common within the Australian lymphoma population. We have also shown that fracture is common following corticosteroid-containing chemotherapy:

12.5% in those with established OP, and 7.1% in those without. These data are consistent with other analyses, reporting fracture rates from 10% at 5 years to 11.4% at 18 months following treatment (1, 2, 11).

This is the first large study in lymphoma patients to assess utility of L1HU in identifying fracture risk, whilst examining for concomitant fracture risk factors. L1HU was more robustly associated with fracture than traditional factors. We identified that L1HU quantification is feasible using routine staging [^{18}F]FDG-PET/CT. Importantly, patients with pre-treatment L1HU<130 had 4-fold fracture rates compared to those with higher L1HU. This finding is consistent with a systematic review comparing lumbar HU value (predominantly at L1) and BMD, inferring a HU value of 90.9–138.7 for the diagnosis of OP (9). Furthermore, vertebral fractures are the commonest fractures associated with glucocorticoid (12). The lumbar spine is therefore the ideal site to evaluate the effect of glucocorticoids on bone strength. Following lymphoma treatment, we demonstrated a mean annualised reduction of -53.7 (SD +/-56.5) over 12 months. A significant association between L1HU reduction and subsequent fracture was not found; but 64% of patients had L1HU scores <130, compared with 40% pre-treatment. Therefore, with longer follow-up, an association between post-treatment L1HU reduction and fracture may emerge.

The benefit of using an existing baseline test to estimate BMD is significant, particularly given that rapid lymphoma diagnosis, staging, and treatment is required, and a separate BMD assessment is not always accessible or prioritised. Lymphoma specialists lack experience managing metabolic bone disease, and utilising a measure such as L1HU to identify patients at high fracture risk may promote referral for expert endocrinological fracture risk assessment and management, thereby improving holistic patient care. Thus far, 3 small prospective randomised studies of 12-month duration each demonstrated BMD loss reduction with bisphosphonate, but only one study found reduced fracture rates, in a cohort with high mean corticosteroid doses (7573mg) (13-15). Larger studies with longer follow-up using standard corticosteroid dosing are desirable, but the capacity to target higher risk patients, potentially using opportunistic tools such as L1HU, may demonstrate more powerful reductions in post-treatment fracture burden.

Our study has important limitations, particularly due to the retrospective nature of clinical data collection. Pre-existing OP, osteopenia, and fracture are likely underreported, given the lack of routine BMD surveillance and reliance on documented evidence of fracture/OP diagnoses. Established risk factors including active thyroid/parathyroid disease, parental hip fracture, early menopause, and sedentary lifestyle could not be included due to inconsistent recording. L1HU was not compared to the gold-standard BMD assessment method of dual x-ray absorptiometry, due to access challenges in our healthcare setting. L1HU cut-off from our study might not be applicable to other [^{18}F]FDG-PET/CT scanners without prior cross-calibration, and might explain the variance in cut-offs reported by other centres.

Despite limitations, L1HU on routine [^{18}F]FDG-PET/CT scans was easily performed, sparing patients from additional radiation exposure and logistics associated with dedicated BMD scans, and was robustly associated with fracture, over any identified traditional risk factors. A prospective study is currently underway to confirm the utility of L1HU in lymphoma patients as an opportunistic flag for those at high risk of fracture. (HREC/79155/Austin-2021).

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Table 1: Baseline cohort characteristics, fracture risk and protective factors

Variables	A: Whole cohort		B: L1HU cohort	
	n	%	n	%
Total	313	100.0	255	100
Median age at diagnosis, years (range)	68 (20-93)		66 (20-93)	
Median follow-up, months (range)	42 (1-122)		42 (2-120)	
Potential fracture risk factors				
Female	131	41.9	102	40.0
Age ≥70	169	54	108	42.4
Osteoporosis pre-treatment	32	10.2	0	0.0
Osteopenia pre-treatment	17	5.4	14	5.5
Bone/bone marrow involvement with lymphoma	82	26.1	60	23.5
Prior malignancy	47	15.0	31	12.1
Hypogonadism	4	1.3	1	0.4
Prior exposure to hormone deprivation therapy	13	4.2	4	1.6
History of malabsorption syndrome	21	6.7	14	5.5
History of rheumatoid arthritis	18	5.8	15	5.9
Prior corticosteroid ≥7.5mg prednisolone equivalent for ≥3 months	24	7.7	17	6.7
BMI ≤18	5	1.6	4	1.6
Current smoker	43	13.7	39	15.3
ETOH ≥3 standard drinks daily	14	4.5	12	4.7
Received pre-phase steroid	112	35.8	88	34.5
Possible protective factors for bone loss				
SERM exposure	3	1.0	1	0.4
Documented vitamin D replacement at lymphoma Rx	100	32.1	73	28.6
Documented calcium replacement at lymphoma Rx	19	6.1	12	4.7
Antiresorptive therapy	12	3.8	2	0.8
HRT	6	1.9	4	1.6
Pre-treatment mean L1HU (+/- SD)	144.9 (+/- 46.8)		145.5 (+/-46.9)	
Post-treatment mean L1HU (+/- SD)	117.1 (+/-44.8)		117.5 (+/-44.9)	
Mean absolute L1HU change (+/- SD)	-27.7 (+/- 22.7)		-28 (+/-22.5)	
Derived annualised L1HU change (+/- SD)	-54.4 (+/- 58.9)		-53.7 (+/-56.5)	
Median total prednisolone equivalent corticosteroid dose	3000mg (IQR 2100-3900)		3000mg (IQR 2230-3700)	
Deaths during follow-up	82	26.2	56	21.9

SERM: selective estrogen receptor modulator, HRT: hormone replacement therapy, DLBCL: diffuse large B-cell lymphoma, cHL: classical Hodgkin lymphoma, PTCL: peripheral t-cell lymphoma, BMI: body mass index, ETOH: alcohol intake

Table 2: Cox regression: association between L1HU, OP risk and protective factors with new fracture

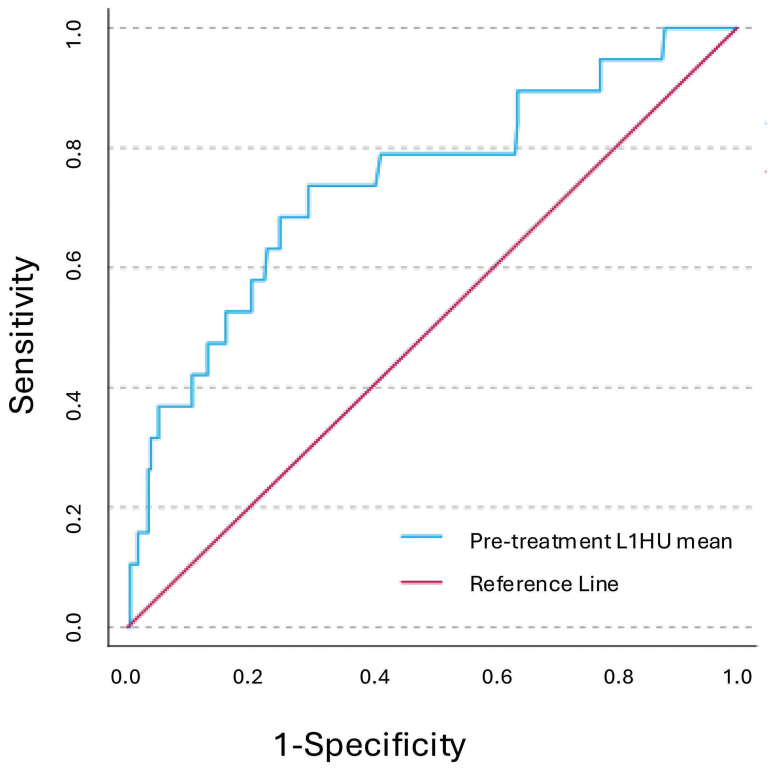
Covariates	Univariable			Multivariable		
	HR	p	95% CI	HR	p	95% CI
Fracture risk factors						
Age >70	3.2	**0.022**	1.2-8.5	1.7	0.324	0.6-4.9
Male	0.9	0.864	0.4-2.3			
Fracture history prior to lymphoma therapy	0.5	0.480	0.1-3.7			
Osteopenia pre-treatment	1.3	0.829	0.2-9.5			
Bone/bone marrow involvement with lymphoma	1.1	0.824	0.4-3.2			
Prior malignancy	2.5	0.157	0.7-8.8			
Hypogonadism	0.1	0.893	0-5x10^7			
Prior exposure to hormone deprivation therapy	0.1	0.844	0-5.5x10^7			
History of malabsorption syndrome	1.5	0.692	0.2-11.6			
History of rheumatoid arthritis	2.5	0.220	0.6-11.1			
Prior ≥7.5mg prednisolone equiv ≥3 months	0.6	0.567	0.1-4.1			
BMI ≤18	11.6	**0.023**	1.4-94.8	14	**0.016**	1.6-121.3
Current smoker	0.3	0.272	0.04-2.4			
ETOH ≥3 standard drinks daily	3.6	0.110	0.8-17.3			
Received pre-phase steroid	1.3	0.564	0.5-3.4			
Total prednisolone equiv corticosteroid	1.0	0.208	0.9-1.0			
Possible protective factors						
SERM exposure	0.1	0.914	0-2.8x10^22			
Documented vitamin D replacement	1.6	0.320	0.6-4.0			
Documented calcium replacement at lymphoma Rx	0.9	0.888	0.1-6.6			
Antiresorptive therapy	0.1	0.869	0-1.9x10^7			
HRT	5.4	0.104	0.7-41.62			
L1HU						
Pre-treatment mean L1HU <130*	5.9	**<0.001**	2.1-16.5	4.8	**0.005**	1.6-14.6
Absolute L1HU change (continuous)	1.0	0.515	0.98-1.04			
Annualised L1HU change (continuous)	1.0	0.340	0.99-1.02			

* cutoff identified using ROC (Figure 1B)

SERM: selective estrogen receptor modulator, HRT: hormone replacement therapy, DLBCL: diffuse large B-cell lymphoma, cHL: classical Hodgkin lymphoma, PTCL: peripheral t-cell lymphoma, BMI: body mass index, ETOH: alcohol intake

Figure 1: Identification of L1HU cutoff for fracture risk, and cumulative risk of fracture comparing L1HU cutoff values
1A: ROC analysis of L1HU predictability for fracture
1B: Cumulative incidence of fracture for patients with pre-treatment L1HU <130 versus L1HU >130, censored at death / last follow-up

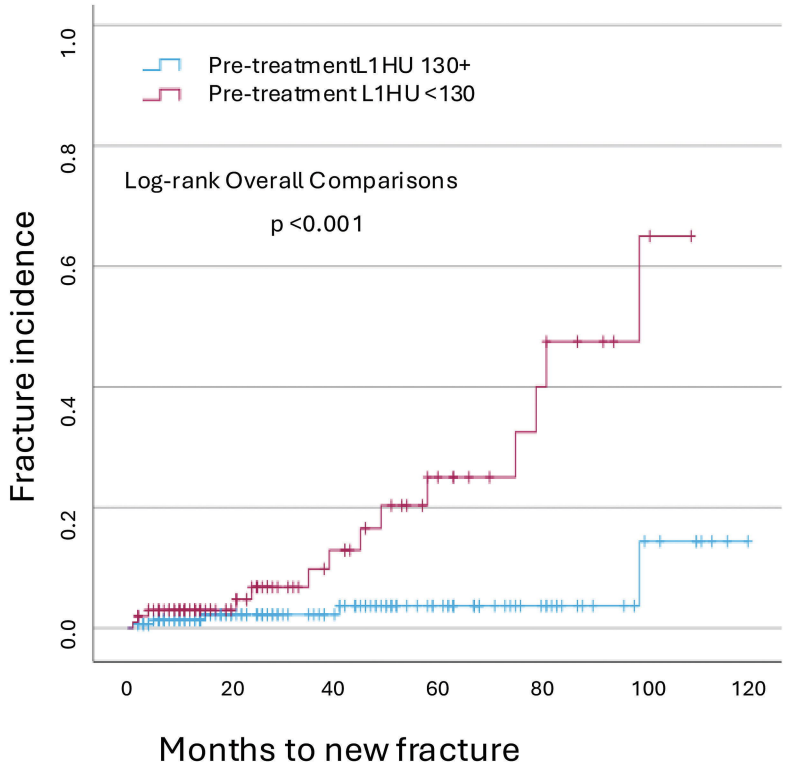
1A



Area under curve	Standard error	95% confidence interval	p value
0.742	0.064	0.616-0.868	0

	Sensitivity %	Specificity %
L1HU 180	89.5	23.6
L1HU 140	78.9	51.5
L1HU 130	73.7	62.4

1B



	At risk						
L1HU <130	102	56	28	15	8	2	
L1HU 130+	153	97	69	40	21	8	1

Table S1: Additional lymphoma, prior fracture and treatment characteristics				
Variables	**A: Whole cohort**		**B: L1HU analysis cohort**	
	n	**%**	**n**	**%**
Total	313	100.0	255	100
Fracture history prior to lymphoma therapy				
Total	37	11.8	24	9.4
Atraumatic	9	2.9	0	0.0
Traumatic	7	2.2	7	2.7
Uncertain trauma level	17	5.4	15	5.9
Pathological	4	1.3	2	0.8
Lymphoma subtype				
DLBCL	268	85.9	213	83.9
cHL	10	3.2	10	3.9
PTCL	2	0.6	2	0.8
Other high-grade lymphoma	28	8.9	26	10.2
Indolent	4	1.3	3	1.2
Missing	1	0.3	1	0.4
First-line treatment delivered				
CHOP +/- rituximab	288	92.0	237	92.9
CVP +/- R	12	3.8	6	2.4
ABVD/escBEACOPP combination	4	1.3	4	1.6
escBEACOPP	1	0.3	1	0.4
Other*	8	2.6	7	2.7

DLBCL=diffuse large B-cell lymphoma; cHL=classical Hodgkin lymphoma; PTCL=peripheral T-cell lymphoma; CHOP=Cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP=cyclophsphamide, vincristine and prednisolone; R=Rituximab; ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine; escBEACOPP=escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, procarbazine

*Other chemotherapy: PVAG (n=2), DA-R-EPOCH (n=6)

Table S2: New fracture / any bone event following commencement of lymphoma treatment

	n	New fracture (%)	Fracture trauma level	New diagnosis of OP (%)	New diagnosis of osteopenia (%)	Any new bone event
No known baseline OP	281	20 (7.1)	Atraumatic: 7 Traumatic: 6 Pathological: 0 Unknown: 7	16 (5.7)	7 (2.5)	31 (11)
Known baseline OP	32	4 (12.5)	Atraumatic: 2 Traumatic: 0 Pathological: 0 Unknown: 2	NA	NA	4 (12.5)

Any new bone event: New fracture and/or diagnosis of OP or osteopenia

Table S3: Detail of fractures identified following commencement of lymphoma therapy		
Fracture details	**Known OP pre-treatment**	**No pre-treatment OP**
All	4	20
Vertebral	2	9
Wrist	1	5
Ribs	0	2
Hip	0	1
Humerus	1	2
Unknown	0	1

Table S4: Detail of prior malignancies	
Prior malignancies	47
Breast cancer	9
Melanoma	8
Myeloproliferative neoplasm	5
Prostate cancer	4
Bowel cancer	4
Gastrointestinal stromal tumour	1
Hepatocellular carcinoma	1
Cervical cancer	1
Nasopharyngeal cancer	1
Germ cell tumour	1
Ovarian cancer	1
Oesophageal cancer	1
Acute lymphoblastic leukemia	1
Bladder cancer	1
Myelodysplastic syndrome	1
2+ prior malignancies	7