Perirenal and subcutaneous fat differently affect outcomes in newly diagnosed classical Hodgkin lymphoma patients

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Title: Perirenal and subcutanous fat differently affect outcomes in newly diagnosed classical Hodgkin lymphoma patients

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Dear Editor,

classical Hodgkin lymphoma (cHL) is a B-cell lymphoid malignancy affecting both young and elderly patients. Cachexia, i.e. weight loss with concomitant loss of muscle and fat mass, is highly prevalent in cancer patients and is associated with functional impairment and worse prognosis.[1,2] Body mass index (BMI) has been widely studied as a prognostic factor in patients with cHL and non-Hodgkin lymphomas with neutral[3], negative[4] and positive[5,6] associations of higher BMI with survival being reported. Subcutaneous and visceral fat show different clinical associations in patients with metabolic diseases[7] and global measurements like body mass index (BMI) might not be reliable for estimation of specific body fat compartments. Thus, we aimed to assess subcutaneous and visceral abdominal fat measurements from baseline computerized tomography (CT) scans of cHL patients and to investigate their clinical and prognostic associations.

We retrospectively analyzed 82 newly diagnosed cHL patients with available data who presented to our institution in period November 2003 – December 2018. Patients were staged by European Organisation for Research and Treatment of Cancer (EORTC) and International Prognostic Score (IPS) cHL prognostic systems and were treated with either ABVD or eBEACOPP chemotherapy regimens and subsequent radiotherapy per physicians' decision. Perirenal fat thickness was assessed from staging CT scans prior to chemotherapy as the largest and the smallest distance from kidney outline to the inner limit of abdominal wall at the transversal level of the renal vein. Subcutaneous fat thickness was assessed as the largest distance between the skin and outer limit of the muscular abdominal wall at the transversal level of the umbilicus. Psoas muscle area are was assessed at the L3 vertebra level. The study was approved by the Institutional Review Board. Statistical analyses were performed using the MedCalc statistical program ver 19.6.

Patients' characteristics and their relationship with perirenal and subcutaneous fat are shown in Table 1. All three abdominal fat thickness measurements correlated positively together, showed moderate positive correlation with BMI (Rho 0.54 to 0.57; $P<0.05$) and weak positive correlation with body weight (Rho 0.31 to 0.44; $P<0.05$) and total psoas muscle area at the L3 level (Rho 0.24 to 0.33; $P<0.05$). Considerable differences were present regarding EORTC disease stage where patients with more advanced disease were significantly more likely to have higher minimal perirenal fat thickness but lower

subcutaneous fat thickness (P<0.05 for both analyses). Similarly, minimal perirenal fat thickness was significantly positively correlated with the IPS (Rho=0.34, P=0.002), whereas subcutaneous fat thickness was significantly negatively correlated with the IPS (Rho=-0.27, P=0.013). No significant associations of BMI with EORTC stages nor IPS were present (P>0.05). Higher minimal and maximal perirenal fat thickness were additionally significantly associated with older age, male sex, lower platelets, lower IgG, higher creatinine, higher ferritin, and higher bone marrow fat percentage. Higher minimal perirenal fat thickness was also significantly associated with higher Ann Arbor stage and palpable splenomegaly. Lower subcutaneous fat thickness was significantly associated with presence of constitutional symptoms but not with other parameters related to perirenal fat thickness measurements.

Using the ROC curve analysis, we have defined optimal cut-off points for survival for minimal perirenal fat thickness (>2 mm; 33/82 [40.2%] patients), maximal perirenal fat thickness (>25 mm; 29/82 [35.4%] patients) and subcutaneous fat thickness (≤22 mm; 54/82 [65.9%] patients). We were also able to define an optimal cut-off point for time to progression for subcutaneous fat thickness (≤22 mm) but not for other two parameters. As shown in Figure 1A-C, higher minimal (HR=8.4; P<0.001), higher maximal perirenal fat thickness (HR=3.15; P=0.049) and lower subcutaneous fat thickness (HR=3.57; P=0.033) were significantly associated with inferior overall survival in univariate analyses. In addition, lower subcutaneous fat thickness (HR=4.45; P=0.005) was also associated with shorter time to disease progression, Figure 1D. Perirenal fat thickness did not show significant associations with time to disease progression. There was no association of BMI with neither survival nor time to progression. Bone marrow fat percentage had no significant association with survival but was significantly associated with shorter time to disease progression (>45%; HR=3.8; P=0.021).

We further analyzed associations of perirenal and subcutaneous fat thickness in the multivariate models adjusted for age, gender, Ann Arbor stage and IPS. Both minimal perirenal fat thickness >2 mm (HR=49.2; P=0.019), subcutaneous fat thickness ≤22 mm (HR=45.7; P=0.038) and IPS (HR=2.44; P=0.025) remained significantly associated with inferior overall survival. Subcutaneous fat ≤22 mm (HR=14.4; P=0.013) and older age (HR=1.04; P=0.043) remained independently associated with shorter time to disease progression. Bone marrow fat percentage did not remain significantly associated with time to progression when added to multivariate model.

We would like to emphasize several important observations. Our data suggest that lesser subcutaneous and greater perirenal fat deposition are associated with more advanced disease features and shorter survival in cHL patients, lesser subcutaneous fat being additionally associated with shorter time to disease progression. BMI is practical and most widely used parameter to assess obesity and underweight, however, it is a composite measure derived from body weight and height and patients with same BMI can have different body composition and different fat tissue distribution. Perirenal fat is a brown adipose tissue and a visceral type of fat with distinct metabolic functions in comparison to subcutaneous fat which is a white adipose tissue. As we show, excess of or depleted abdominal fat might have different clinical associations and differently affect outcomes in cHL patients depending on its distribution. Distinction between different abdominal adipose tissue compartments is necessary to better understand relationship between obesity, cachexia and prognosis in patients with cHL.

Limitations of our work are single center experience, retrospective study design and small number of patients. Nevertheless, our data show for the first time that localization of abdominal fat has important prognostic implications in patients with cHL. The question emerges, could CT measurements of different abdominal fat deposits also be used to further refine current standard of prognostication, PET-CT obtained information on interim PET-CT scans. Further research on this issue is needed.

References

1. Dunne RF, Loh KP, Williams GR, Jatoi A, Mustian KM, Mohile SG. Cachexia and Sarcopenia in Older Adults with Cancer: A Comprehensive Review. *Cancers.* 2019;11(12):1861.
2. Lucijanić M, Huzjan Korunic R, Ivić M, et al. Psoas muscle index at the time of diagnosis might reflect the prognosis of classical Hodgkin's lymphoma patients. *Wien Klin Wochenschr.* 2021.
3. Hong F, Habermann TM, Gordon LI, et al. The role of body mass index in survival outcome for lymphoma patients: US intergroup experience. *Ann Oncol.* 2014;25(3):669-674.
4. Scheich S, Enßle JC, Mücke VT, et al. Obesity is associated with an impaired survival in lymphoma patients undergoing autologous stem cell transplantation. *PLoS One.* 2019;14(11):e0225035.
5. Landgren O, Andrén H, Nilsson B, Ekbom A, Björkholm M. Risk profile and outcome in Hodgkin's lymphoma: is obesity beneficial? *Ann Oncol.* 2005;16(5):838-840.
6. Weiss L, Melchardt T, Egle A, et al. Influence of body mass index on survival in indolent and mantle cell lymphomas: analysis of the StiL NHL1 trial. *Ann Hematol.* 2017;96(7):1155-1162.
7. Gelber RP, Gaziano JM, Orav EJ, Manson JE, Buring JE, Kurth T. Measures of obesity and cardiovascular risk among men and women. *J Am Coll Cardiol.* 2008;52(8):605-615.

Table 1: Patients' characteristics and their relationship with minimal and maximal perirenal fat and subcutaneous fat thickness.

	Overall	**Min. perirenal fat** (mm)	**Max. perirenal fat** (mm)	**Subcutaneous fat** (mm)
Age (years)	36 IQR (26.5 - 55.75)	Rho=0.53 **P<0.001***	Rho=0.39 **P<0.001***	Rho=-0.12 P=0.275
Sex		Median	Median	Median
Male	46/82 (56.1%)	3	26	17.5
Female	36/82 (43.9%)	1	14.5	19.5
		P<0.001*	**P<0.001***	P=0.349
Pathohistological type		Median	Median	Median
Nodular sclerosis	61/82 (74.4%)	1	20	18.5
Mixed cellularity	6/82 (7.3%)	5	28.5	15.5
Lymphocyte depletion	2/82 (2.4%)	5.5	23	21
Lymphocyte predomination	2/82 (2.4%)	4.5	45.5	18
Unclassifiable	11/82 (13.4%)	2	20.5	17
		P=0.075	P=0.113	P=0.877
Ann Arbor staging		Median	Median	Median
I	6/82 (7.3%)	3	23	23
II	43/82 (52.4%)	1	19	17
III	17/82 (20.7%)	5	26	19
IV	16/82 (19.5%)	2	19.5	15.5
		P=0.032*	P=0.130	P=0.486
Ann Arbor staging		Median	Median	Median
I-II	49/82 (59.8%)	1	19	18
III-IV	33/82 (40.2%)	3	24	19
		P=0.016*	P=0.077	P=0.626

	Overall	Min. perirenal fat (mm)	Max. perirenal fat (mm)	Subcutaneous fat (mm)
EORTC staging		Median	Median	Median
Early favorable	11/82 (13.4%)	1	19	31
Early unfavorable	38/82 (46.3%)	1	19.5	15.5
Advanced	33/82 (40.2%)	3	24	19
		P=0.050*	P=0.196	**P=0.002***
IPS score	2 IQR (1 - 3)	Rho=0.34	Rho=0.17	Rho=-0.27
		P=0.002*	P=0.129	**P=0.013***
B symptoms		Median	Median	Median
Yes	47/82 (57.3%)	2	20	17
No	33/82 (40.2%)	2	22	22
		P=0.773	P=0.879	**P=0.007***
Bulky disease		Median	Median	Median
Yes	22/82 (26.8%)	1	20	15.5
No	60/82 (73.2%)	2	21.5	20
		P=0.176	P=0.164	P=0.063
Extra-nodal disease		Median	Median	Median
Yes	16/82 (19.5%)	1	18.5	16
No	66/82 (80.5%)	2	22	19
		P=0.434	P=0.303	0.268
Splenomegaly		Median	Median	Median
Yes	12/82 (14.6%)	3.5	25	20.5
No	70/82 (85.4%)	1.5	20	18
		P=0.047*	P=0.077	P=0.723
Hemoglobin (g/L)	127 IQR (110 - 138)	Rho=0.01	Rho=0.15	Rho=0.2
		P=0.922	P=0.194	P=0.079
Platelets ($x10^9$/L)	320 IQR (246 - 423.5)	Rho=-0.3	Rho=-0.29	Rho=-0.2
		P=0.008*	**P=0.010***	P=0.077
WBC ($x10^9$/L)	8.8 IQR (6.73 - 11.35)	Rho=-0.17	Rho=-0.06	Rho=-0.15
		P=0.122	P=0.605	P=0.194

	Overall	**Min. perirenal fat** (mm)	**Max. perirenal fat** (mm)	**Subcutaneous fat** (mm)
Aps. lymphocyte count ($x10^9$/L)	1.4 IQR (0.93 - 2.18)	Rho=0.05 P=0.636	Rho=0.15 P=0.173	Rho=0.06 P=0.617
Rel. lymphocyte count (%)	14.9 IQR (9.95 - 22.68)	Rho=0.04 P=0.715	Rho=0.11 P=0.348	Rho=0.17 P=0.129
Albumin (g/L)	42 IQR (37.25 - 45.75)	Rho=-0.12 P=0.287	Rho=0.1 P=0.367	Rho=0.18 P=0.098
ESR (mm/h)	45 IQR (23 - 73.25)	Rho=0.14 P=0.210	Rho=0.04 P=0.748	Rho=-0.18 P=0.100
CRP (mg/L)	63.3 IQR (10.1 - 113.05)	Rho=0.15 P=0.202	Rho=-0.03 P=0.831	Rho=-0.2 P=0.087
LDH (U/L)	227 IQR (159.5 - 281)	Rho=0.13 P=0.252	Rho=0.06 P=0.621	Rho=0.12 P=0.293
Creatinine (µmol/L)	79 IQR (69.5 - 92)	Rho=0.41 **P<0.001***	Rho=0.4 **P<0.001***	Rho=-0.01 P=0.966
Ferritin (µg/L)	266 IQR (96 - 412.5)	Rho=0.38 **P=0.003***	Rho=0.28 **P=0.032***	Rho=-0.04 P=0.769
IgG (g/L)	14.1 IQR (10.72 - 16.38)	Rho=-0.24 **P=0.047***	Rho=-0.27 **P=0.028***	Rho=-0.09 P=0.442
Body weight (kg)	79 IQR (67.25 - 90)	Rho=0.37 **P=0.001***	Rho=0.44 **P<0.001***	Rho=0.31 **P=0.005***
Body weight <60 kg 60-90 kg >90 kg	 7/82 (8.5%) 53/82 (64.6%) 22/82 (26.8%)	Median 1 1 3 **P=0.043***	Median 12 20 26 **P=0.008***	Median 16 17 21 P=0.084
BMI (kg/m^2)	25.6 IQR (21.85 - 28.63)	Rho=0.54 **P<0.001***	Rho=0.57 **P<0.001***	Rho=0.56 **P<0.001***
Bone marrow fat (%)	32.5 IQR (20 - 50)	Rho=0.36 **P=0.001***	Rho=0.3 **P=0.010***	Rho=-0.08 P=0.514

	Overall	**Min. perirenal fat** (mm)	**Max. perirenal fat** (mm)	**Subcutaneous fat** (mm)
Total psoas area L3 (mm^2)	1571.5 IQR (1200.75 - 2157.5)	Rho=0.28 **P=0.012***	Rho=0.33 **P=0.003***	Rho=0.24 **P=0.031***
Min. perirenal fat (mm)	2 IQR (0.5 - 6)	-	Rho=0.83 **P<0.001***	Rho=0.32 **P=0.003***
Max. perirenal fat (mm)	20.5 IQR (12 - 28.75)	Rho=0.83 **P<0.001***	-	Rho=0.32 **P=0.003***
Subcutaneous fat (mm)	18.5 IQR (12.25 - 24)	Rho=0.32 **P=0.003***	Rho=0.36 **P=0.001***	-

*statistically significant at level P<0.05 /the Mann Whitney U test, the Kruskal-Wallis ANOVA test and the Spearman rank correlation were used /Abbreviations: EORTC - European Organisation for Research and Treatment of Cancer; IPS – International Prognostic Score; WBC – white blood cell count; ESR – erythrocyte sedimentation rate; CRP – C reactive protein; LDH – lactate dehydrogenase; IgG – immunoglobulin G; BMI – body mass index.

Figure 1: Overall survival stratified according to the **A)** minimal (min.) perirenal fat, **B)** maximal (max.) perirenal fat and **C)** subcutaneous fat thickness. **D)** Time to progression stratified according to the subcutaneous fat thickness. The log-rank test was used. HR – hazard ratio.