Thymus is the Barometer of Aging in HIV Patients, Associated With Metabolic Syndrome and Frailty

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759

Background

Thymus size and function involve across time. This physiological process varies from one individual to another, and can be influenced by several pathological conditions that affect the immune system, such as HIV.

Thymic function can be evaluated by estimation of thymus size through CT chest scan. Larger volume is associated with higher thymic output, smaller volume with short- and long-term inadequate CD4+ cell recovery, and faster disease progression despite effective cART. The impact of thymus detection and size in HIV individuals on relevant ageing outcomes has not been evaluated yet.

We sought to investigate the relationship between thymus imaging detection and size with metabolic syndrome, multi-morbidity and frailty in PLWH.

Methods

Study design

This was a cross-sectional observational study including 665 consecutive HIV patients attending Modena HIV Metabolic Clinic (MHMC), a tertiary care teaching Hospital in Northern Italy. Inclusion criteria were being on cART for at least 6 months and having a thoracic CT scan performed for routine cardiovascular disease screening by mean of coronary artery calcium.

Thymus detection and size was retrospectively graded by using a semi-quantitative score describing the size and appearance of thymic solid tissue in the anterior mediastinum (0=not detected; 1=minimal soft tissue barely recognizable; 2=minimal soft tissue more obvious; 3=moderate soft tissue; 4=moderate soft tissue almost mass-like; 5=mass-like soft tissue), as depicted in figure 1.

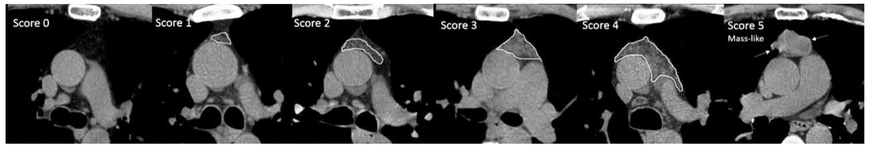


Figure 1. *Images depicting semi-quantitative score of thymus appearance*

Outcome measures

Metabolic Syndrome (MS) was defined according to ATPIII criteria: if three or more of the following five criteria were met: waist circumference over 40 inches (men) or 35 inches (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar over 100 mg/dl. Comorbidity diagnoses were based on guidelines defined criteria and included: cardiovascular disease (CVD), hypertension (HTN), type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), dyslipidaemia (DLM), liver cirrhosis, cancer. Multimorbidity (MM) was defined as ≥3 comorbidities in the same individual. Polypharmacy was defined as ≥5 drug components other than ARVs. Frailty was measured with both the frailty phenotype (FP) and a 37-item Frailty index (FI) previously validated at MHMC. In the logistic analyse FI>0.4 was used to identify most frail individuals. Disability was assessed for any impairment in Advanced Instrumental activity of Daily Living (AIADL). Quality of life was measured with EQ 5D5L questionnaire.

Statistical analyses

Results were expressed as mean ± SD, or median and interquartile range for continuous variables based on the normality of distribution, and as frequencies and percentages for categorical variables. Student's t-test was applied to identify statistical difference for the continuous variables with normal distribution while Mann-Whitney test was used for those without normal distribution. $\chi 2$ test was preformed to assess the frequency for the categorical variables.

A logistic regression analyses was conducted to identify independent predictors for thymus detection, by using as covariates: age, gender and statistically significant predictors identified in univariate analyses. To avoid collinearity between age and duration of HIV, the latter was expressed as "Residual HIV duration" derived from univariate linear regression between age and duration of HIV infection: depicting the effect of HIV duration after correlation for age. A logistic regression analyses was conducted to identify independent predictors for MS MM, FI, Disability and QoL by using as covariates age, gender, thymus detection and statistically significant predictors identified in univariate analyses.

All statistical analyses were performed by using R software, version 3.4.1.

Results

665 HIV infected patients (81% males), median age 53 years and median current CD4=730/μL and HIV-RNA<40c/mL in 98.5% were included.

Table 1*: The table describes demographic, anthropometric, relevant HIV and immuno-metabolic markers, comorbidities and study outcomes according to thymus detection and size*

	Total	THY=0	THY 1-2	THY 3+	p
Thymus detection	665	485(72.93%)	128(19.25%)	52(7.82%)	
Demographics and anthropometry					
Age (yrs ± SD) [n°]	53.11 (7.98) [665]	54.59 (7.86)[485]	50.92 (6.36)[128]	44.69 (6.13)[52]	<0.001
Male, %	539 (81.05%)	412 (84.95%)	92 (71.88%)	35 (67.31%)	<0.001
BMI, Kg/m2	24.15 (3.78) [615]	24.57 (3.97)[449]	23.22 (3.05)[120]	22.45 (2.51)[46]	<0.001
Waist circumf. (cm±SD) [n°]	89.67 (10.89) [618]	91.27 (10.94)[450]	86.65 (9.86)[122]	82.03 (7.78)[46]	<0.001
Appendicular skeletal muscle index [ASMI (kg)/height (m)²]	6.97 (1.39) [531]	7.02 (1.39)[382]	6.86 (1.48)[106]	6.73 (1.14)[43]	0.161
No lypodistrophy	96 (28.15%)	49 (19.84%)	28 (41.79%)	19 (70.37%)	<0.001
Lipoatrophy	102 (29.91%)	74 (29.96%)	22 (32.84%)	6 (22.22%)	<0.001
Lipohypertrophy	36 (10.56%)	32 (12.96%)	2 (2.99%)	2 (7.41%)	<0.001
Mixed form	107 (31.38%)	92 (37.25%)	15 (22.39%)	0 (0%)	<0.001
HIV related variables					
HIV duration, (months) [n°]	262 (183.25-323) [658]	267 (197-327.5)[479]	259 (180-319.5)[127]	171 (87.25-251.75)[52]	<0.001
HIV Risk: IVDU (%) [n°]	174 (26.17%)	141 (29.07%)	28 (21.88%)	5 (9.62%)	0.022
HIV Risk: MSM (%) [n°]	234 (35.19%)	167 (34.43%)	42 (32.81%)	25 (48.08%)	0.022
HBV-co-infection	13 (2.13%) [611]	12 (2.67%) [450]	1 (0.87%) [115]	0 (0%) [46]	0.286
HCV co-infection	159 (26.46%) [601]	116 (26.13%) [444]	36 (31.03%) [116]	7 (17.07%) [41]	0.209
Nadir CD4, (median c/µL, IQR [n°])	200.5 (94.25-300) [642]	200 (88-300)[473]	216.5 (99-301)[120]	240 (110-318)[49]	0.356
Current CD4/CD8, (mean c/µL ± SD) [n°]	0.96 (0.62) [539]	0.96 (0.68)[399]	0.95 (0.48)[99]	0.97 (0.36)[41]	0.399
Current CD4, (mean c/µL ± SD) [n°]	730.61 (330.52) [652]	718.2 (342.38)[476]	758.19 (287.33)[126]	779.26 (313.92)[50]	0.102
HIV-RNA<40 c/mL, n (%)	655 (98.5%)	478 (98.56%)	128 (100%)	49 (94.23%)	0.015
Immuno-metabolic variables					
Total Cholesterol, mg/dL (±SD) [n°]	184.78 (40.2) [630]	183.57 (40.25)[463]	188.96 (38.47)[120]	186.06 (43.96)[47]	0.415
Tryglycerides, mg/dL (±SD)	159.42 (113.15) [628]	169.98 (123.63)[461]	133.1 (71.42)[120]	123 (64.65)[47]	<0.001
HOMA-IR, (±SD)	2.96 (5.31) [498]	3.39 (6.09)[368]	1.87 (1.23)[92]	1.38 (0.69)[38]	<0.001
HbA1C, mmol/mol (±SD) [n°]	27.49 (16.21) [487]	28.62 (16.68)[356]	26.4 (13.91)[90]	20.14 (15.01)[41]	0.005
CKD-EPI ml/min (±SD) [n°]	88.6 (18.17) [607]	86.42 (18.69)[445]	93.05 (15.29)[117]	98.61 (14.24)[45]	<0.001
CRP mg/L (±SD) [n°]	0.3 (0.37) [617]	0.31 (0.38)[450]	0.29 (0.38)[120]	0.22 (0.19)[47]	0.013
Calcium score	2 (0-78.25) [640]	11 (0-112.75) [462]	0 (0-23.5)[127]	0 (0-0)[51]	<0.001
Co-morbidities					
Dislypidemia, n (%)	574 (86.32%)	431 (88.87%)	106 (82.81%)	37 (71.15%)	0.001
Hypertension, n (%)	337 (50.68%)	276 (56.91%)	51 (39.84%)	10 (19.23%)	<0.001
CVD, n (%)	43 (6.47%)	39 (8.04%)	3 (2.34%)	1 (1.92%)	0.025
T2-Diabetes Mellitus, n (%)	120 (18.05%)	110 (22.68%)	8 (6.25%)	2 (3.85%)	<0.001
CKD, n (%)	101 (15.19%)	83 (17.11%)	17 (13.28%)	1 (1.92%)	0.012
COPD, n (%)	42 (6.32%)	31 (6.39%)	10 (7.81%)	1 (1.92%)	0.335
Osteoporosis, n (%)	173 (26.02%)	131 (27.01%)	31 (24.22%)	11 (21.15%)	0.576
Liver cirrhosis, n (%)	85 (12.78%)	68 (14.02%)	14 (10.94%)	3 (5.77%)	0.187
Outcome variables					
Metabolic syndrome	106 (17.21%)	95 (21.16%)	7 (5.83%)	4 (8.51%)	<0.001
Multi-Morbidity, n(%)	275 (41.35%)	222 (45.77%)	45 (35.16%)	8 (15.38%)	<0.001
Polypharmacy, n (%)	112 (17.31%)	100 (21.1%)	10 (8%)	2 (4.17%)	<0.001
Frailty Phenotype, n (%)	6 (2.17%)	6 (2.83%)	0 (0%)	0 (0%)	0.396
37-item Frailty Index, Median (IQR), [n°]	0.29 (0.23-0.35) [588]	0.3 (0.24-0.37)[434]	0.25 (0.19-0.32)[108]	0.23 (0.16-0.26)[46]	<0.001
Disability (KATZ)	14 (6.17%)	13 (7.39%)	1 (2.5%)	0 (0%)	0.349
Quality of life impaired	255 (76.81%)	187 (75.4%)	52 (80%)	16 (84.21%)	0.540

Figure 2*: Relationship between thymus detection and size and age*

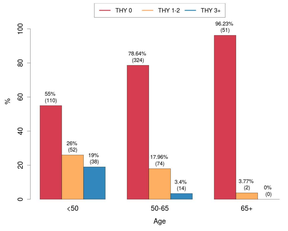


Figure 3*: Relationship between thymus detection and size and HIV duration*

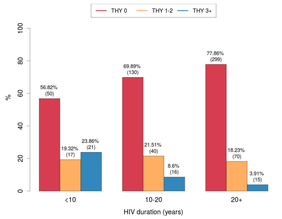
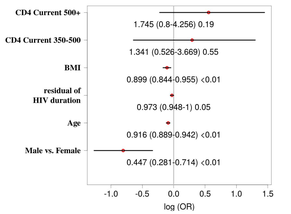


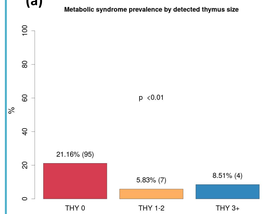
Figure 4 *. Predictors of thymus detection at multivariate logistic model.*



CD4 was Included in the model due to a significant cell count difference (p=0.035) in THY0 (CD4=730/µL) versus THY>0 (CD4=782/µL)

Figure 5*: Association between thymus detection and size and Metabolic Syndrome. Panel (a) prevalence, Panel (b) univariate analyses, Panel (c) multivariate regression analyses*

(a)



(b)

	OR	lower	upper	p value
Age (years)	1,057	1,03	1,086	<0,01
Male	1,483	0,845	2,765	0,19
CD4 Nadir 100-350	0,898	0,558	1,465	0,66
CD4 Nadir 350-500	0,911	0,435	1,82	0,80
CD4 Nadir 500+	0,914	0,252	2,637	0,88
HIV duration (years)	1,033	1,005	1,063	0,03
CD4/CD8	1,021	0,681	1,419	0,91
CD4 Current 350-500	0,75	0,334	1,716	0,49
CD4 Current 500+	0,569	0,296	1,155	0,10
BMI	1,204	1,136	1,279	<0.01
THY 1-2	0,229	0,094	0,474	<0.01
THY 3+	0,341	0,101	0,868	0,04

(c)

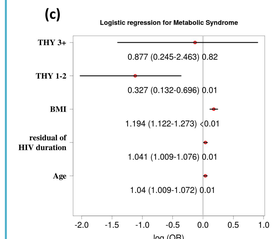
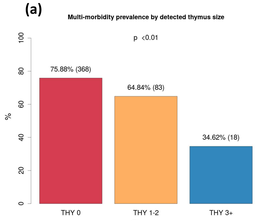


Figure 6*: Association between thymus detection and size and Multi-Morbidity. Panel (a) prevalence, Panel (b) univariate analyses, Panel (c) multivariate regression analyses*

(a)



(b)

	OR	lower	upper	p value
Age (years)	1,174	1,138	1,214	<0.01
Male	1,109	0,721	1,681	0,63
CD4 Nadir 100-350	0,408	0,257	0,634	<0.01
CD4 Nadir 350-500	0,38	0,205	0,703	<0.01
CD4 Nadir 500+	0,316	0,132	0,782	0,01
HIV duration (years)	1,098	1,074	1,123	<0.01
CD4/CD8	1,143	0,839	1,65	0,44
CD4 Current 350-500	0,449	0,199	0,959	0,04
CD4 Current 500+	0,554	0,266	1,061	0,09
BMI	1,091	1,04	1,149	<0.01
THY 1-2	0,596	0,392	0,913	0,02
THY 3+	0,167	0,089	0,304	<0.01

(c)

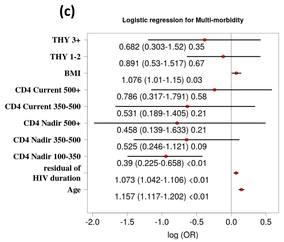
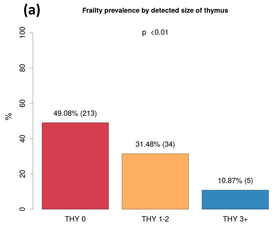


Figure 7*: Association between thymus detection and size and Frailty. Panel (a) prevalence, Panel (b) univariate analyses, Panel (c) multivariate regression analyses*

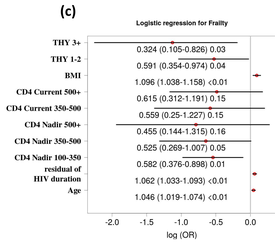
(a)



(b)

	OR	lower	upper	p value
Age (years)	1,062	1,039	1,086	<0.01
Male	0,965	0,635	1,472	0,87
CD4 Nadir 100-350	0,609	0,414	0,893	0,01
CD4 Nadir 350-500	0,424	0,235	0,752	<0.01
CD4 Nadir 500+	0,396	0,144	0,993	0,06
HIV duration (years)	1,07	1,046	1,096	<0.01
CD4/CD8	1,003	0,744	1,335	0,99
CD4 Current 350-500	0,511	0,253	1,015	0,06
CD4 Current 500+	0,471	0,263	0,83	0,01
BMI	1,098	1,047	1,153	<0.01
THY 1-2	0,474	0,3	0,738	<0.01
THY 3+	0,124	0,042	0,293	<0.01

(c)



Discussion

- Thymus was detected in 27% of our cohort, being still present in 19.4% of HIV patients over 50 years of age. HIV duration (studied as the residual from age) impacts thymus detection and size and therefore may modulate the association between this lymphoid tissue and aging trajectories in PLWH.
- Thymus detection and size are associated with immune-metabolic disarrangements depicted by metabolic syndrome and with biological age depicted by frailty. In our study patients with higher thymic size show significant lower prevalence of MS and frailty, and a trend towards lower MM.
- The lack of association between thymus detection and disability and impaired QoL may be attributed to the relatively healthy profile of our cohort.
- In consideration of the "inflammaging" construct and the strong association between Frailty and immune-system dysfunction we hypothesize that thymus detection and size underline a complex immunologic phenotype not detected by immunological parameters traditionally used in HIV patients.

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