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MAJOR ARTICLE

Thymus Imaging Detection and Size Is Inversely Associated With Metabolic Syndrome and Frailty in People With HIV

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Background. People with HIV (PWH) may experience accentuating aging in relation to immuno-activation. Little is known regarding thymus (THY) involution in this process. We sought to investigate the relationship between THY imaging detection/size and clinically relevant aging outcomes such as metabolic syndrome (MetS), multimorbidity (MM), and frailty in PWH.

Methods. This was a cross-sectional observational study including 665 HIV patients (81% males; median age, 53 years) attending Modena HIV Metabolic Clinic from 2014 to 2017. They underwent thoracic computed tomography scan as part of the medical assessment for cardiovascular disease, in which THY detection and size were reported using a semiquantitative score. Outcome measures were MetS, MM, and frailty.

Results. THY was detected in 27.0% of subjects; 71.1% showed THY size of grade 1–2, and 28.9% exhibited grade ≥3. Covariates that inversely correlated with THY detection were age, male gender, body mass index (BMI), and HIV duration. Covariates that inversely correlated with MetS were age, HIV duration, BMI, and THY grade 1–2. Covariates that inversely correlated with MM were age, HIV duration, and CD4 nadir. Covariates that inversely correlated with frailty were age, HIV duration, CD4 nadir, BMI, and THY detection.

Conclusions. THY is inversely associated with MetS and frailty in PWH.

Keywords. aging; frailty; HIV; metabolic syndrome; thymus.

Thymus (THY) is a primary lymphoid organ, visible in the upper mediastinum beneath the sternum. It is the primary site of T-cell selection, development, and maturation. THY size and function decline across time: They are more conspicuous at the onset of puberty [1]; afterwards, they decrease by ~3% per year until middle age, and subsequently by 1% per year [2]. Loss of THY function has been described as an independent predictor of all-cause mortality in uninfected elderly humans [3].

Although THY involution affects all individuals, this physiological process may vary from one subject to another. Moreover, it can be greatly influenced by several pathological conditions that affect the immune system, such as HIV infection [4, 5].

THY size has been shown to predict CD4 recovery and higher CD4/CD8 ratio after antiretroviral therapy (ART) initiation [6] and to be related to the dramatic increase in CD4 T-cell count found in late presenters [5]. Furthermore, age-related THY decline may have an impact on the inability of either children or adults to restore immune function following HIV infection [7].

Much less is known regarding the role of THY in immune activation, which characterizes accentuating aging processes in people with HIV (PWH), as defined by the increased prevalence of age-related comorbidity and frailty observed in comparison with the general population [8, 9]. At a clinical level, this immuno-metabolic phenomenon is often described as "inflammaging" [10, 11], and it is pathogenically linked with metabolic syndrome (MetS) [12], noninfectious comorbidities (NICMs) [13, 14], functional decline [15], and geriatric syndromes including frailty [16]. Geriatric syndromes are better suited than single comorbidities to predicting age-related outcomes in PWH [17]. Frailty, in particular, measures the biological age of individuals regardless of their chronological age. It is conceptualized as a reduction of physiologic reserves related to a greater risk of hospitalization, disability, and mortality [18, 19].

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We hypothesized that THY may play an important role in clinically relevant aging outcomes in PWH, and thus we sought to investigate the association between thymus imaging detection/size and metabolic syndrome, multimorbidity, and frailty in PWH.

METHODS

Study Design

This was an observational study including HIV patients attending Modena HIV Metabolic Clinic (MHMC) from 2014 to 2017. In this tertiary care teaching hospital in Northern Italy, all individuals are screened by a multidisciplinary team for immuno-metabolic disorders, HIV-associated NICMs, geriatric syndromes, and frailty. In this center of excellence, the national health service offers patients, free of charge, thoracic and abdominal computed tomography (CT) to detect coronary artery calcium (CAC), lung parenchyma abnormalities, visceral adipose tissue, and liver steatosis. CAC assessment is routinely used as a risk modifier for cardiovascular risk stratification. THY detection is reported in the description of radiological findings.

In this cross-sectional study, we included 665 consecutive HIV patients undergoing ART for at least 2 years with a stable undetectable viral load (<40 copies/mL). No exclusion criteria were defined. Patients were evaluated for immuno-metabolic abnormalities, NICM, and frailty on the same day when thoracic CT scan was performed.

THY detection and size were retrospectively graded using a semiquantitative score describing the size and appearance of THY solid tissue in the anterior mediastinum (0 = not detected; 1 = minimal soft tissue barely recognizable, 1%–25%; 2 = minimal soft tissue more obvious, 26%–50%; 3 = moderate soft tissue, 51%–75%; 4 = moderate, almost mass-like, soft tissue, 75%–100%; 5 = mass-like soft tissue), as previously described [20–22].

In this semiquantitative grading system, THY is detected and evaluated by tissue density and size (picture examples from this cohort are shown in Supplementary Figure 1, where borders are manually drawn to visually show THY size).

This study was approved by the University of Modena and Reggio Emilia ethics committee according to the Declaration of Helsinki. All patients provided written consent before participating in the study.

Outcome Measures

Metabolic disorder was defined using MetS ATPIII classification [23], including 3 or more of the following 5 criteria: waist circumference >102 cm (men) or >88 cm (women), blood pressure >130/85 mmHg, fasting triglyceride (TG) level >150 mg/dL, fasting high-density lipoprotein (HDL) cholesterol level <40 mg/dL (men) or <50 mg/dL (women), and fasting blood glucose >100 mg/dL. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR = [fasting glucose (mg/dL) × fasting insulin (mU/mL)]/405 [24].

NICMs were defined according to European AIDS Clinical Society (EACS) guidelines [25]. Cardiovascular disease (CVD) included myocardial infarction, coronary artery disease, peripheral vascular disease, stroke, and angina pectoris, as well as coronary artery bypass grafting and angioplasty, based on diagnoses recorded in patient files. Hypertension (HTN) was defined as 2 consecutive measurements of blood pressure >140/90 mmHg; dyslipidemia (DLP) as elevated total or low-density lipoprotein cholesterol or low high-density lipoprotein cholesterol above laboratory limits; type 2 diabetes mellitus (T2DM) as fasting serum glucose levels >126 mg/dL or HbA1C >6.5%; chronic kidney disease (CKD) as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation; osteoporosis in postmenopausal women and men aged ≥50 years as a bone mass index (BMD) T-score ≤−2.5 and in premenopausal women and men aged <50 years as a BMD Z-score ≤−2 and fragility fracture; chronic obstructive pulmonary disease (COPD) as postbronchodilator FEV1/FVC <0.70 with spirometry. Liver cirrhosis was assessed in every patient and was defined through noninvasive assessment with either serum biomarkers (FIB-4) or transient elastography [26]. Lipodystrophy was described as lipoatrophy, lipohypertrophy, or mixed form a fat redistribution [27]. Laboratory values for the diagnosis of CKD and DLP were confirmed in 2 consecutive measurements. Diagnoses of DLP, HTN, and T2DM were also identified based on current use of lipid-lowering, antihypertensive, or antidiabetic drugs. The following comorbidities were not included if they had not been collected routinely and in a standardized fashion: cancer, sexual dysfunction, neurocognitive impairment, or depression.

Multimorbidity (MM) was defined as presence ≥3 comorbidities in the same individual. Frailty was measured with both the frailty phenotype (FP) and a 37-item frailty index (FI) previously validated at MHMC and constructed from health variables collected at the same study visit [28]. Each variable included in the FI was coded with a value of 1 when a deficit was present and 0 when it was absent. Missing values were removed from both the numerator and the denominator of the FI [29]. In the logistic analyses, FI >0.4 was used to identify most frail individuals. The FP is based on a predefined set of 5 criteria exploring the presence/absence of signs or symptoms (involuntary weight loss, exhaustion, slow gait speed, poor handgrip strength, and sedentary behavior). The number of criteria (a 6-level ordinal variable ranging from 0 to 5) is categorized as a 3-level variable depicting robustness (meets none of the criteria), prefrailty (meets 1 or 2 criteria), and frailty (meets ≥3 criteria) [30].

Statistical Analyses

Results were expressed as mean and standard deviation or median and interquartile range (IQR) for continuous variables based on the normality of distribution, and as frequencies and percentages for categorical variables. The Student *t* test was applied to identify statistical difference for continuous variables with normal distribution, whereas the Mann-Whitney test was used for those without normal distribution. The χ^2 test was performed to assess the frequency of the categorical variables.

A backwards stepwise logistic regression analysis was conducted to identify independent predictors for THY detection by using as covariates age, gender, and statistically significant predictors identified in univariate analyses, including cumulative exposure to ART. To avoid collinearity between age and duration of HIV, the latter was calculated from univariate linear regression between age and duration of HIV infection, depicting the effect of HIV duration after correction for age (in Figure 1, called "residual of HIV duration").

A logistic regression analysis was conducted to identify independent predictors for MetS, MM, and FI by using as covariates age, gender, THY detection (using THY = 0 as reference), and statistically significant predictors identified in univariate analyses.

A *P* value cutoff <.05 was chosen for all statistical analyses, performed using R software, version 3.4.1.

RESULTS

A total of 665 HIV-infected patients (81% males) were included (median age, 53 years; median CD4, 730/μL).

Thymus Detection and Associated Factors

THY was detected in 180 (27.0%) of 665 subjects. In these individuals, the mean age was 49.1 ± 6.9 years, and the current CD4 count was 764.7 ± 298.1 c/μL. In patients in whom THY was not detected, the mean age was 45.6 ± 7.9 years, and the current CD4 count was 718.2 ± 342.4 c/μL. Among subjects with a detectable THY, 128 (71.1%) showed a size of grade 1–2, and 52 (28.9%) exhibited grade 3 or higher.

THY was detected in 45.0% of HIV patients aged <50 years (26.0% THY 1–2 and 19.0% THY ≥3), 21.4% of HIV patients aged 50–65 years (18.0% THY 1–2 and 3.4% THY ≥3), and 3.8% of HIV patients >65 years (all THY 1–2) (Supplementary Figure 2A). THY was found in 43.2%, 30.1%, and 22.1% of subjects with <10, 10–20, and >20 years of HIV duration, respectively (Supplementary Figure 2B).

Univariate analysis was built to describe demographic, anthropometric, and HIV variables and study outcomes according to THY detection and size. High statistically significant differences were found between THY detection and size and the following demographic and anthropometric measures: age, male sex, BMI, waist circumference, lipodystrophy, and cumulative exposure to PI and NRTI ($P < .001$) but not NNRTI and INSTI (Table 1).

Shorter HIV duration expressed in months was associated with a higher prevalence of THY detection in our cohort ($P < .001$), whereas other traditional HIV variables used in routine clinical assessment in PWH were not statistically significant.

Lower levels of immuno-metabolic measures such as total cholesterol, triglycerides, HOMA-IR, HbA1C, CKD-epi, CRP, and CAC were related to THY detection and size, all of which reached statistical significance.

With regard to comorbidities, DLP, HTN, and T2DM were significantly and inversely associated with THY detection and size ($P < .001$).

In a multivariate logistic model, negative predictors for THY detection were older age (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.89–0.94), male gender (OR, 0.43; 95% CI, 0.27–0.70), and higher BMI (OR, 0.90; 95% CI, 0.84–0.96), as depicted in Figure 1. Cumulative exposure to NRTI and PI were not independently associated with study outcome.

Thymus and Clinical Outcomes

THY detection and size were evaluated in relation to the following clinical outcomes: MetS, MM, and FI. An inverse association was found between THY and MetS ($P < .01$) (Figure 2A), MM ($P < .01$) (Figure 2B), and FI ($P < .01$) (Figure 2C) prevalence.

Univariate analysis demonstrated that age (OR, 1.06; 95% CI, 1.03–1.09), BMI (OR, 1.20; 95% CI, 1.14–1.28), THY 1–2 (OR, 0.23; 95% CI, 0.09–0.47), THY ≥3 (OR, 0.34; 95% CI, 0.10–0.87), and HIV duration (OR, 1.03; 95% CI, 1.01–1.06) were significantly related to MetS, whereas traditional HIV factors did not correlate with it. MM and FI were associated with higher BMI (MM OR, 1.09; 95% CI, 1.04–1.15; FI OR, 1.10; 95% CI, 1.05–1.15), older age (MM OR, 1.17; 95% CI, 1.14–1.21; FI OR, 1.06; 95% CI, 1.04–1.09), nadir CD4 100–350 c/μL (vs 100 c/μL; MM OR, 0.41; 95% CI, 0.26–0.63; FI OR, 0.61; 95% CI, 0.41–0.89), nadir CD4 350–500 c/μL (vs 100 c/μL; MM OR, 0.38; 95% CI, 0.21–0.70; FI OR, 0.42; 95% CI, 0.24–0.75), current CD4 count ≥500 c/μL (vs 350 c/μL; MM OR, 0.55; 95% CI, 0.27–1.06; FI OR, 0.47; 95% CI, 0.26–0.83), and longer HIV duration (MM OR, 1.10; 95% CI, 1.07–1.12; FI OR, 1.07; 95% CI, 1.05–1.10) (Supplementary Table 1).

To better explore these associations, multivariate logistic models were built. Independent predictors for MetS were older age (OR, 1.04; 95% CI, 1.01–1.07), longer HIV duration (OR, 1.04; 95% CI, 1.01–1.08), higher BMI (OR, 1.19; 95% CI, 1.12–1.27), and THY 1–2 (OR, 0.33; 95% CI, 0.13–0.70), as shown in Figure 3A. Independent predictors for MM were older age (OR, 1.16; 95% CI, 1.12–1.20), longer HIV duration (OR, 1.07; 95% CI, 1.04–1.11), and nadir CD4

Table 1. Demographic, Anthropometric, Relevant HIV and Immuno-Metabolic Markers, Comorbidities, and Study Outcomes According to THY Detection and Size

	Total	THY = 0	THY 1–2	THY ≥ 3	*P*
THY detection	665	485 (72.93)	128 (19.25)	52 (7.82)	
Demographics and anthropometry					
Age, mean (SD) [No.]	53.11 (7.98) [665]	54.59 (7.86) [485]	50.92 (6.36) [128]	44.69 (6.13) [52]	<.001
Male, No. (%)	539 (81.05)	412 (84.95)	92 (71.88)	35 (67.31)	<.001
BMI, mean (SD), kg/m^2 [No.]	24.15 (3.78) [615]	24.57 (3.97) [449]	23.22 (3.05) [120]	22.45 (2.51) [46]	<.001
Waist circumference, mean (SD), cm [No.]	89.67 (10.89) [628]	91.27 (10.94) [450]	86.65 (9.86) [122]	82.03 (7.78) [46]	<.001
Lipoatrophy, No. (%) [No.]	102 (29.91) [665]	74 (29.96) [485]	22 (32.84) [128]	6 (22.22) [52]	<.001
Lipohypertrophy, No. (%) [No.]	36 (10.56) [665]	32 (12.96) [485]	2 (2.99) [128]	2 (7.41) [52]	<.001
Mixed form, No. (%) [No.]	107 (31.38) [665]	92 (37.25) [485]	15 (22.39) [128]	0 (0) [52]	<.001
HIV-related variables					
HIV duration, median (IQR), mo [No.]	262 (183.25–323) [658]	267 (197–327.5) [479]	259 (180–319.5) [127]	171 (87.25–251.75) [52]	<.001
HIV risk: IVDU, No. (%) [No.]	174 (26.17) [665]	141 (29.07) [485]	28 (21.88) [128]	5 (9.62) [52]	.022
HIV risk: MSM, No. (%) [No.]	234 (35.19) [665]	167 (34.43) [485]	42 (32.81) [128]	25 (48.08) [52]	.022
HBV co-infection, No. (%) [No.]	13 (2.13) [611]	12 (2.67) [450]	1 (0.87) [115]	0 (0) [46]	.286
HCV co-infection, No. (%) [No.]	159 (26.46) [601]	116 (26.13) [444]	36 (31.03) [116]	7 (17.07) [41]	.209
Nadir CD4, median (IQR), c/μL [No.]	200.5 (94.25–300) [642]	200 (88–300) [473]	216.5 (99–301) [120]	240 (110–318) [49]	.356
Current CD4/CD8, mean (SD) [No.]	0.96 (0.62) [539]	0.96 (0.68) [399]	0.95 (0.48) [99]	0.97 (0.36) [41]	.399
Current CD4, mean (SD), c/μL [No.]	730.61 (330.52) [652]	718.2 (342.38) [476]	758.19 (287.33) [126]	779.26 (313.92) [50]	.102
Current CD38, mean (SD), c/μL [No.]	59.5 (86.22) [321]	59.83 (89.76) [235]	47.74 (61.99) [66]	94.5 (105.05) [20]	.120
Cumulative exposure to NRTI, median (IQR), mo [No.]	158.5 (87.75–210.25) [628]	167.5 (98–213) [458]	142 (79.25–201.25) [122]	100.5 (57.75–169.25) [48]	<.001
Cumulative exposure to NNRTI, median (IQR), mo [No.]	61 (25–115) [485]	61.5 (24.25–114.75) [358]	64 (26–132) [93]	50.5 (25.5–92.5) [34]	.551
Cumulative exposure to PI, median (IQR), mo [No.]	97.5 (48–154.75) [542]	105 (51.5–162.5) [407]	93 (46–137) [97]	55.5 (30–97.5) [38]	<.001
Cumulative exposure to INSTI, median (IQR), mo [No.]	39 (17–68.5) [251]	37 (16–69.25) [200]	48.5 (34–64.75) [38]	35 (17–68) [13]	.538
Immuno-metabolic variables					
Total cholesterol, mean (SD), mg/dL [No.]	184.78 (40.2) [630]	183.57 (40.25) [463]	188.96 (38.47) [120]	186.06 (43.96) [47]	.415
Tryglycerides, mean (SD), mg/dL [No.]	159.42 (113.15) [628]	169.98 (123.63) [461]	133.1 (71.42) [120]	123 (64.65) [47]	<.001
HOMA-IR, mean (SD) [No.]	2.96 (5.31) [498]	3.39 (6.09) [368]	1.87 (1.23) [92]	1.38 (0.69) [38]	<.001
HbA1C, mean (SD), mmol/mol [No.]	27.49 (16.2) [487]	28.62 (16.68) [356]	26.4 (13.91) [90]	20.14 (15.01) [41]	.005
CKD-Epi, mean (SD), mil/min [No.]	88.6 (18.17) [607]	86.42 (18.69) [445]	93.05 (15.29) [117]	98.61 (14.24) [45]	<.001
CRP, mean (SD), mg/L [No.]	0.3 (0.37) [617]	0.31 (0.38) [450]	0.29 (0.38) [120]	0.22 (0.19) [47]	.013
CAC, median (IQR) [No.]	2 (0–78.25) [640]	11 (0–112.75) [462]	0 (0–23.5) [127]	0 (0-0) [51]	<.001
Comorbidities					
DLP, No. (%) [No.]	574 (86.32) [665]	431 (88.87) [485]	106 (82.81) [128]	37 (71.15) [52]	.001
HTN, No. (%) [No.]	337 (50.68) [665]	276 (56.91) [485]	51 (39.84) [128]	10 (19.23) [52]	<.001
CVD, No. (%) [No.]	43 (6.47) [665]	39 (8.04) [485]	3 (2.34) [128]	1 (1.92) [52]	.025
T2DM, No. (%) [No.]	120 (18.05) [665]	110 (22.68) [485]	8 (6.25) [128]	2 (3.85) [52]	<.001
CKD, No. (%) [No.]	101 (15.19) [665]	83 (17.11) [485]	17 (13.28) [128]	1 (1.92) [52]	.012
COPD, No. (%) [No.]	42 (6.32) [665]	31 (6.39) [485]	10 (7.81) [128]	1 (1.92) [52]	.335
Osteoporosis, No. (%) [No.]	173 (26.02) [665]	131 (27.01) [485]	31 (24.22) [128]	11 (21.15) [52]	.576
Liver cirrhosis, No. (%) [No.]	85 (12.78) [665]	68 (14.02) [485]	14 (10.94) [128]	3 (5.77) [52]	.187

Abbreviations: BMI, body mass index; CAC, coronary artery calcium; CKD, chronic kidney disease; CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; DLP, dyslipidemia; HBV, hepatitis B virus; HCV, hepatitis C virus; HOMA-IR, homeostatic model assessment-insulin resistance; HTN, hypertension; INSTIs, integrase strand transfer inhibitors; IQR, interquartile range; IVDU, intravenous drug user; MetS, metabolic syndrome; MM, multimorbidity; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; T2DM, type 2 diabetes mellitus; THY, thymus.

100–350 vs <100 c/μL (OR, 0.39; 95% CI, 0.23–0.66) (Figure 3B). Independent predictors for FI were older age (OR, 1.05; 95% CI, 1.02–1.07), longer HIV duration (OR, 1.06; 95% CI, 1.03–1.09), nadir CD4 100–350 vs <100 c/μL (OR, 0.58; 95% CI, 0.38–0.90), higher BMI (OR, 1.10; 95% CI, 1.04–1.16), THY 1–2 (OR, 0.59; 95% CI, 0.35–0.97), and THY ≥3 (OR, 0.32; 95% CI, 0.11–0.82) (Figure 3C).

DISCUSSION

This is the first study to explore the relationship between detection and size of the thymus and metabolic syndrome, multimorbidity, and frailty in PWH. In fact, to the best of our knowledge, even general population studies have never explored THY as a predictor of immuno-metabolic and geriatric outcomes in large cohorts [31].

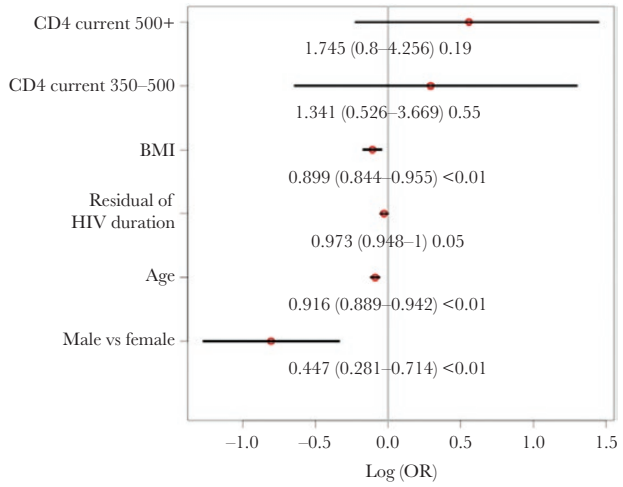

Figure 1. Predictors of thymus detection at multivariate logistic model. Abbreviations: BMI, body mass index; OR, odds ratio.

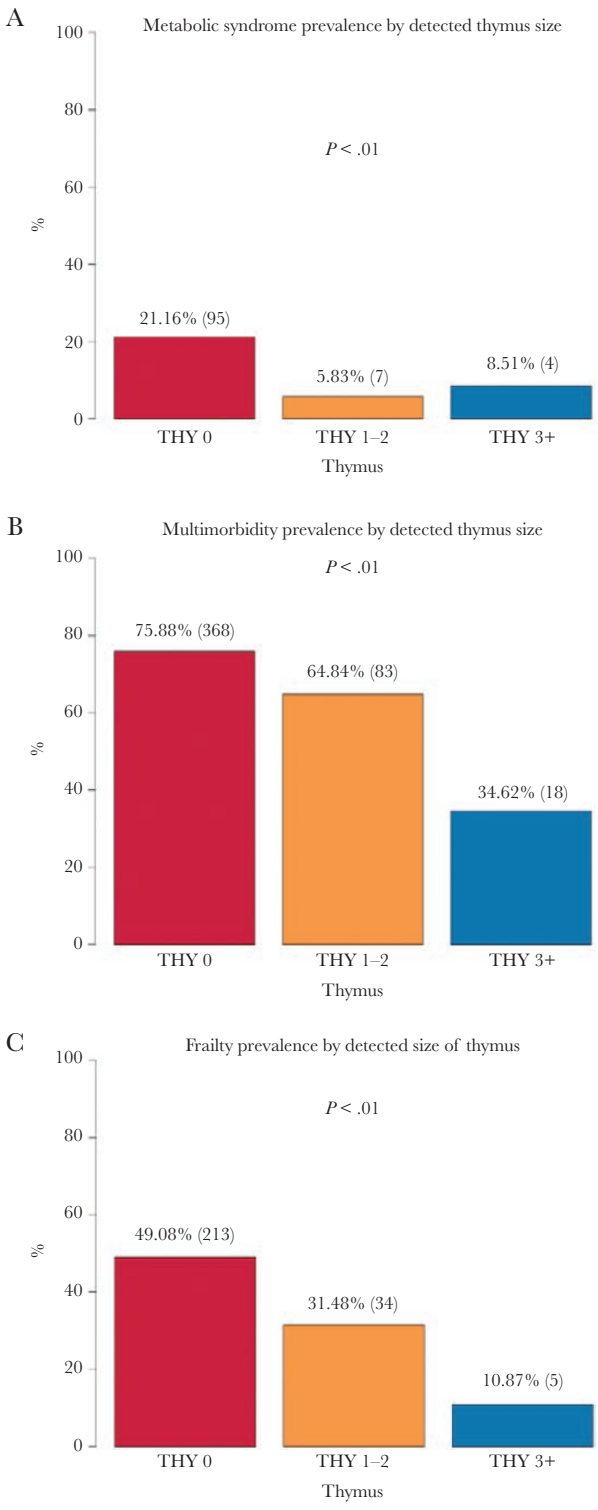

Figure 2. Association between thymus detection and size, and metabolic syndrome (A), multimorbidity (B), and frailty index (C) prevalence. Abbreviation: THY, thymus.

THY was detected in 27.0% of PWH in our cohort, showing a decreasing prevalence with age, along with a presence of 19.4% in PWH over 50 years of age (although in only in 3.8% of patients >65 years). The lack of a control group in our study prevents us from comparing these data with the general population. In a previous study comparing 99 HIV-positive patients with 32 HIV-negative controls with median age <40 years, THY tissue persisted in HIV-positive patients only [32], suggesting that this organ involution might be specific to PWH. Interestingly, the authors from this study suggested a possible survival bias to explain this phenomenon in HIV patients. The same bias cannot be ruled out in our cohort either. Moreover, it must be taken into account that a functional thymus has been described in healthy centenarians [33].

THY involution is a time-dependent variable that is definitively associated with age but, independently from that, is also associated with HIV duration. This finding from our cohort is consistent with previous studies [34]. We argue that this HIV duration effect may be related to the chronic immuno-activation process specific to PWH, regardless of exposure to effective ART [34, 35] and not captured by HIV variables routinely used to monitor HIV disease. It is therefore not surprising that CD4 count and viral load were not associated with THY.

THY was inversely associated with CRP and a constellation of metabolic disorders, reinforcing the conceptualization of immune-metabolic disorder. We believe that these findings fit the "metaflammation" construct [36]. Metaflammation has been described as an inflammatory cell action present in the liver, brain, pancreas, adipose tissue, lymph nodes, and presumably in THY, as the result of inflammatory cell interactions within the stromal components in these organs. These tissues and mediators cause systemic inflammatory responses and disrupt metabolic homeostasis. As a result, immuno-metabolic diseases often emerge as clusters and promote aging, disability, and premature death. We therefore suggest that "metaflammation" justifies the inverse statistical association between THY detection/size and DLP, HTN, CKD, CVD, and T2DM found in our study.

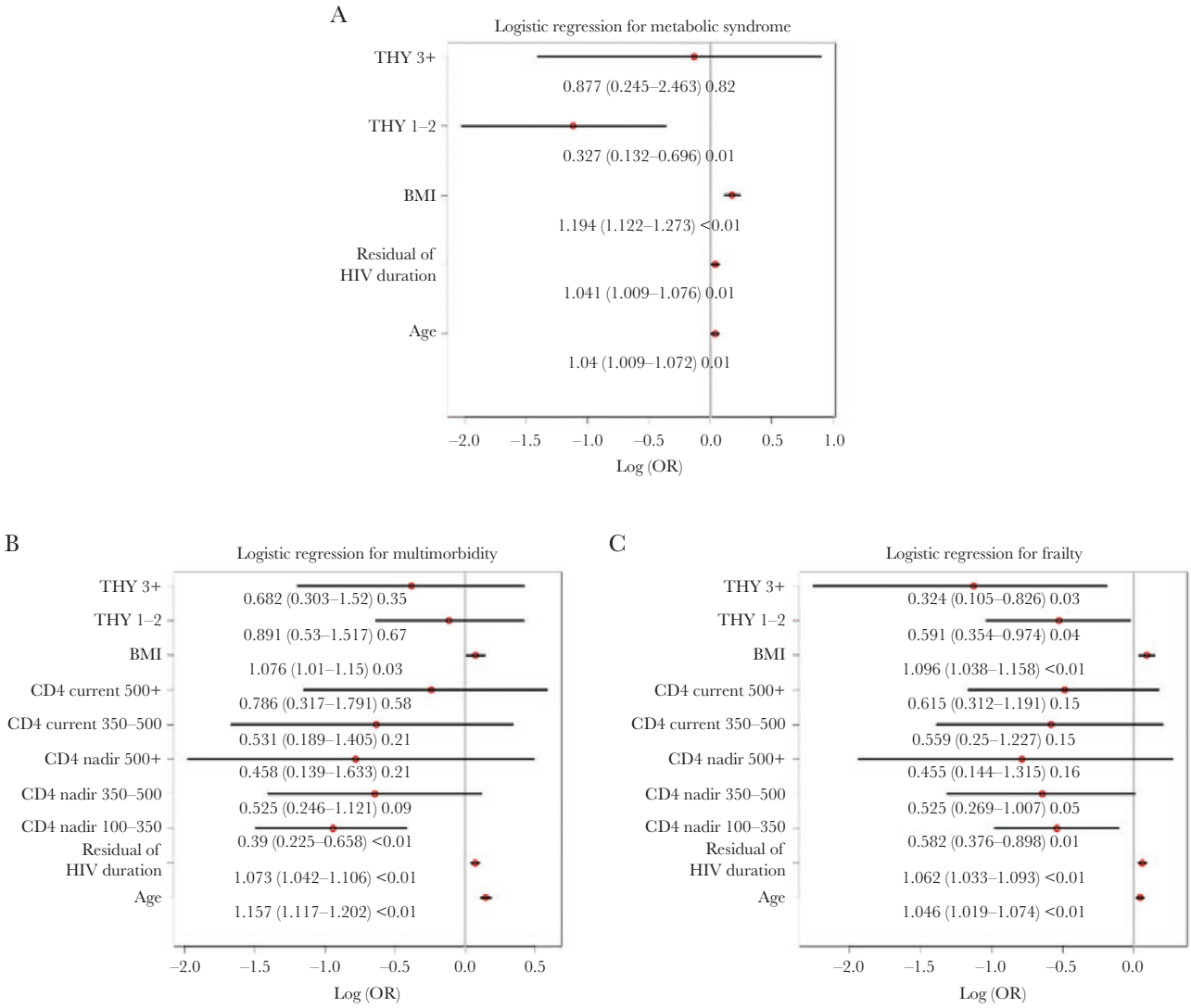

Figure 3. Multivariate analysis for the association between thymus detection and size, and metabolic syndrome (A), multimorbidity (B), and frailty index (C). Abbreviations: BMI, body mass index; OR, odds ratio; THY, thymus.

This study chose MetS, MM, and frailty as relevant geriatric outcomes. THY was an independent predictor for MetS after correction for BMI, age, and HIV duration. The lack of association between these outcomes and THY size (THY ≥ 3) may just reflect the small sample size of this group.

As the NICM-and-MM construct does not necessarily reflect the clinical complexity of aging, we sought to portray biological age with regards to frailty [17]. The association between THY and age is expected; on the contrary, the association with a measure of biological age, which depicts health outcomes better than chronological age, has never been described even in the general population. We have previously compared FP and FI in our cohort. Although these 2 tools display similar characteristics in our cohort, FI had a stronger association with age, comorbidities, geriatric syndromes, and disability [29]. Therefore, we were not surprised that FI, but not FP, was associated with THY.

The strong correlation between FI and smaller THY size, after correction for age, BMI, CD4 nadir, and HIV duration, confirms that this geriatric syndrome, possibly measured with an index, is connected with immune system dysfunction. Smaller THY size reflects reduced THY function [4]. We therefore believe that THY involution is a component of the complex clinical spectrum of aging in PWH. This is meant to be a hypothesis-generating study regarding a novel mechanism that regulates aging trajectories in PWH. Prospective studies comparing children who acquired HIV at birth with noninfected children to confirm this observation are needed. THY is an organ in which T cells differentiate and mature, giving origin to all peripheral T-cell populations, which have different functions and activities. Indeed, cells that derive from THY not only include those that regulate and dampen the immune response (ie, regulatory T cells),

but also those capable of triggering inflammatory pathways (such as Th17). Thus, it is unclear whether THY may actually have a protective role in the "inflammaging" process, or if the same pathogenic pathways leading to chronic inflammation, metabolic changes, and ultimately disability lead to faster THY involution. Future research should focus on the pathogenic mechanisms behind THY involution, on the ways to preserve its function, and on the frequency of different categories of peripheral T cells.

This study has a number of limitations. Some of these are intrinsic to the cross-sectional nature of the study, which cannot reveal any causative association between variables. Moreover, we cannot prove that smaller THY size is associated with reduced THY function. The absence of a control group does not allow us to show whether HIV variables associated both with THY and outcome measures represent a true specificity of these findings in PWH, compared with the general population.

The retrospective nature of our study did not allow us to measure THY function. The correlation of thymic mass with thymic function remains under investigation. Evidence exists for extrathymic thymopoieseis, non-thymic-dependent T-cell maturation mechanisms, IL-7-related effects, and others factors affecting T-cell function. It is unknown how these factors interact in treated PWH and whether there are age-related differences in these mechanisms.

On the other hand, as previously mentioned, this is one of the largest cohorts ever to describe THY detection and size in an HIV setting.

In conclusion, our study defines THY as an indicator of biological aging in PWH predicting metabolic syndrome and frailty. Future studies should focus on assessing the impact of THY detection in relation to function and to other relevant health variables such as hospitalization, disability, and quality of life.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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