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ORIGINAL RESEARCH

# Lymphoma Severity and Type Are Associated With Aortic FDG Uptake by $^{18}$F-FDG PET/CT Imaging

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## ABSTRACT

**BACKGROUND** There is evidence that metabolic disease burden in lymphoma influences patient outcome. However, the impact of disease severity on the cardiovascular system is unknown.

**OBJECTIVES** The aim of this study was to examine whether lymphoma is associated with arterial inflammation by investigating the relationship between disease metabolic burden and arterial fluorodeoxyglucose (FDG) uptake.

**METHODS** Sixty-two chemotherapy-naïve patients with active Hodgkin's or non-Hodgkin's lymphoma were matched (2:1) to individual control groups of lymphoma patients previously treated and free of active disease. All groups underwent $^{18}$F-FDG position emission tomography–computed tomography imaging. Disease severity was quantified by metabolic tumor volume (MTV) and total lesion glycolysis corresponding to standardized uptake values (SUVs) ≥41% or ≥2.5 of the maximum SUV within lymphoma regions, and aortic FDG uptake was quantified through the target-to-background ratio (TBR). Inflammatory and disease severity biomarkers were also measured.

**RESULTS** MTV and total lesion glycolysis measurements were significantly correlated with inflammatory and disease biomarkers. Aortic TBR was higher in patients with active non-Hodgkin's lymphoma compared with control subjects (median difference 0.51; 95% confidence interval [CI]: 0.28 to 0.78; $p < 0.001$). Similarly, patients with active Hodgkin's lymphoma had higher values of aortic TBR compared with control subjects (median difference 0.31; 95% CI: 0.15 to 0.49; $p < 0.001$). In addition, aortic TBR was modestly increased in patients with stage III to IV disease compared with those with stage I to II disease (median aortic TBR: 2.23 [interquartile range: 2.01 to 2.54] vs. 2.06 [interquartile range: 1.83 to 2.27; $p = 0.050$). In multivariable analysis, aortic FDG uptake and $MTV_{\geq 2.5}$ values were independently associated ($\beta = 0.425$; 95% CI: 0.189 to 0.662; $p = 0.001$; $R^2 = 0.208$), as were aortic FDG uptake and $MTV_{\geq 41\%}$ ($\beta = 0.407$; 95% CI: 0.167 to 0.649, $p = 0.001$; $R^2 = 0.191$).

**CONCLUSIONS** Aortic wall FDG uptake is related with disease severity indicative of a possible vascular effect of lymphoma. This work highlights a new potential role of molecular imaging in cardio-oncology for evaluating disease severity and its consequences on the vasculature. (J Am Coll Cardiol CardioOnc 2020;2:758–70) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Inflammation plays a pivotal role in the pathogenesis of both Hodgkin's and non-Hodgkin's lymphoma. Specifically, it is involved in complex interactions between stromal, lymphoid, and malignant cells in the tumor microenvironment, regulating several stages of tumor progression (1). In Hodgkin's lymphoma in particular, the reactive milieu can form up to 99% of the cellular background (2). Furthermore, a number of studies have demonstrated the prognostic significance of inflammatory biomarkers, such as the C-reactive protein, albumin, and neutrophil counts values in patients with lymphoma (3). In various clinical settings, the release of cytokines and chemokines by inflammatory cells in the circulation induces a systemic proinflammatory response eliciting prothrombotic and atherosclerotic effects, such as endothelial dysfunction, vascular inflammation, and atherosclerotic plaque destabilization (4).

A major characteristic of cancer pathophysiology is the increased metabolic need and use of glucose as the main substrate for energy production via glycolysis, resulting in increased glucose uptake from cancer cells across a broad range of malignancies. Furthermore, upregulation of glucose metabolism promotes an acidic cellular milieu due to lactic acid formation, inducing carcinogenesis. Beyond cancer cells, metabolically active cells within the tumor microenvironment, such as neutrophils and macrophages, also present elevated glucose uptake (3).

$^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography-computed tomography (PET/CT) is a versatile tool with an established role not only in oncology, but also in inflammatory diseases for the assessment of arterial inflammation in various settings such as rheumatoid arthritis, psoriasis, and HIV infection (5–7). $^{18}$F-FDG PET/CT imaging demonstrates good performance for the diagnosis and assessment of disease severity in different types of vasculitis (8,9). Subclinical atherosclerosis has also been evaluated on the basis of selective FDG uptake by metabolically active macrophages within atherosclerotic plaques (10,11). Importantly, arterial FDG uptake has been associated with risk of subsequent cardiovascular events (12).

The potential impact of systemic inflammatory activation on arterial inflammation in lymphoma remains unexplored. The aim of the present study was to test the hypothesis that lymphoma is associated with arterial inflammation by examining the relationship between disease metabolic burden and arterial FDG uptake in Hodgkin's and non-Hodgkin's lymphoma.

## METHODS

**STUDY POPULATION.** Between July 2015 and July 2018, 62 consecutive patients with a histologically confirmed new diagnosis of lymphoma were prospectively enrolled across 4 centers. Patients provided written informed consent to undergo 2 PET scans (one clinically indicated at 60 min and a second one at 120 min for assessment of aortic uptake). The study was approved by the Institutional Research Ethics Committee of the coordinating center and conducted according to institutional guidelines and the Declaration of Helsinki.

Clinical staging of lymphoma was based on Ann Arbor classification (Cotswolds modification) (13). Sociodemographic data, history of cerebrovascular and cardiovascular events, cardiovascular risk factors, and current medical therapy of patients, as well as routine laboratory tests, were collected for all patients. Family history of cardiovascular disease (CVD) included history of acute myocardial infarction and nonembolic stroke, and dyslipidemia was defined if the patient had already been categorized as dyslipidemic or was already on treatment for dyslipidemia. The Framingham 10-year CVD risk score (body mass index [BMI]-based formula) was used to assess each patient's CVD risk (14,15). Exclusion criteria were recent (<6 months) cardiovascular event, aortitis, active infection or systemic autoimmune disease, venous thromboembolic disease, renal failure, and treatment with anti-inflammatory agents. Patients with inadequate images for analysis owing to excessive spillover within the arterial wall from

**ABBREVIATIONS AND ACRONYMS**

**$^{18}$F-FDG** = $^{18}$F-fluorodeoxyglucose

**BMI** = body mass index

**CI** = confidence interval

**CT** = computed tomography

**CVD** = cardiovascular disease

**hsCRP** = high-sensitivity C-reactive protein

**LDH** = lactate dehydrogenase

**MTV** = metabolic tumor burden

**PET** = positron emission tomography

**SUV** = standardized uptake value

**SUVmax** = maximum standardized uptake value

**SUVmean** = mean standardized uptake value

**TBR** = target-to-background ratio

**TLG** = total lesion glycolysis

**WBC** = white blood cell count

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surrounding nodal or extranodal FDG uptake were also excluded. Each of the active lymphoma group were matched (2:1) for age, sex, and cardiovascular risk factors to 2 prospectively selected control groups. Control groups consisted of patients who had been diagnosed with lymphoma and had been disease-free for more than 1 year (mean 19.3 [range 12 to 48] months after last treatment), free of active malignancy or active systemic inflammatory disorder at the time of $^{18}$F-FDG PET/CT imaging, and scheduled to undergo an $^{18}$F-FDG PET CT scan for clinical purposes.

**$^{18}$F-FDG PET/CT IMAGING.** Patients with newly diagnosed lymphoma underwent $^{18}$F-FDG PET/CT imaging within 7 days prior to the initiation of chemotherapy, after fasting for at least 6 h prior to the study. None of the patients had blood glucose levels >180 mg dl$^{-1}$ before injection. FDG was injected intravenously (5 MBq/kg), and scanning was performed at 60- and 120-min post-injection for disease staging evaluation and aortic tracer uptake assessment, respectively. Patients were scanned from the base of the skull to the upper third of the thighs on a hybrid PET/CT scanner (Biograph 6, Siemens, Forchheim, Germany). For the second scan, acquisition was restricted to the thoracic and abdominal region. A low-dose CT scan in supine position was obtained, with patients' arms placed above their heads. No CT intravenous contrast was administered. CT images were acquired with 30 mA, 130 KV, axial slice thickness of 5 mm, and table feed rotation of 27 mm per tube rotation. PET scanning followed immediately over the same predefined body region, and the images were reconstructed using a standard iterative ordered subset expectation maximization algorithm. The image reconstruction matrix employed was 168 × 168. The reconstruction scheme of choice in this work consisted of 4 iterations and 8 subsets.

**IMAGE ANALYSIS.** Lymphoma sites were manually analyzed using a consensus-based assessment by 3 nuclear medicine physicians, 2 with >5 years' experience in PET/CT reporting (N.P. and A..G) and a third (C.D.A.) with >10 years' experience. Pathological uptake was distinguished from physiological or uptake unrelated to lymphoma according to the lesions' distribution and the CT features. Regions of interest were drawn around nodal or extranodal pathological lesions. Measurements of FDG uptake in the spleen, liver, and bone marrow were performed in cases of focal uptake. The spleen was also included in the analysis, in cases of diffusely increased uptake in the absence of bone marrow reactive changes. Conversely, the bone marrow was included in the analysis, only in patients with intense diffuse FDG uptake and a positive biopsy confirming bone marrow involvement.

Metabolic burden was quantified by metabolic tumor volume (MTV) and total lesion glycolysis (TLG) based on mean and maximum derived standardized uptake values (SUVs). SUV, MTV, and TLG values were calculated according to the following equations:

$$SUV = \frac{Patient\ Weight \bullet Activity\ on\ the\ Image}{Decay\ Factor \bullet Injected\ Activity}$$

$$MTV\ (cm^3) = \frac{Number\ of\ Voxels\ \text{Within}\ Disease\ Region \times Voxel\ Size^3}{1,000}$$

$$TLG = MTV \times SUV_{mean}$$

Volumes with SUV ≥41% or ≥2.5 of the maximum SUV were selected and the corresponding MTV and TLG values were calculated (16,17). The total MTV was summed over the total volumes of interest.

**AORTIC FDG UPTAKE ASSESSMENT.** $^{18}$F-FDG PET/CT images were assessed in consensus by 2 investigators with experience in cardiovascular PET/CT image analysis (reader 1 [P.K.] and reader 2 [I.K.]) without knowledge of patients' data. Aortic FDG uptake quantification has been previously described (18,19). In brief, regions of interest around the aortic wall were manually drawn along the entire aorta in consecutive axial slices at intervals of 5 mm. Metabolic activity within each arterial region of interest was measured by maximum SUV (SUVmax). In the next step, 6 consecutive circular regions of interest of 3 mm diameter were drawn within the superior vena cava and an average venous SUVmean value was calculated. The arterial target-to-background ratio (TBR) was then derived by dividing the mean aortic SUVmax to the average value of venous SUVmean. Finally, aortic TBR was calculated as the sum of TBRs of the ascending and descending aorta, aortic arch, and suprarenal and infrarenal abdominal aorta divided by 5. For corroboration of our results, we proceeded with the same analyses using aortic TBR that was derived by dividing the mean aortic SUVmax to the average value of liver SUVmean (20,21).

**AORTIC CALCIFICATION ASSESSMENT.** CT images were assessed by an experienced investigator (E.S.). A semi-quantitative method was used to examine the scans for the presence of calcified plaque in the walls of the same arterial segments studied with $^{18}$F-FDG PET. The amount of calcification was ranked according to a scale modified from previous investigations

**TABLE 1 Characteristics of the Study Population**

| | Newly Diagnosed Non-Hodgkin's Lymphoma (n = 28) | Non-Hodgkin's Lymphoma Without Active Disease Control Group 1 (n = 14) | p Value | Newly Diagnosed Hodgkin's Lymphoma (n = 34) | Hodgkin's Lymphoma Without Active Disease Control Group 2 (n = 17) | p Value |
|---|---|---|---|---|---|---|
| Age, yrs | 63.3 ± 14.0 | 63.3 ± 10.1 | 0.993 | 54.1 ± 20.1 | 54.1 ± 16.5 | 0.996 |
| Male | 20 (71.4) | 10 (71.4) | 1.000 | 22 (64.7) | 11 (64.7) | 1.000 |
| Weight, kg | 78.1 ± 14.3 | 88.4 ± 16.0 | 0.041 | 78.9 ± 19.5 | 86.5 ± 13.6 | 0.157 |
| Height, cm | 169.6 ± 10.6 | 172.9 ± 8.3 | 0.324 | 169.0 ± 8.9 | 171.0 ± 7.8 | 0.261 |
| BMI, kg/m$^2$ | 27.2 ± 5.0 | 29.8 ± 6.5 | 0.156 | 27.54 ± 6.3 | 29.5 ± 5.7 | 0.295 |
| Risk factor | | | | | | |
| Diabetes | 3 (10.7) | 3 (21.4) | 0.383 | 3 (8.8) | 2 (11.8) | 1.000 |
| Hypertension | 13 (46.4) | 7 (50) | 0.824 | 7 (20.6) | 1 (5.9) | 0.242 |
| Dyslipidemia* | 11 (39.3) | 6 (42.9) | 0.824 | 4 (11.8) | 1 (5.9) | 0.654 |
| Smokers | 8 (28.6) | 5 (35.7) | 0.723 | 14 (41.2) | 6 (35.3) | 0.685 |
| Framingham risk score, %† | 27.7 ± 20.2 | 28.6 ± 16.5 | 0.889 | 23.4 ± 21.6 | 20.0 ± 17.6 | 0.574 |
| Medication | | | | | | |
| Aspirin | 5 (17.9) | 1 (7.1) | 0.645 | 4 (11.8) | 1 (5.9) | 0.654 |
| ADP receptor inhibitor | 2 (7.1) | 0 | 0.545 | 1 (2.9) | 0 | 1.000 |
| ACE inhibitors | 2 (7.1) | 1 (7.1) | 1.000 | 1 (2.9) | 0 | 1.000 |
| ARB | 9 (32.1) | 0 | 0.016 | 3 (8.8) | 0 | 0.542 |
| Beta-blocker | 5 (17.9) | 2 (14.3) | 1.000 | 7 (20.6) | 1 (5.9) | 0.242 |
| CCB | 5 (17.9) | 0 | 0.151 | 3 (8.8) | 0 | 0.542 |
| Statin | 10 (35.7) | 1 (7.1) | 0.067 | 4 (11.8) | 1 (5.9) | 0.654 |
| Ann Arbor stage | | | | | | |
| I/II | 12 (42.9) | – | – | 17 (50.0) | – | – |
| III/IV | 16 (57.1) | – | – | 17 (50.0) | – | – |
| Blood tests | | | | | | |
| WBC count, per μl‡ | 7,400 (5,890–13,270) | 5,729 (4,554–6,702) | 0.001 | 8,760 (6,005–11,085) | 6,603 (4,753–7,835) | <0.001 |
| N/L | 3.23 (1.86–4.06) | – | – | 3.22 (2.48–5.64) | – | – |
| hsCRP, mg/l§ | 5.4 (2.2–40.0) | 1.9 (1.3–2.5) | 0.023 | 13.6 (4.5–53.6) | 1.9 (1.3–3) | <0.001 |
| LDH, IU/l | 293 (211–435) | – | – | 225 (185–359) | – | – |
| Albumin, g/l | 38.5 (34.0–42.0) | – | – | 39.5 (33.5–42.0) | – | – |
| PET/CT findings | | | | | | |
| Aortic calcifications | 3.0 (0.0–8.0) | 5.0 (2.0–8.3) | 0.163 | 2.0 (0.0–8.3) | 2.0 (0.0–8.0) | 0.967 |
| $TLG_{\geq 41\%}$, cm$^3$ | 281 (89–463) | – | – | 196 (80–416) | – | – |
| $TLG_{\geq 2.5}$, cm$^3$ | 389 (199–1,398) | – | – | 430 (93–802) | – | – |
| $MTV_{\geq 41\%}$, cm$^3$ | 25.9 (7.9–69.0) | – | – | 29.7 (9.8–56.0) | – | – |
| $MTV_{\geq 2.5}$, cm$^3$ | 64 (28–143) | – | – | 79 (18–129) | – | – |
| Aortic TBR | 2.29 (1.96–2.60) | 1.78 (1.45–2.05) | <0.001 | 2.07 (1.83–2.29) | 1.76 (1.61–1.92) | <0.001 |

Values are mean ± SD, n (%), or median (interquartile range). For the control group populations, only relevant inflammatory biomarkers are demonstrated (WBC count, hsCRP, aortic TBR) because disease burden biomarkers (LDH, albumin, $MTV_{\geq 2.5}$, $MTV_{\geq 41\%}$, $TLG_{\geq 2.5}$, $TLG_{\geq 41\%}$) are not applicable. *Dyslipidemia was diagnosed if the patient was already diagnosed with dyslipidemia or was already on treatment for dyslipidemia. †Ten-year cardiovascular risk was calculated via Framingham risk score using patients' BMI. ‡10 of 14 patients from the non-Hodgkin's control group had WBC measured and 10 of 17 patients from the non-Hodgkin's control group had WBC measured. §Fourteen of 17 patients from the non-Hodgkin's group had hsCRP measured.

ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate; ARB = angiotensin II receptor blocker; BMI = body-mass index; CCB = calcium-channel blocker; CT = computed tomography; CVD = cardiovascular disease; hsCRP = High-sensitivity C-reactive protein; LDH = lactate dehydrogenase; MTV = metabolic tumor volume; N/L = neutrophil-to-lymphocyte ratio; PET = positron emission tomography; TBR = target-to-background ratio; TLG = total lesion glycolysis; WBC = white blood cell.

(22,23): a score of 0 was assigned when calcified plaque was absent; 1 was assigned when a small calcified plaque covering <10% of the vessel circumference was found; 2 was assigned when the calcified plaque involved 10% to 25% of the vessel circumference; 3 was assigned when 25% to 50% of the circumference was involved; and 4 was assigned when more than 50% of the vessel circumference was involved. The calcified plaque scores were summed for ascending aorta, aortic arch, descending aorta, and suprarenal and infrarenal abdominal aorta (total score range 0 to 20).

**EVALUATION OF SYSTEMIC INFLAMMATION.** Before $^{18}$F-FDG PET/CT imaging, blood was obtained and serum was separated by centrifugation at 4,000 rpm for 10 min at 4°C and stored at −81°C. Serum biomarkers of systemic inflammation such as high-sensitivity C-reactive protein (hsCRP), white blood cell (WBC) count, ratio of neutrophils to lymphocytes,

and surrogate markers of lymphoma's severity, such as serum lactate dehydrogenase (LDH) and albumin, were also measured at each participating center.

**STATISTICAL ANALYSIS.** Sample size calculation was performed a priori (Supplemental Appendix). Quantitative data are presented as mean ± SD or median (interquartile range), while qualitative variables are presented as frequencies with percentages. Variables were tested for normality using the Kolmogorov-Smirnov test.

Student's *t*-test and chi-square or Fisher's exact test were employed for between-groups comparisons for continuous and categorical variables, respectively. Differences between groups in non-normal variables were assessed by the Mann-Whitney *U* test. To assess the relationship between disease severity indices and markers of systemic and vascular inflammatory process, Pearson's correlation ($r_p$) coefficient was used. Correlations between the sum of the aortic calcification score and aortic inflammation or disease burden were evaluated by the Spearman's correlation coefficient ($r_s$).

Measures of aortic inflammation (aortic TBR) and imaging disease burden ($TLG_{\geq 41\%}$, $TLG_{\geq 2.5}$, $MTV_{\geq 41\%}$, or $MTV_{\geq 2.5}$), and associations with demographic variables and clinical characteristics were determined in univariable analyses. Multivariable linear regression analyses with aortic TBR or $MTV_{\geq 2.5}$ as dependent variables, adjusted for potential confounders, were then performed. Covariates for the multivariable modeling were chosen based on their clinical relevance or known association with aortic TBR or $MTV_{\geq 2.5}$ and cardiovascular risk. Age, sex, and BMI were used as covariates for the models evaluating the association between aortic TBR (dependent variable) and $MTV_{\geq 2.5}$ (dependent variable) with circulating biomarkers. Furthermore, for the models evaluating aortic TBR and associations with $TLG_{\geq 41\%}$, $TLG_{\geq 2.5}$, $MTV_{\geq 41\%}$, or $MTV_{\geq 2.5}$, the following covariates were considered: 10-year Framingham risk score, aortic calcification, dyslipidemia, and family history of CVD. Similarly, for the comparison between patients (non-Hodgkin's lymphoma or Hodgkin's lymphoma and control subjects) regarding aortic TBR levels, the following covariates were considered: age, sex, BMI, 10-year Framingham risk score, family history of CVD, and aortic calcification. For the regression models, parameters that exhibited a non-normal distribution were log-transformed (logAortic TBR or $logMTV_{\geq 2.5}$). Standardized β coefficients with 95% confidence intervals (CIs) are presented. $R^2$ is reported to assess amount of variability accounted for by the covariates in the model.

In order to further describe our results, we categorized patients according to increased levels of $^{18}$F-FDG uptake: 1) aortic TBR equal to or more than 2.68 (n = 8 of 62), a proposed cutoff for increased inflammation of the aorta as used in previous studies (24,25); and 2) metabolic burden ($MTV_{\geq 2.5}$ equal to or more than 268 [n = 6 of 62]), which has been shown to be a marker of severity of disease and predictor of worse outcome in lymphoma patients (26). To explore factors associated with increased aortic FDG uptake ≥2.68, a univariable logistic regression analysis with the covariates including an increased metabolic burden ($MTV_{\geq 2.5}$ equal to or more than 268) and lymphoma type were evaluated. Results are presented as odds ratio (OR) with 95% CI.

Intraclass correlation coefficients with 95% CIs were calculated to test the intraobserver variability (2-way random-effects model with absolute agreement) and also to assess interobserver agreement (2-way mixed-effects model with absolute agreement) (27) for TBR assessment. For reader 1, the 95% CI was between 0.991 and 0.999 ($p < 0.001$). For reader 2, the 95% CI was between 0.981 and 0.997 ($p < 0.001$). The interrater agreement between reader 1 and reader 2 was strong, with a 95% CI from 0.913 to 0.989 ($p = 0.001$). Bland-Altman plots to assess interreader variability are also provided (Supplemental Figure 1).

A 2-tailed p value <0.05 was considered significant. All statistical analyses were performed with the SPSS version 20.0 (IBM, Armonk, New York).

## RESULTS

**STUDY POPULATION.** In total, 62 consecutive patients (42 men, mean age 58.2 years) with newly diagnosed Hodgkin's (n = 34) or non-Hodgkin's lymphoma (n = 28) and 2 control groups of 17 and 14 patients, respectively, previously treated for Hodgkin's and non-Hodgkin's lymphoma without active disease, were enrolled in the study. In **Table 1**, the demographic, clinical, laboratory, and PET characteristics of all patients are summarized.

**ASSOCIATION BETWEEN CANCER DISEASE BURDEN AND SERUM BIOMARKERS.** In univariable analysis, PET-derived indices of disease severity were associated with serum markers of disease severity (**Table 2**). In particular, an inverse association was found between MTV values ($logMTV_{\geq 2.5}$) and plasma albumin levels. In addition, patients with increased MTV values had elevated serum LDH levels and serum inflammatory markers. In particular, MTV values correlated with hsCRP levels, and individuals with higher MTV values had increased neutrophil-to-

lymphocyte ratio levels. All associations remained significant after adjustment for age, sex, and BMI (Table 2). No significant association was observed between $MTV_{\geq 2.5}$ values and WBC count. Similar findings were observed for disease severity as assessed by $TLG_{\geq 2.5}$ and $TLG_{\geq 41\%}$ and serum biomarkers (Supplemental Table 1)

**ASSOCIATION BETWEEN AORTIC FDG UPTAKE AND SERUM BIOMARKERS.** In univariable models, aortic TBR was associated with hsCRP, neutrophil-to-lymphocyte ratio, LDH, and albumin levels, while no significant correlation was observed with WBC count values. After adjustment for age, sex, and BMI, the observed associations remained significant (Supplemental Table 2).

**COMPARISON OF AORTIC TBR BETWEEN HODGKIN'S OR NON-HODGKIN'S PATIENTS AND CONTROL GROUPS.** Aortic TBR was higher in patients with newly diagnosed non-Hodgkin's lymphoma compared with the control group without active disease (median difference 0.51; 95% CI: 0.28 to 0.78); $p < 0.001$). Similarly, patients with Hodgkin's lymphoma had higher values of aortic TBR compared with the control group (median difference 0.31; 95% CI: 0.15 to 0.49); $p < 0.001$) (Table 1). In models adjusted for age, sex, BMI, aortic calcifications, Framingham risk score and family history of CVD, results were similar, with higher values of aortic TBR in groups with active lymphoma (Supplemental Table 3). However, the aortic liver TBR was not significantly different between groups, and there was no significant correlation with hsCRP, suggesting that the liver might also be affected by this underlying inflammatory process (Supplemental Tables 4 to 6).

**COMPARISON OF PET DERIVED INDICES BETWEEN INDIVIDUALS WITH STAGE I TO II VERSUS STAGE III TO IV LYMPHOMA.** Patients with stage III to IV lymphoma had increased $MTV_{\geq 41\%}$ and $MTV_{\geq 2.5}$ values compared with individuals with stage I to II disease. In addition, aortic TBR in patients with stage III to IV disease was modestly elevated, with borderline statistical significance ($p = 0.050$), compared with individuals with stage I to II disease (Table 3). The results were similar for TLG-related parameters (Supplemental Table 7).

**ASSOCIATION BETWEEN AORTIC FDG UPTAKE, DISEASE BURDEN, AND AORTIC CALCIFICATION.** With respect to aortic calcification, 19 of 34 (56%) patients with Hodgkin's lymphoma and 17 of 28 (61%) patients with non-Hodgkin's lymphoma demonstrated aortic calcification of grade 1 to 3 in one of the segments. There was no significant difference in aortic calcification between patients with active Hodgkin's lymphoma and the control group (Table 1). Similarly, patients with active non-Hodgkin's lymphoma did not demonstrate significant differences in aortic calcification compared with control subjects (Table 1). Furthermore, no correlation was observed between aortic TBR and the sum of the aortic calcification score in lymphoma patients ($r_s = 0.020$; 95% CI: -0.231 to 0.269; $p = 0.877$). There was also no association between aortic calcification and disease burden (correlation with $MTV_{\geq 2.5}$, $r_s = 0.229$; 95% CI: -0.025 to 0.454; $p = 0.076$).

**ASSOCIATION OF LYMPHOMA DISEASE SEVERITY AND AORTIC FDG UPTAKE.** In univariable analysis, there was a moderate correlation between both $MTV_{\geq 41\%}$ or $MTV_{\geq 2.5}$ and aortic TBR ($p < 0.001$ and $p = 0.004$, respectively) (Figure 1). There was no association between aortic TBR and 10-year Framingham cardiovascular risk score ($r_p = -0.008$; 95% CI: -0.257 to 0.243; $p = 0.952$).

In multivariable analysis, aortic TBR remained significantly associated with $MTV_{\geq 41\%}$ or $MTV_{\geq 2.5}$ after adjustment for the Framingham cardiovascular risk score, aortic calcification, dyslipidemia, and family history of CVD. In particular, after adjusting for all the previous covariates, aortic TBR remained positively associated with $MTV_{\geq 41\%}$ ($\beta = 0.407$; 95% CI: 0.167 to 0.649; $p = 0.001$; $R^2 = 0.191$) and $MTV_{\geq 2.5}$

**TABLE 2 Associations of Disease Severity ($logMTV_{\geq 2.5}$) With Biomarkers in Patients With Active Hodgkin's or Non-Hodgkin's Lymphoma**

| | Unadjusted Correlations | | | Multivariable Associations | | |
|---|---|---|---|---|---|---|
| | $r_p$ | 95% CI | p Value | β | 95% CI | p Value |
| Albumin | -0.385 | -0.597 to -0.122 | 0.005 | -0.362 | -0.662 to -0.086 | 0.012 |
| LDH | 0.561 | 0.350 to 0.718 | <0.001 | 0.527 | 0.289 to 0.763 | <0.001 |
| hsCRP | 0.378 | 0.139 to 0.575 | 0.003 | 0.371 | 0.123–0.647 | 0.005 |
| N/L | 0.420 | 0.154 to 0.629 | 0.003 | 0.434 | 0.154–0.717 | 0.003 |
| WBC | 0.141 | -0.124 to 0.389 | 0.295 | – | – | – |

The dependent variable was $logMTV_{\geq 2.5}$. Unadjusted correlations using Pearson's correlation coefficients demonstrates correlation of disease severity as assessed by $^{18}$F-FDG PET/CT by means of $MTV_{\geq 2.5}$ and biomarkers. Multivariable analysis using linear multiple regression analysis demonstrates the correlation between $MTV_{\geq 2.5}$ and biomarkers after adjustment for age, sex, and BMI.

$^{18}$F-FDG = F-18 fluorodeoxyglucose; other abbreviation as in Table 1.

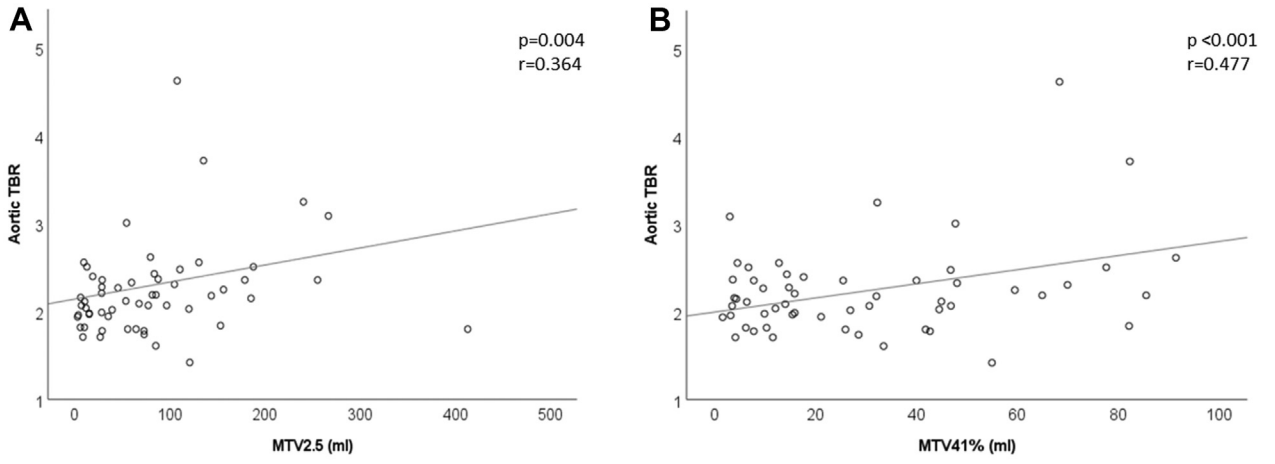
**TABLE 3 Metabolic Burden and Aortic FDG Uptake According to Lymphoma Stage**

| PET-Derived Measurements | Ann Arbor Stages I/II | Ann Arbor Stages III/IV | Median Difference (95% CI) | p Value |
|---|---|---|---|---|
| $MTV_{\geq 41\%}$, $cm^3$ | 15.1 (6.7–44.1) | 33.5 (12.7–82.3) | 17.9 (32.2 to 0.3) | 0.041 |
| $MTV_{\geq 2.5}$, $cm^3$ | 28.6 (10.5–55.6) | 105.0 (77.5–240.5) | 73.8 (109.8 to 51.3) | <0.001 |
| Aortic TBR | 2.06 (1.83–2.27) | 2.23 (2.01–2.54) | 0.20 (0.39 to 0.00) | 0.050 |

Values are median (interquartile range), unless otherwise indicated. Analysis performed in 60 patients (2 patients excluded due to rapid progression of disease).

CI = confidence interval; other abbreviations as in Table 1.

**FIGURE 1** Scatterplots of the Aortic TBR and $MTV_{\geq 41\%}$ and $MTV_{\geq 2.5}$ of the Maximum Standardized Uptake Value




Significant association between **(A)** metabolic tumor volume (MTV) >41% and **(B)** MTV≥2.5 and aortic target-to-background ratio (TBR).

(β = 0.425; 95% CI: 0.189 to 0.662; p = 0.001; $R^2$ = 0.208) (Table 4). Illustrative cases of these findings are shown in Figures 2 to 4. The results were similar for TLG-related parameters (Supplemental Table 8).

### PREDICTORS OF INCREASED AORTIC FDG UPTAKE.

Aortic TBR was ≥2.68 in 8 of 62 patients and the $MTV_{\geq 2.5}$ ≥268 in 6 of 62 patients. We then explored for potential associations between lymphoma type and metabolic burden and aortic inflammation.

Increased metabolic burden was associated with an increased likelihood of increased aortic FDG uptake (Table 5). Non-Hodgkin's lymphoma tended towards, but was not significantly associated with increased aortic FDG uptake compared with Hodgkin's lymphoma.

## DISCUSSION

In the present study, we demonstrate that aortic FDG uptake quantified by PET is higher in patients with newly diagnosed lymphoma compared with control groups comprising lymphoma patients without active disease. Moreover, aortic FDG uptake is associated with disease burden as assessed by MTV and TLG (Central Illustration).

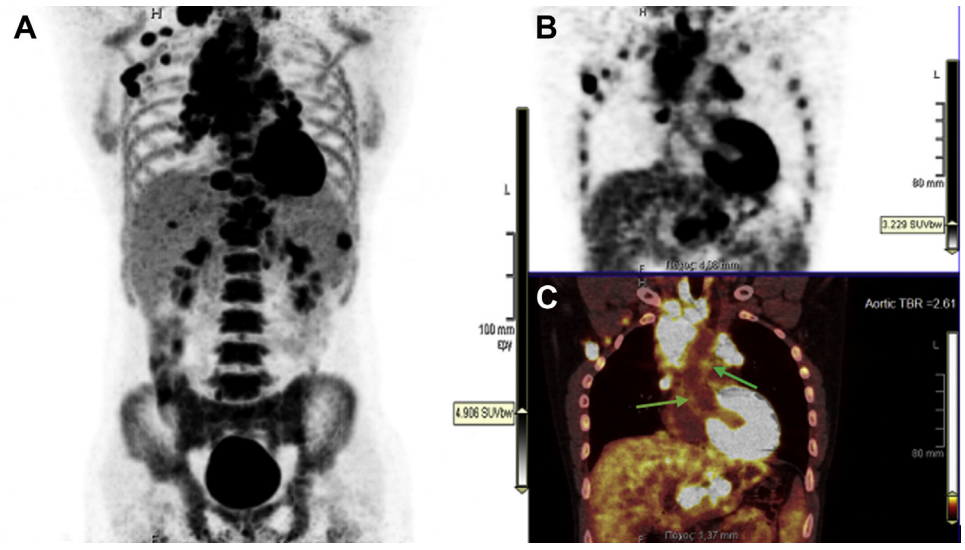
**TABLE 4** Results of Univariable Analysis and Multivariable Analysis Demonstrating the Association of Aortic TBR With $MTV_{\geq 41\%}$ and $MTV_{\geq 2.5}$

| | Univariable Analysis (LogAortic TBR) | | Multivariable Analysis (LogAortic TBR) | |
|---|---|---|---|---|
| | β (95% CI) | p Value | β (95% CI) | p Value |
| $MTV_{\geq 41\%}$* | | | | |
| Dyslipidemia (yes/no) | 0.242 (-0.008 to 0.493) | 0.058 | 0.283 (0.023 to 0.540) | 0.033 |
| Framingham 10-yr CVD risk score | 0.022 (-0.237 to 0.280) | 0.868 | 0.062 (-0.215 to 0.338) | 0.655 |
| Family history of CVD | 0.162 (-0.092 to 0.417) | 0.207 | 0.120 (-0.122 to 0.360) | 0.325 |
| Aortic calcification | -0.088 (-0.345 to 0.169) | 0.496 | -0.300 (-0.580 to -0.021) | 0.036 |
| $LogMTV_{\geq 41\%}$ | 0.347 (0.103 to 0.593) | 0.006 | 0.407 (0.167 to 0.649) | 0.001 |
| $MTV_{\geq 2.5}$† | | | | |
| Dyslipidemia (yes/no) | 0.242 (-0.008 to 0.493) | 0.058 | 0.251 (-0.006 to 0.507) | 0.055 |
| Framingham 10-yr CVD risk score | 0.022 (-0.237 to 0.280) | 0.868 | 0.012 (-0.260 to 0.284) | 0.928 |
| Family history of CAD | 0.162 (-0.092 to 0.417) | 0.207 | 0.142 (-0.097 to 0.381) | 0.239 |
| Aortic calcification | -0.088 (-0.345 to 0.169) | 0.496 | -0.251 (-0.522 to 0.020) | 0.069 |
| $LogMTV_{\geq 2.5}$ | 0.393 (0.154 to 0.634) | 0.002 | 0.425 (0.189 to 0.662) | 0.001 |

*Framingham 10-year general CVD risk score prediction using BMI, aortic calcification, dyslipidemia, family history of CVD, and $MTV_{\geq 41\%}$ were included as independent factors. $R^2$ of model = 0.191. †Framingham 10-year general CVD risk score prediction using BMI, aortic calcification, dyslipidemia, family history of CVD, and $MTV_{\geq 2.5}$ were included as independent factors. $R^2$ of model = 0.208.

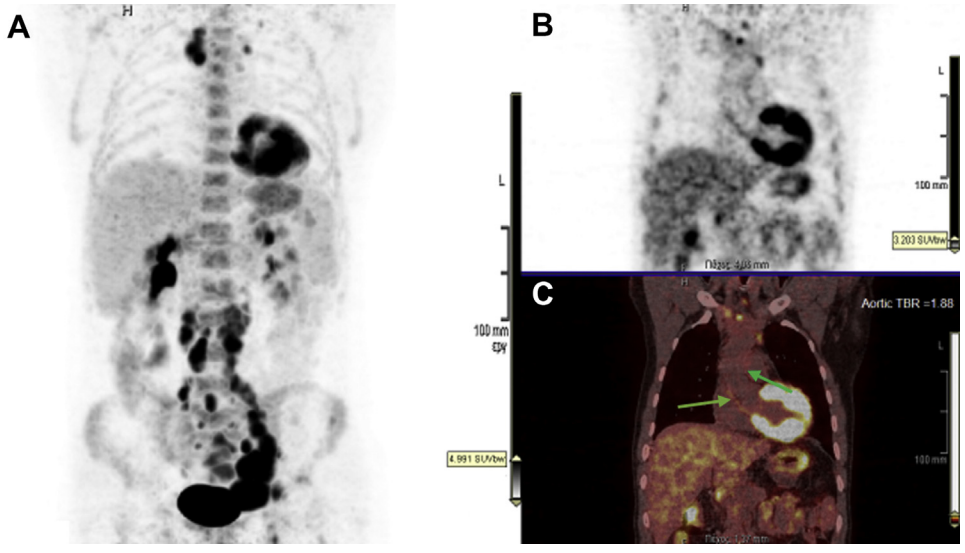
CAD = coronary artery disease; SUV = standardized uptake value; other abbreviations as in Tables 1 and 3.

**FIGURE 2** **A 33-Year-Old Patient With Hodgkin's Lymphoma Without Cardiovascular Risk Factors and With Aortic TBR of 2.61**



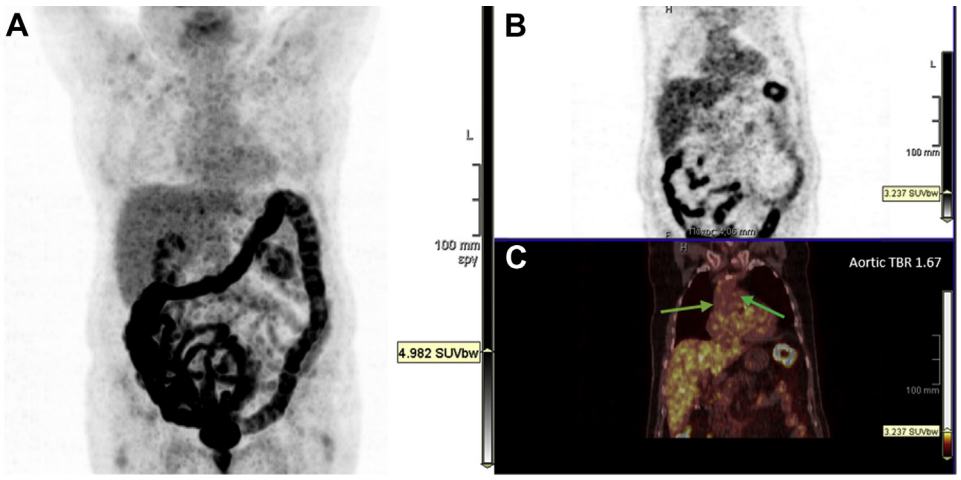

**(A)** Maximum intensity projection, **(B)** coronal positron emission tomography, and **(C)** fused positron emission tomography-computed tomography of a 33-year-old patient with Hodgkin's lymphoma without cardiovascular risk factors but significant disease burden and increased aortic fluorodeoxyglucose uptake. **Arrows** indicate the aortic wall area with $^{18}$F-FDG uptake. SUV = standardized uptake value; TBR = target-to-background ratio.

**FIGURE 3** **A 41-Year-Old Patient With Hodgkin's Lymphoma Without Cardiovascular Risk Factors and With Aortic TBR of 1.88**




**(A)** Maximum intensity projection, **(B)** coronal positron emission tomography, and **(C)** fused positron emission tomography-computed tomography of a 41-year-old patient with Hodgkin's lymphoma without cardiovascular risk factors and lower disease burden and aortic fluorodeoxyglucose uptake than the patient illustrated in Figure 2. **Arrows** indicate the aortic wall area with $^{18}$F-FDG uptake. Abbreviations as in Figure 2.

**FIGURE 4 A 72-Year-Old Patient From Control Group Without Cardiovascular Risk Factors and With Aortic TBR of 1.67**




**(A)** Maximum intensity projection, **(B)** coronal positron emission tomography, and **(C)** fused positron emission tomography–computed tomography of a 72-year-old patient from control group without cardiovascular risk factors and lower aortic fluorodeoxyglucose uptake than the patients illustrated in Figures 2 and 3. **Arrows** indicate the aortic wall area with $^{18}$F-FDG uptake. Abbreviations as in Figure 2.

**SYSTEMIC AND VASCULAR INFLAMMATION IN LYMPHOMA: PREVIOUS KNOWLEDGE AND NOVEL FINDINGS.** We found significant associations between disease metabolic burden and inflammatory indices. Although the pathophysiology of the relationship between glucose metabolism within the malignant cell and inflammatory activation has not been thoroughly investigated, our findings are in line with prior work on lymphoma (28-30) demonstrating a direct relationship between nodal or extranodal FDG uptake with hsCRP, LDH, and albumin. A recent study in pediatric patients with lymphoma reported no significant association between PET-derived metabolic indices and erythrocyte sedimentation rate, serum albumin, and WBC count (31). In contrast, a number of studies on solid tumors support a strong relationship between tumor metabolic activity and inflammatory biomarkers such as hsCRP, WBC count, and neutrophil-to-lymphocyte ratio (32-34).

**TABLE 5 Univariable Associations Between Aortic TBR ≥2.68 and Lymphoma Type and MTV**

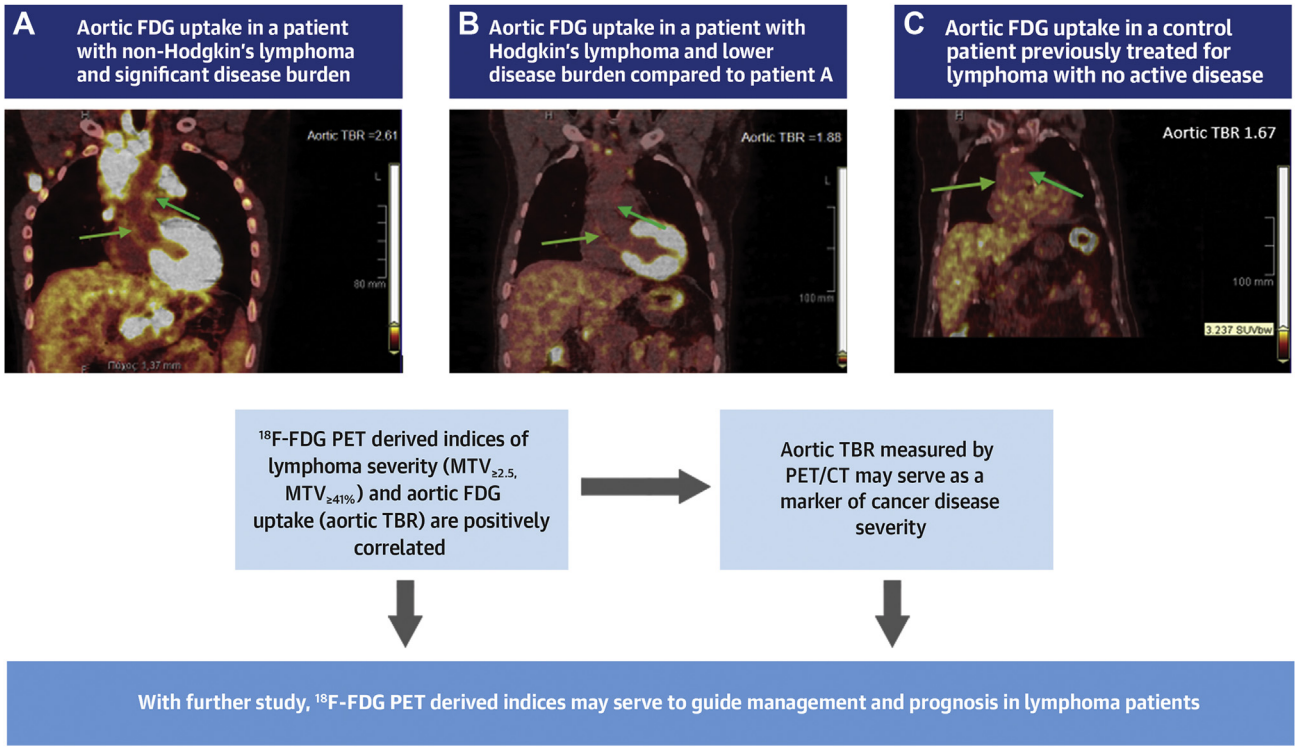
| | Odds Ratio | 95% CI | p Value |
|---|---|---|---|
| Type of lymphoma (reference: Hodgkin's lymphoma) | 4.36 | 0.81–23.65 | 0.087 |
| $MTV_{\geq 2.5}$ ≥268 (reference: <268) | 10.00 | 1.58–63.32 | 0.014 |

Abbreviations as in Tables 1 and 3.

Moreover, it has been shown previously that tumor-associated macrophages' functionality is influenced by tumor histological grade (35). There are also sporadic reports that include case series demonstrating that vasculitis is related to lymphoma; however, to the best of our knowledge, this is the first study to demonstrate a direct association between disease metabolic burden and aortic FDG uptake (36,37). In our study, aortic TBR was associated with neutrophil-to-lymphocyte ratio and hsCRP. The association of aortic TBR with inflammatory markers can be explained on the basis that increased $^{18}$F-FDG uptake in the arterial wall reflects low-grade inflammation of the arterial wall. Indeed, previous work in this field has demonstrated a positive correlation between hsCRP and arterial inflammation as assessed by $^{18}$F-FDG PET/CT (38,39). However, other studies have demonstrated an inconsistent relationship between C-reactive protein and arterial FDG uptake even in the presence of vasculitis (40). Therefore, our findings remain to be validated in future large-scale studies.

The lack of association between arterial calcification and arterial FDG uptake may be related to the fact that calcification represents a late stage of atherosclerosis, whereas FDG uptake reflects an active inflammation process that could potentially be reversible (39), and further implies that the metabolic tumor burden, rather than aortic atherosclerosis, may

**CENTRAL ILLUSTRATION** **Severity and Type of Lymphoma Are Associated With Aortic $^{18}$F-FDG Uptake Assessed by PET/CT**




**Vlachopoulos, C.V. et al. J Am Coll Cardiol CardioOnc. 2020;2(5):758–70.**

Positron emission tomography–computed tomography (PET/CT)–derived indices can provide an evaluation of disease severity and its consequences to the arterial wall with a single examination, in patients with lymphoma—a potential role of molecular imaging in cardio-oncology. $^{18}$F-FDG = $^{18}$F-fluorodeoxyglucose; MTV = metabolic tumor volume; TBR = target-to-background ratio.

be the determinant of arterial inflammation in our population.

**ASSOCIATION BETWEEN DISEASE BURDEN AND AORTIC FDG UPTAKE: POSSIBLE UNDERLYING MECHANISMS.** Several mechanisms may explain the link between lymphoma grade and systemic and arterial inflammation. Gene mutations that lead to carcinogenesis promote local and systemic inflammation. This may occur through several mechanisms, such as stimulation of the secretion of proinflammatory mediators, differentiation and consequently activation of local immune cells (neutrophils and monocytes) within tumor microenvironment (41), formation of neutrophil extracellular traps (42), activation of nuclear factor-kappa B, and dysregulation of efferocytosis (phagocytosis of proinflammatory cellular necrotic remnant), all of which lead to the augmentation of inflammation (43–45). Consequently, monocytes enter systemic circulation and differentiate to macrophages, which are then inserted within the arterial wall, promoting vascular inflammation. Importantly, the Warburg effect that occurs also in the context of inflammatory immune response during progression of atherosclerosis may explain the relationship between disease severity and systemic and arterial inflammatory activation observed in the present study (46,47).

**POTENTIAL CLINICAL RELEVANCE.** Aortic inflammation as assessed by $^{18}$F-FDG PET/CT imaging has been associated with cardiovascular events in various

populations, patients with a history of cancer, and symptomatic or healthy subpopulations (23,48,49). Subclinical arterial inflammation has also been related to worsening arterial stiffness (50), which is an important predictor of cardiovascular events (51–53). Our results should be regarded as hypothesis-generating, and we acknowledge that they do not demonstrate causality. However, the results support the hypothesis that the increased cardiovascular risk of lymphoma survivors could be mediated (at least in part) by vascular impairment. In patients with lymphoma, aortic TBR may not only be a prognostic marker of cardiovascular events, but conceptually, an additional surrogate marker of disease severity. With future study, PET/CT-derived indices can be assessed early during the course of the disease and potentially guide cardiovascular management (i.e., closer follow-up in high-risk patients), predict outcomes, and serve to gauge the effects of disease-targeting or specific cardioprotective strategies.

**STUDY LIMITATIONS.** First, a relatively small number of patients with lymphoma were enrolled, preventing a detailed comparison between Hodgkin's and non-Hodgkin's lymphoma. As such, we were also unable to use propensity matching; however, the number of patients studied was based on a priori power sample size calculation, and our statistical approach was robust. Second, the correlation between MTV or TLG, or circulating markers of disease severity, and aortic TBR may suggest specific pathophysiologic pathways; however, these associations cannot prove causality. Furthermore, correlations between disease burden indices and arterial FDG were modest; however, our study generates important hypotheses and motivates additional studies. Finally, the study design does not allow detailed mechanistic insights into the complex relationship between lymphoma and inflammation or the natural history and change over time. Moreover, no recommendations as of yet can be made for the management of individuals with elevated FDG aortic uptake. However, these aspects were beyond the scope of the present observational study and need to be addressed in larger prospective multicenter studies.

## CONCLUSIONS

Aortic FDG uptake is elevated in patients with lymphoma and associated with metabolic tumor burden. These findings indicate a potential role of molecular imaging in cardio-oncology, which can provide an evaluation of disease severity and its consequences to the arterial wall with a single examination.

## AUTHOR DISCLOSURES

The study was funded by the Hellenic Society of Lipidology, Atherosclerosis and Vascular disease. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Our findings suggest an association between lymphoma disease burden and arterial inflammation and highlight a potential role of $^{18}$F-FDG PET/CT imaging in cardio-oncology risk assessment.

**TRANSLATIONAL OUTLOOK:** Further research is needed in order to further understand the relationship between lymphoma and inflammation and the natural history of these findings. Additional research is necessary to determine optimal management of individuals with elevated aortic FDG uptake.

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**KEY WORDS** arterial inflammation, lymphoma, metabolic burden, positron emission tomography

**APPENDIX** For expanded Methods and References sections as well as supplemental tables and a figure, please see the online version of this paper.