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ORIGINAL RESEARCH

Prevalence and distribution of vascular calcifications at CT scan in patients with and without large vessel vasculitis: a matched cross-sectional study

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ABSTRACT

Objectives The aim of this study was to compare the prevalence, entity and local distribution of arterial wall calcifications evaluated on CT scans in patients with large vessel vasculitis (LVV) and patients with lymphoma as reference for the population without LVV.

Methods All consecutive patients diagnosed with LVVs with available baseline positron emission tomography-CT (PET-CT) scan performed between 2007 and 2019 were included; non-LVV patients were lymphoma patients matched by age (±5 years), sex and year of baseline PET-CT (≤2013; >2013). CT images derived from baseline PET-CT scans of both patient groups were retrospectively reviewed by a single radiologist who, after setting a threshold of minimum 130 Hounsfield units, semiautomatically computed vascular calcifications in three separate locations (coronaries, thoracic and abdominal arteries), quantified as Agatston and volume scores.

Results A total of 266 patients were included. Abdominal artery calcifications were equally distributed (mean volume 3220 in LVVs and 2712 in lymphomas). Being in the LVVs group was associated with the presence of thoracic calcifications after adjusting by age and year of diagnosis (OR 4.13, 95% CI 1.35 to 12.66; p=0.013). Similarly, LVVs group was significantly associated with the volume score in the thoracic arteries (p=0.048). In patients >50 years old, calcifications in the coronaries were more extended in non-LVV patients (p=0.027 for volume).

Conclusion When compared with patients without LVVs, LVVs patients have higher calcifications in the thoracic arteries, but not in coronary and abdominal arteries.

INTRODUCTION

Large vessel vasculitides (LVVs) are systemic diseases that primarily affect the aorta and its major branches.[1] The most common LVVs include Takayasu arteritis (TAK) and giant cell arteritis (GCA), which present many similarities in clinical manifestations and imaging

findings, and they are mainly differentiated based on the age of onset. GCA is a disease of elderly people, affecting subjects older than 50 years, whereas TAK affects younger patients.[2 3]

Disease activity assessment in LVVs is multimodal, including clinical and imaging evaluation. Physicians evaluate the presence of signs and symptoms related to inflammation and ischaemic complications and laboratory findings. In LVV, a dense inflammatory infiltrate affects the arterial walls leading to vascular damage (ie, stenoses, dilations and aneurysms); thus, imaging is used to complement the clinical assessment and includes functional and morphologic studies.[4] ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) detects the degree of

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Cardiovascular risk is well known in large vessel vasculitis and imaging studies have described features of accelerated atherosclerosis in patients with Takayasu arteritis, probably due to vascular inflammation.

WHAT THIS STUDY ADDS
⇒ Patients with large vessel vasculitis present a higher prevalence and extension of vascular calcifications in the thoracic aorta than age-matched and gender-matched patients without vasculitis.
⇒ There might be a protective effect of large vessel vasculitis on the coronary arteries calcifications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Inflammation may play a role in the development of vascular calcifications. Further studies are needed to understand the direction of this association.

vascular inflammation, CT and MR angiography (MRA) assess inflammation and vascular damage.[5] Nowadays, both studies tend to be combined, permitting evaluation of both sides of the vascular involvement.

Imaging studies have described features of accelerated atherosclerosis in TAK patients, probably due to vascular inflammation.[6] In GCA, data are scarce, but necropsy studies have demonstrated calcium deposition in the arterial walls.[7–9] Arterial wall calcifications in the aorta and peripheral arteries are better detected with CT, and they correlate with the extent of atherosclerosis, thus becoming a risk factor for developing cardiovascular complications.

Comparative data about the presence of atherosclerosis between TAK or GCA versus patients with risk factors for atherosclerosis, such as hyperlipidemia, have shown that vascular calcification throughout the aorta is more common in LVV. In contrast, calcifications in coronary arteries seem to be more common in patients with hyperlipidaemia.[10] However, data about the prevalence, distribution and burden of calcifications in LVV compared with the general population are scarce.

Although cardiovascular risk is well known in LVV, guidelines currently do not suggest to monitor and manage this risk differently from the general population.[11 12] Evaluating the presence of vascular calcification in an LVV population of TAK and GCA compared with a population not selected for having any vascular disease or risk factor could inform better about the development of accelerated atherosclerosis. The burden and localisation of calcifications, when compared with the general population, is also important to evaluate if it is necessary to initiate a treatment to prevent this condition.

The aim of the study was to compare the prevalence, entity and local distribution of arterial wall calcification evaluated on CT scans in patients with LVVs and patients without LVVs, matched for age, sex and PET-CT scan date.

METHODS
Study design, population
This was a retrospective matched study comparing the prevalence and quantity of calcifications in two groups, one exposed to the LVV disease and one chosen as a surrogate for the general population, that is, lymphoma patients at their first diagnosis, without vascular manifestation of disease. The presence of the outcome (calcifications) and of the exposure (LVV) is considered at the same time point in the patient's lifetime, thus the study has a cross-sectional design. Eligible patients were all consecutive patients diagnosed with LVV who were referred to the Rheumatology Unit of the Santa Maria Nuova Hospital of Reggio Emilia (Northern Italy) between 2007 and 2019. In this tertiary referral centre for vasculitis, patients with suspected, early or established LVV are admitted for diagnosis confirmation and disease activity assessment. All patients satisfied the modified inclusion criteria of the GiACTA trial for GCA,[13] and the 1990 American College of Rheumatology classification criteria for TAK[14]; the diagnosis of LVV, confirmed by imaging, was defined as the presence of circumferential wall thickening/oedema with or without contrast enhancement and/or the presence of vascular stenosis/occlusion and/or dilation/aneurysm on CTA or MRA and/or the presence of vascular uptake on PET-CT. Patients under age 50 at symptom onset were classified as TAK and those over 50 as GCA[15 16]

Only patients who had at least one PET-CT performed at our institution during the study period were included. For patients who underwent more than one PET-CT, only the first one was evaluated. Patients with aortic or coronary stents, grafts or previous bypass surgery preventing a correct assessment of calcifications were excluded.

The non-LVV group was composed by lymphoma patients who underwent PET-CT scan for staging purposes between 2007 and 2019, matched with LVV patients by age (in a±5-year interval), sex and year of PET-CT scan (considered in two periods, 2007–2013 and 2014–2019). The matching for PET-CT date was applied in order to take into account the technical changes in the PET-CT equipment from the first to the second time frame, which may have increased CT sensitivity for calcifications. Furthermore, during the study period, mortality for cardiovascular diseases decreased by one-third, probably reflecting a reduction of the prevalence of underlying vascular risk factors such as calcification.[17]

Assessment of vessel wall calcification
^{18}F-FDG PET-CT scan performed for LVV disease assessment or staging of lymphoma were acquired using a hybrid PET-CT scanner (Discovery STE 16, GE Healthcare, USA) with 3.30 min emission scan/bed and CT-attenuation correction. Free-breathing, low dose, non-contrast-enhanced helical CT images acquired for PET coregistration (slice thickness of 3.75 mm) were used to evaluate vessel wall calcifications. Retrospective radiologic assessment of vascular calcifications was performed using Carestream Vue PACS software (Carestream Health, Rochester, New York, USA) for evaluation of CT images derived from PET-CT studies. An automated thresholding tool was used to define areas of vascular calcifications with a minimum of 130 Hounsfield units.[18] Artefacts were qualitatively excluded from the analysis. A semiautomated analysis was performed to compute vascular calcifications in three specific locations, that is, coronary arteries, thoracic arteries (thoracic aorta and main branches) and abdominal arteries (abdominal aorta and main branches). Contouring of vessel wall calcifications was performed using a specific tool allowing quantification of vascular calcium through the drawing of regions of interest (ROIs) on calcific portions of main thoracoabdominal vessels. The operator (a radiologist with 10 years of experience in body and cardiac CT) selected true calcifications by circling the ROIs and assigning them to one of the locations

mentioned above. Agatston score and volume of coronary, thoracic and abdominal vascular calcifications were collected.

Statistical analyses

Paired t-test was used to compare the mean Agatston score and volume of calcifications in LVV and lymphoma patients in the three locations.

Since the matching for age and year of PET-CT scan was not precise (in a 5-year interval for age and in two periods for the year of PET-CT), residual confounding was considered a relevant issue, therefore regression analyses were adjusted for age and PET-CT year. Conditional logistic regression analyses adjusted by age and year of PET-CT were conducted to evaluate the association between the LVV group and the presence of vessel wall calcification in the three considered locations, in terms of OR with respective 95% CI. Linear regressions adjusted by age, sex and year of PET-CT were used to evaluate the association between the LVV group and the extent of calcifications (in terms of Agatstone score and volume) in the three considered locations. Subgroup analyses were conducted by repeating the abovementioned regressions in patients <50 years and in patients >50 years, as well as in patients with newly diagnosed LVVs and in patients with a disease duration ≥1 month (at the moment of PET-CT scan).

In the absence of a suitable match among controls, unmatched LVV patients were included only in non-paired analyses (regressions) and excluded from paired analyses (paired t-test and conditional logistic regressions).
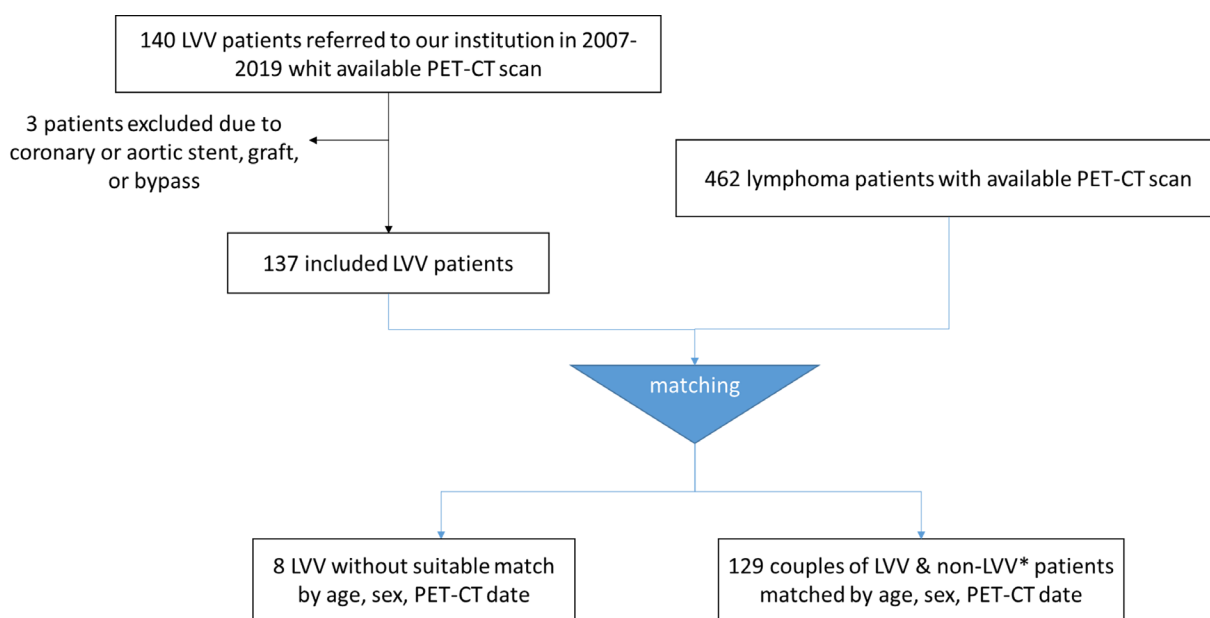
RESULTS

Study population

After exclusion of three patients due to coronary or aortic stent, graft or bypass,137 LVV patients referred to our institution in 2007–2019 with an available PET-CT scan were included. The control group was constituted by 129 matched non-LVV patients, while for 8 LVV patients a suitable match was not found (figure 1).

Of the 137 LVV patients included, 80 were GCA and 57 were TAK, 111 (81%) were females and mean age at inclusion was 54.6±18.8 years (table 1). LVV patients aged >50 years at first PET-CT in our institution were 85 (62%), 5 of them with TAK which was previously diagnosed. These five patients were all females, aged between 52 and 59 years, with a mean disease duration of 64 months.

Calcification burden and location

Compared with matched non-LVV patients, LVV patients had a higher burden of thoracic artery calcifications (table 2). Although the difference was borderline in significance (p=0.054 for volume), the absolute difference was striking.

Calcification burden was slightly higher in abdominal arteries and lower in coronary arteries in LVV patients compared with matched non-LVV patients, but differences were compatible with random fluctuation (p=0.371 for abdominal calcification volume and p=0.13 for coronary calcification volume). Figure 2 shows the distribution of calcification volumes in the three districts in LVV and non-LVV patients. The extremely high values

Figure 1 Flow chart representing patient inclusion in LVV and non-LVV groups. LVV, large vessel vasculitis; PET-CT, positron emission tomography-CT.

Table 1 Clinical characteristics of LVV patients, overall and subdivided according to age at PET-CT (<50 and >50 years old)

		LVV patients (n=137)	LVV patients <50 years (n=52)	LVV patients >50 years (n=85)
Age (years), mean±SD		54.6±18.8	33.9±9.7	66.6±9.3
Female gender, n (%)		111 (81.0)	47 (90.4)	64 (75.3)
LVV type	TAK, n (%)	57 (41.6)	52 (100)	5 (5.9)
	GCA, n (%)	80 (58.4)	–	80 (94.1)
Disease duration from diagnosis to PET-CT (months), mean±SD		23.0±47.4	43.5±66.4	12.2±24.7

GCA, giant cell arteritis; LVV, large vessel vasculitides; PET-CT, positron emission tomography-CT; TAK, Takayasu arteritis.

(>10 000) for the thoracic district are more frequent in LVV patients (6 vs 2).

Representative images of LVV and non-LVV patients with different calcification burdens and distributions are reported in figures 3 and 4.

Association between LVV and the presence of calcifications

In conditional logistic regression analyses adjusted by age and year of PET-CT scan, being in the LVV group was associated with the presence of calcifications in the thoracic aorta and main branches (OR 4.13, 95% CI 1.35 to 12.66; p=0.013) (table 3). The associations of the LVV group with the presence of calcifications in coronary arteries and abdominal aorta and main branches were compatible with random fluctuations (p=0.575 and p=0.328), however, the direction was towards a higher prevalence of abdominal calcifications and a lower prevalence of coronary calcifications.

Association between LVV and calcification burden

In the regression analyses including both matched patients and the eight patients without a suitable match, adjusted by age, sex and year of PET-CT, the LVV group was significantly associated with higher calcification burden (in terms of score and volume) in the thoracic aorta and main branches (coefficient=1091; 95% CI 65 to 2116; p=0.037 for volume) (table 4). The direct relationship between LVV and calcification burden in the abdominal location and the inverse relationship between LVV and calcification burden in the coronaries were compatible with random fluctuations.

Subgroup analysis by age and disease duration

In subgroup analyses conducted in patients aged <50 years and >50 years at PET-CT, the association between LVV and the presence of thoracic arteries calcifications was stronger in patients <50 years (OR 8.48, 95% CI 0.65 to 111; p=0.103) (online supplemental table 1). Both in LVV and non-LVV patients, the prevalence of calcification in the coronaries was extremely low below the age of 50 years. The association between LVV and coronary calcification in patients >50 years, as well as abdominal calcification in both age groups, was largely compatible with random fluctuations.

The association of LVV with calcification burden in the thoracic aorta and main branches remained similar in patients <50 and >50 years (p for interaction 0.73) (online supplemental table 2). A similar difference was observed for the abdominal aorta and main branches (p for interaction 0.63). Calcifications in the coronaries were more extended in LVV patients when considering only younger patients, while in patients >50 years old they were more frequent/extended in non-LVV patients: test for interaction between age and group suggests a different effect but random fluctuation cannot be excluded (p=0.06).

A higher excess of prevalence of calcifications was found restricting the analyses to patients who were not

Table 2 Comparison of coronary, thoracic and abdominal calcium score and volume in large-vessel vasculitis versus lymphoma groups

|	Large-vessel vasculitis group (n=129) Mean (SD)	Lymphoma group (n=129) Mean (SD)	P value*
Coronary calcium score	103.35 (373.75)	197.46 (693.64)	0.161
Coronary calcium volume (mm3)	103.68 (347.04)	198.85 (643.26)	0.130
Thoracic calcium score	2464.22 (7276.27)	1213.45 (2759.03)	0.059
Thoracic calcium volume (mm3)	2025.94 (5774.63)	1012.96 (2258.70)	0.054
Abdominal calcium score	3870.32 (7142.97)	3266.12 (6300.76)	0.381
Abdominal calcium volume (mm3)	3219.93 (5801.47)	2712.5 (5227.42)	0.371

*Paired t-test.
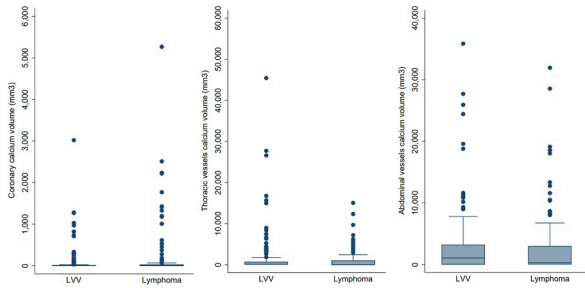
Figure 2 Distribution of the volume of calcifications in coronary, thoracic and abdominal vessels in the LVV group (including non-matched patients) and lymphoma group. LVV, large vessel vasculitis.

newly diagnosed with LVV at the moment of PET-CT scan (online supplemental table 1) (OR for thoracic calcifications 8.07; 95% CI 1.36 to 47.75; OR for abdominal calcifications 3.66; 95% CI 0.58 to 22.89). This behaviour was not found for calcification burden (online supplemental table 2). Within LVV patients, we observed an increased prevalence of thoracic calcifications with increasing disease duration (OR for 1-month increase 1.04, 95% CI 1.01 to 1.06), while a small if any effect was appreciable for coronary and abdominal vessel calcification (ORs for 1-month increase 1.003, 95% CI 0.989 to 1.017, and 1.008, 95% CI 0.998 to 1.018, respectively).

DISCUSSION

In this matched cross-sectional study, LVV patients had a higher prevalence and a larger extension of calcifications in the thoracic aorta and main branches when compared with non-LVV patients. The difference in extension was striking, with twice as much thoracic calcification volume in LVV patients, even if the clinical relevance of such difference is difficult to define in the absence of validated cut-offs. Importantly, the difference was similar in both younger (<50 years old, mostly TAK) and older patients

Figure 3 Multiplanar reconstructions on the sagittal (A) and coronal (B) plane, and volume rendering reconstructions of the CT images of representative PET-CT scan of an LVV patient (A) and a non-LVV patient (B). Calcification burden in the thoracic aorta was much higher in the patient with LVV. LVV, large vessel vasculitis; PET-CT, positron emission tomography-CT.
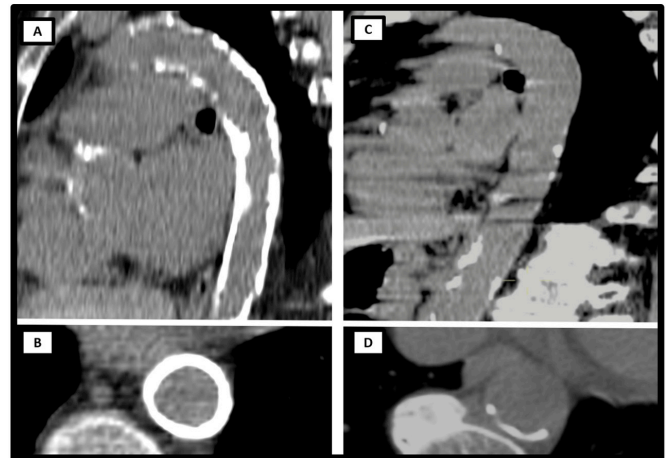

Figure 4 PET-CT images comparing the aortic calcium plaque density in an LVV patient (A,B) and a non-LVV patient (C,D). LVV patient exhibit consistently high plaque density (> 800 HU) as evident in the long axis sagittal view (A) and short axis axial view (B). In contrast, the plaque density in this lymphoma is notably lower (around 400 HU), as illustrated in the long axis sagittal view (C) and short axis axial view (D). HU, Hounsfield units; LVV, large vessel vasculitis; PET-CT, positron emission tomography-CT.

(mostly GCA), while it was appreciable only in non-newly diagnosed patients.

Coronary vessels in LVV patients did not show an overall excess of calcifications. On the contrary, in older patients only, we observed a lower prevalence/extension in LVV patients. The difference in extension found in older patients (an excess of almost 200 mm^3 on average in non-LVV patients) may be not irrelevant.[19] Abdominal vessels showed an excess in prevalence and extension of calcification only in non-newly diagnosed LVV patients.

A few non-matched studies previously described calcification extent and distribution in patients with LVV compared with patients with other risk factors, reporting a high prevalence of calcification in TAK patients, still much lower than in patients with atherosclerosis[20] and a burden of calcifications higher in patients with LVV than in patients with hyperlipidaemia[10] In this last study, the location of calcifications was comparable, with the exception of a lower prevalence of calcifications in the coronary arteries of patients with LVVs[10] In the only available study comparing TAK patients with healthy controls, age-adjusted analyses showed that TAK patients had a significantly higher prevalence of thoracic calcifications, as well as a higher prevalence of coronary calcifications, although the difference in the coronaries was compatible with random fluctuation.[6] Importantly, our results differ, showing an excess of calcification in the non-LVV group, only when compared with the subgroup of patients >50 years old, who were almost exclusively GCA patients.

Since the thoracic aorta and main branches are the main target of vessel wall inflammation in LVVs, and on the contrary coronary arteries are not commonly affected, it could be inferred from our results that inflammation has a role in the development of calcifications. However,

Table 3 Association of LVV group with the presence of calcification in different locations

	LVV group prevalence of calcification	Lymphoma group prevalence of calcification	OR (95%CI) of calcification in LVV versus lymphoma group*
Coronary calcification	35/129 (27.1%)	38/129 (29.5%)	0.79 (0.35 to 1.78)
Thoracic calcification	93/129 (72.1%)	71/129 (55.0%)	4.13 (1.35 to 12.66)
Abdominal calcification	93/129 (72.1%)	86/129 (66.7%)	2.05 (0.48 to 8.71)

*Conditional logistic regression analyses on matched patients (n=129 for each group).
LVV, large vessel vasculitis.

the cross-sectional design does not allow us to establish the direction of the observed associations, that is, we do not know if one is the cause of the other or the two are both consequences of a common cascade of vessel wall alterations consequent to the autoimmunity disorder. Nevertheless, we can observe that the two phenomena often occur in the same vascular districts. Furthermore, the strong association with disease duration strengthens the hypothesis of a causal link between inflammation and calcifications.

Our stratification by age is almost perfectly consistent with the type of LVV with only five exceptions. We preferred to maintain age at PET-CT as the main stratification variable because calcifications in the general population are strictly related to age and any comparison with the general population should take into account this factor. Nevertheless, we cannot distinguish if differences in the association between LVV and calcifications in the two age groups are related to a different progression of calcifications by age common to both LVV types or to differences between TAK and GCA in the effect on calcifications.

Possible explanations for the lower prevalence of coronary calcifications in older (GCA) patients compared with the general population could be better control of risk factors (lower smoking prevalence, better cholesterol control) while a survival bias is not plausible due to the low lethality of the disease. Unfortunately, we lacked information on other cardiovascular risk factors, including smoking and dyslipidaemia, which could not be retrospectively found in the non-LVV group. Finally,

since coronary calcifications are a surrogate marker for atherosclerosis[21] and inflammation plays a central role in atherosclerosis, we can speculate that the long-term exposition to anti-inflammatory therapy in older LVV patients may have slowed down the progression of atherosclerosis and coronary calcium deposition.

Other limitations included the control group of lymphoma patients which may not be representative of the general population. Nevertheless, there is no evidence of association between lymphoma and cardiovascular diseases. LVV disease duration was highly variable, however, we conducted stratified analyses. PET-CT scans are not ideal for measuring calcifications; however, the acquisition parameters and measurement technique were identical across groups, and matching for PET-CT scan date accounted for small technical differences that could have been introduced over time. Residual confounding by age and PET-CT period matching was addressed by adjusting the main analyses. We also performed non-matched analyses that confirmed the direction of all the observed associations with slightly higher statistical power and precision. Beyond the statistical significance, for thoracic vessels the analyses are consistent.

In conclusion, LVV patients, compared with matched controls, had a higher prevalence and extension of vessel wall calcifications in the thoracic district but not in abdominal and coronary arteries. Older LVV patients, mostly GCA, had lower prevalence and extension of coronary artery calcifications than controls. Further studies are needed to understand the direction of the association between vessel wall inflammation and calcifications, and

Table 4 Association between LVV group and calcification burden in terms of score and volume in different locations

	Coeff (95% CI) for LVV group*	P value*
Coronary calcium score	−80.80 (−210.65 to 49.05)	0.222
Coronary calcium volume	−80.36 (−200.28 to 39.55)	0.188
Thoracic calcium score	1351.62 (63.76 to 2639.47)	0.040
Thoracic calcium volume	1090.63 (65.44 to 2115.81)	0.037
Abdominal calcium score	868.48 (−598.04 to 2335)	0.245
Abdominal calcium volume	726.84 (−473.70 to 1927.37)	0.234

*Regression analyses included both matched patients and LVV patients without a suitable match (n=137 LVV patients and n=129 lymphoma patients).
LVV, large vessel vasculitis.

the reasons behind the protective effect of LVV on coronary artery calcifications in older patients.

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