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Association between vascular FDG uptake at diagnosis and evolution in aortic dimensions in giant cell arteritis: a prospective study

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- 22
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- 26
- 27

28 Abstract

29 Background: Retrospective studies have shown that giant cell arteritis (GCA) patients with

vascular 18F-fluorodeoxyglucose (FDG) uptake at diagnosis are at increased risk of
 developing aortic complications.

- 32 **Objective:** To evaluate the association between vascular FDG uptake at diagnosis and the
- 33 evolution of aortic dimensions in GCA patients.
- 34 **Design:** Prospective cohort study
- 35 Setting: University Hospitals Leuven, 2012-2020
- 36 **Patients:** 100 GCA patients with FDG PET imaging at diagnosis \leq 3 days after initiation of 37 glucocorticoids and followed for \geq 2 years.
- 38 Measurements: PET scans were scored (0-3) at 7 vascular areas and a total vascular score
- 39 (TVS) was calculated. PET scans were considered positive in case of FDG uptake \geq grade 2
- in any large vessel. Patients underwent CT imaging at diagnosis and yearly thereafter for a
 maximum of 10 years. The association between vascular FDG uptake and aortic dimensions
- 42 was estimated by linear mixed effect models with random intercept and slope.
- 43 **Results:** The increase in ascending and descending aortic diameter and in thoracic aortic
- 44 volume was higher in patients with a positive PET scan compared to those without (p=0.009,
- 45 p=0.01, and p=0.008, respectively). This increase was also significantly associated with TVS
- 46 (p=0.007, p=0.03, and p=0.003, respectively). FDG uptake was not associated with an 47 increase in abdominal aortic dimensions. Thoracic aortic aneurysms were more frequently
- 48 observed in patients with a positive PET scan (aOR 7.19, 95%-CI 1.55-54.18, p=0.02).
- 49 **Limitations:** The lengthy inclusion and follow-up period resulted in the use of different PET 50 machines and missing data.
- 51 Conclusion: Higher TVS was associated with greater yearly increase in thoracic aortic
- 52 dimensions. Performing PET imaging at diagnosis may help to estimate the risk of aortic
- 53 aneurysm formation.
- 54 Primary funding source: none
- 55 Registration: NCT01588483
- 56
- 57
- 58

59 Introduction

60 Giant cell arteritis (GCA) is a large vessel vasculitis that preferentially affects the cranial 61 arteries, the aorta, and its proximal branches (1). The prevalence of GCA increases with age 62 and is estimated at 125-250 per 100 000 in people over 50 years old in northern Europe and 63 North America (2).

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For the diagnosis of GCA, the European Alliance of Associations for Rheumatology (EULAR) recommends early imaging (3). Ultrasound is recommended for the assessment of GCA with cranial artery involvement with magnetic resonance imaging (MRI) as an alternative (3). Our group has introduced ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET)scintigraphy in the assessment of large vessel vasculitis (4,5). PET/computed tomography (CT) and MRI are currently recommended for the assessment of large vessel involvement with similar diagnostic accuracy (6).

72

Two severe complications of GCA are sudden irreversible vision loss and aortic aneurysm formation and dissection. Vision loss most frequently occurs before or within the first days of initiation of treatment with glucocorticoids (7). In contrast, aortic aneurysm may be present at diagnosis, but typically occurs during follow-up. However, the exact timing of aortic aneurysm

- 77 formation in GCA patients remains unclear.
- 78

79 Patients with GCA have a 3 to 17-fold increased risk of developing thoracic aortic aneurysms 80 (8–11). A meta-analysis of studies with systematic imaging reported a pooled prevalence of 81 thoracic aortic aneurysm of 15% (12). GCA patients have no or only a slightly increased risk 82 of abdominal aortic aneurysms (8-11). Predictors for thoracic aneurysms were reported with 83 inconsistent results (12). However, four retrospective studies have indicated that FDG uptake 84 in large vessels at diagnosis increases the risk of developing aortic complications during follow-85 up (13–16). Prospective studies confirming these findings are lacking. The aim of this study was to evaluate the association between FDG uptake in large vessels at diagnosis and the 86 87 evolution of aortic dimensions in a prospective cohort of GCA patients. 88

89 Methods

90 Patient population

We prospectively included patients with GCA, who were evaluated by the Department of General Internal Medicine of the University Hospitals Leuven between 2012 and 2020 and who had undergone FDG PET imaging at diagnosis within 3 days after initiation of glucocorticoids. Patients with a previous diagnosis of GCA, in whom a PET scan and yearly CT of the aorta were available, were also included. Patients who were followed for less than two years were excluded.

97

98 The study was conducted in accordance with the Declaration of Helsinki and approved by the 99 ethical committee of the University Hospitals Leuven. All patients gave informed consent. The 100 study was registered in advance in ClinicalTrials.gov (NCT01588483).

- 101
- 102 Data collection

103 We collected the following patient data from the electronic health record: age, sex, date of

104 diagnosis, duration of symptoms until diagnosis, symptoms at diagnosis, cardiovascular risk

- 105 factors and medication, erythrocyte sedimentation rate (ESR; mm/h), C-reactive protein (CRP;
- 106 mg/l), temporal artery biopsy (TAB) result, duration of follow-up, total duration (in weeks) and

cumulative dose in the first two years of glucocorticoid treatment, use of glucocorticoid-sparing
 agents, relapses, aortic complications (dilatation or dissection and region), vascular stenosis,
 vascular surgery, myocardial infarction, cerebrovascular accident (CVA), anterior ischemic
 optic neuropathy (AION), and mortality during follow-up.

- 111
- 112 Definitions

113 The diagnosis of GCA was based on the judgement of two experienced clinicians (DB and 114 SV), considering all available information (clinical data, biochemical, radiological, PET and 115 TAB results, and evolution during follow-up). Relapse was defined as recurrence of clinical 116 symptoms compatible with GCA or polymyalgia rheumatica (PMR) and/or increase of inflammatory markers requiring escalation of treatment. We created a cardiovascular risk score 117 118 by adding the following cardiovascular risk factors with a maximum of 10 points: history of 119 myocardial infarction or angor, peripheral vascular disease, and stroke were assigned 2 points; 120 diabetes, smoking, use of statins, and use of antihypertensive medication were assigned 1 121 point.

121 poil

123 PET imaging and analysis

124 Patients were required to fast for at least 6 hours before intravenous injection of 4-5 MBg/kg 125 of FDG, and glycemia levels were determined in all patients (as per procedure, to be < 140 126 mg/dl). A whole-body PET scan was performed 60 min after tracer administration. PET scans 127 were performed between 2003 and 2020, acquired on a ECAT HR + PET camera, Hirez 128 Biograph 16 PET/CT, Truepoint Biograph 40 PET/CT (Siemens, Knoxville, TN, USA) or GE 129 Discovery MI 4-ring PET/CT system (GE, Milwaukee, WI, USA). Because of scan duration, 130 HR+ data were not corrected for attenuation using transmission scanning. On the PET/CT 131 systems, either a low-dose non-diagnostic CT scan or a diagnostic CT scan was performed 132 immediately before PET acquisition. Non-attenuation corrected PET images were available for 133 all included patients and attenuation-corrected PET images were only available for the patients 134 who were scanned with a PET/CT system (n=63). PET data were corrected for scatter and 135 randoms. Data were reconstructed using iterative OSEM reconstruction, with parameters 136 optimized over the years (FWHM HR+ 6-7 mm, for the Truepoint 5 mm).

137

138 Reconstructed PET images were re-evaluated visually by a specialist in nuclear medicine (LB), who was blinded for all other patient information. FDG PET uptake was scored semi-139 140 quantitatively at 7 vascular regions (thoracic and abdominal aorta, subclavian, axillary, carotid, 141 iliac, and femoral arteries) as 0 (no FDG uptake), 1 (minimal but not negligible FDG uptake), 2 142 (clearly increased FDG uptake), or 3 (very marked FDG uptake). PET scans were considered 143 positive in case of FDG uptake \geq grade 2 in any large vessel. Additionally, a total vascular 144 score (TVS) was calculated ranging from 0 (no vascular FDG uptake in any of the 7 vascular 145 regions) to 21 (vascular FDG uptake scored 3 in all 7 segments) (17). Subclavian, axillary, 146 carotid, iliac, and femoral arteries were counted as 1 vascular region each: when the score 147 differed from right to left artery, the highest score was taken for that vascular region. The intensity of FDG uptake in affected vessels was measured by dividing TVS by the number of 148 149 vessels with FDG uptake \geq grade 2. In addition, to assess cranial vasculitis, the vertebral, 150 maxillary, occipital and temporal arteries were scored similarly.

151

152 CT imaging and analysis

153 Patients underwent a CT scan of the thorax and abdomen at diagnosis and yearly thereafter 154 for a maximum of 10 years. CT scans were preferentially performed without intravenous 155 contrast. A contrast-enhanced CT scan or PET/CT scan was used if a non-enhanced CT scan 156 was not available. The aortic diameter was measured perpendicular to the axis of blood flow 157 at six different levels (ascending aorta, aortic arch, descending thoracic aorta, suprarenal, 158 juxtarenal and infrarenal aorta) and the thoracic and abdominal aortic volumes were measured. 159 To obtain the volume, the thoracic and abdominal aorta were segmented semi-automatically 160 using MMWP Volume software (Siemens, Erlangen, Germany). Next, the volumes of both 161 parts were calculated automatically. To avoid interobserver variability, the measurements were 162 performed by the same author (diameters by LM and volumes by WC). Both were unaware of the PET findings. The ascending aorta, aortic arch, descending aorta, and abdominal aorta 163 164 were considered aneurysmatic when the diameter was \geq 45, \geq 40, \geq 35 and \geq 30 mm respectively 165 (14,15).

166

167 Statistical analysis

168 Categorical and continuous variables were expressed as count and percentage and as mean 169 and standard deviation or median and interguartile range (IQR) as appropriate. Chi square 170 tests, Fisher's exact test, unpaired t-test, or Mann-Whitney U tests were used to compare 171 characteristics between patients with a positive and negative PET scan and between patients 172 with and without thoracic aortic aneurysm as appropriate. The associations between a positive 173 PET scan and aortic diameters and volumes were estimated by linear mixed effect models 174 with random intercept and slope in time with and without adjustment for age, sex, 175 cardiovascular risk score, CT or PET/CT scan, and intravenous contrast. These confounding 176 factors were chosen for biological and technical reasons. Subgroup analyses comparing 177 patients with a positive and negative PET scan in the thoracic and abdominal aorta were performed. In addition, the association between TVS, the number of vessels with FDG uptake 178 179 \geq grade 2 and the intensity of FDG uptake in affected vessels on the one hand and evolution 180 of the aortic diameters and volumes on the other hand were assessed. Logistic regression 181 models were fitted to analyze the association between a positive PET scan and thoracic aortic 182 aneurysm with and without adjustment for the same variables. All statistical tests were two-183 tailed with significance set at the p<0.05 level. Statistical analysis was performed in R Studio 184 (version 2022.06.23, The R Foundation for Statistical Computing) with inclusion of the Ime4, 185 siPlot, and ggplot2 packages.

186

187 Role of the funding source

188 This study received no funding.

189

190 Results

191 136 GCA patients underwent a PET scan between 2003 and 2020 and signed informed 192 consent. Twenty patients were excluded because they received treatment with glucocorticoids 193 for more than three days prior to PET imaging. Sixteen patients were followed less than two 194 years. Finally, 100 patients (mean age 70 years, 68% females) were included, of whom 74 (74%) patients had FDG uptake \geq grade 2 in any large vessel, 60 (60%) in the thoracic aorta, 195 196 and 49 (49%) in the abdominal aorta. In these patients, 603 CT scans were performed, of 197 which 507 (84%) non-enhanced CT scans, 14 (2%) contrast-enhanced CT scans and 82 (14%) 198 PET/CT scans. Median follow-up was 80 months (IQR 47-110). Fifteen (15%) patients 199 received glucocorticoids for less than three days prior to PET imaging; 85 (85%) were steroid-200 naive. Median TVS was 14 (IQR 6-16, range 2-21) in the PET positive group and 0 (IQR 0-1, 201 range 0-3) in the PET negative group. FDG uptake \geq grade 2 was most frequently observed in 202 the subclavian arteries (64%), followed by ascending aorta (59%), aortic arch (57%),

descending aorta (57%), abdominal aorta (49%), carotid arteries (48%), axillary arteries (48%),
iliac arteries (22%), and femoral arteries (20%). Forty eight percent of patients had increased
FDG uptake in the cranial arteries, all of whom had FDG uptake in the vertebral arteries. The
maxillary, temporal, and occipital arteries were affected in 36%, 15%, and 11% respectively.

207

208 The baseline characteristics are presented in Table 1. Patients with a positive PET scan were 209 younger (68 versus 74 years, p=0.001) and more frequently female (77% versus 42%, p=0.001) compared to those with a negative PET scan. The symptom duration until diagnosis 210 211 was significantly longer in patients with a positive PET scan (8 versus 3 weeks, p<0.001). 212 Patients without vascular FDG uptake more frequently had cranial symptoms (96% versus 213 69%, p=0.006) and tended to have more PMR (54% versus 34%, p=0.07), whereas those with 214 vascular FDG uptake more often had constitutional symptoms (95% versus 65%, p<0.001). 215 There were no significant differences in cardiovascular risk factors, proportion of patients with 216 a positive temporal artery biopsy, or inflammatory markers between the PET positive and PET 217 negative group.

218

219 The increase in ascending and descending aortic diameter and in thoracic aortic volume was 220 higher in patients with a positive PET scan compared to those without (p=0.009, p=0.01 and p=0.008, respectively) (Table 2 and Supplementary Tables 1 and 2). In patients with a positive 221 222 PET scan in the thoracic aorta, the increase was only significantly higher in the ascending 223 aortic diameter and in thoracic aortic volume (both p=0.005) (Table 2 and Supplementary 224 Tables 3 and 4). However, there was also a trend to a greater increase in the diameter of the 225 descending aorta and aortic arch (p=0.06 and p=0.07, respectively). Vascular FDG uptake was 226 not associated with an increase in abdominal aortic diameters nor volume (Table 2 and 227 Supplementary Tables 5 and 6). The thoracic aortic diameters and volume were positively 228 associated with TVS (Table 3, Figure 1 and Supplementary Tables 7 and 8). There was no 229 significant association between the abdominal aortic diameters and volume on the one hand 230 and TVS on the other hand. The ascending and descending aortic diameter and thoracic aortic 231 volume were also positively associated with the number of vessels with FDG uptake \geq grade 232 2 and with the intensity of FDG uptake in affected vessels (Supplementary Tables 9-12). As 233 expected, TVS, the number of affected vessels, and the intensity of FDG uptake in affected 234 vessels are correlated with each other, with the strongest correlation between TVS and the 235 number of affected vessels (Supplementary Table 13). 236

237 Twenty-one patients developed an aortic aneurysm, which was already present on the first CT 238 scan in six patients. The median time since diagnosis to develop an aortic aneurysm was 37 239 months (IQR 19-60) for any aneurysm and 40 months (IQR 18-61) for thoracic aortic aneurysm. 240 Eighteen patients had an aneurysm in the descending aorta, five in the ascending aorta, five 241 in the aortic arch, and four in the abdominal aorta. In three of the four patients with an 242 abdominal aortic aneurysm, the aneurysm was located in the suprarenal aorta and these 243 patients also had a thoracic aortic aneurysm. The patient with an isolated abdominal aortic 244 aneurysm had an infrarenal aneurysm. Logistic regression analysis revealed that thoracic 245 aortic aneurysms occurred more frequently in patients with a positive PET scan (24% versus 246 8%, aOR 7.19, 95%-CI 1.55-54.18, p=0.02) and in patients with a positive PET scan in the 247 thoracic aorta (27% versus 10%, aOR 6.06, 95%-CI 1.68-27.62, p=0.01) (Supplementary 248 Tables 14 and 15). Aortic aneurysm occurred in 16 of the 18 (89%) PET positive patients in a 249 region with FDG uptake at diagnosis. Two patients with high TVS (15 and 16, maximum 21) 250 needed elective surgery for ascending aortic aneurysm. Histopathological examination showed

degenerative changes, cystic media necrosis and mild lymphocytic inflammation in theadventitia in both patients and also in the media in one patient.

253

254 As an exploratory analysis, we examined differences between patients with and without 255 thoracic aneurysms (Table 4). Patients who developed a thoracic aneurysm, tended to have 256 higher TVS (14 versus 6, p=0.05) with both higher number of affected vessels (5 versus 2, 257 p=0.03), and higher intensity of FDG uptake in affected vessels (2.8 versus 2.7, p=0.04). They 258 also had a longer symptom duration until diagnosis (8 versus 6 weeks, p=0.04), and higher inflammatory markers at diagnosis (CRP 121 versus 78 mg/l, p=0.02 and ESR 98 versus 67 259 260 mm/h, p=0.04). There were no significant differences in age, sex, cardiovascular risk factors, 261 symptoms at diagnosis, temporal artery biopsy results, duration of glucocorticoids, cumulative 262 dose of glucocorticoids in the first two years, use of glucocorticoid-sparing agents, relapse rate, 263 cardiovascular events during follow-up, or mortality.

265 Discussion

266 In this prospective study, we found that GCA patients with a positive PET scan had a greater 267 increase in ascending and descending aortic diameter and thoracic aortic volume compared 268 to those with a negative scan. There were no differences in abdominal aortic diameters and 269 volume. In addition, higher TVS was associated with greater yearly increase in thoracic aortic 270 diameters and volume. In patients without elevated vascular FDG uptake, the increase in aortic 271 diameters seems to be similar to the general population with a reported yearly increase of 272 about 0.1-0.2 mm (18). Vascular and more specifically thoracic aortic FDG uptake at diagnosis 273 was an independent risk factor for developing thoracic aortic aneurysms.

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264

275 These findings are consistent with earlier retrospective studies (13–16). Our group first showed 276 that patients with aortic FDG uptake at diagnosis had a significantly larger ascending and 277 descending aortic diameter and thoracic aortic volume during follow-up (13). In a multicenter 278 study of de Boysson et al. 9% of patients developed aortic dilatation, all of whom had FDG 279 uptake in large vessels at diagnosis or during follow-up (14). Afterwards, they confirmed that 280 large vessel inflammation is a predictor of aortic dilatation in a larger, multicenter, retrospective 281 cohort (15). Muratore et al. reported significantly larger thoracic and abdominal diameters in 282 patients with FDG uptake grade 3 compared to those with FDG uptake \leq grade 2 (16).

283

284 The mechanism of aneurysm formation in GCA patients remains unclear. It is sometimes 285 hypothesized that persistent subclinical vasculitis activity leads to cumulative damage to the 286 aortic wall (12,19). However, histopathological examination of the aorta after surgery mostly revealed extensive disruption of elastic fibers in the media with only mild and scattered 287 inflammation in the media and/or adventitia (20-22), which we also found in two patients who 288 required elective surgery for an ascending aortic aneurysm in our cohort. In 89% of PET 289 290 positive patients aortic dilatation occurred in a vascular region with elevated FDG uptake at 291 diagnosis. In addition, we found a dose-response relation with a positive association between 292 TVS and thoracic aortic diameters and volume. Both the number of vessels with FDG uptake 293 \geq grade 2 and the intensity of FDG uptake in affected vessels were associated with the 294 evolution in the ascending and descending aortic diameter and thoracic aortic volume. 295 However, the extent and the intensity of vessel involvement were correlated, which we assume 296 to be related to patients with severe large vessel vasculitis having both larger extent of affected 297 vessels and a higher intensity of inflammation in the affected vessels. Moreover, patients who 298 developed a thoracic aneurysm, had a longer symptom duration until diagnosis and had higher

299 inflammatory markers at diagnosis. Inflammatory markers were also higher in patients with 300 aortic aneurysms in the study of Gonzalez-Gay et al. (23), but this was not significant in several 301 other studies (13,14,16,19,24,25). Blockmans et al. and Nuenninghoff et al. also found a longer 302 symptom duration until diagnosis in patients with aortic dilatation (13,26), but this was not 303 confirmed in two other studies (19,23). There were no significant differences in cardiovascular 304 risk factors in patients with and without thoracic aneurysms. Our findings suggest that the 305 intensity, duration and extent of initial inflammation rather than the persistence of inflammatory 306 activity determines the risk of subsequent aortic dilatation. This intense inflammation probably 307 weakens the aortic wall, which then undergoes progressive dilatation due to deficient vascular 308 remodeling and mechanical forces.

309

310 There is no consensus on the screening for the development of aortic aneurysms in GCA 311 patients. EULAR and American College of Rheumatology (ACR) guidelines currently do not 312 recommend routinely screening for aortic dilatation (3,27,28). In contrast, the American Heart Association (AHA)/American College of Cardiology (ACC) Joint Committee recommends 313 314 annual surveillance imaging with CT, MRI, or PET/CT (29). This study confirms that vascular 315 FDG uptake is an independent predictor of thoracic aortic aneurysms with a higher increase in 316 thoracic aortic diameters and volume in patients with higher TVS. One fourth of patients with 317 a positive PET scan developed a thoracic aortic aneurysm. These aneurysms most frequently 318 occurred in the descending aorta in a median time since diagnosis of 40 months, but the two 319 patients who needed surgery, had an ascending aortic aneurysm. Follow-up of aortic 320 dimensions seems to be warranted in GCA patients, especially in those with high intensity and 321 broad extent of vascular inflammation. However, the added value of screening and the interval 322 required should be addressed in future studies.

323

324 Consistent with previous studies (15,30,31), we found that patients with a positive PET scan 325 were younger, were more frequently female, and had a longer symptom duration until 326 diagnosis. Patients with vascular FDG uptake more often had constitutional symptoms, 327 whereas cranial symptoms and PMR more frequently occurred in those without vascular FDG 328 uptake. However, these symptoms are not specific enough to differentiate patients with and without large vessel vasculitis clinically. Thus, to estimate the future risk of aortic aneurysm 329 330 formation, performing PET imaging at diagnosis before or shortly after the start of glucocorticoid treatment in GCA patients would be advisable. 331 332

333 Strengths of this study include that it is the first prospective study which addresses the impact 334 of vascular FDG uptake on the evolution of aortic dimensions. In addition, a large cohort of 335 GCA patients was followed for a long time in this study. Our study also has several limitations. 336 First, due to the long inclusion period PET scans were performed on different PET systems 337 with increasing device quality over time. In addition, CT scans were preferentially performed 338 without intravenous contrast, but a contrast-enhanced CT scan or a PET/CT scan was used if 339 a non-enhanced CT scan was not available. However, we corrected for this in the linear mixed 340 model and logistic regression analyses. Third, due to the long follow-up a substantial number 341 of CT scans were missing. Fourth, this was a single-center study, which probably limits the 342 generalizability. Finally, the treatment was at the discretion of the physician, so we cannot 343 exclude an effect of differences in treatment on the evolution of aortic dimensions. However, 344 the duration of glucocorticoid treatment, the cumulative glucocorticoid dose in the first two 345 years and the use of glucocorticoid-sparing agents were not significantly different in patients 346 with and without thoracic aneurysms.

347

In conclusion, higher TVS was associated with greater yearly increase in thoracic aortic diameters and volume. Vascular FDG uptake was not associated with an increase in abdominal aortic diameters nor volume. Vascular and more specifically thoracic aortic FDG uptake at diagnosis is an independent risk factor for developing thoracic aortic aneurysms in GCA patients. In addition to diagnostic information, performing PET imaging at diagnosis in GCA patients would help to estimate the future risk of aortic aneurysm formation. Follow-up of aortic dimensions may be warranted in patients with thoracic aortic FDG uptake or a high TVS.

356 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

359

360 Author Contributions

361 LM: Conceptualization, Methodology, Validation, Investigation, Formal analysis, Writing -362 Original Draft, Writing – Review & Editing, Visualization; WC: Conceptualization, Methodology, Validation, Investigation, Writing - Review & Editing; LB: Methodology, Validation, 363 364 Investigation, Writing - Review & Editing; AB: Conceptualization, Methodology, Writing -365 Review & Editing; GM: Methodology, Formal analysis, Writing - Review & Editing; SV: 366 Investigation, Writing - Review & Editing, Supervision; KVL: Writing - Review & Editing, supervision; EC: Investigation, Writing - Review & Editing, DB: Conceptualization, 367 368 Methodology, Investigation, Writing – Review & Editing, Supervision 369

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470 **Tables and figures**

471 Table 1: Baseline characteristics of patients with (PET positive) and without (PET negative)

vascular FDG uptake ≥ grade 2 472

Characteristics	Total	PET positive	PET negative	
Characteristics	(n = 100)	(n = 74)	(n = 26)	p-value
Age at inclusion, years, mean (SD)	70 (8)	68 (7)	74 (8)	0.001
Sex, no. of females, n (%)	68 (68)	57 (77)	11 (42)	0.001
Symptom duration until diagnosis, weeks,	6 (3-14)	8 (4-17)	3 (2-5)	< 0.001
median (IQR)				
Cardiovascular risk factors/events				
 Active or past tobacco use, n (%) 	46 (49) ⁶	35 (49) ²	11 (50) ⁴	0.91
 Antihypertensive medication, n (%) 	47 (47)	32 (43)	15 (58)	0.20
 Diabetes mellitus, n (%) 	5 (5)	3 (4)	2 (8)	0.60
 Statin use, n (%) 	30 (30)	20 (27)	10 (38)	0.27
 History of stroke, n (%) 	4 (2)	2 (3)	2 (8)	0.28
• History of myocardial infarction or angor, n (%)	2 (2)	2 (3)	0 (0)	1
 History of peripheral vascular, disease, n (%) 	2 (2)	1 (1)	1 (4)	0.45
 Cardiovascular risk score, median (IQR) 	1 (0-2)	1 (0-2)	1 (1-2)	0.35
Symptoms at diagnosis				
 Cranial symptoms, n (%) 	76 (76)	51 (69)	25 (96)	0.006
o PMR, n (%)	37 (37)	25 (34)	14 (54)	0.07
 Constitutional symptoms, n (%) 	87 (87)	70 (95)	17 (65)	< 0.001
 Limb claudication, n (%) 	4 (4)	4 (5)	0 (0)	0.57
Laboratory tests				
 ESR, mm/h, median (IQR) 	69 (48-105) ¹⁴	70 (47-109) ¹¹	66 (52-90) ³	0.45
 CRP, mg/l, median (IQR) 	87 (43-130)	86 (45-125)	92 (43-136)	0.70
Positive temporal artery biopsy, n (%)	49 (63) ²²	31 (60) ²²	19 (73)	0.24
Duration of follow-up, months, median (IQR)	80 (47-110)	75 (43-107)	91 (59-117)	0.26

473 474 475 Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; IQR, interquartile

range; no., number; PET, positron emission tomography; PMR, polymyalgia rheumatica; SD, standard deviation

Number of missing values are reported in superscript.

476

478 **Table 2:** Evolution of the aortic diameters (in mm) and volumes (in cm³) per year in patients with (PET positive) and without (PET negative)

479 FDG uptake \geq grade 2 in large vessels

FDG uptake 2 grade 2 in any large vessel								
		Crude regression coefficient (95% CI)*		p-value	Adjusted regression coefficient (95% CI)°		p-value	
		PET negative	PET positive		PET negative	PET positive		
Volum	ne of thoracic aorta	3.62 (0.69-6.57)	7.84 (6.07-9.61)	0.02	2.39 (-0.42-5.20)	6.82 (5.11-8.55)	0.008	
Volum	ne of abdominal aorta	-0.38 (-1.29-0.54)	-0.73 (-1.270.20)	0.52	0.27 (-0.48-1.04)	0.12 (-0.33-0.57)	0.73	
Diame	eter of thoracic aorta							
0	Ascending aorta	0.06 (-0.14-0.26)	0.34 (0.22-0.46)	0.02	0.10 (-0.11-0.30)	0.41 (0.29-0.53)	0.009	
0	Aortic arch	0.20 (0.04-0.35)	0.31 (0.22-0.41)	0.21	0.21 (0.05-0.37)	0.35 (0.25-0.45)	0.14	
0	Descending aorta	0.11 (-0.05-0.27)	0.34 (0.24-0.44)	0.02	0.11 (-0.06-0.27)	0.34 (0.25-0.45)	0.01	
Diameter of abdominal aorta								
0	Suprarenal aorta	0.08 (-0.02-0.19)	0.12 (0.06-0.18)	0.53	0.07 (-0.04-0.17)	0.11 (0.04-0.17)	0.51	
0	Juxtarenal aorta	0.12 (0.00-0.23)	0.10 (0.03-0.16)	0.78	0.14 (0.03-0.25)	0.14 (0.07-0.21)	0.98	
0	Infrarenal aorta	0.15 (0.07-0.23)	0.07 (0.03-0.12)	0.10	0.15 (0.07-0.23)	0.08 (0.03-0.12)	0.11	
FDG u	ıptake ≥ grade 2 in thorac	ic aorta						
		Crude regression coefficient (95% CI)*		p-value	Adjusted regression coefficient (95% CI)°		p-value	
	_	PET negative	PET positive		PET negative	PET positive		
Volum	ne of thoracic aorta	4.27 (1.90-6.66)	8.35 (6.41-0.30)	0.009	3.11 (0.83-5.40)	7.34 (5.46-9.24)	0.005	
Diame	eter of thoracic aorta							
0	Ascending aorta	0.11 (-0.05-0.27)	0.37 (0.24-0.50)	0.01	0.14 (-0.02-0.31)	0.45 (0.31-0.58)	0.005	
0	Aortic arch	0.21 (0.08-0.33)	0.33 (0.23-0.43)	0.13	0.22 (0.09-0.35)	0.37 (0.27-0.48)	0.07	
0	Descending aorta	0.19 (0.06-0.32)	0.34 (0.23-0.45)	0.09	0.18 (0.05-0.32)	0.35 (0.24-0.46)	0.06	
FDG u	ıptake ≥ grade 2 in abdom	ninal aorta						
		Crude regression coefficient (95% CI)*		p-value	Adjusted regression coefficient (95% CI)°		p-value	
	_	PET negative	PET positive		PET negative	PET positive		
Volum	ne of abdominal aorta	-0.49 (-1.14-0.16)	-0.78 (-1.440.14)	0.52	0.08 (-0.46-0.61)	0.23 (-0.33-0.78)	0.68	
Diameter of abdominal aorta								
0	Suprarenal aorta	0.09 (0.01-0.16)	0.13 (0.06-0.21)	0.37	0.07 (-0.00-0.14)	0.12 (0.04-0.20)	0.33	
0	Juxtarenal aorta	0.10 (0.02-0.18)	0.10 (0.02-0.18)	0.95	0.13 (0.05-0.20)	0.15 (0.07-0.23)	0.70	
0	Infrarenal aorta	0.13 (0.07-0.18)	0.06 (0.01-0.12)	0.11	0.12 (0.07-0.18)	0.06 (0.00-0.12)	0.12	

480 481 ^{*} Linear mixed model without adjustment for confounders

^o Linear mixed model adjusted for age, sex, cardiovascular risk score, CT or PET/CT scan, and intravenous contrast

482 Abbreviations: 95% CI, 95% confidence interval; FDG, fluorodeoxyglucose; PET, positron emission tomography

Table 3: Association between total vascular score and the evolution in aortic diameters (mm) and volumes (cm³)

		Crude regression coefficient of interaction term ^{*+} (95% Cl)	p-value for interaction term ¹	Adjusted regression coefficient of interaction term ^{°+} (95% CI)	p-value for interaction term ¹	
Volume	e of thoracic aorta	0.31 (0.09-0.52)	0.005	0.31 (0.11 – 0.52)	0.003	
Volume of abdominal aorta		-0.03 (-0.10-0.04)	0.38	0.00 (-0.05 – 0.06)	0.95	
Diameter of thoracic aorta						
0	Ascending aorta	0.02 (0.00-0.03)	0.03	0.02 (0.01 – 0.04)	0.007	
0	Aortic arch	0.01 (0.00-0.02)	0.11	0.01 (0.00 – 0.02)	0.05	
0	Descending aorta	0.01 (0.00-0.02)	0.04	0.01 (0.00 – 0.03)	0.03	
Diameter of abdominal aorta						
0	Suprarenal aorta	0.00 (-0.00-0.01)	0.34	0.00 (-0.00 – 0.01)	0.29	
0	Juxtarenal aorta	0.00 (-0.01-0.01)	0.59	0.00 (-0.00 – 0.01)	0.31	
0	Infrarenal aorta	-0.01 (-0.010.00)	0.05	-0.01 (-0.01 – -0.00)	0.05	
Linear mixed model without adjustment for confounders						

486 ^{*} Li

487 ° Linear mixed model adjusted for age, sex, cardiovascular risk score, CT or PET/CT scan, and intravenous contrast

488 ⁺ Interaction between evolution in time (in year) and total vascular score

489 **Abbreviations:** 95% CI, 95% confidence interval

491 Table 4: Characteristics of patients with and without thoracic aneurysm

	Tetal	Thoracic	No thoracic	
Characteristics		aneurysm	aneurysm	p-value
	(n = 100)	(n = 20)	(n = 80)	
Age at inclusion, years, mean (SD)	70 (8)	69.5 (6)	70 (8)	0.80
Sex, no. of females, n (%)	68 (68)	11 (55)	57 (71)	0.16
Symptom duration until diagnosis, week, median	6 (3-14)	8 (6-18)	6 (3-13)	0.04
(IQR)				
Cardiovascular risk factors/events at diagnosis	0			
 Active or past tobacco use, n (%) 	46 (49) ⁶	13 (65)	33 (45) ⁶	0.11
• Antihypertensive medication, n (%)	47 (47)	10 (50)	37 (46)	0.76
• Statin use, n (%)	30 (30)	5 (25)	25 (31)	0.58
• Diabetes mellitus, n (%)	5 (5)	0 (0)	5 (6)	0.59
• History of stroke, n (%)	4 (2)	1 (5)	3 (4)	1
• History of myocardial infarction or angor, n (%)	2 (2)	0 (0)	2 (3)	1
• History of peripheral vascular, disease, n (%)	2 (2)	0 (0)	2 (3)	1
• Betablocker at diagnosis, n (%)	34 (34)	8 (40)	26 (33)	0.53
• Betablocker during follow-up, n (%)	49 (49)	13 (65)	36 (45)	0.11
• Cardiovascular risk score, median (IQR)	1 (0-2)	1 (1-2)	1 (0-2)	0.56
Symptoms at diagnosis	70 (70)	40 (00)	C4 (00)	0.00
• Craniai symptoms, n (%)	76 (76)	12 (60)	64 (80)	0.08
• PMR, n (%)	39 (39)	4 (20)	35 (44)	0.05
• Constitutional symptoms, n (%)	85 (85)	19 (95)	68 (85) 2 (4)	0.46
Lind claudication, if (%)	4 (4)	1 (5)	3 (4)	I
Eabliatory tests at diagnosis	60 (48 105)14	08 (57 126)2	67 (43 104)12	0.04
\circ CRP mg/l median (IQR)	87 (43-100)	90 (07-120) 121 (80-146)	07 (43-104) 78 (41 - 123)	0.04
Positive temporal artery bionsy n (%)	49 (63)22	6 (46) ⁷	<u>44 (68)¹⁵</u>	0.02
PFT results	40 (00)	0 (40)	++ (00)	0.20
\sim Positive PET n (%)	74 (74 0)	18 (90.0)	56 (70.0)	0.07
• Positive PET in thoracic aorta n (%)	60 (60 0)	16 (80.0)	44 (55 0)	0.07
• TVS median (IOR)	8 (2-14)	14 (8-16)	6 (1-14)	0.05
\circ Number of vessels with FDG uptake > grade 2	3 (0-5)	5 (4-6)	2 (0-5)	0.03
median (IQR)	0 (0 0)	0(10)	2 (0 0)	0.00
 Intensity of FDG uptake in affected vessels, median 	2.8 (0-3)	2.8 (2.5-3.0)	2.7 (0-2.9)	0.04
(IQR)°	2.0 (0 0)	2.0 (2.0 0.0)	(0)	
Treatment				
 Duration of GC treatment, months, median (IQR) 	34 (24-65) ³	44 (25-94) ¹	34 (23-60) ²	0.32
• Cumulative GC dose in first 2 years after diagnosis,	4.7 (1.4) ⁶	4.8 (1.5)	4.7 (1.3) ⁶	0.73
g methylprednisolone, mean (SD)		()		
• Use of glucocorticoid-sparing agents during follow-	32 (33) ²	7 (37) ¹	25 (32) ¹	0.66
up, n (%)				
Duration of follow-up, months, median (IQR)	80 (47-110)	107 (74-123)	71 (41-99)	0.01
Relapse, n (%)	68 (68)	15 (75)	53 (66)	0.10
Cardiovascular event during follow-up		· · ·		
 Aortic dissection, n (%) 	0 (0)	0 (0)	0 (0)	/
 Vascular stenosis, n (%) 	14 (14)	5 (25)	9 (11)	0.15
 Vascular surgery, n (%) 	7 (7)	2 (10)	5 (6)	0.62
 Myocardial infarction, n (%) 	2 (2)	0 (0)	2 (3)	1
○ CVA, n (%)	10 (10)	3 (15)	7 (9)	0.41
• AION, n (%)	2 (2)	0 (0)	2 (3)	1
Mortality, n (%)	13 (13)	3 (15)	10 (13)	0.72

492 493 494 495 Abbreviations: AION, anterior ischemic optic neuropathy; CRP, C-reactive protein; CVA, cerebrovascular accident; ESR,

erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; GC, glucocorticoids; IQR, interquartile range; no., number; PET,

positron emission tomography; PMR, polymyalgia rheumatica; SD, standard deviation; TVS, total vascular score

Number of missing values are reported in superscript.

496 ° Calculated as total vascular score divided by the number of vessels with FDG uptake ≥ grade 2

Figure 1: Association between total vascular score and the evolution in (A) volume of thoracic aorta, (B) diameter of ascending aorta, (C) diameter of aortic arch, (D) diameter of descending aorta, (E) volume of abdominal aorta, (F) diameter of suprarenal aorta, (G) diameter of juxtarenal aorta, and (H) diameter of infrarenal aorta. The linear mixed models were adjusted for age, sex, cardiovascular risk score, CT or PET/CT scan, and intravenous contrast.



504 Abbreviations: TVS, total vascular score