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Introduction

Rupture of an abdominal aortic aneurysm (AAA) remains a catastrophic event, with in-hospital mortality after emergency repair ranging from 40% to 50% [1]. Approximately 30% of patients with a ruptured AAA die before reaching the hospital [1]. By contrast, 30-day mortality after elective repair of an unruptured AAA is markedly lower, respectively 2% for endovascular aneurysm repair (EVAR) and 3% for open surgical repair [1]. Therefore, early diagnosis, close surveillance and timely treatment are the only effective strategies to reduce AAA-related mortality. Generally asymptomatic until they rupture, AAAs exhibit variable and often non-linear growth patterns, making it difficult to predict their progression and their risk of rupture [2]. Current management of asymptomatic AAA relies on periodic imaging, control of cardiovascular risk factors and preventive pharmacotherapy, with elective repair generally indicated when the maximal diameter exceeds the thresholds recommended by the guidelines. However, size alone is not a perfect predictor, and improved tools for identifying high-risk patients are needed.

Molecular imaging with ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) has emerged as a promising complement to detect increased metabolic activity in the AAA wall, which reflects increased local inflammatory activity, characterised by macrophage infiltration and degradation of the extracellular matrix in the aortic wall. Sakalihan et al. [3] previously demonstrated that focal [^{18}F]FDG uptake in the aneurysmal wall was observed in areas of maximal wall stress and in patients with large, rapidly expanding, or symptomatic AAAs at risk of rupture [2,4,5]. Since then, PET/CT has been routinely integrated into the evaluation of AAA at our institution, both at baseline and during follow-up. However, the prognostic value of repeated PET/CT scans over time remains uncertain.

In this study, we pooled PET/CT data from AAA patients and examined long-term outcomes. We sought to determine whether successive changes in PET/CT scans were associated with aneurysm growth, rupture risk, and mortality, and whether this follow-up provides prognostic information complementary to conventional morphological assessment.

Materials and methods

Population

Between 2008 and 2012, patients with a diagnosis of abdominal aortic aneurysm (AAA) referred to the

Department of Cardiovascular Surgery at the University Hospital of Liège (Liège, Belgium) were invited to participate in the multicentre FAD (*Fighting Aneurysmal Disease*) research project on aortic diseases. As part of this protocol, all included patients underwent whole-body [^{18}F]FDG PET/CT imaging at baseline. Exclusion criteria were: known connective tissue disorders, thoracoabdominal aortic aneurysms, aortitis, malignancy, congestive heart failure, and renal insufficiency (serum creatinine $>1.8\text{mg/dL}$). This study was approved by the institutional ethics committee (n°200647, 7 February 2011), and all participants provided written informed consent.

A total of 197 patients with AAA were included in the study and underwent whole-body [^{18}F]FDG PET/CT imaging at baseline (Figure 1). Among them, 164 patients had been included in a previous publication on blood biomarker assessment [6]. Of the study population, 40 patients had histological analysis of their aneurysm; the results are presented in this manuscript. In addition, 121 patients underwent at least one follow-up imaging examination (PET/CT, CT, or ultrasound) to assess the evolution of the aneurysm, and 148 patients ultimately underwent surgical repair (EVAR or open surgery).

Follow-up and AAA diameter progression

The evolution of aortic diameter in the 121 patients was monitored by computed tomography (CT), positron emission tomography combined with CT (PET/CT), or ultrasound until December 2016. All imaging acquisitions were performed in the same department by experienced vascular specialists, according to standardised protocols and with standardised equipment. The maximum diameter of the aneurysm determined the frequency of the follow-up imaging examinations. Specifically, follow-up was performed at 6 or 12 months depending on the size of the aneurysm and according to an internationally recognised algorithm [2]. Furthermore, critical diameter measurements obtained by US were confirmed by CT or PET/CT scan measurements. Any decision regarding surgery was based solely on the diameters determined by CT or PET/CT. For AAA diameter measurements by CT or PET/CT, the anteroposterior and transverse planes were perpendicular to the aortic axis.

Growth rates were calculated from serial CT or PET/CT measurements with a known time interval between the two measurements [7]. Rapid aneurysm growth was defined as an increase in size $\geq 1\text{cm}$ per year, consistent with previous work [8]. A patient was considered to have rapid growth if at least one episode of rapid growth occurred between two successive measurements. Open

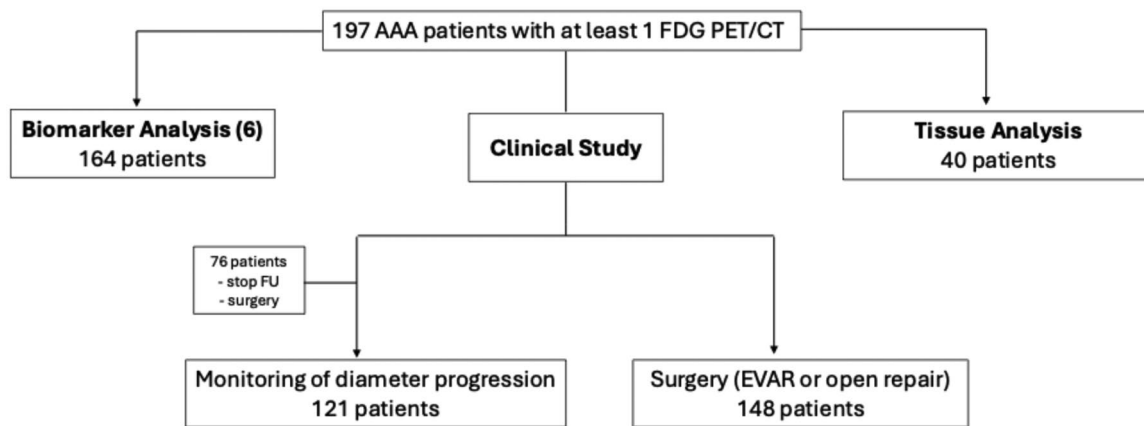


Figure 1. Flowchart illustrating subgroups of AAA patients: 197 AAA patients underwent baseline [^{18}F]FDG PET/CT, 76 were excluded due to early surgery or loss to follow-up, and the remaining 121 patients, with at least 2 preoperative diameter measurements, were included in the longitudinal analysis for diameter progression evaluation. Furthermore, all 148 patients who proceeded to surgery were included in the analysis of the indications for surgical intervention.

surgery was the treatment of choice for patients with short, angled and/or calcified aortic neck and/or superior mesenteric artery stenosis. An aortic wall biopsy was performed during open surgery. EVAR was performed with infrarenal deployment of Zenith (Cook Medical, Bloomington, IN, USA) or Endurant (Medtronic, Minneapolis, MN, USA) bifurcated stent grafts.

[^{18}F]FDG PET/CT image acquisition

For [^{18}F]FDG PET/CT imaging, patients fasted for at least 6h prior to intravenous injection of [^{18}F]FDG (3.7 MBq/kg body weight) via an indwelling catheter. Plasma blood glucose levels were normal in all cases before tracer injection. PET/CT acquisition was started after an average uptake period of 60min, according to the protocol described in Courtois A et al. [5]. Briefly, PET/CT scans were acquired on a Gemini BB or a Gemini TF (16-slice CT scanner, Philips Healthcare, Best, The Netherlands). Low-dose CT (thickness 5mm, increment 5mm, voltage 120kV, current 25mA/slice) was acquired first, followed by PET emission scan from the skull to the upper thighs (1–3min per bed position depending on the patient's body habitus). The study was completed with an arterial CT phase (thickness 2mm, increment 1mm, 120keV, 100mA/slice). Data were corrected for radioactive decay, scatter, randomness, and attenuation, and reconstructed with an iterative 3D algorithm. Attenuation correction was based on low-dose CT images. Oasis software (version 1.8.3; Segami Corporation, Columbia, MD, USA) was used for PET analysis. All the [^{18}F]FDG PET/CT scans were independently evaluated. Qualitative and quantitative evaluation of the [^{18}F]FDG PET/CT was performed by analysing the hypermetabolic zones.

[^{18}F]FDG PET/CT quantitative image analysis

As previously described [6], quantitative assessment of [^{18}F]FDG uptake was performed on transaxial sections only. Any aortic wall region showing visually increased

activity compared to the other areas of the aortic wall was considered as an abnormal focus. To quantify the [^{18}F]FDG uptake in the tissues, a region of interest (ROI) was placed over the abnormal focus of the aortic wall or the normal liver, to measure the maximum pixel value standardised uptake values (SUVmax). Because SUVs may vary depending on the PET/CT device and protocol, results were expressed as the ratio between the uptake in the AAA and the liver (SUVr). The SUVr was calculated for each patient. This approach has been validated and the liver has been chosen as a reference tissue because its uptake has been shown to have low intra-patient variability in test–retest studies [8,9].

[^{18}F]FDG PET/CT visual image analysis

For qualitative or visual analysis, the fused CT and PET images were independently evaluated by a nuclear medicine physician and a vascular surgeon experienced in PET imaging. The PET/CT scan was considered positive when focal or segmental [^{18}F]FDG uptake was observed in the aneurysmal aortic wall at baseline, and the patient was then classified as PET+; otherwise, PET–. The evolution of [^{18}F]FDG uptake was analysed in patients monitored by PET/CT. A patient was classified as PET+ if at least one PET scan was positive.

Tissue collection and sample analysis

Due to clinical and/or technical factors (such as absence of open surgery, failure to obtain a biopsy, or inadequate sample quality or quantity), the number of usable samples varied across the different analyses. In total, aortic tissues were collected in 40 AAA patients: 26 PET– patients and 14 PET+ patients. Three type of biopsies were collected at the time of surgery in the anterior-lateral aneurysmal wall, biopsies of PET– patients (A0), biopsies of PET+ patients at the site of [^{18}F]FDG uptake (A+_{pos}), localised by using anatomical landmarks and CT images as previously explained [5], and biopsies of PET+ patients at a distant site negative

for [^{18}F]FDG uptake (A_{Neg}). A full thickness slice of the biopsy was fixed in 4% paraformaldehyde for histological and immunohistochemical analysis. Sections of 5 μm of paraffin-embedded samples were coloured with Elastica von Giesen staining to visualise elastic fibres in the aortic wall. Semi-quantification of elastin amount was performed using Image J software. Masson's trichrome staining was performed using the standard protocol to visualise collagen deposition. Briefly, sections were incubated in Weigert's iron haematoxylin to stain nuclei, followed by Biebrich scarlet-acid fuchsin solution to stain cytoplasm and muscle fibres. Collagen fibres were differentiated using phosphomolybdic-phosphotungstic acid solution and counterstained with aniline blue. Slides were then rinsed in acetic acid, dehydrated, cleared, and mounted with a coverslip. Collagen appeared blue, smooth muscle and cytoplasm red, and nuclei dark brown to black. Stained sections were scanned at high resolution and analysed using QuPath software v0.4.4, where the collagen-positive area was quantified by colour deconvolution and threshold-based segmentation. Sections were also stained with toluidine blue to visualise nuclei in dark blue and extracellular matrix components. Proteoglycan deposits were identified as purple regions. Digital whole-slide images of toluidine staining were analysed using QuPath software v0.4.4. Regions of interest (the media of the aortic wall) were annotated and purple stained areas were quantified using positive pixel count algorithm. Proteoglycan content was expressed as percentage of positive area relative to total surface of the annotated region.

Statistical analysis

Quantitative data were expressed as mean and standard deviation (SD), or as median and interquartile range (IQR) for skewed data. Frequency tables (number, percent) were used for summarising categorical findings. The Spearman correlation coefficient was calculated to measure the association between quantitative variables. Skewed data were also log-transformed to normalise their distributions. The unpaired Student *t*-test or the Kruskal–Wallis' test for non-normal distributions was used to compare groups for quantitative variables, while the chi-square test was used to compare proportions. To assess the relationship between a binary variable (e.g. presence/absence of AAA rapid growth) and a set of covariates, stepwise logistic regression analysis was applied to the data. Results were expressed as odds ratio (OR) with 95% confidence interval (95%CI). Test results were considered significant at the 5% critical level ($p < 0.05$). All statistical calculations were always performed on the maximum number of data available (missing data were neither replaced nor imputed) using SAS (version 9.4 for Windows) and R (version 4.1.1) programs. Prism GraphPad was used for graphs.

Results

Patient characteristics at baseline

The 197 AAA patients had a mean age of 72.0 ± 8.5 years and were mainly males (89.8%). Twenty-seven (13.7%) of

them were diabetic, 74 (37.6%) current smokers, 123 (62.4%) suffered hypertension, 74 (37.6%) chronic obstructive pulmonary disease (COPD), and 119 (60.4%) hyperlipidaemia. Chronic medications included aspirin (56.4%), betablockers (33.7%), and statins (61.7%). (Table 1).

Risk factors did not differ between female and male patients (Supplementary Table 1).

The mean AAA diameter at baseline was 51.8 ± 11.8 mm, with 50% of patients having a diameter ≥ 50 mm and 75% a diameter ≥ 45 mm. The distribution of AAA diameter at baseline was more dispersed in male than in female patients (Figure 2).

At baseline, a significant positive correlation was found between age and AAA diameter ($r = 0.29$, $p < 0.0001$). Larger aneurysms were observed in patients with renal failure ($p = 0.028$), COPD ($p = 0.037$) and aspirin use ($p = 0.022$), while hypertension was associated with smaller aneurysms ($p = 0.042$) (Supplementary Table 2).

At baseline, 158 (80.2%) patients had a PET visually negative (PET-) with a median SUVr of 0.74 (IQR 0.65–0.83), and 39 (19.8%) patients had a PET visually positive (PET+) with median SUVr of 1.04 (IQR 0.88–1.17). The SUVr difference between the two groups of patients was highly significant ($p < 0.0001$). By contrast, no association could be evidenced between the diameter of AAA and the PET status (53.3 ± 11.1 mm for PET+ vs. 51.5 ± 12.0 mm for PET-; $p = 0.44$) and similarly for the uptake SUVr ($r = -0.015$, $p = 0.83$) (Figure 3).

There was no significant association between risk factors and visual PET at baseline except for gender ($p = 0.033$) and hyperlipidaemia ($p = 0.016$). The proportion of PET+ was higher in female (40%) than in male patients (17%) and lower in patients with hyperlipidaemia (14% v. 28%) (Table 2).

The proportion of PET+ among patients with a history of cancer was slightly higher than the proportion of PET+ among patients without history of cancer (25% vs. 19%, $p = 0.46$).

Table 1. Baseline demographic and clinical characteristics of AAA patient ($N = 197$).

Variable	Mean $\pm$ SD N (%)
Age (years)	72.0 ± 8.5
Gender (Male)	177 (89.8)
Smoking	74 (37.6)
Diabetes	27 (13.7)
Hypertension	123 (62.4)
Chronic obstructive pulmonary disease	74 (37.6)
Renal failure	32 (16.2)
Stroke	34 (17.3)
Hyperlipidaemia	119 (60.4)
AMI	63 (32.0)
PAD	55 (27.9)
Aspirin	111 (56.3)
Statins	121 (61.7)
Betablockers	66 (33.7)
Family history	25 (12.7)
History of cancer	28 (14.2)
Aneurysm diameter (mm)	51.8 ± 11.8
PET SUVr	0.77 (0.70–0.90)*
PET + (visual)	39 (19.8)
SUVr ≥ 1	28 (14.2)

*Median (IQR); COPD chronic obstructive pulmonary disease; AMI acute myocardial infarction; PAD peripheral artery disease.

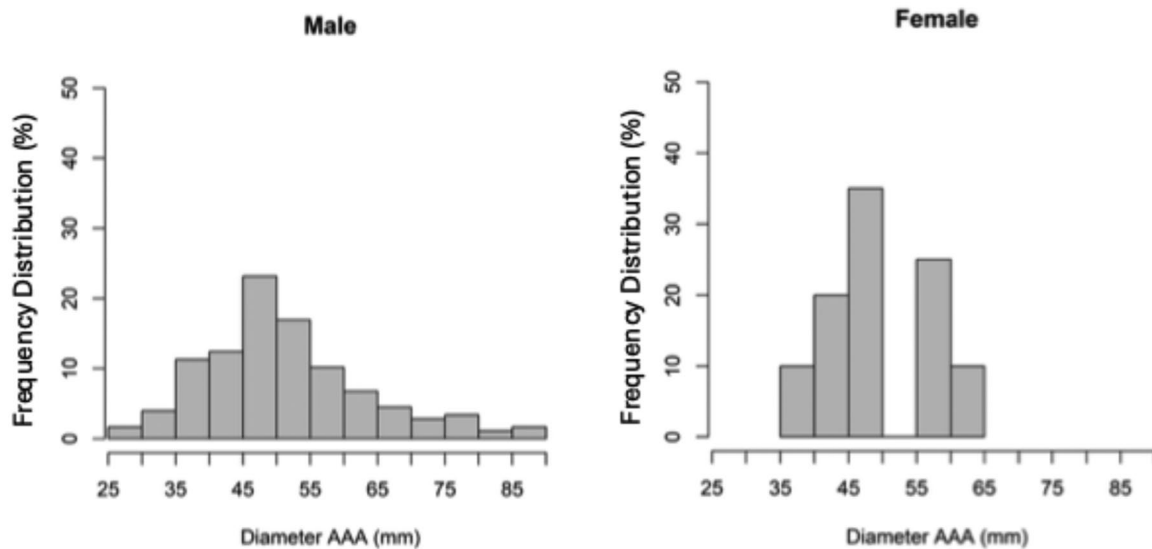


Figure 2. Distribution of AAA diameter according to gender at baseline ($N=197$ AAA patients).

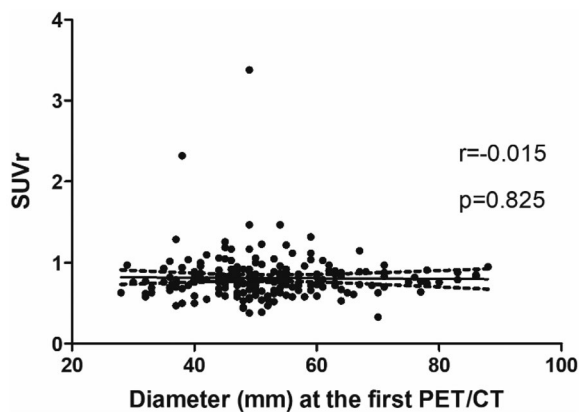


Figure 3. Relationship between PET SUVr and AAA diameter at baseline ($N=197$ patients).

Table 2. Distribution of risk factors according to their visual PET at baseline ($N=197$ AAA patients).

Variable	PET- Mean $\pm$ SD N (%)	PET+ Mean $\pm$ SD N (%)	P-value
No. of patients	158	39	
Age (years)	71.9 $\pm$ 8.5	72.5 $\pm$ 8.6	0.69
Gender (Female)	12 (7.6)	8 (20.5)	0.033
Smoking (Current/Former)	135 (85.4)	33 (84.6)	0.98
Diabetes	23 (14.6)	4 (10.3)	0.48
Hypertension	100 (63.3)	23 (59.0)	0.62
COPD	60 (38.0)	14 (35.9)	0.81
Renal failure	27 (17.1)	5 (12.8)	0.52
Stroke	25 (15.8)	9 (23.1)	0.28
Hyperlipidaemia	102 (64.6)	17 (43.6)	0.016
AMI	51 (32.3)	12 (30.8)	0.86
PAD	43 (27.2)	12 (30.8)	0.66
Aspirin	90 (57.0)	21 (53.8)	0.73
Statins	99 (63.1)	22 (56.4)	0.44
Betablockers	54 (34.4)	12 (30.8)	0.67
History of cancer	21 (13.3)	7 (17.9)	0.46

COPD: chronic obstructive pulmonary disease; AMI: acute myocardial infarction; PAD: peripheral artery disease.

Patients follow-up by PET/CT and evolution of AAA diameter

During a median follow-up period of 33 (IQR15-70) months, 354 PET/CT were performed and distributed as follows: 2 PET/CT (93 patients), 3 PET/CT (47 patients), 4 PET/CT (14 patients), and 5 PET/CT (3 patients). The mean time interval between 2 PET/CT scans was 11.7 ± 12.9 months. Throughout the study, PET remained positive in 10 patients and negative in 70 patients.

Among the 121 patients who underwent imaging assessment of AAA size progression prior to surgery, AAA diameter was measured 439 times: twice in 25.6% of cases, three times in 21.5% of the cases, and four times in 28.1% of cases. Those individual AAA size progressions are depicted in Figure 4.

As seen in Figure 5, a small but statistically significant positive correlation was noted between initial AAA diameter and AAA growth rate ($r=0.19$, $p=0.0008$).

Among the 121 patients, 36 (29.8%) had at least one rapid growth during follow-up. From a univariate standpoint, the risk of rapid growth was higher in women ($OR = 4.6$, $p=0.013$) and lower in case of hyperlipidaemia ($OR = 0.37$, $p=0.016$) (Table 3). Baseline AAA diameter was also associated with AAA rapid growth ($OR = 1.1$, $p=0.0037$). Visual PET positivity and SUVr measurement at baseline were not associated with rapid AAA growth (Table 3).

It is worth adding that in patients with rapid growth, the percentage of at least one PET+ during follow-up was 41.7% compared to 22.4% in the other patients ($p=0.031$).

When combining all risk factors in a stepwise logistic regression analysis, it turned out that the risk of rapid growth was higher in female patients ($OR = 5.62$, $p=0.011$), in patients taking betablockers ($OR = 3.11$, $p=0.029$) and in patients with a family history ($OR = 3.76$, $p=0.042$). The risk was lower in patients with hyperlipidaemia ($OR = 0.28$, $p=0.008$) (Table 4).

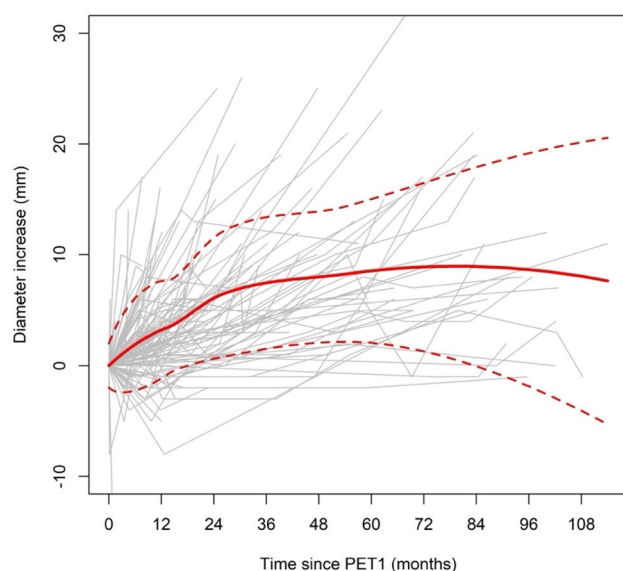


Figure 4. AAA diameter evolution since baseline in patients with at least two diameter assessments (PET/CT or imaging) ($N=121$). LOESSs fitting curve with 95% confidence region.

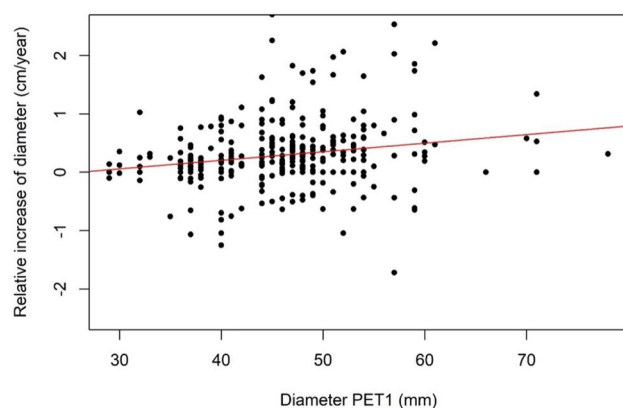


Figure 5. Relationship between AAA size growth rate and baseline AAA diameter in patients with at least two diameter assessments (PET/CT or imaging) ($N=121$).

Risk factors associated with symptomatic patients

During the 9-year follow-up period, 109 patients underwent AAA open surgery and 39 had EVAR. Reasons for intervention were an AAA diameter > 55 mm ($n=104$), a rapid symptomatic AAA growth ($n=17$), AAA rupture ($n=4$), onset of symptoms ($n=9$), and other undetailed reasons ($n=14$). Symptomatic patients at the time of intervention were comparable to asymptomatic patients in terms of age (71.9 ± 8.7 vs. 71.7 ± 7.9 years), gender, major cardiovascular risk factors (smoking, diabetes, hypertension), COPD, and medications. Of note, PET positivity at baseline, which was not considered as a surgical criterion, tended to be observed more frequently in symptomatic patients ($p=0.055$). Interestingly, when considering only patients with positive PET before surgery, the association with symptoms was more marked ($p=0.0053$) (Table 5).

Table 3. Individual assessment of baseline risk factors with respect to rapid growth status in patients with at least two AAA diameter measurements (PET/CT or imaging) ($N=121$).

Variable	Rapid Growth		OR	95%CI	P-value
	No ($N=85$) Mean $\pm$ SD N (%)	Yes ($N=36$) Mean $\pm$ SD N (%)			
Age at baseline (years)	70.5 $\pm$ 7.3	71.1 $\pm$ 10.0	1.01	0.96–1.06	0.73
Gender (Female)	5 (5.9)	8 (22.2)	4.57	1.38–15.1	0.013
Smoking					0.32
Never	13 (15.3)	3 (8.3)	1.00		
Former	41 (48.2)	15 (41.7)	1.59	0.40–6.35	
Current	31 (36.5)	18 (50.0)	2.52	0.63–10.0	
Diabetes	15 (17.6)	3 (8.3)	0.42	0.12–1.57	0.20
Hypertension	50 (58.8)	27 (75.0)	2.10	0.88–5.01	0.094
COPD	28 (32.9)	10 (27.8)	0.78	0.33–1.85	0.58
Renal Failure	13 (15.3)	4 (11.1)	0.69	0.21–2.29	0.55
Stroke	15 (17.6)	4 (11.1)	0.58	0.18–1.90	0.37
Hyperlipidaemia	60 (70.6)	17 (47.2)	0.37	0.17–0.83	0.016
AMI	25 (29.4)	8 (22.2)	0.69	0.27–1.71	0.42
PAD	22 (25.9)	12 (33.3)	1.43	0.61–3.34	0.41
Aspirin	48 (56.5)	21 (58.3)	1.08	0.49–2.38	0.85
Statins	55 (65.5)	20 (55.6)	0.66	0.30–1.46	0.31
Betablockers	22 (26.2)	15 (41.7)	2.01	0.89–4.58	0.095
Family History	9 (10.6)	7 (19.4)	2.04	0.70–5.98	0.19
History of cancer	12 (14.1)	3 (8.3)	0.55	0.15–2.09	0.38
Baseline AAA diameter(mm)	46.5 $\pm$ 8.34	52.3 $\pm$ 10.8	1.07	1.02–1.12	0.0037
SUVr (log scale)*	0.77 $\pm$ 0.24	0.80 $\pm$ 0.23	1.55	0.36–6.73	0.56
Baseline Positive Visual PET	9 (10.6)	7 (19.4)	2.04	0.70–5.98	0.19

*Median (IQR) in both groups (0.74 (0.63–0.86) and 0.75 (0.67–0.83)); COPD: chronic obstructive pulmonary disease; AMI: acute myocardial infarction; PAD: peripheral artery disease.

Table 4. Multivariate assessment of baseline risk factors (stepwise logistic regression analysis) with respect to rapid growth status in patients with at least two AAA diameter measurements (PET/CT or imaging) ($N=121$).

Variable	OR	IC95% OR	p-value
Gender (Female vs. Male)	5.62	1.48–21.4	0.011
Hyperlipidaemia (Yes vs. No)	0.28	0.11–0.72	0.0080
Betablockers (Yes vs. No)	3.11	1.13–8.58	0.029
Family History (Yes vs. No)	3.76	1.05–13.5	0.042

Table 5. Distribution of PET/CT results according to the absence/presence of symptoms before surgery in surgical patients ($N=148$).

	Asymptomatic at surgery ($n=118$)	Symptomatic at surgery ($n=30$)	P-value*
PET at entry			
PET+	20 (17%)	9 (30%)	0.055
SUVr (log-scale)	0.78 $\pm$ 0.17	0.83 $\pm$ 0.23	0.17
SUVr ≥ 1	10 (8.5%)	8 (27%)	0.0066
Diameter	54.9 $\pm$ 12.1	50.2 $\pm$ 9.4	0.27
Last PET before surgery			
PET+	25 (21%)	14 (47%)	0.0053
SUVr (log-scale)	0.80 $\pm$ 0.17	0.88 $\pm$ 0.27	0.25
SUVr ≥ 1	13 (11%)	9 (30%)	0.012
Diameter	56.3 $\pm$ 12.0	52.7 $\pm$ 10.8	0.11

*Derived by logistic regression.

Risk factors associated with mortality

Among the 197 patients, 112 died. Considering each risk factor separately, death increased with age (OR = 1.1,

Table 6. Relationship between risk factors and mortality in patients with at least two AAA diameter measurements (PET/CT or imaging) ($N=121$).

Risk factor	OR	95%CI	P-value*
Age at baseline (years)	1.086	1.03–1.14	0.0012
Gender female	5.039	1.31–19.37	0.019
Smoking			0.21
Former vs Non-smokers	0.714	0.23–2.21	
Current vs Non-smokers	1.453	0.47–4.53	
Diabetes	0.441	0.15–1.33	0.14
Hypertension	1.619	0.76–3.46	0.21
COPD	2.709	1.23–5.97	0.013
Renal Failure	1.534	0.55–4.29	0.41
Stroke	1.525	0.57–4.07	0.40
Hyperlipidaemia	0.321	0.15–0.69	0.0038
AMI	1.535	0.69–3.43	0.30
PAD	1.201	0.54–2.66	0.65
Aspirin	0.643	0.31–1.33	0.23
Statins	0.244	0.11–0.53	0.0004
Betablockers	1.166	0.53–2.54	0.70
Family History	0.254	0.068–0.94	0.041
History of cancer	1.141	0.39–3.38	0.81
SUVr (log scale)	0.936	0.24–3.66	0.92
Visual PET	0.998	0.35–2.88	0.99
SUVr ≥ 1	2.577	0.81–8.21	0.11
Diameter max PET-CT	1.079	1.03–1.13	0.0012
Type of surgery			0.42
Operated vs Non operated	0.572	0.25–1.32	
EVAR vs Non operated	0.656	0.24–1.81	
Diameter Rapid Growth	3.244	1.439–7.31	0.0045

*Logistic regression; COPD: chronic obstructive pulmonary disease; AMI: acute myocardial infarction; PAD: peripheral artery disease.

$p < 0.0001$), female gender (OR = 3.4, $p = 0.036$), in case of COPD (OR = 2.2, $p = 0.0086$), AMI (OR = 2.0, $p = 0.028$), and AAA diameter at baseline (OR = 1.1, $p = 0.0001$). The risk of death was lower for statin users (OR = 0.40, $p = 0.0052$) and hyperlipidemic patients (OR = 0.40, $p = 0.002$). PET positivity at baseline was unrelated to mortality (OR = 1.5, $p = 0.31$).

When restricting the analysis to the 121 patients (53 deaths) with at least two AAA measurements (PET/CT or imaging), similar findings were obtained (Table 6). Interestingly, the risk of death was increased in patients with larger diameters (OR = 1.1, $p = 0.0012$) and in those with AAA rapid growth (OR = 3.2, $p = 0.0045$).

Correlation between tissue staining and PET results

Sections of aneurysmal aortic wall were stained to reveal elastic fibres. As expected, the general structure of aortic wall showed a substantial degradation of extracellular matrix with fragmented elastin fibres in all aneurysmal samples (Figure 6). The semi-quantification of the number of elastic fibres showed a significant decrease in the media at the site of [^{18}F]FDG uptake in PET+ patients as compared to the negative site and as compared to PET– patients. Moreover, the number of elastic fibres was negatively correlated with SUVr ($r = -0.381$, $p = 0.012$). Despite the limited number of female patient biopsies ($n = 3$; two PET+ samples and one PET– sample), the level of elastin amount appeared to be lower in PET+ female patients [$n = 2$, median (IQR): 0.07 (0.5–0.9) %] compared to PET+ male patients [$n = 11$, median (IQR): 0.17 (0.09–1.07) %].

Collagen content in the aneurysmal aortic wall of 5 PET positive patients was estimated from Masson Trichrome staining (Figure 7). There was no statistically significant difference in collagen content in the aortic wall at the positive versus negative site.

Sections of aneurysmal aortic wall were also stained with toluidine blue to visualise cellular and extracellular components. More proteoglycan-rich areas were observed in PET+ regions, indicating more media degradation, compared to PET– regions of the same patients, although the difference was not statistically significant (Figure 8). The percentage increase in proteoglycan deposition in PET+ areas compared with PET– areas was 124% ($n = 13$), with a 96% increase in males ($n = 11$) and a 156% increase in females ($n = 2$).

Discussion

In this prospective cohort of patients with AAA, PET positivity at baseline was not significantly associated with rapid growth or mortality, although it was more frequent in patients who later developed symptoms. In contrast, PET positivity emerging or persisting during follow-up was clearly linked to faster aneurysm expansion and a higher risk of symptomatic presentation before repair, highlighting the added prognostic value of serial imaging.

Value of PET in AAA risk stratification

Our findings support previous evidence that focal [^{18}F]FDG uptake in the aneurysmal wall reflects ongoing inflammatory activity and extracellular matrix degradation, implicated in aneurysm progression and rupture [3,10–14]. Earlier studies, including the work by Reeps et al. [11] demonstrated that PET-positive AAAs are more likely to exhibit histological features of inflammation and proteolysis, and may be associated with higher growth rates. In our cohort, baseline PET positivity was associated with female gender and higher SUVr values, but not with aneurysm size or immediate progression risk. Histological analyses confirmed a significantly lower elastin content in PET-positive wall segments compared to PET-negative segments, and this loss was inversely correlated with SUVr values. Clinically, PET positivity at baseline tended to be more frequent in patients who presented with symptoms prior to surgery, suggesting that metabolic activity on PET may identify aneurysms in a biologically more unstable state, even if not yet reflected in size-based risk metrics. These findings indicate that a single PET/CT at diagnosis may have limited standalone prognostic value but can unveil pathological features linked to both structural wall weakening and symptomatic presentation.

Interest of serial PET/CT monitoring

A key finding of this study is that repeated PET/CT assessments provide temporal information on the biological activity of the aneurysmal wall that is not captured by a single baseline measurement. Patients who were initially

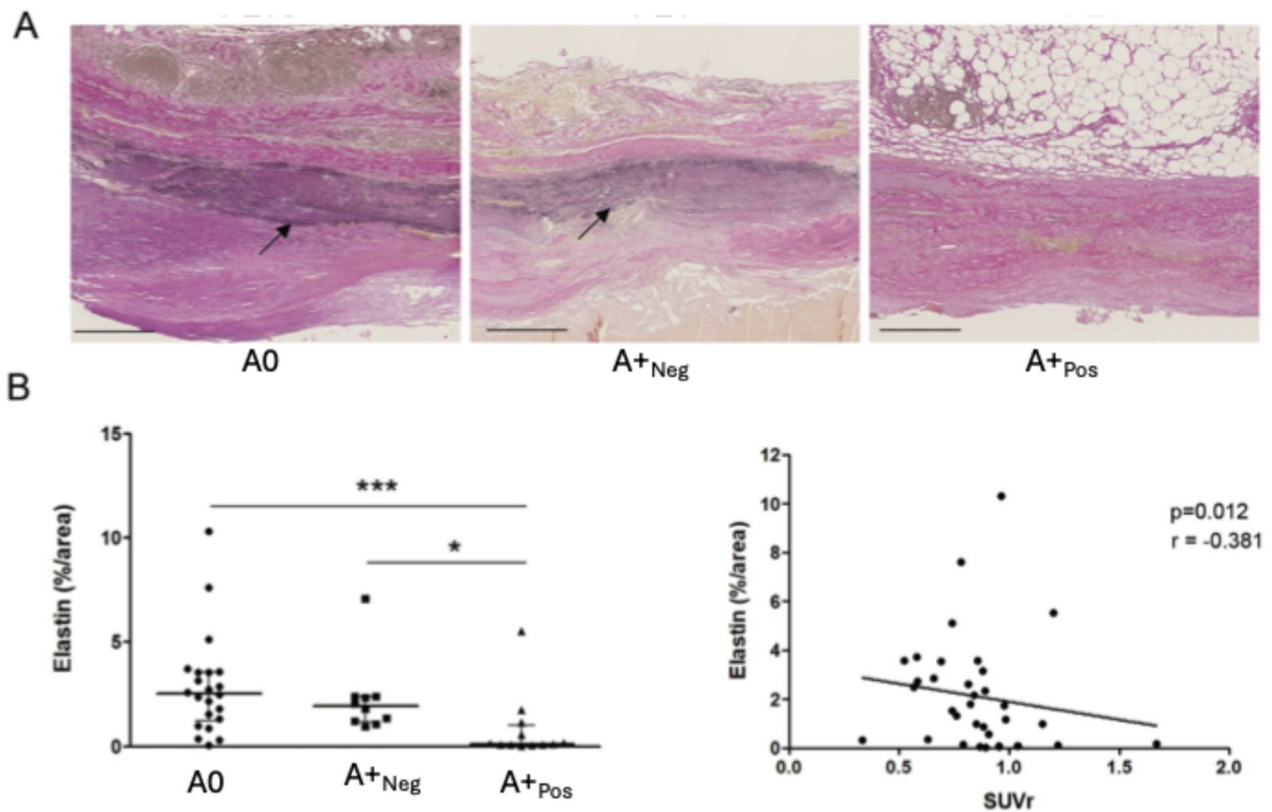


Figure 6. Elastin content (arrows) in AAA wall and its relationship with PET/CT metabolic activity. (A) Representative histological sections (Elastica van Gieson staining) of aneurysmal aorta of PET – patients (A0), of PET negative regions (A+N_{eg}) and of PET positive regions (A+P_{os}) of aneurysmal aorta of PET+ patients, showing reduced elastic fibres in PET+ areas. (B) Quantitative analysis illustrating lower elastin content in PET positive compared to PET negative regions. (C) Correlation plot of elastin content and SUVr showing their inverse relationship.

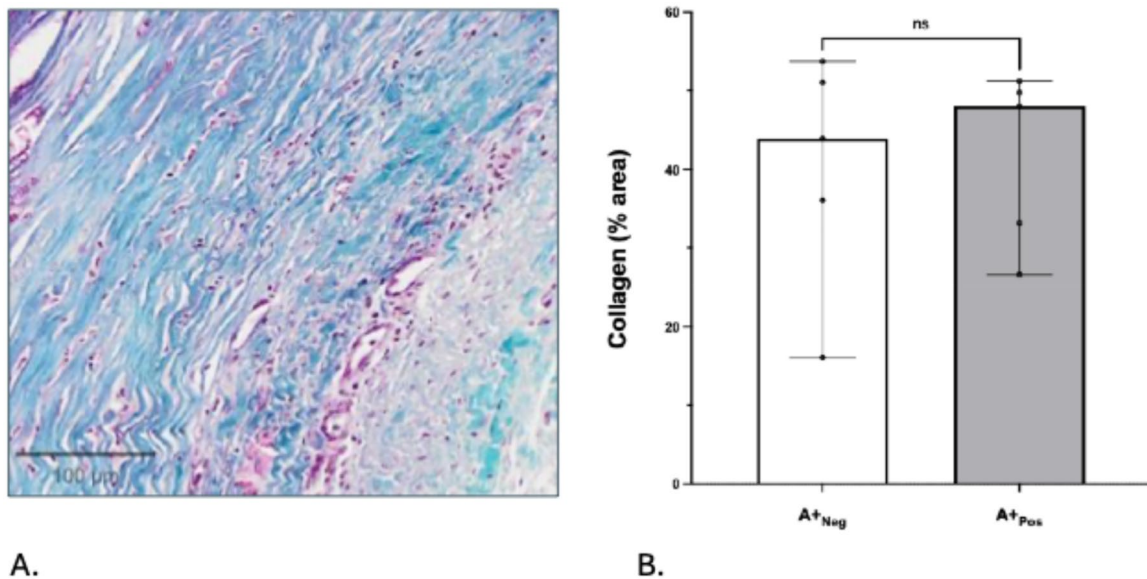


Figure 7. Collagen content estimated from Masson Trichrome staining (A) in AAA wall and its relationship with PET/CT metabolic activity. Comparison of collagen content between PET negative and PET positive sites in the aortic wall of 5 PET positive patients (B).

PET-negative but developed PET positivity during follow-up had a significantly higher incidence of rapid aneurysm growth and symptomatic presentation

compared with those who remained PET-negative. This pattern indicates that metabolic activation within the aneurysm wall is not constant over time but may occur

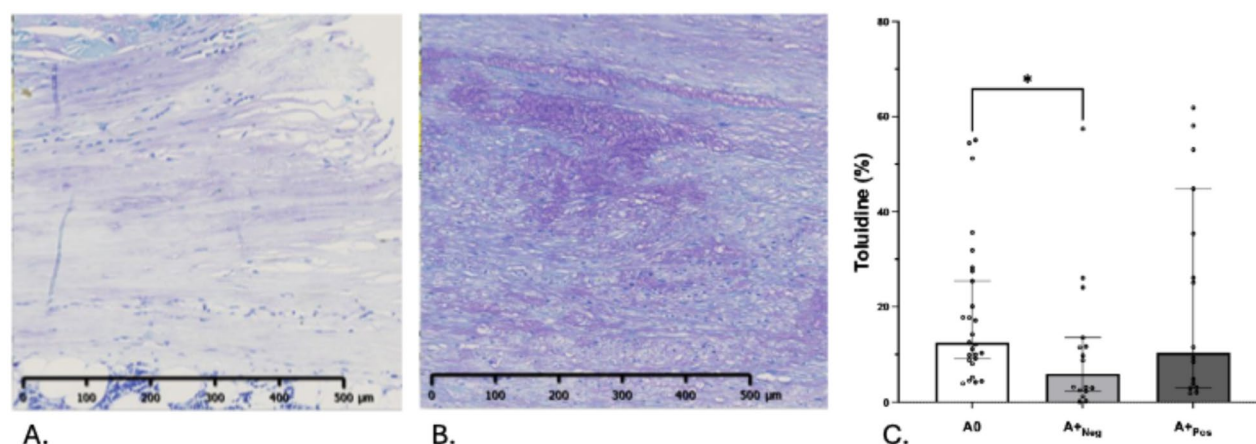


Figure 8. Toluidine staining in AAA wall and its relationship with PET/CT metabolic activity. Representative histological sections of toluidine blue staining (A. PET- area and B. PET+ area of the same patient). Nuclei appear dark blue, collagen and elastin rich areas show a light blue shade (turquoise for elastin and light blue for collagen). Proteoglycan deposits are stained in purple. C. Semiquantitative analysis of proteoglycan content in the tissues of 27 patients with PET negative at the moment of surgery (A0) and 13 tissues from PET+ patients in an area PET negative A+Neg and in PET positive area, A+Pos.

intermittently, potentially influenced by changes in local hemodynamic stress, systemic inflammatory status, or intercurrent clinical events [3,6].

From a mechanistic standpoint, conversion from PET-negative to PET-positive status may reflect a shift from a relatively quiescent phase to one characterised by active extracellular matrix degradation. Uptake of [^{18}F]FDG corresponds to the presence of metabolically active inflammatory cells, predominantly macrophages, which secrete proteolytic enzymes such as matrix metalloproteinases (MMPs) that contribute to elastin fragmentation and weakening of the aortic wall [4,14–16]. This is reflected in the decrease observed in elastin and increase in proteoglycans in PET+ areas compared to PET- areas, although differences are not statistically significant for proteoglycan content. Overall, collagen content did not differ between positive and negative sites; however, when considering adventitia only, collagen was lower at the positive sites compared to the negative sites, likely due to increased cellular infiltrates in these regions. These results are in line with smaller longitudinal studies [17]. For instance, Reeps et al. found an association between higher [^{18}F]FDG uptake, faster aneurysm growth, and increased inflammatory cell infiltration, although most earlier investigations relied on single time-point imaging [11,18]. The present data indicate that the temporal change in PET status provides additional prognostic information beyond baseline measurements, particularly in patients with aneurysm diameters below surgical thresholds who may undergo abrupt biological activation.

Male and female differences

Although no risk factors differences were found associated with gender, the proportion of PET+ was higher in females compared to males (40% vs 17%, $p=0.033$), as well as in patients with AAA rapid growth (OR = 4.6, $p=0.013$). Being female also increased the risk for mortality (OR = 3.4, $p=0.036$). At the tissular level, the amount

of elastin was lower in female and the percentage of elastin decrease in PET+ areas compared to PET- areas was more pronounced compared to males. There are well-known gender differences in AAA already reported in the literature [19]. Although not scientifically proven, population studies show an inverse association between reproductive time (i.e. shorter life-time exposure to endogenous estradiol) and AAA size in women. Gender hormones, in particular the loss of oestrogen after menopause, may lead to increased protease activity and reduced inhibition of elastolysis, explaining why women have less elastin and higher MMP-9 levels (elastolytic enzyme) compared to men [20].

Hyperlipidaemia and statin use

Statins (hydroxymethylglutaryl-coenzyme A reductase inhibitors) are primarily known for their cholesterol-lowering effects. On the other hand, several studies have suggested an association between statins treatment and improvement of AAA [21]. In fact, by reducing arterial wall inflammation, known to play a critical role in aneurysm development and rupture, statins may slow down AAA progression. Moreover, a recent meta-analysis concluded that statin therapy was associated with reduced arterial wall inflammation, as evidenced by decreased [^{18}F]FDG uptake on PET/CT scans [22]. In the present study, patients with hyperlipidaemia or those taking statins had smaller AAA diameters compared to their counterparts, although the difference was not statistically significant. On the other hand, hyperlipidaemia, but not statin use, was associated with PET negative status and with an AAA non-rapid growth. A meta-analysis including 14 studies with 38,749 patients indicated that statin therapy was associated with a significantly reduced AAA growth rate, (mean annual drop: -1.5 mm , $p<0.00001$) and reduced significantly short and long-term mortality after AAA repair [23]. Another meta-analysis conducted by Salata et al. revealed that statins are associated with

reduced AAA growth rates, lower rupture risk, and decreased perioperative mortality [24]. In accordance with the literature [23–25], our study confirmed a significantly lower risk of death in case of statin use.

While statins appear to offer benefits in reducing AAA growth rates and improving survival outcomes post-repair, they are not currently established as a primary treatment to prevent AAA progression. The evidence from randomised controlled trials specifically focused on statins for AAA progression remains limited, and further research is needed to confirm these observational findings and to establish definitive correlations between statin therapy, AAA progression, and PET/CT imaging findings.

Clinical implications

The potential integration of serial [^{18}F]FDG PET/CT into AAA surveillance protocols raises important considerations for day-to-day management. Beyond static anatomical thresholds, repeated metabolic imaging can detect a shift from a stable to an active inflammatory phase, signalling a period of increased risk of rupture. In such cases, shortening surveillance intervals, intensifying clinical follow-up, or bringing forward surgical referral may be warranted, even if maximal diameter criteria are not yet met. This strategy may be particularly relevant in intermediate-sized aneurysms, in patients with recent symptom onset, or in those with other high-risk features such as rapid recent growth or female gender. Conversely, patients with persistently negative serial PET/CT could be followed with standard or extended imaging intervals, thereby reducing unnecessary radiation exposure, procedural risk, and healthcare costs. Embedding PET/CT findings into multidisciplinary decision-making could therefore help refine patient selection for early intervention and optimise timing of repair.

Study limitations

Several limitations should be acknowledged. First, although our cohort is among the largest with serial PET/CT in AAA, the observational design precludes establishing causality between PET positivity and outcomes. Second, the study was conducted in specialised tertiary centres, which may limit generalisability. Third, PET/CT acquisition protocols and devices evolved over the study period, which could have influenced SUV measurements, although the use of SUV ratio to liver uptake mitigated this variability. Fourth, the number of patients with histological correlation was limited, particularly among women, reducing our ability to fully explore gender-specific pathophysiological differences. Finally, radiation exposure and cost considerations remain relevant obstacles to the routine use of serial PET/CT.

Conclusion

Our findings indicate that baseline [^{18}F]FDG PET/CT positivity, when considered in isolation, shows no consistent

association with rapid AAA progression or mortality after adjustment for other risk factors. In contrast, the emergence or persistence of PET positivity during follow-up was associated with accelerated aneurysm growth and a higher likelihood of symptom development. These observations support the potential role of serial PET/CT within surveillance strategies, particularly for patients at intermediate surgical thresholds. Further prospective, multicentre studies, including cost-effectiveness analyses, are needed to determine whether PET-guided monitoring can improve outcomes and refine the timing of intervention in AAA management.

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Disclosure statement

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