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OBSERVATIONAL STUDY

Total Luminal Volume Predicts Risk after Endovascular Aneurysm Repair

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WHAT THIS PAPER ADDS

Maximum aortic diameter has been recognised as an independent risk factor for endovascular aneurysm repair (EVAR) failure. However, the reason may relate to the size of the lumen free of thrombus. Larger luminal volume may allow for subtle, progressive movement of the endograft within the aneurysm sac, leading to sealing related complications over time. This study shows that lumen volume represents an important risk factor for late complications after EVAR, mainly caused by neck related events. As such, lumen volume may be relevant for informed consent and surveillance protocols.

Objective: Large aneurysm diameter represents a well known predictor of late complications after endovascular aneurysm repair (EVAR). However, the role of the thrombus free lumen inside the abdominal aortic aneurysm (AAA) sac is not clear. It was hypothesised that greater luminal volume represents a relevant risk factor for late complications after EVAR.

Methods: A retrospective cohort analysis was performed including all patients undergoing EVAR from 2005 to 2016 at a tertiary referral institution. Pre-operative AAA lumen volume was measured in centre lumen line reconstructions and patients were stratified into quartiles according to luminal volume. The primary endpoint was freedom from AAA related complications. Secondary endpoints were freedom from neck events (type 1A endoleak, migration >5 mm or any pre-emptive neck related intervention), iliac related events (type 1B endoleak or pre-emptive iliac related intervention), and overall survival.

Results: Four hundred and four patients were included: 101 in the first quartile (Q1; <61 cm^3). Patients with higher luminal volumes had wider, shorter, and more angulated proximal necks. There were more ruptured AAAs, more aorto-uni-iliac implanted devices and patients outside neck instructions for use in the 4th quartile. Five year freedom from AAA related complications was 79%, 66%, 58% and 56%, respectively ($p = .007$). At five years, freedom from neck related events was 86%, 84%, 73%, and 71%, respectively, for the four groups ($p = .009$), and freedom from iliac related events was 96%, 91%, 88%, and 88%, respectively ($p = .335$). On multivariable analysis, luminal volume was an independent predictor of late complications (Q4 *vs.* Q1 — hazard ratio: 1.91, 95% confidence interval 1.01—3.6, $p = .046$). Overall survival at five years was not affected by lumen volume ($p = .75$).

Conclusion: AAA luminal volume represents an important risk factor for AAA related complications. This information may be considered when deciding tailoring surveillance protocols after EVAR. However, larger studies are needed to validate this hypothesis.

Keywords: Aortic aneurysm, Abdominal, Complications, Endovascular procedures, Lumen volume
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INTRODUCTION

Endovascular aneurysm repair (EVAR) has become the preferred modality for abdominal aortic aneurysm (AAA) repair. However a low but persistent risk of rupture and high rate of secondary interventions remain the main drawbacks and lifelong imaging surveillance is therefore warranted.[1–3]

AAA diameter is a well known anatomical characteristic linked to an increased risk of late complications.[4–7] In most patients, even with larger AAA diameters, the sac is partially filled with thrombus, which may limit the endograft's mobility within the sac over time. Conversely, in large patent lumens, regardless of total sac diameter, there is a greater propensity for the stentgraft to dislodge, leading to seal complications.

It was hypothesised that AAA luminal volume may represent an important risk factor for AAA related complications over time, because of a higher propensity for graft dislodgement.

METHODS

Design and population

A retrospective cohort study was designed based on a prospectively maintained database, including all patients undergoing EVAR in a single tertiary referral centre. Informed consent was not required according to institutional policy on retrospective research. All consecutive patients undergoing standard EVAR between January 2005 and December 2016 for infrarenal AAA were included. Patients with previous aortic surgery, with a diagnosis other than degenerative AAA and isolated iliac aneurysm were excluded. Additionally, patients who died perioperatively and those without a pre-operative contrast enhanced computed tomography angiogram (CTA) with adequate quality for luminal volume measurement were excluded.

Post-operative surveillance

At the beginning of the study period, contrast enhanced CTA was routinely performed at one, six, 12 months, and yearly thereafter. Since then, the six month CTA has been progressively reserved only for selected patients with, or at an increased risk of developing aneurysm related complications. Alternatively, if patients were considered by the treating physician to be at low risk of complications or had renal function impairment, coloured duplex ultrasound and or non-contrasted CT was preferred. On detection of an adverse event on these imaging modalities, such as enlargement >5 mm or an endoleak other than a type 2 endoleak, the patient would undergo a CT scan.

Data management

At the time of intervention, baseline demographic data were collected, and anatomical measurements were performed. At outpatient visits and or at regular and predefined intervals, patient records were assessed and subsequent follow up data were acquired prospectively.

Image analysis and measurements

All measurements were obtained on CT imaging using semi-automatically generated centre lumen line reconstructions performed on dedicated reconstruction software (3mensio Vascular 4.2; Medical Imaging B.V., Bilthoven, The Netherlands). All imaging data were acquired by four observers with experience in image analysis (FBG, NO, JOP, RF).

The total volume of the aneurysm was calculated, as previously reported and validated.[8,9] In brief, AAA volume was semi-automatically calculated using dedicated software and measured from 10 mm distal to the lower renal to 10 mm above the aortic bifurcation. For calculation of the luminal volume, the same anatomical references were adopted (10 mm distal to the lower renal to 10 mm above the aortic bifurcation; Fig. 1). Luminal volumes were obtained from the pre-operative CT scan, and no luminal measurements were performed after endograft implantation.

Luminal AAA volume medians and quartiles were calculated, and patients were classified accordingly: 1st quartile (Q1), 2nd quartile (Q2), 3rd quartile (Q3), and 4th quartile (Q4).

AAA diameter and total volumes were also stratified into quartiles and their respective impact on the occurrence of AAA related complications was also assessed in a separate sensitivity analysis.

The intra-observer variability for pre-operative AAA volume, endograft migration, and proximal sealing length measurements were tested in a sample of 40 patients, with very good agreement (Spearman's correlation coefficient for AAA volume of .996 [$p < .001$], for graft migration .971 [$p < .001$], and for proximal sealing length .993 [$p < .001$]).

Inter-observer variability for pre-operative AAA volume and pre-operative AAA diameter were also analysed. High agreement was found between the measurements (Spearman's correlation coefficient for pre-operative AAA volume of .987 [$p < .001$] and for pre-operative AAA diameters .970 [$p < .001$]).

Aneurysm neck length was defined as the distance from the lowest renal artery to the level where the aortic diameter increased more than 10%. Aneurysm neck angulation was also measured according to previously validated methodology.[8,9] The angles between the suprarenal aorta and the aneurysm neck (α) and between the aneurysm neck and sac (β) were measured.

The maximum aortic diameter was measured in the transverse plane after centre lumen line reconstruction.

Aneurysm neck thrombus and calcification were categorised according to infrarenal aortic neck circumferential involvement. Neck configuration was classified according to published methodology.[10] In a previous report, the present study group has demonstrated high rates of inter-observer agreement regarding aneurysm

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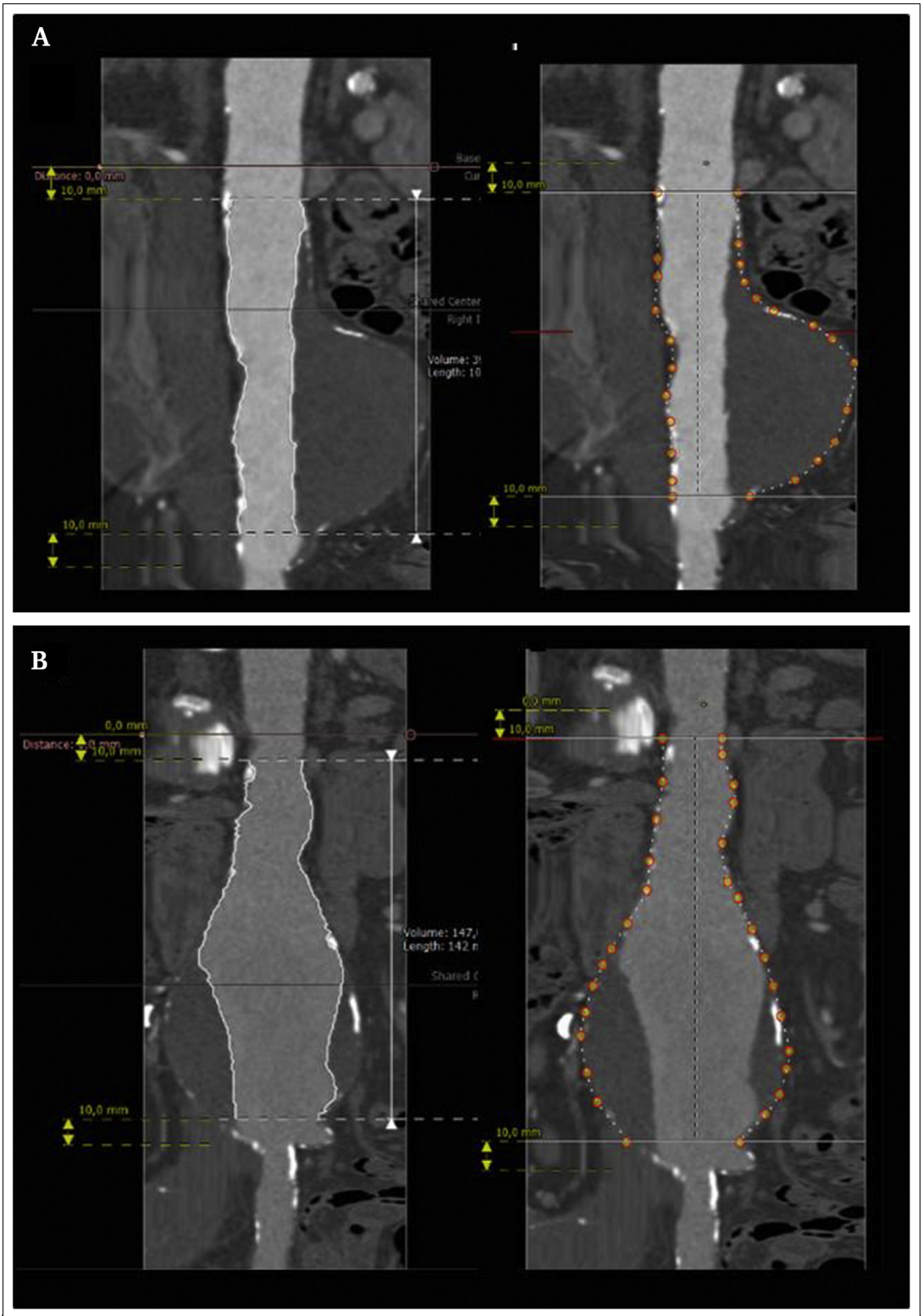

Figure 1. Illustrative representation of lumen volume measurement of abdominal aortic aneurysm (AAA). Lumen volume is surrounded by white line (contrasted area). Total AAA volume is surrounded by orange dots. A = Large AAA with small lumen; B = Large AAA with large lumen.

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Table 1. Baseline demographic, morphological, and peri-operative characteristics of endovascular aneurysm repair (EVAR) patients according to lumen volume

Characteristics	Aneurysm lumen volume divided into quartiles				*p* value
	Q1 <61 mL (*n* = 101)	Q2 61–84.9 mL (*n* = 101)	Q3 85–118.9 mL (*n* = 101)	Q4 ≥119 mL (*n* = 101)	
Mean age ± SD – years	71.6 ± 7.4	73.8 ± 8.2	72.1 ± 6.9	73.0 ± 7.6	.17*
Age > 70 – years	61	68	63	63	.79
Male	83	90	93	93	.080
SVS/AAVS Cardiac Status	17	18	16	18	.93
Hypertension	75	69	76	67	.55
Antiplatelet therapy	69	64	61	58	.43
Smoking	77	77	69	69	.63
Diabetes	18	17	19	19	.97
PAD	19	14	19	15	.73
Creatinine clearance <60 mL/min/1.73m^2	20	25	30	28	.36
Ruptured AAA	5	6	11	35	<.001
AAA Ø	54 (47–60)	58 (54–63)	60 (55–68)	74 (62–89)	<.001†
AAA volume – mL	120 (94–156)	163 (133–201)	198 (159–262)	333 (213–475)	<.001†
Reverse taper neck	20	23	21	26	.80
Neck Ø – mm	24 (22–26)	25 (22–27)	25 (23–28)	25 (23–28)	.010†
Neck Ø > 28 mm	10	18	16	24	.11
Neck length – mm	29 (20–38)	29 (20–38)	27 (18–40)	24 (16–35)	.030†
Neck length < 15 mm	7	6	9	15	.13
Neck thrombus >25%	46	37	42	34	.27
Neck calcification >25%	23	23	18	16	.49
α Angle – °	16 (9–25)	20 (12–30)	24 (14–35)	33 (19–51)	<.001†
α Angle > 45°	5	6	8	33	<.001
β Angle – °	32 (21–44)	36 (25–52)	37 (28–49)	53 (41–69)	<.001†
β Angle > 60°	9	17	11	43	<.001
Baseline oversizing	18.4 (12–22)	18.4 (12–22)	19.1 (13–27)	19.1 (13–27)	.94†
Proximal seal length	23 (14–16)	23 (16–27)	20 (15–29)	17 (20–23)	.002†
Right iliac seal length – mm	30 (22–41)	29.5 (20–41)	31 (24–43)	30 (22–45)	.81†
Left iliac seal length – mm	30 (20–43)	32 (21–37)	28 (20–41)	31 (22–40)	.77†
Outside IFU	12	14	13	37	<.001
AUI graft configuration	7	4	5	20	<.001
Graft model					
Endurant	61	63	67	75	
Excluder	30	34	27	22	
Talent	2	2	4	2	
Zenith	0	1	1	1	
Other	7	0	1	1	

Data are presented as median (interquartile range) for continuous data and as *n* for categorical data, unless stated otherwise. AAA = abdominal aortic aneurysms; AAVS = American Association for Vascular Surgery; AUI = aorto-uni-iliac; eGFR = estimated glomerular filtration rate; IFU = instructions for use; PAD = peripheral arterial disease; SVS = Society for Vascular Surgery; Ø = diameter; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile.
Univariable differences were assessed with χ^2 test, except *one way ANOVA and †Kruskal–Wallis Test.

diameter, neck diameter, neck length, and proximal seal length measurements.[11]

Definitions

Patient comorbidities and aneurysm related outcomes were reported according to the guidelines from the Society for Vascular Surgery/American Association of Vascular Surgery ad hoc Committee for Standardised Reporting Practices in Vascular Surgery.[12]

Luminal volume was defined as the volume free of thrombus within the aneurysm sac (as shown in the left panels of Fig. 1A and B).

Oversizing was calculated by dividing the difference between the implanted main body diameter and the reference neck diameter in the first 15 mm of the infrarenal neck by the latter.

AAA related complications were defined as a composite of the following: type 1 or 3 endoleak, aneurysm sac expansion, migration >5 mm, graft infection or thrombosis, device integrity failure, AAA related death, post-implant rupture, or any AAA related secondary intervention. Secondary interventions were considered to be AAA related if performed to resolve or prevent a possible complication and included proximal cuff and stent implant,

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Table 2. Mid term outcomes of endovascular aneurysm repair (EVAR) patients, according to abdominal aortic aneurysm (AAA) lumen volume, occurring after hospital discharge

Complications	Patients classified in quartiles according to aneurysm lumen volume				*p*
	Q1 *n* = 101	Q2 *n* = 101	Q3 *n* = 101	Q4 *n* = 101	
Follow up − years	3.8 (2.2–6.4)	3.5 (1.9–6.4)	3.7 (1.8–5.9)	5.1 (2.3–7.3)	.20
CT follow up − years	2.5 (1.1–5.7)	2.7 (1.1–5.7)	2.1 (1.1–5.7)	3.5 (1.5–6.3)	.09
Mortality − *n*	31	34	35	34	.75*
ARM − *n*	1	2	1	3	.30*
Aneurysm related complications	27	26	37	45	.007*
Post-implant ruptures	1	0	0	2	.30
Type 1A endoleak	3	4	7	7	.46
Type 1B endoleak	3	3	4	4	.96
Type 2 endoleak	16	11	10	18	.29
Type 3 endoleak	0	0	1	0	.39
Aneurysm sac growth	18	14	14	13	.72
Volume > 5%	16	13	14	12	.87
Diameter > 5 mm	9	7	6	11	.57
Migration > 5 mm	9	9	14	9	.58
Limb thrombosis	0	4	2	5	.14
Graft infection	1	1	1	3	.27
Secondary interventions	9	15	21	30	.004*
Proximal re-intervention	4	5	12	17	.006*
Proximal cuff	1	3	7	9	.038
Fenestrated cuff	0	2	2	2	.57
Relining	0	1	1	2	.57
Distal extension	3	7	9	10	.23
Embolisation/ligation collaterals	1	0	1	1	.80
Other	1	3	1	6	.10
Open conversion	3	2	5	5	.60
Iliac related events	4	7	9	12	.335*

Data presented as *n* for dichotomous data and as median (interquartile range) for continuous data. *p* values obtained from log rank test are marked as *. ARM = aneurysm related mortality; CT = computed tomography; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile.

distal extension, catheter based thrombolysis, iliac angioplasty, coil or glue embolisation of aortic branch vessels, balloon thrombectomy, femorofemoral crossover, conversion to open repair, and open or laparoscopic ligation of collaterals.

Aneurysm sac expansion was assessed between the first post-operative and last available CTA. Sac growth was defined as a >5% increase in aneurysm sac volume or as > 5 mm increase in sac diameter.

Type 1A endoleak, device migration >5 mm, or pre-emptive neck related intervention were registered as infrarenal neck related events.

An iliac related event was defined as the occurrence of type 1B endoleak or any iliac related intervention.

All adverse events reported above occurred during follow up and not as part of the primary procedure.

Endpoints

The primary endpoint was freedom from AAA related complications. Secondary endpoints were freedom from secondary interventions, neck related adverse events, iliac related events, and overall and AAA related mortality. Individual components of AAA related complications were also explored individually: aneurysm rupture, sac expansion, type 1A, type 1B, type 2 and type 3 endoleaks, secondary interventions, limb thrombosis, graft infection, conversion to open repair, or death as a result of aneurysm rupture or aneurysm related treatment.

Statistical analysis

Categorical variables are presented as count and percentage and compared using the Pearson's chi-square test. Where there were low numbers of cases per group ($n < 5$), the Fisher exact test was used. Continuous variables are presented as mean and standard deviation (SD) or as median and interquartile range (IQR) and differences between groups were analysed using the Kruskal–Wallis test for independent samples with non-normal distributions or with the one way ANOVA for non-related variables with normal distributions, and the overall *p* value is shown.

Survival curves for freedom from aneurysm related adverse events were estimated by Kaplan–Meier methods, and equality between quartiles was tested using the Mantel–Cox log rank test. Aneurysm related complications (primary endpoint) were assessed by Cox hazards regression models. Multivariable regression was performed to include demographic, morphological, and procedural features with an α level <.1 in univariable analysis and results are presented using quartile 1 as reference. Confidence intervals (CIs) of 95% were used and

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statistical significance was considered if $p < .05$. All statistical analysis was performed using SPSS 24.0 (IBM, Armonk, NY, USA).

RESULTS

From 2005 to 2016, 604 patients underwent primary standard EVAR. Seventy-two patients were considered ineligible for this study: 33 anastomotic or other pseudoaneurysms, 27 isolated iliac aneurysms, 11 infected and one traumatic rupture. Among the remaining 532 patients, 25 died in hospital and five patients were converted to open repair intra-operatively. Additionally, pre-operative lumen volume was not accessible in 98, leaving a final study population of 404 patients. The mean age was 72.6 years and 89% were male.

Patients were classified according to their luminal AAA volumes into four quartiles: Q1 if AAA lumen volume <61 cm^3 ($n = 101$), Q2 from 61 to 84.9 cm^3 ($n = 101$), Q3 from 85 to 118.9 cm^3 (n = 101), and Q4 if AAA lumen $\geq$ 119 cm^3 ($n = 101$).

Patients with higher luminal volume had wider proximal necks (neck diameter (mm): 24 [22–26] *vs.* 25 [22–27] *vs.* 25 [23–28] *vs.* 25 [23–28], $p = .010$) and also shorter proximal necks (neck length (mm): 29 [20–38] *vs.* 29 [20–38] *vs.* 27 [18–40] *vs.* 24 [16–35], $p = .030$, respectively). Neck angulation was also greater among those patients within the Q4 (α angle: 16 [9–25] *vs.* 20 [12–30] *vs.* 24 [14–35] *vs.* 33 [19–51], $p < .001$ and β angle: 32 [21–44] *vs.* 36 [25–52] *vs.* 37 [28–49] *vs.* 53 [41–69], $p < .001$). At baseline, there were more ruptured AAA (rAAA) in Q4 (5 in Q1; 6 in Q2; 11 in Q3 and 35 in Q4, $p < .001$). Baseline endograft oversizing was similar among groups (18% [12–22%] *vs.* 18% [12–22%] *vs.* 19% [13–27%] *vs.* 19% [13–27%] respectively, $p = .94$). Seventy-six patients were outside neck IFU for the respective endograft: 12 in Q1, 14 in Q2, 13 in Q3, and 37 in Q4, $p < .001$. Breached IFU was neck length in 13 patients and neck angulation in 66 patients. Baseline clinical and anatomical characteristics are shown in Table 1.

Regarding procedural details, patients with quartile 4 aortic luminal volume had more AUI devices implanted (7 *vs.* 4 *vs.* 5 *vs.* 20, $p < .001$; Table 1).

Aneurysm related complications

Over a median follow up of 3.7 years (IQR 1.8–6.5), 135 (33.4%) patients had aneurysm related complications: 27 in Q1, 26 in Q2, 37 in Q3, and 45 in Q4 (Table 2). CT follow up was 2.5 years (1.1–5.7) in Q1, 2.7 (1.1–5.7) in Q2, 2.1 (1.1–5.7) in Q3, and 3.5 (1.5–6.3) in Q4 ($p = .090$).

Five year freedom from AAA related complications was 79% ($n = 36$, SE = .053), 66% ($n = 29$, SE = .063), 58% ($n = 27$, SE = .062), and 56% ($n = 31$, SE = .060), respectively ($p = .007$) (Fig. 2). In a subanalysis excluding patients treated in the context of AAA rupture, five year freedom from AAA related complications was 80% ($n = 35$, SE = .054), 67% ($n = 28$, SE = .064), 60% ($n = 25$, SE = .062), and 59% ($n = 20$, SE = .074), respectively ($p = .008$).

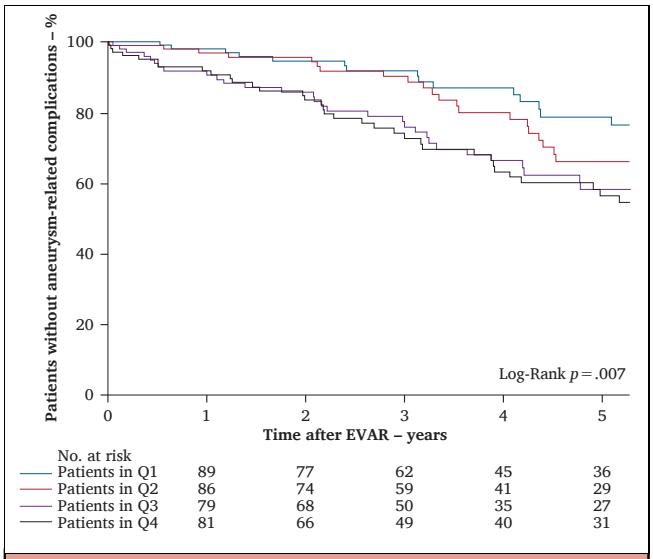

Figure 2. Cumulative Kaplan–Meier estimate of freedom from aneurysm related complications after endovascular aneurysm repair (EVAR) according to abdominal aortic aneurysm (AAA) lumen volume.

Aneurysm sac growth occurred similarly between groups (18 *vs.* 14 *vs.* 14 *vs.* 13, respectively, $p = .72$) (Table 2). Three patients had post-implant ruptures: one in Q1 and two in Q4 ($p = .30$). The patient in Q1 had a rupture secondary to an isolated type 1B endoleak. This patient was offered limb extension but, because of clinical deterioration, was considered unfit for further interventions. In Q4, two post-implant ruptures occurred: the first patient was 88 years old with a sharply angulated neck, who had a type 1A endoleak but was considered unsuitable for endovascular repair and unfit for open surgery. Another patient had a rupture because of type 1c endoleak through an occluder positioned on the left common iliac artery after AUI EVAR.

On multivariable analysis, correcting for baseline and procedural differences (gender, AAA diameter, α and beta angulation, proximal sealing length, neck diameter, rupture as indication, and AUI devices), AAA luminal volume represented an independent predictor of aneurysm related complications (Q4 *vs.* Q1 – HR: 1.91, 95% CI 1.01–3.6, $p = .046$), while aneurysm diameter did not (HR: 0.99, 95% CI 0.98–1.01, $p = .45$) (Table 3). A multivariable analysis correcting for compliance with IFU was performed. Both Q3 and Q4 remained independent predictors of complications after EVAR (Q4 *vs.* Q1 – HR: 1.98, 95% CI 1.08–3.64, $p = .028$, and Q3 *vs.* Q1 – HR: 1.76 95% CI 1.03–3.02, $p = .039$).

Secondary interventions

During follow up, 88 secondary interventions were performed in 75 (18.6%) patients: nine patients in Q1, 15 patients in Q2, 21 patients in Q3, and 30 patients in Q4. Freedom from secondary interventions at five years was 91% ($n = 36$, SE = .039), 79% ($n = 29$, SE = .057), 75%

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Table 3. Multivariable analysis for freedom from aneurysm related complications after endovascular aneurysm repair (EVAR), between different lumen volume quartiles

Risk factor	Univariable analysis			Multivariable analysis					
				Adjusted for AAA diameter only			Adjusted for gender, AAA diameter, α and β angulation, PSL, neck diameter, rupture as indication, AUI devices		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p*
Q1	Ref			Ref			Ref		
Q2	0.98	0.57–1.68	.94	0.97	0.56–1.68	.91	1.05	0.59–1.9	.88
Q3	1.65	0.99–2.72	.051	1.63	1.05–3.31	.062	1.67	0.97–2.9	.066
Q4	1.91	1.18–3.08	.008	1.86	1.05–3.31	.035	1.91	1.01–3.6	.046

AAA = abdominal aortic aneurysm; AUI = aorto-uni-iliac; HR = hazard ratio; 95% CI = 95% confidence interval; PSL = proximal sealing length; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile.

(*n* = 27, SE = .054), and 66% (*n* = 31, SE = .059), respectively (*p* = .001) (Fig. 3). Detailed data regarding secondary interventions are presented in Table 2.

Indications for secondary interventions are listed in Table S1.

Neck related events

During the study period, neck related events occurred in 84 patients (21%): 16 in Q1, 13 in Q2, 28 in Q3, and 27 in Q4. Estimates for freedom from neck related events at five years were 86% (*n* = 38, SE = .044), 84% (*n* = 34, SE = .048), 73% (*n* = 31, SE = .050), and 71% (*n* = 35, SE = .058), respectively (*p* = .009).

There were no significant differences between groups regarding Type 1A endoleaks (3 *vs.* 4 *vs.* 7 *vs.* 7%, *p* = .46) or migration >5 mm (9 *vs.* 9 *vs.* 14 *vs.* 9, *p* = .58). Thirty-eight patients had neck related interventions: four in Q1, five in Q2, 12 in Q3, and 17 in Q4 (Table 2).

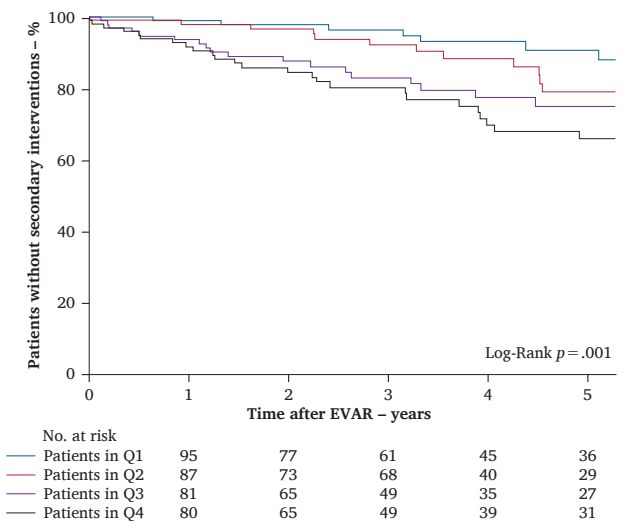

Figure 3. Cumulative Kaplan–Meier estimate of freedom from secondary interventions after endovascular aneurysm repair (EVAR).

Estimates of freedom from neck related intervention at five years were 97% (*n* = 39, SE = .023), 93% (*n* = 38, SE = .037), 87% (*n* = 32, SE = .040), and 79% (*n* = 39, SE = .051), respectively (*p* = .006).

Iliac related events

Iliac related events occurred in 32 patients (7.9%): four in Q1, seven in Q2, nine in Q3, and 12 in Q4 (*p* = .20).

The Kaplan–Meier estimates for freedom from iliac related events at five years were 96% (*n* = 37, SE = .029), 91% (*n* = 31, SE = .039), 88% (*n* = 32, SE = .045), and 88% (*n* = 46, SE = .038), respectively (*p* = .34).

Fourteen iliac related events were type 1B endoleaks: three in Q1, three in Q2, four in Q3, and four in Q4 (*p* = .961). Twenty-nine patients underwent distal extension because of type 1b endoleak or loss of iliac seal: three in Q1, seven in Q2, nine in Q3, and 10 in Q4 (*p* = .23) (Table 2).

Overall and AAA related mortality

Over the follow up period, 134 patients died: 31 in Q1, 34 in Q2, 35 in Q3, and 34 in Q4. Estimates for overall survival at five years were 75% (*n* = 47, SE = .049), 76% (*n* = 43, SE = .046), 70% (*n* = 40, SE = .052), and 72% (*n* = 54, SE = .048), respectively (*p* = .75) (Fig. 4). There were seven AAA related deaths: one in Q1 (graft infection) two in Q2 (graft infection and following secondary intervention), one in Q3 (graft infection), and three in Q4 (post-implant rupture in two and endograft infection in one). In a sub-analysis excluding patients treated in the context of rupture, overall survival estimates at five years were 75% in Q1 (*n* = 43, SE = .052), 77% in Q2 (*n* = 41, SE = .047), 72% in Q3 (*n* = 37, SE = .054), and 74% in Q4 (*n* = 36, SE = .058) (*p* = .78). In this subset of patients there were five aneurysm related deaths: one in Q1 (graft infection) two in Q2 (graft infection and following secondary intervention), one in Q3 (graft infection), and one in Q4 (post-implant rupture).

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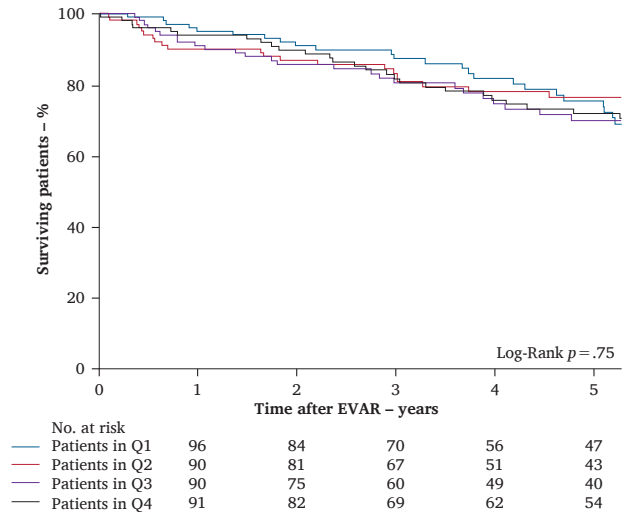

Figure 4. Cumulative Kaplan–Meier estimate for overall survival after endovascular aneurysm repair (EVAR) according to abdominal aortic aneurysm (AAA) lumen volume.

AAA diameter and volume and AAA related complications: Sensitivity analysis

When stratifying patients according to AAA diameter, AAA related complications occurred in 30 patients in Q1, 40 patients in Q2, 28 patients in Q3, and 37 patients in Q4. Five year freedom from AAA related complications was 76% in Q1, 63% in Q2, 62% in Q3, and 55% in Q4 ($p = .060$). In multivariable analysis, correcting for gender, neck diameter, rupture as indication, α and β angle, lumen volume, AUI device and proximal sealing length, diameter was not significantly associated with higher risk of complications (Q4 *vs.* Q1 HR: 1.34, 95% CI 0.70–2.6, $p = .38$; Q3 *vs.* Q1 HR: 1.18, 95% CI 0.67–2.07, $p = .57$; Q2 *vs.* Q1 HR: 1.24, 95% CI 0.75–2.05, $p = .41$).

When stratifying patients according to AAA volume, AAA related complications occurred in 31 patients in Q1, 26 patients in Q2, 34 patients in Q3, and 44 patients in Q4. Five year freedom from AAA related complications was 73% in Q1, 69% in Q2, 67% in Q3, and 50% in Q4, $p = .004$). In multivariable analysis patients, correcting for gender, neck diameter, rupture as indication, α and β angle, AUI device and sealing length at 30 days, AAA total volume was not significantly associated with higher risk of complications (Q4 *vs.* Q1 HR: 1.6, 95% CI 0.90–2.9, $p = .11$; Q3 *vs.* Q1 HR: 1.1, 95% CI 0.64–1.9, $p = .73$; and Q2 *vs.* Q1 HR: 0.81, 95% CI 0.47–1.40, $p = .45$).

DISCUSSION

To the best of the authors' knowledge, this is the first study focusing on the impact of free luminal space on outcomes after EVAR. It is well known that patients with a larger AAA diameter are at greater risk of complications;[5–7] however, it is not defined whether this higher complication risk is attributable to the actual total diameter or to the space free from thrombus inside the AAA sac, the luminal space. The present results suggest that patients with higher AAA luminal volumes are at a significantly greater risk of AAA related complications irrespective of the total diameter of the AAA sac or sealing lengths at baseline. It is hypothesised that AAA sacs with large luminal spaces offer conditions for subtle but significant graft movements within the sac. As the newly formed thrombus after endograft implant is softer and does not have the consistency of previously existing laminated mural thrombus,[13–15] this movement may ultimately compromise sealing zones. However, in smaller luminal spaces, the graft remains imprisoned against the thrombus wall, with less space for movement and consequently fewer sealing related complications. Proving the concept, the recent update of the Nellix System® IFUs, also considered the luminal AAA space. The thrombus index, expressed as a ratio between maximum aneurysm sac and maximum flow lumen diameter should be less than 1.4 and aneurysm lumen diameter less than 60 mm.[16]

Despite a higher proportion of AAA treated in the context of rupture being present in Q4, a subanalysis excluding these patients showed a significantly higher rate of complications in Q4. The authors acknowledge that the timing of repair may affect long term mortality and AAA related complications, even though several studies have reported similar long term survival in patients treated in the context of rupture when compared with elective patients, as long as they survive the in hospital period.[17,18]

Although more patients were treated outside the IFU in quartiles with larger lumen volumes, when correcting for "IFU compliance" Q3 and Q4 remained independent predictors of future complications when compared with Q1. These results further support the independent impact of luminal size in the occurrence of future complications, beyond the other well established risk factors. Despite higher complication rates in the larger quartiles, similar growth rates were seen in all groups. This can be explained by the fact that more secondary interventions were needed in the larger quartile groups, with many of them performed because of progressive loss of proximal seal, but before any serious complication or significant growth was established.

Contradictory data have been reported regarding the impact of AAA sac thrombus on the occurrence of graft related complications. Some studies suggest that thrombus has a protective effect for complications whereas others describe a detrimental effect.[19,20] Sadek *et al.*[19] describe a lower incidence of type 2 endoleak and sac enlargement among patients with higher thrombus volume (and consequently lower luminal volume) in a single centre study ($n = 136$, mean follow up 11 months). In the present study, the type 2 endoleak rates were similar among groups, as were the rates of AAA sac enlargement. On the other hand, Sirignano *et al.*, in a single centre study ($n = 191$, mean follow up 32 months), suggested that higher thrombus proportion within the sac was associated with higher re-intervention rates, which is opposite to the findings of the present study.[20] However, the former was limited by small sample size, no data were presented regarding baseline or

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procedural characteristics for each group, and consequently, all analyses were unadjusted and thus less reliable.

In another single centre report, Yeung *et al.* ($n = 100$; median follow up 31 months) also reported that a higher volume of thrombus represented a risk factor for absence of AAA sac shrinkage.[21] Similar to the previous reports, no anatomical details were provided for patients among both groups. Besides, by 24 months the influence of pre-operative thrombus burden had disappeared. Furthermore, the methods used for classifying the amount of thrombus were subjective and operator dependent. Despite the absence of an established optimal method to quantify aneurysm thrombus, the present study used centre lumen line reconstructions with quantitative analysis, which are more accurate and less operator dependent. In contrast to the abovementioned studies, which focused on the role of thrombus, in the present study, it was hypothesised that larger luminal space might be a more important risk factor for AAA related complications, as the availability of a greater space might allow for a greater amplitude of progressive endograft dislocation within the sac. As previous reports show that sideways displacement of the graft within the AAA sac is associated with late adverse events, indeed, large lumens may increase the risk of graft movements and, consequently, the risk of long term complications after EVAR.[22]

A sensitivity analysis addressing the impact of AAA diameter and volume in the occurrence of AAA-related events showed that patients with larger total volumes and diameters also had more complications. However, only lumen volume reached significance on multivariable analysis. Although this finding may be related to potential lack of power to show significant results, this may also mean that lumen size is a more sensitive measure to predict complications and should be considered an important additional anatomical determinant when planning and following EVAR patients.

In the present study, the increased risk of aneurysm related complications seems mostly to be a result of a higher rate of neck related adverse events. Despite no significant differences regarding type IA endoleaks or migration among groups, significantly more proximal secondary interventions were performed in the larger quartiles, which means that progressive and significant loss of seal was perceived, and patients were pre-emptively treated before clinical consequences. Multivariable analyses for neck events were not performed because of a low number of events.

As no differences were found regarding iliac related events, it is considered that larger lumens may also contribute to limb movements, with subsequent retraction resulting in seal loss.[23] The absence of clinical consequences in the present study may be related to the increased awareness of the consequences of insufficient iliac seal as described previously.[23] As such, at the study institution the iliac seal is optimised by extending limbs close to the iliac bifurcation. With longer follow up, clinical consequences may arise from progressive seal loss as a result of continuous retraction. Significantly greater risks of AAA related complications, mainly at the cost of more neck related events, were found in the larger quartile groups. However, all the well established anatomical risk factors associated with EVAR failure also need to be individually considered when planning EVAR and surveillance strategies.

Of note, according to recent ESVS guidelines, patients at low risk of complications (no endoleak, anatomy within IFU, and seal of >10 mm proximal and distally) can be considered for a limited follow up.[24] However, in subgroups of patients with larger luminal volumes, sporadic CT scans may be advised to analyse how sealing zones have evolved over time and allow pre-emptive treatment.

Although this study shows that free lumen, measured as luminal volume, is associated with aneurysm related complications, it cannot clarify the exact mechanism for this. Instead, the study creates awareness of the fact, irrespective of the underlying cause. Although it is hypothesised that small graft displacement over time in large lumens may occur and compromise sealing zones, further studies with detailed and serial sealing measurements are necessary to prove this hypothesis.

Some other limitations warrant consideration: aneurysm length was not considered and may underestimate the impact of luminal volume in shorter AAA while overestimating its impact in longer AAA. The use of lumen diameter instead of volume would be simpler to interpret in a clinical setting; however, this can be misleading as a fixed reference point should be used for diameter measurements. Given lumen irregularity, this measure could not be representative of the real luminal space. As such, a more precise method was adopted for calculation, despite the acknowledgement that it is less simple to use in daily practice.

Measuring volumes is relatively laborious and not universally adopted in the clinical setting. However volumetry represents a significantly more reliable and precise method for detecting aneurysm sac changes and is a better predictor of clinical success.[25–27] Additionally, volumetry is more sensitive to predict secondary problems.[28] Furthermore, this represents a retrospective single centre study, and consequently there is potential for selection bias. Several operators were included in AAA repair during the study period and endograft selection was left to the surgeon's discretion. Lastly, there is a risk of multicollinearity among variables included in the multivariable model. Therefore, multivariable analysis must be interpreted with caution.

In conclusion, AAA luminal volume represents a risk factor for AAA related complications, neck related events, and secondary interventions after standard EVAR. Although further studies are needed, both to clarify the mechanism of how larger lumens contribute to more complications, and to validate the study hypothesis, this information might be considered when tailoring surveillance protocols after EVAR.

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CONFLICTS OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2020.02.011.

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