Preoperative prediction of type II endoleak following standard EVAR

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Abstract:

Introduction: Type II endoleak (T2EL) consists the most common complication after the endovascular repair of an abdominal aortic aneurysm (EVAR). Despite been generally considered as a benign condition, aortic sac expansion is possible, and for this reason patients should be kept under close surveillance. Aim of the study was to identify preoperative parameters that are related with a T2EL and create a predicting-scoring model.

Methods: A prospective clinical study was made. All patients who underwent EVAR throughout a 12-month period in two hospitals, were included. Patients were followed for 12 months using a pre-specified protocol. Various clinical, anatomical and device specific parameters were examined as potential factors of T2EL, using univariate and multivariable analysis.

Results: Overall, 73 patients were included. Three patients were excluded due to Type I endoleak. From the rest 70 patients, 17 (24.3%) developed a T2EL (Endoleak group). These patients were compared to the patients who did not develop a T2EL (No-Endoleak group, N=53). The analysis demonstrated that 3 parameters were related with the development of T2EL: the preoperative anticoagulant treatment, the number of patent arteries in the preoperative CT scan, and the nitinol skeleton of the endograft. Based on the multivariable analysis, the ***ABS-10*** risk scoring system for the preoperative prediction of a T2EL was created as following: 4 points for prior chronic use of ***A***nticoagulants, 1 point for each patent arterial ***B***ranch from the aneurysm sac, and 5 points for a nitinol endograft ***S***keleton. A score of 7 presented sensitivity 88%, specificity 62%, positive predictive value 43%, and negative predictive value 94%.

Conclusions: A risk scoring system for the prediction of T2EL after standard EVAR was created. A score of less than 7 practically excludes the possibility of T2EL. External validation in larger populations is needed.

INTRODUCTION

Endovascular aortic aneurysm repair (EVAR) of infrarenal abdominal aortic aneurysms has been established as an accepted alternative to open surgery. EVAR is associated with lower rates of surgical mortality and morbidity, less invasiveness, and shorter hospital stay[1]. An inherent problem of the method is the development of endoleaks due to persistent, post-interventional perfusion of the aneurysmal sac[1].

Although it has been agreed that type I and type III endoleaks require urgent treatment[2], there is no such consensus at this time regarding treatment of type II endoleaks (T2EL). However, this is the most frequently occurring endoleak in approximately 10-25 % of patients who undergo EVAR[2,3]. This type of endoleak is related to retrograde filling of the aneurysm sac from aortic side branches. Typical sources of T2EL are the inferior mesenteric artery (IMA), one or more lumbar arteries, the median sacral artery, or even accessory renal arteries. These endoleaks are usually transient and get thrombosed spontaneously within the first 6 months in up to 80% of cases[4,5].

However, T2EL that persist longer than 6 months are associated with a higher probability of a complicated course[3] and, despite being small, the risk of aneurysm rupture due to an increasing intrasaccular pressure exists. Data from the EUROSTAR registry on 2463 patients suggested a cumulative 2-year incidence of rupture after T2EL of 1.8%, although this rate was no different in patients without any detected endoleak (0.9%)[6]. The increase of the aneurysmal sac size is observed significantly more often in patients with a persistent T2EL (24-52%) than in patients without it (13%)[4,5,7-9]. In the follow-up period of patients after EVAR, the increase of the aneurysmal sac size is a matter of concern and generally is an accepted criterion for reintervention[10]. In patients with a T2EL after EVAR, about a quarter will need to be treated due to aortic aneurys-

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mal sac enlargement[11], although the treatment of T2EL without changes of the aneurysmal sac remains controversial[12-19].

Little is known about the factors that can predict a T2EL preoperatively. A high suspicion of a postoperative T2EL after EVAR would be helpful for the proper selection of patients regarding the proper type of treatment they would receive including open repair. On the contrary, a minimal risk of T2EL will allow treating physicians choosing patients who will benefit of an EVAR without the question of a potential long-term hazard. Aim of this study was to determine factors that may be potentially predictive of early T2EL after standard EVAR, taking into consideration patients' clinical data, aneurysm anatomic features, and endograft details.

METHODS

A prospective clinical study was designed. The study population included all consecutive patients with AAA disease who underwent a standard EVAR throughout a 12-month period in two tertiary care hospitals in Athens area (G. Gennimatas Athens General Hospital, and Attikon University Hospital). Patients who underwent an endovascular treatment for complex aortic cases such as fenestrated grafts, parallels grafts, or iliac-branch devices were excluded from the study. All patients consented, and the Ethics Commitees of both hospitals approved the study. Patients who developed a type I endoleak were excluded from the study. The rest patients were divided in two groups: the No-endoleak group (N=53), which consisted of the patients who did not develop a T2EL, and the Endoleak group (N=17), which consisted of the patients who developed a T2EL.

The primary outcome was the existence or absence of a T2EL. All patients underwent a high-resolution multislice computed tomography angiography (CTA) with 0.5 - 1.5 mm thickness, preoperatively. Postoperatively, they entered a strict follow-up protocol, which included clinical examination and an aorta CTA scan at previously specified time-intervals (1, 6 and 12 months). A patient was considered to have a T2EL if this was diagnosed in one of the postoperative CT scans. For each patient, the endoleak type was classified according to the EVAR reporting criteria[20].

Specific sets of variables regarding the patient, the aneurysm and the endograft were examined as possible factors that could relate to the outcome (Tables 1, 2, 3). The study of the anatomic characteristics of the aneurysm was based on the preoperative aortic CTA. The CTAs were analyzed using the 3mensio Medical Imaging / Pie Medical Imaging (Bilthoven, The Netherlands) software. Two authors (DD, AML) examined independently the CT scan and when a disagreement was found this was dealt with a consensus of both.

Statistical analysis

Means and standard deviations were used for the description of the continuous data, while percentages for the description of the binary data. Each of the parameters / variables was examined as a potential factor for a T2EL on a univariable analysis using various tests based on the type of parameter (continuous or binary), and its distribution (normal or abnormal) when it regarded continuous data. A normal distribution for a continuous variable was assumed when the two-sided F test between the two groups for this specific parameter was not statistically significant ($p>.05$). The tests used for the univariable analysis were: Unpaired t test, Mann Whitney U test, Chi-square test, Yates corrected Chi-square test, and Fisher's Exact test. Descriptive statistics were presented as mean with standard deviation or rates.

Variables that were found to have a statistically significant difference between the two groups ($p< .05$) were considered as potential predictors of T2EL and were entered into a multivariable analysis as independent variables, using the outcome (endoleak or no-endoleak) as the dependent variable. Using a logistic regression analysis, the most significant factors ($p< .05$) were extracted and presumed as the definitive predicting factors for a T2EL.

Based on this logistic regression equation, a simplified risk-scoring model for the prediction of a T2EL was created. The extracted simplified risk-scoring model was subsequently tested for calibration or good-fitness (Hosmer & Lemeshow test) and discrimination (Harrell's c statistic). The ROC curve of the risk-scoring model was designed, the area under the curve was calculated, and sensitivity, specificity, and positive and negative predictive values at the relevant score cut-off levels were measured.

The Statsdirect Software for medical statistics (version 2.8.0)[10], and the MedCalc Medical Statistical software (version 12.5.0; Broekstraat, Mariakerke, Belgium) were used for the statistical analyses.

RESULTS

From a total of 73 patients, 3 patients (4.1%) developed a type 1 endoleak and were excluded from the analysis. Overall, 17 patients (23.3%) developed a T2EL. The patients were divided in two groups: the No-Endoleak group (N=53), and the Endoleak group (N=17).

Most of the patients were male (94%) and their mean age was 73±9.3 years. Regarding atherosclerosis risk factors, 76% were smokers, 84% ⅝ suffered by arterial hypertension, 79% by dyslipidemia, 44% were diabetic, and 39% had any degree of renal impairment. Nine patients (13%) were on therapeutic anticoagulant treatment on admission, whereas 46% were on antiplatelet, and 47% on lipid control treatment (Table 1). As it regards the aneurysm characteristics, the mean diameter of the aneurysm was 62.2±17.6 mm, while 26% of them had an abnormal proximal aortic neck, either due to large angulation or short length. Thirty three percent of the patients had a patent inferior mesenteric artery on the preoperative CT scan while the mean number of patent lumbar arteries from the aneurysmal sac was 3.1 (Table 2). Six different types of endografts were used: Cook Zenith™, Metronic Endurant™, Vascutek Anaconda ™, Gore Excluder ™, Bolton Treo ™, and Cordis Incraft ™. Two different types of Cook Zenith ™ endografts were used, Cook Zenith Flex and Cook Zenith LP, the skeleton of which are different: stainless steel for the Flex™ and nitinol for the LP™. Overall, nitinol skeleton was used in 61% of the cases. Additionally, most of the grafts used, 84%, had suprarenal fixation (Table 3).

In the total cohort of patients, there was no perioperative death, and not any other significant morbidity apart endoleak was noted.

		No--endoleak N=53	Endoleak N=17	p (two--sided)
Demographic data				
Age (years)	mean ± SD	72.7 ± 9.7	73.8 ± 7.8	.682 a
Gender: male	N (%)	49 (92%)	17 (100%)	.568 e
Risk factors				
Tobacco use	N (%)	41 (77%)	12 (71%)	.746 e
Arterial hypertension	N (%)	45 (85%)	14 (82%)	>.999 e
Dislipidemia	N (%)	41 (77%)	14 (82%)	>.999 e
Diabetes Mellitus	N (%)	22 (42%)	9 (53%)	.586 d
Chronic Renal Failure	N (%)	20 (38%)	7 (41%)	>.999 d
Blood tests on admission				
CRP (mg/L)	mean ± SD	12.2 ± 18.6	17.6 ± 44.8	.662 b
Hemoglobin (g/L)	mean ± SD	13.3 ± 2	13.2 ± 2	.768 a
White blood cells (x 10^3 /mm^3)	mean ± SD	8.9 ± 3.8	8.4 ± 2.6	.611 a
Platelets (x 10^3 /mm^3)	mean ± SD	231 ± 86	222 ± 47	.906 b
Abnormal coagulation tests	N (%)	5 (9%)	2 (12%)	>.999 e
Medications on admission				
Anticoagulants	N (%)	4 (8%)	5 (29%)	.033 e
Antiplatelets	N (%)	25 (47%)	7 (41%)	.879 d
Statins	N (%)	25 (47%)	8 (47%)	>.999 d

Table 1. Patients' characteristics include demographic data, atherosclerosis risk factors, blood test examinations, and patients' medications (a: Unpaired t-test, b: Mann Whitney U test, c: Uncorrected Chi^2, d: Yates-corrected Chi^2, e: Fisher's Exact test).

		No--endoleak N=53	Endoleak N=17	p (two--sided)
AAA measurements				
Abnormal suprarenal angle	N (%)	1 (2%)	1 (6%)	.429 e
Abnormal infrarenal angle	N (%)	4 (8%)	3 (18%)	.349 e
Abnormal proximal angle	N (%)	5 (9%)	3 (18%)	.387 e
Abnormal length of proximal neck	N (%)	8 (15%)	5 (29%)	.283 e
AAA diameter (mm)	mean ± SD	61.4 ± 16.7	64.8 ± 20.6	.489 a
AAA lumen diameter (mm)	mean ± SD	38.8 ± 12.6	41.1 ± 12.5	.516 a
Aortic bifurcation diameter (mm)	mean ± SD	35.9 ± 11.8	37.4 ± 16.6	.694 a
Patent any lumbar artery	N (%)	37 (70%)	17 (100%)	.008 e
Number of patent lumbar arteries	mean ± SD	2.7 ± 2.1	4.1 ± 1.3	.030 b
Patent IMA	N (%)	14 (26%)	9 (53%)	.115 d
Number of patent arterial branches	mean ± SD	3 ± 2.3	4.6 ± 1.5	.008 a
AAA volume (mL)	mean ± SD	208.6 ± 137.4	269.9 ± 204.5	.392 b
Lumen volume (mL)	mean ± SD	94.7 ± 65.1	105.5 ± 66	.567 a
Thrombus volume (mL)	mean ± SD	103.2 ± 98	154.7 ± 151.4	.308 b
Volumes ratio: Thrombus / AAA (%)	mean ± SD	51.3 ± 18.7	52.7 ± 23.6	.825 a
Volumes ratio: Thrombus / Lumen (%)	mean ± SD	140.3 ± 103.2	154.9 ± 105.1	.629 a
Volumes ratio: Lumen / AAA (%)	mean ± SD	48.6 ± 18.7	47.3 ± 23.6	.825 a

Table 2. Aneurysms' details (a: Unpaired t-test, b: Mann Whitney U test, c: Uncorrected Chi^2, d: Yates-corrected Chi^2, e: Fisher's Exact test).

		No--endoleak N=53	Endoleak N=17	p (two--sided)
Endograft characteristics				
Suprarenal fixation	N (%)	44 (83%)	15 (88%)	>.999 e
Fabric type: polyester	N (%)	51 (96%)	16 (94%)	>.999 e
Skeleton type: Nitinol	N (%)	28 (53%)	15 (88%)	.020 d
Endograft type				
Cook Zenith™	N (%)	39 (74%)	11 (65%)	.543 e
Medtronic Endurant™	N (%)	1 (2%)	2 (12%)	.144 e
Vascutek Anaconda™	N (%)	7 (13%)	1 (6%)	.669 e
Gore Excluder™	N (%)	2 (4%)	1 (6%)	>.999 e
Bolton Treo™	N (%)	4 (8%)	1 (6%)	>.999 e
Cordis Incraft™	N (%)	0 (0%)	1 (6%)	.243 a

Table 3. Devices' specifications (a: Unpaired t-test, b: Mann Whitney U test, c: Uncorrected Chi^2, d: Yates-corrected Chi^2, e: Fisher's Exact test).

Univariate analysis

Initially, the two groups were compared regarding each one of the variables on a univariable analysis (Tables 1, 2, and 3). The most statistically significant factors (p<.05) found were patient been on chronic anticoagulant treatment (8% in the No-Endoleak group versus 29% in the Endoleak group, p=.033), the existence of at least one patent lumbar artery in the pre-operative CT scan (70% in the No-endoleak group versus 100% in the Endoleak group, p=.008), the number of patent lumbar arteries (2.7 in the No-endoleak group versus 4.1 in the Endoleak group, p=.030), the total number of any patent arterial branch from the aortic sac, lumbar artery, or inferior mesenteric artery (3 in the No-endoleak group versus 4.6 in the Endoleak group, p=.008), and a Nitinol skeleton on the endograft (29% in the No-endoleak group versus 88% in the Endoleak group, p=.028).

Mutlivariable analysis / risk model creation

After the multivariable analysis, the variables found to be statistically significant were the chronic use of anticoagulants, the total number of any patent arterial branch from the aortic sac on the preoperative CT scan, and the type of skeleton material of the endograft (Table 4). These parameters were included in a risk scoring model, the ABS-10 risk scoring for the prediction of T2EL after standard EVAR. On this scoring model, each of the parameters scores as follows:

Chronic use of ***A***nticoagulants: 4 points

Patent arterial ***B***ranch from the aortic sac on the preoperative CT scan: 1 point / each patent artery

Nitinol ***S***keleton of the endograft: 5 points

The ABS-10 predicting score model was well-fitted (Hosmer & Lemeshow test 3.5, p=0.75) and presented a good discriminative ability (Harrell's c statistic 0.81, 95% CI 0.70 - 0.89, at an optimum cut-off score of 7) (Figure 1). Overall, 25 patients had a score above 7 in the No-endoleak group (47%) and 16 (94%) in the Endoleak group (Figure 2). At this score level, the model presented 88% sensitivity, 62% specificity, 43% positive predictive value, and 94% negative predictive value.

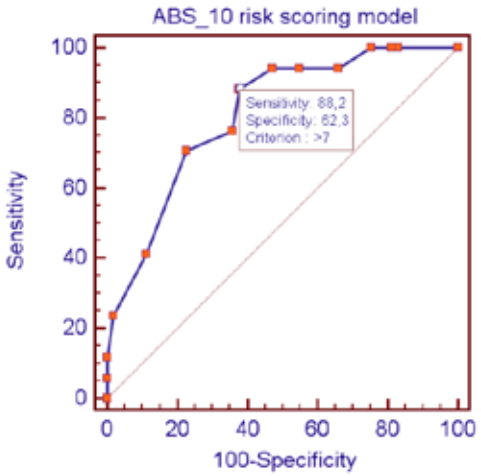

Figure 1. ROC analysis of the ABS-10 risk-scoring model. A value of 7 consists the optimum cut-off point, giving the best combination of sensitivity and specificity.

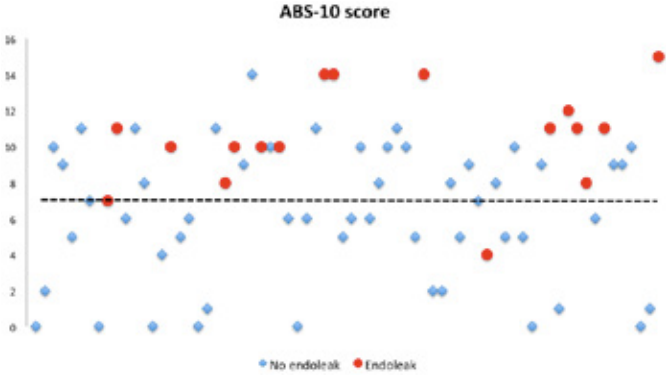

Figure 2. Scatterplot indicates the value of ABS-10 score for each of the patients of the study. Almost no patient with a value of ABS-10 less than 7 had a type II endoleak (red points).

DISCUSSION

In the current study of patients with AAA disease, being treated with a standard EVAR procedure, T2EL occured in 23.3% of the population. According to the analysis, three variables were related with the T2EL: the preoperative chronic use of anticoagulant treatment, the number of patent arterial branches from the aortic sac in the preoperative CT scan, and the nitinol skeleton of the endograft. Based on these findings, the ***ABS-10*** risk scoring system for the preoperative prediction of a T2EL was created as following: 4 points for prior chronic use of ***A***nticoagulants, 1 point for each patent arterial ***B***ranch from the aortic sac, and 5 points for nitinol endograft ***S***keleton.

Atherosclerosis risk factors were not found to be associated with T2EL. Current use of tobacco, arterial hypertension, and dislipidemia did not show any statistically significant difference between the two groups. In a meta-analysis regarding the possible risk factors associated with T2EL, gender, diabetes, hypertension, and dyslipidemia were not found to have a role[21]. On the contrary, smoking was considered to act protectively, something that was not seen in the current study.

The use of anticoagulant treatment has been considered as a potential predisposing factor for T2EL after EVAR[22,23], but this is not a constant finding. In a study of 127 patients with AAA s who underwent EVAR, Bobadilla et al.[24] reported that anticoagulation with warfarin appears to be linked to an increased risk for the development of endoleak after EVAR, specifically type II. Similarly, previous reports have demonstrated that the chronic anticoagulation drugs' use can lead to a long-term poor outcome[25,26]. This is consistent with our univariate and multivariable analysis, which found that patients been on ongoing treatment with anticoagulants were in higher risk for T2EL (8% in the No-Endoleak group vs. 29% in the Endoleak group, p=.033).

The existence of patent arterial branches from the aneurysm sac seems to be related to the development of T2EL[27-30]. The patent lumbar arteries, the inferior mesenteric artery, or any accessory renal arteries are such arterial branches. Each of them has been described as a potential risk factor for the development of a T2EL[27-29]. In our study, although in the unviariate analysis both the number of patent lumbar arter-

ies and the patent IMA were found to be associated with the T2EL, both were excluded in the multivariable analysis. On the contrary, the total number of patent arterial branches from the aneurysm sac, either lumbar arteries or IMA, was found to be a risk factor for a T2EL. It seems reasonable to consider that the existence of any patent branch is important and not any particular vessel, either named IMA or lumbar artery[30].

In the present analysis, we were not able to confirm any relationship between aneurysmal thrombus and T2EL. No thrombus-associated parameter of the AAA such as thrombus volume, thrombus-to-AAA ratio, thrombus-to-lumen ratio proved to be a predictive factor for the development of T2EL. Brountzos et al[30] have reported that the percentage of aortic perimeter covered by thrombus at the level of the sac lumbar arteries' ostia is an independent predictor of T2EL. Similarly, no relation between the material of the endograft (polyester or PTFE) and T2EL was found.

However, the material of the endograft skeleton was significantly associated with T2EL (nitinol skeleton was found in 29% in the No-endoleak group versus 88% in the Endoleak group, p=.028). Nitinol, an approximately equiatomic alloy of nickel and titanium, belongs to a group of materials named as shape-memory alloys, due to its remarkable properties of thermal shape-memory[31]. It is more compliant than other alloys such as stainless steel, and has a broad array of applications in vascular surgery[32]. Nitinol is considered to produce a limited inflammatory response[33] but there are conflicting reports with regard to the effect of inflammation magnitude to the development of endoleaks. Some authors support that that an increased inflammatory reaction post EVAR increases the possibility of T2EL[34], while other studies have shown that an increased inflammation after EVAR is associated with a decreased incidence of T2EL[35]. In our study, there was no specific investigation with regard to inflammation markers, nevertheless CRP was found similar in both groups (Table 1). Irrespective to the controversial effect on inflammation, it seems that nitinol exhibits reduced thrombogenicity as compared to stainless steel stents. In an animal study of Thierry et al[36], nitinol stents were found to present lower thrombogenicity as compared to stainless steel stents. This was proven by assessing the local fibrinogen absorption and was confirmed by scanning electron observations showing different thrombus morphologies between nitinol and stainless steel. As the metallic skeleton of the aortic graft usually lies outside the fabric, it is in constant contact to the content of the aneurysmal sac. The decreased thrombogenicity of nitinol can be considered an advantage when it regards bare metal stents as it may reduce the possibility of stent thrombosis. However, in aortic stent grafts, as it lies (in most devices) on the outer surface of the graft, its constant contact with the aortic sac content might be considered a factor for decreased aortic sac thrombosis and thus a risk factor for T2EL development. Nevertheless, today this finding has literally a theoretical value and no clinical impact, since the skeletons of most endografts existing in the market today are made of nitinol. The only company still using stainless steel on grafts exoskeleton is Cook Medical™, which uses skeletons made of stainless steel in a small portion of its AAA products (Zenith® Flex and Zenith® Fenestrated AAA Endovascular Graft™).

This study has several limitations. Despite being a prospective study, the number of patients was small, and limited the general relevance of the results. Additionally, as the decision for the selection of the graft type was made per surgeons' preference, the number of the various types of endografts used varied. Thus, the potential effect of specific devices could not been tested. Another limitation concerns the methodology for measuring the morphological characteristics of the aneurysm based on the CTA images. Although the measurements were performed by two independent researchers (DD, AML,) intraobserver or interobserver variability may exist[37]. Definitely, external validation of the model in large cohorts of patients is needed in order to accept of reject the results of the study. Finally, the ABS-10 prediction model does not identify the T2EL that would need intervention, as this definitely would need further follow-up.

CONCLUSIONS

Three variables were found to be related to the development of T2EL after standard EVAR: the preoperative chronic use of anticoagulants, the number of patent lumbar arteries in the preoperative CT scan, and the nitinol skeleton of the endograft. The produced ABS-10 predicting score model could be used to potentially identify low-risk patients for the development of this complication. Further studies involving larger numbers of patients will improve our understanding on T2EL.

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