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Prospective Evaluation of Post-implantation Inflammatory Response After EVAR for AAA: Influence on Patients' 30 Day Outcome

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WHAT THIS PAPER ADDS

The impact of post-implantation syndrome (PIS) on the outcome of patients after elective endovascular aneurysm repair (EVAR) is still unknown. In the present study PIS after EVAR was prospectively evaluated and its association with various clinical and laboratory parameters, as well as the clinical outcome of the patients was investigated. It was found that a systematic inflammatory response is observed in almost one third of the patients after EVAR. For the first time in the literature it has been shown that the intensity of the inflammation, as assessed mainly by the post-operative high sensitivity C-reactive protein values, correlates with the presence of a cardiovascular or any other adverse event during the first 30 days after the procedure.

Objectives: The aim was to prospectively evaluate post-implantation syndrome (PIS) after elective endovascular aneurysm repair (EVAR) of abdominal aortic aneurysms (AAAs) and to investigate its association with clinical and laboratory parameters and the clinical outcome of the patients.

Methods: From January 2010 till June 2013, 214 consecutive patients treated electively by EVAR for AAA were prospectively included. PIS was defined according to systemic inflammatory response syndrome criteria. Adverse events included any major adverse cardiovascular events (MACE), acute renal failure, re-admission and death from any cause.

Results: PIS was diagnosed in 77 (34%) patients. Pre-operative white blood cell (WBC) count values ($p < .001$), endograft material (polyester) ($p < .001$), and heart failure ($p = .03$) were independent predictors of PIS. Mean post-operative temperature ($p < .001$), length of hospital ($p < .001$) and intensive care unit ($p = .008$) stay, as well as maximum post-operative WBC count ($p < .001$) and hs-CRP values ($p < .001$) were significantly higher in the PIS group. Post-operative hs-CRP ($p = .001$) and duration of fever ($p = .02$) independently predicted the occurrence of MACE. Post-operative hs-CRP ($p = .004$), maximum temperature ($p = .03$), and the presence of PIS ($p = .01$) were independent predictors of an adverse event during the first 30 days. A threshold of post-operative hs-CRP value of 125 mg/L was highly associated with the occurrence of MACE, with a sensitivity of 82% and specificity of 75%.

Conclusions: A systematic inflammatory response is observed in a significant number of patients after EVAR. The type of endograft material seems to play a significant role in this inflammatory process. The intensity of inflammation, as assessed mainly by the post-operative hs-CRP values, correlates with the presence of a cardiovascular or any other adverse event during the first 30 days after the procedure.

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INTRODUCTION

Post-implantation syndrome (PIS) has been used to describe a clinical entity characterized by systemic inflammation after endovascular repair of an abdominal aortic aneurysm (EVAR).[1] The impact of the syndrome on patient outcome is still unknown. The post-operative inflammatory response raises concerns of increased morbidity, especially in patients at high cardiovascular risk. In most cases, PIS is

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generally well tolerated, but even then it may result in a more demanding post-operative recovery leading to prolonged hospitalization, and thus it might be considered a moderate complication of the procedure.[2,3] Rarely, the inflammatory process has been reported to lead to the development of serious complications such as pulmonary dysfunction, cardiovascular events, renal insufficiency, even multisystem organ failure.[4–7] However, in several large EVAR papers the association of these clinical reactions with PIS has not been yet reported.

In 2010, this group published some preliminary results of 40 consecutive EVAR patients, evaluating the association of PIS with clinical and laboratory parameters.[3] PIS was diagnosed in 35% of the patients. Patients with PIS showed significantly greater changes of inflammation marker levels, including high sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6), than the non-PIS group. PIS was also associated with longer hospitalization. In another publication the readmission of five EVAR patients and one thoracic EVAR (TEVAR) patient during the first 30 days after the procedure due to a systemic inflammatory response syndrome (SIRS) was reported.[7] All these patients had PIS post-operatively. It was concluded that in some patients, the initial inflammatory response following EVAR is not always benign and therefore patients developing an excessive inflammatory response may need close surveillance. Other groups have also investigated possible factors that may influence PIS after EVAR. Voûte et al.[8] found that polyester stent grafts were independently associated with an increased risk of PIS, while Moulakakis et al.[9] confirmed these results in a later report. However, the association between PIS and patient outcome, including cardiovascular or other adverse events, has not been prospectively investigated in any study so far.

Based on the results of two previous studies, the hypothesis that there might be a relationship between PIS occurrence and patient outcome after EVAR was tested, and the present study was designed to prospectively evaluate PIS after elective endovascular aneurysm repair of abdominal aortic aneurysm (AAA) and to investigate its association with various clinical and laboratory parameters, as well as the clinical outcome of the patients.

METHODS

Definition

PIS fulfills at least two of the SIRS criteria (i.e., fever and leukocytosis).[10] Therefore, PIS was defined as the presence of fever (persisting body temperature $>$ 38 °C lasting for more than 1 day during hospitalization) and leukocytosis (white blood cell count $>$ 12.000/μL) with negative blood culture results.

Study sample

In a prospective study approved by the institutional review committee, all patients having EVAR between January 2010 and June 2013 were eligible for inclusion. During this time, endovascular repair was offered to all suitable patients according to the ESVS practice guidelines for the management of AAA.[11] Exclusion criteria included:

- Clinical and/or laboratory evidence of infection pre-operatively, including leukocytosis (white blood cell count [WBC] $>$ 10.000/μL) and elevated body temperature.
- Signs of gangrene.
- Previous trauma or surgery two months prior to enrollment.
- Previous implantation of endoprosthesis.
- Any autoimmune disease or systemic inflammatory condition.
- Any malignancy.
- Use of anti-inflammatory drugs, chemotherapeutic agents, immunosuppressants, or anticoagulants.

Procedure

All patients were treated by the same surgical and anesthesiology team in a fully equipped operating room with the patient under general anesthesia. Every effort was made to follow the selection criteria recommended by the manufacturer of the stent graft, however, the surgeon's decision as to which device to use was based on the anatomical characteristics of the proximal neck, the iliac artery configuration, and the presence of thrombus or calcification. Systemic heparinization was achieved with 5,000 IU of heparin. Every effort was made to deploy the endovascular device just below the level of the lowest renal artery. The stent grafts implanted were Endurant (Medtronic Inc, Santa Rosa, CA, USA), Anaconda (Vascutek, a Terumo company, Inchinnan, UK), Zenith (Cook Inc., Indianapolis, IN, USA), Aorfix (Lombard Medical Technologies, Oxfordshire, UK), Powerlink (Endologix, Irvine, California), and Excluder (W.L. Gore & Associates, Flagstaff, AZ, USA). The material of the first four devices is polyester, while the last two devices are made from ePTFE. All the devices were bifurcated systems. All patients received antibiotic prophylaxis (teicoplanin 400 mg, and ceftriaxone 1 g) half an hour pre-operatively and for the day of operation, as well as 3500 IU of low molecular weight heparin (tinzaparin) from the first post-operative day until discharge. In all patients, demographics, intra-operative and post-operative complications, the incidence of PIS, the diameter of the aneurysm, the type of the graft deployed, the operation time, the amount of contrast media administered (Optiray 320, Mallinckrodt Inc, St. Louis, MO, USA), and length of post-operative stay, were recorded. Temperature was recorded eight times daily for the duration of hospitalization. Blood tests including troponin levels were measured on the first and third post-operative day and the day before discharge. Post-operative pain was controlled with intravenous tramadol, while in cases of fever $>$38.5 °C lasting more than 2 hours intravenous paracetamol (1 g) was administered. According to the protocol no anti-inflammatory drugs (steroids or non-steroids) were used during the post-operative period. All patients presenting with fever during

the post-operative period, whether or not fulfilling the PIS criteria, underwent a thorough work up for possible infection. If any of these tests revealed evidence of an early pulmonary, urinary tract or any other kind of infection, the patient was not considered to suffer from PIS. Patients were discharged in the absence of any complications, with a body temperature $<37.5\ ^{\circ}C$ for at least 24 hours and a WBC $<12.000/\mu L$.

Variables of interest

Demographics, risk factors, pre-operative medication, maximum aneurysm diameter, contrast media used, duration of the procedure, type of endograft, the occurrence of PIS, maximum temperature, peri-operative complications, and duration of hospital stay were recorded for each patient. Adverse events included any major adverse cardiovascular events (MACE), acute renal failure, readmission, and death by any cause. MACE was defined as a composite of death from cardiac causes, non-fatal acute myocardial infarction (ST and non-ST), ischemic stroke, or transient ischemic attack.[12,13] Aneurysm volume was calculated from the computed tomography using a workstation with dedicated reconstruction software (3Mensio, Medical imaging B.V., Bilthoven, The Netherlands) by the same operator. At first the total AAA volume from pre-operative computed tomography angiography (CTA) was calculated. Furthermore, from CTA in the first month, the amount of newly formed thrombus was calculated by subtracting the endograft volume and the pre-operative thrombus volume from the total AAA volume.

Medication

All patients were on antiplatelet therapy (aspirin 100 mg once daily) for at least 3 weeks prior to the procedure. Pre-operative medications were continued immediately after surgery. Patients who were enrolled and were already receiving a statin continued their medication. For patients not already on statin, atorvastatin (20 mg once daily) was initiated at the screening visit.

Blood samples

Venous blood was collected, without tourniquet, pre-operatively and at days 1 and 3 post-operatively. Full blood cell counts (WBC and platelets) were measured in an automated hematology analyzer (model SE-9500; Sysmex Corporation, Kobe, Japan). A high sensitivity assay was used for the determination of serum CRP levels (hs-CRP Beckman Coulter, Miami, FL, USA). The serum CRP levels were determined via the scatter of light produced by the formation of immune complexes in the test solution (Beckman Coulter, Immage Immunochemistry System). IL-6 was determined by immunosorbent assays in duplicated samples according to the manufacturer's instructions (Bender MedSystems, Vienna, Austria). The detailed process has been previously reported.[3] In brief, serum and standard samples were incubated into the micro wells of an enzyme linked immunosorbent assay (ELISA) plate, coated with a mouse monoclonal antibody against the corresponding human molecule. During the incubation a bound complex of antigen—antibody was formed. After the removal of the unbound material, a mixture of streptavidine—horseradish peroxidase (HRP) and a biotin-conjugated detector monoclonal antibody against the complex was added. Following the incubation step, the excess unbound material was removed and a substrate solution reactive with the HRP was added. During a new incubation step, a colored product was formed in proportion to the serum amount of IL-6. The enzymatic reaction was stopped and the absorbance of the colored product was measured at 450 nm. A standard curve of various IL-6 concentrations is used for the determination of IL-6 concentration in the tested sample. Troponin concentrations were measured by Immunolite 2000 troponin I, a solid phase, two site chemiluminescent assay (Diagnostic Products Corporation, Corporate Offices, Louisiana, USA).

Statistical analysis

Since there was a lack of adequate data regarding the exact frequency or the effect of PIS on adverse events rates after EVAR, no reliable sample size estimation was feasible. In the preliminary report, there was evidence of PIS in 35% of the patients, while five of 148 EVAR patients in another report from this group needed re-admission due to symptoms of severe inflammation. Based on these rates and given financial restrictions, the study was designed to include nearly 200 patients, so that the PIS group ($\approx$70 patients) should have a relatively adequate size for estimation of events differences. Data were expressed as mean $\pm$ standard deviation (SD) as appropriate, except for non-Gaussian parameters, which were presented as median (range). Comparisons of continuous variables were performed by Student t test for normally distributed variables and Mann—Whitney U test for non-normally distributed variables, while the chi-square test was used for categorical variables. To assess the effect of the independent variables observed within the study context, each one was initially examined separately and the significant predictors at level $p_1 = .25$ were identified. These were used in a binary logistic regression model. The formerly non-significant factors were then considered again at level $p_2 = .10$. Interactions between the main effects of the final model were examined. The enter method with significance level $p_3 = .05$ was used to obtain p values and odds ratios for the main effects and interactions. All analyses were carried out with SPSS 20.0 statistical package for Windows (IBM Corporation, Armonk, New York).

RESULTS

A total of 214 patients (72.3 $\pm$ 8.1 years, 97% males) were included in the study. Stent deployment was technically successful in all patients, with no intra-operative complications. PIS was diagnosed in 77 (36%) patients. Baseline and peri-operative characteristics in patients with and without PIS are shown in Table 1. In terms of baseline characteristics, traditional cardiac risk factors were equally

distributed among the groups (Table 1). Sixteen patients (7.5%) had MACE within 30 days of surgery, resulting in one death. More specifically, 11 patients sustained a non-fatal acute myocardial infarction, three a transient ischemic attack, and one patient had a stroke. Four patients suffered from acute renal failure, and four patients were readmitted due to symptoms of severe inflammation.

Predictors of PIS

Pre-operative WBC count values ($p < .001$), endograft material (polyester) ($p < .001$), and heart failure ($p = .03$) were independent predictors of PIS, as shown by multiple logistic regression analysis. For every 1,000 units increase in pre-operative WBC count the chance of PIS increased by 95.5% (95% CI 50—255%). The use of polyester raised (95% CI 5,3—29,5 times) the possibility of PIS 12 times compared with the use of ePTFE. Patients suffering from heart failure were three times (95% CI: 1.1—8.5 times) more likely to have PIS than those who did not. The endografts that were deployed are shown in Table 2. The relationship between the different endografts deployed and the occurrence of PIS is shown in Fig. 1A. 127 grafts were made of polyester, and 87 were ePTFE. Endografts made of polyester had significantly higher rates of PIS development than endografts made from ePTFE (polyester group 52.8% vs. PTFE group 11.5%, $p < .001$) (Fig. 1B). There were no differences recorded either in total pre-operative AAA volume, pre-operative endoluminal thrombus, or in the amount of newly formed thrombus between the two groups (Fig. 2).

PIS qualitative and quantitative characteristics

PIS characteristics are shown in Table 1. Mean post-operative temperature ($p < .001$), length of hospital

Table 1. Baseline characteristics and peri-operative clinical data of the study population.

	No PIS $n = 137$	PIS $n = 77$	p
Age, years	72 ± 8.1	72.9 ± 8	.440
Male gender, *n* (%)	132 (96.4)	74 (96.1)	.927
BMI, kg/m^2	27.7 ± 5	28.5 ± 5.5	.283
AAA diameter, cm	5.8 ± 1.1	5.9 ± 1.3	.558
AAA volume preop	195.4 ± 178.7	204.5 ± 99.6	.767
Endoluminal thrombus pre-op	104.3 ± 73.3	123.3 ± 73.7	.190
Patent IMA	99 (72.3)	53 (68.8)	.639
Inflammatory AAA	10 (7.3)	6 (7.8)	.895
Risk factors			
Hypertension, *n* (%)	118 (86.1)	69 (89.6)	.462
CAD, *n* (%)	66 (47.8)	45 (58.4)	.149
COPD, *n* (%)	58 (42.3)	42 (54.5)	.086
Smoking, *n* (%)	82 (59.9)	47 (61)	.865
CHF, *n* (%)	17 (12.4)	15 (19.5)	.164
Diabetes mellitus, *n* (%)	27 (19.7)	18 (23.4)	.527
Hyperlipidemia, *n* (%)	106 (77.4)	62 (80.5)	.591
Peri-operative characteristics			
White blood cell count pre-op (× 10^3/μL)	6.6 ± 1.4	7.7 ± 1.3	.101
White blood cell count post-op (max, × 10^3/μL)	10 ± 2.5	15.9 ± 3.8	<.001
hs-CRP preop (mg/L)	3.2 (0.2—49)	4.3 (0.1—49)	.374
hs-CRP post-op (max, mg/L)	88 ± 61.6	132 ± 63.3	<.001
IL-6 pre-op (pg/mL)	5.2 (3.5—9.1)	6.4 (4.5—9.2)	.640
IL-6 post-op (max, pg/mL)	36.9 (21.3—66.8)	98.4 (63.6—126.8)	<.001
PLT pre-op	196.8 ± 51.5	217.5 ± 53.9	.006
PLT post-op (max)	151.4 ± 54	149.7 ± 49.9	0.834
Duration of operation (min)	108 ± 49.2	112.9 ± 53	.521
Media contrast (mL)	151.6 ± 88.4	149 ± 111.3	.852
Radiation Burden (mGym^2)	2.1 (0.75—312)	2.1 (0.89—15.7)	.351
Radiation time (min)	21 ± 16.2	23.2 ± 15.2	.318
ICU stay (days)	0 (0—5)	0 (0—7)	.008
Temperature maximum (°C)	37.8 ± .7	38.6 ± 0.5	<.001
Temperature duration (days)	0.78 ± 0.3	2.8 ± 1.3	<.001
Days of stay (days)	3 (2—29)	6 (3—26)	<.001
Accessory renal artery covered	5 (3.6)	3 (3.9)	.954
Newly formed thrombus at first month	64.6 ± 119.7	54.5 ± 59	.620

BMI = body mass index; AAA = abdominal aortic aneurysm; IMA = inferior mesenteric artery; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; hs-CRP: high sensitivity C reactive protein; IL-6 = interleukin 6; PLT = platelets.

Table 2. The stent grafts deployed in the two groups.

	Total $n = 214$	No PIS $n = 137$	PIS $n = 77$
Endurant	108	52	56
Excluder	86	76	10
Anaconda	11	2	9
Zenith	7	6	1
Powerlink	1	1	0
Aorfix	1	0	1

($p < .001$) and ICU ($p = .008$) stay, as well as maximum post-operative WBC count ($p < .001$), IL-6 ($p < .001$), and hs-CRP values ($p < .001$) were significantly higher in the PIS group. In the vast majority (73/77, 94.8%) of patients in the PIS group, the syndrome was evident from the first post-operative day. In all patients who sustained an adverse event, PIS occurred before that event.

Influence on outcome

Major adverse cardiovascular events. None of the patients was lost to follow up. During the first 30 days, three of 137 patients (2.2%) in the non-PIS group had MACE, compared with 13 out of 77 patients (16.8%) in the PIS group ($p < .001$). More specifically, multiple logistic regression analysis showed that the presence of coronary artery disease ($p = .01$), post-operative hs-CRP ($p = .001$), and duration of fever ($p = .02$) independently predicted the occurrence of MACE. Patients suffering from CAD were 7.9 times (95% CI 1.6—38.6 times, $p = .011$) more likely to sustain MACE during the first 30 days after the procedure. For every additional day of post-operative fever after the first, the chance of MACE increased by 67.9% (95% CI 9.8—260%, $p = .017$), while for every 10 unit increase in the post-operative hs-CRP the chance for MACE increased by 15% (95% CI 6—24%, $p = .001$). The ROC curve analysis showed that post-operative hs-CRP is an important value in predicting the occurrence of MACE during the first 30 days after the procedure (area under the curve [AUC] 0.804; $p < .001$; Fig. 3). A threshold value of 125 mg/L was highly associated with the occurrence of MACE, with a sensitivity of 82% and specificity of 75%.

Adverse events. During the first 30 days, four of 137 patients (2.9%) in the non-PIS group had an adverse event, compared with 20 of 77 patients (25.9%) in the PIS group ($p < .001$). Multiple logistic regression analysis showed that hs-CRP post-operative values ($p = .004$), post-implantation syndrome ($p = .01$), maximum temperature ($p = .02$), and history of smoking ($p = .02$) were independent predictors of an adverse event during the first 30 days after the procedure. For every 10 unit rise in the value of post-operative hs-CRP the chance of an adverse event increased by 12% (95% CI 4—19%, $p = .004$), while for every 1 degree rise in maximum temperature the risk increased 3.1 times (95% CI 1.15—8.5 times higher, $p = .03$). Patients diagnosed with PIS after implantation were about five times (95% CI 1.5—17.6, $p = .011$) more likely to suffer an adverse event than non-PIS patients, while smokers were about 4.3 times (95% CI 1.25—15.1, $p = .02$) more likely than non-smokers. The ROC curve analysis showed that post-operative hs-CRP is an important value in predicting the occurrence of an adverse event during the first 30 days after the procedure (area under the curve [AUC] 0.79; $p < .001$, Fig. 4). A threshold value of 125 mg/L was highly associated with the occurrence of an adverse event, with a sensitivity of 72% and specificity of 75%.

DISCUSSION

This study shows that PIS affects nearly one third of patients after EVAR for AAA. The reported incidence of PIS in the literature varies widely from 14% to 60%.[14—17] The lack of a universally accepted definition may account for this variation. Some authors described PIS as the presence of fever coinciding with an elevated serum CRP level, whereas others regard it as the presence of fever combined with a leukocytosis of different cut off values.[8,9,14—17] This group has proposed a definition of the syndrome according to SIRS, as PIS actually fulfills at least two of the SIRS criteria

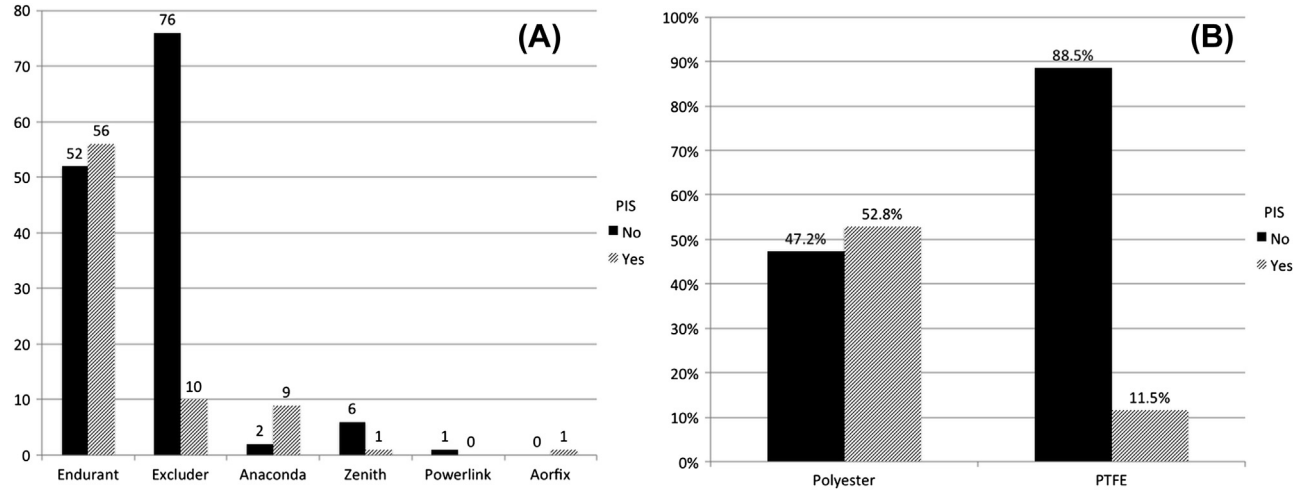

Figure 1. (A) The relation between the different endografts deployed and the occurrence of post-implantation syndrome (PIS). (B) The material the endografts made and its relation to PIS.

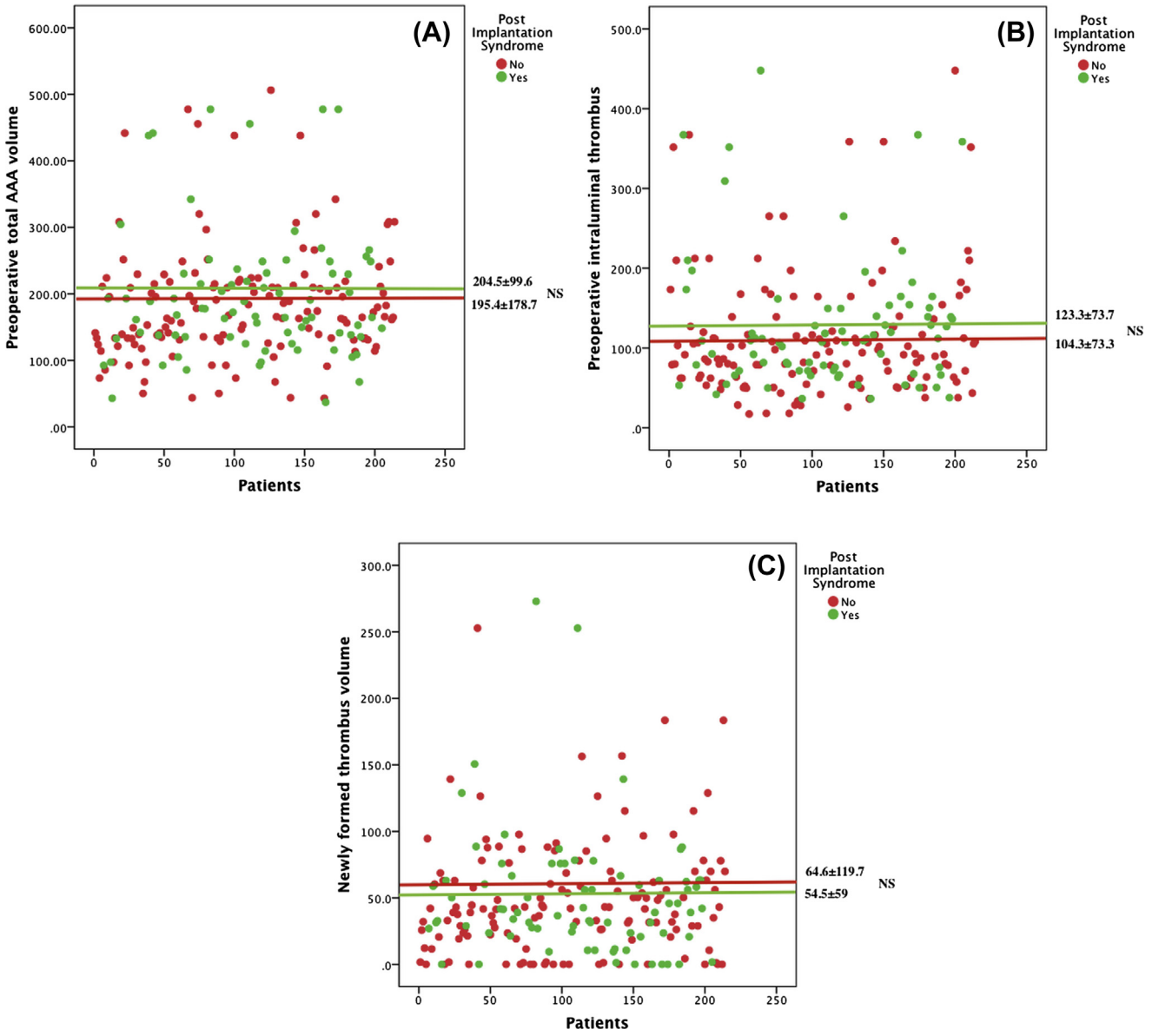

Figure 2. Scatterplot showing (A) total abdominal aortic aneurysm volume in the two groups, (B) the volume of thrombus pre-operatively, and (C) the newly formed thrombus after the first post-operative month.

(fever and leukocytosis).[18] In this study PIS was defined as the presence of fever (>38 °C) and leukocytosis (>12.000/μL). However, hs-CRP values were strongly related to the presence of PIS and also emerged as an important predictor of the 30 day outcome. Thus hs-CRP probably expresses the intensity of the inflammatory response to endograft deployment more consistently and reliably. It is likely that this biomarker is more appropriate in defining PIS than WBC count and the definition of the syndrome might be based mainly on hs-CRP values. Voûte et al.[8] in their report included CRP in the PIS definition and described PIS as fever >38 °C coinciding with an elevated serum CRP level above 10 mg/L. In any case, a universally accepted definition is needed for use in everyday clinical practice and for reporting standards when comparing different studies.

The cause of the inflammatory response after EVAR has not been clearly defined. It is important to identify the primary event causing the inflammatory reaction. In open AAA repair, a more pronounced elevated systemic inflammatory response has been observed than in EVAR, probably due to the more significant invasiveness of the procedure.[19] The magnitude of this response may cover any effect of other co-factors such as the type of the graft, although this has not been studied so far. In EVAR cases, the amount of contrast media, the endograft material, or the amount of mural thrombus within the aneurysm sac have all been implied as possible causative factors.[8,9,20,21] The type of anesthesia may also have a role by influencing the inflammatory cytokine response.[22] As most of the patients worldwide are operated on under general anesthesia, to avoid any possible bias all patients in this study were operated on under general anesthesia. In the present study the contrast media used as well as the aneurysm's thrombus load were not correlated with PIS. This finding is

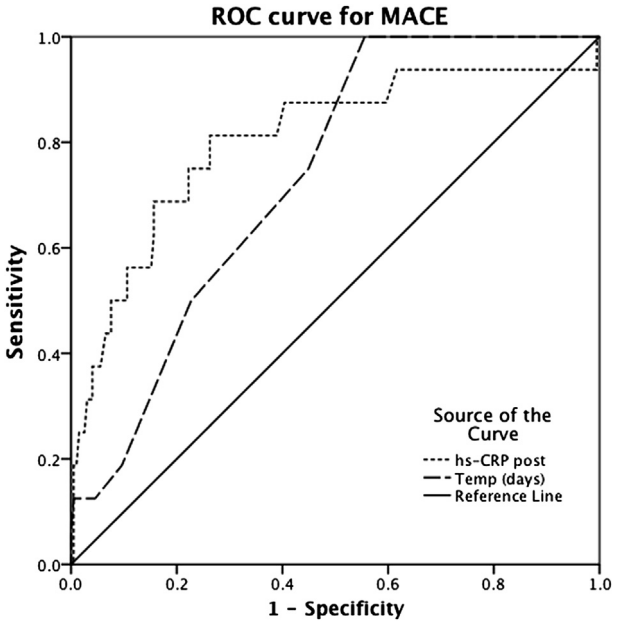

Figure 3. Major adverse cardiac event (MACE) plot of receiver operating characteristic (ROC) curve for high sensitivity C-reactive protein (hs-CRP) measured post-operatively, as well as for fever duration. Diagonal segments are produced by ties.

in accordance with the recent publication of Voûte et al.[8] However, in the same report the authors showed that the implantation of stent grafts based on polyester was independently associated with a stronger inflammatory response.[8] Moulakakis et al.,[9] observing a milder inflammatory activation in patients with a PTFE endograft, have confirmed this finding in a later report. In accordance with these reports it was found that the use of polyester endograft independently predicted PIS and was correlated with a greater than 10 times higher risk for an inflammatory response. Although other endograft parameters such as the exoskeleton material (nitinol vs. stainless steel) have not been investigated in the present study, the wide application of these materials in cardiac and peripheral arterial stenting with no reports of a remarkable inflammatory response show that differences in the application of nitinol among stent grafts is unlikely to influence PIS. Based on the three studies mentioned above (450 patients overall), it is quite obvious that the polyester fabric of the endograft can predict the occurrence of PIS in more than 50% of patients. Nevertheless, as shown in the multivariate analysis, some other parameters seem to influence PIS occurrence and perhaps the primary event causing the inflammatory reaction is still unidentified and further study is therefore required.

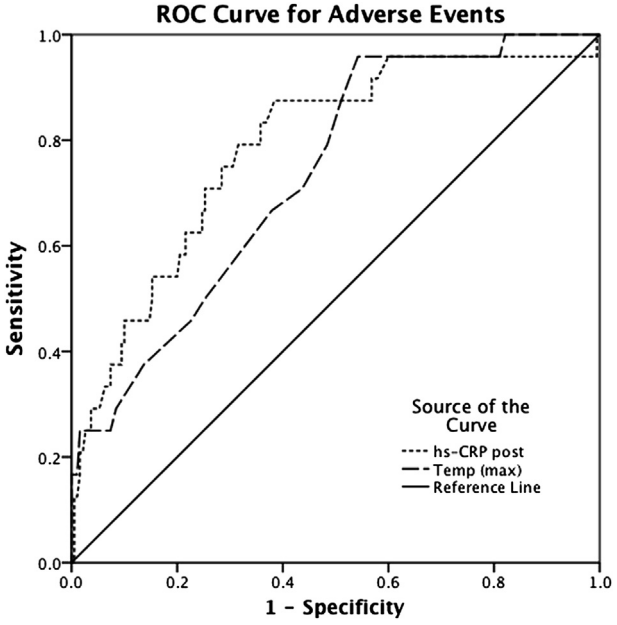

Figure 4. Adverse event plot of receiver operating characteristic (ROC) curve for high sensitivity C-reactive protein (hs-CRP) measured post-operatively, as well as maximum post-operative temperature. Diagonal segments are produced by ties.

Coagulation disturbances after EVAR occur either as a result of aneurysm sac thrombosis or by direct platelet stimulation by the endograft material.[23] A significant decrease in platelet count, an indirect index of platelet activation and consumption, has been observed post-operatively in a substantial proportion of EVAR patients.[3,9] The amount of mural thrombus has also been proposed to incur a role in the inflammatory response, as PIS initially was linked with the release of inflammatory mediators from the aneurysm thrombus.[15,16] Kakisis et al.[24] recently evaluated nearly 85 patients after EVAR and reported an association between new onset thrombus and PIS. However, Voûte et al.[8] by investigating the relation of PIS with new onset thrombus formation in 136 patients after EVAR did not find any correlation. This finding is in accordance with the results here, as there was no difference either in total pre-operative AAA volume and pre-operative endoluminal thrombus, or in the amount of newly formed thrombus between the two groups.

The effect of the syndrome on the outcome of the patients has not been well defined. In most studies PIS is generally well tolerated, showing a benign course during the post-operative period.[9] Most series have failed to demonstrate any connection between PIS and post-operative complications.[9,14] However, no study so far has focused on cardiovascular and other adverse events, by prospectively evaluating the treated patients during the 30 day post-operative period. In many vascular centers, EVAR is considered to be a quite simple procedure and most patients are discharged home the day after the procedure. This could lead to non-awareness of some cardiovascular or other adverse events that might happen during the post-operative period, as patients might be referred to other medical specialties or even hospitals. There is some evidence that in some patients the initial inflammatory response following EVAR is not always spontaneously attenuated and could lead to the development of serious complications even several days after the operation.[7] For example Chang et al.[6] evaluated the effect of the inflammatory response on post-operative renal function after

endovascular repair of thoracoabdominal aneurysms and found that the severity of the inflammation correlated with post-operative renal dysfunction. In a previous publication by the group, five EVAR patients and one TEVAR patient who needed re-admission during the first 30 days after the procedure due to intense SIRS were reported.[7] In the present prospective study patients of the PIS group had significantly more adverse events during the first month after the procedure (9.3% vs. 1.8%). The intensity of the inflammatory process, as shown from the post-operative values of hs-CRP and the characteristics of fever, independently predicted the occurrence of a cardiovascular or any other adverse event during the first month after EVAR. Based on these results, it seems reasonable that patients who develop an excessive inflammatory response post-operatively might be better kept under surveillance for the first post-operative month. A cut off value of hs-CRP of 125 mg/dL in the immediate post-operative period could probably distinguish those patients that need the extended surveillance. Such a policy could lead to early identification of any cardiovascular or other adverse event that would then be adequately treated.

The results of the present study certainly raise the question about the need for PIS-specific treatment, focusing on reducing the post-deployment inflammatory response. Current literature provides scarce evidence and no established algorithm concerning the type and duration of such treatment. Some authors recommended aggressive routine use of anti-inflammatory drugs while most others prefer a more conservative approach.[15,25] Akin et al.[26] did not observe any clinical benefit of prolonging antibiotic treatment beyond the day of endovascular intervention in PIS patients. Bischoff et al.[17] in a recent survey of vascular surgery departments in Germany reported that 71% of the vascular centers treated PIS with non-steroidal anti-inflammatory agents (NSAIDs). A recently published, prospective randomized trial evaluated the effect of pre-operative high dose glucocorticoid on PIS and reported an attenuated inflammatory response with a faster recovery for those EVAR patients treated with anti-inflammatory drugs.[27] However, the routine administration of drugs like steroids or NSAIDs is of serious concern because of their side effects, especially in patients with several comorbidities, including renal failure, heart failure, or coronary artery disease.[7] It is reasonable that some patients presenting with an intense inflammatory response, leading to prolonged hospitalization or even a readmission, might benefit from anti-inflammatory therapy. Future studies might focus on the effect of routine or symptom based anti-inflammatory therapy on the outcome of patients developing PIS after EVAR.

These results should be interpreted in the light of certain limitations, including the small number of cardiovascular events and the effect of this on the statistical analysis. This was not a randomized trial, though graft selection was based strictly on anatomical criteria and not on any characteristic of the inflammatory response. Furthermore, the recording of detailed data on AAA anatomy such as the length or angulation of the neck was not part of the present protocol. Although their potential effect on PIS cannot be excluded, it was not considered that these parameters were related to the inflammatory response after EVAR and they have not been included in any PIS study so far. The lack of a control group to better quantify the inflammatory response should also be acknowledged. However, the creation of a control group with AAA patients undergoing bilateral femoral cut down alone without graft deployment would be unethical. Inflammatory markers were only measured on the first and third post-operative day. Therefore, although PIS is usually evident in the first three post-operative days, any rises in inflammatory markers occurring later may have been missed by the study protocol.

In conclusion, a systematic inflammatory response is observed in almost one third of patients after EVAR for AAA. The type of endograft material (polyester) seems to play a significant role in this inflammatory process. Although PIS is well tolerated in the majority of patients, the intensity of the inflammation, as assessed mainly by post-operative hs-CRP values, seems to correlate with the presence of a cardiovascular or any other adverse event during the first 30 days after the procedure.

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CONFLICT OF INTEREST

None.

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