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# Clinical features and prognostic value of stent-graft-induced post-implantation syndrome after thoracic endovascular aortic repair in patients with type B acute aortic syndromes

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## Abstract

**OBJECTIVES**: The aim of this study was to investigate the incidence, the biomarker profile and the clinical impact of post-implantation syndrome (PIS) after thoracic endovascular aortic repair (TEVAR) for type B acute aortic syndromes (AASs).

**METHODS**: This retrospective study included 133 patients with type B AASs undergoing TEVAR; PIS was defined as fever >38°C, white blood cells (WBCs) >12.0/nl and C-reactive protein (CRP) >10 mg/dl within 72 h after TEVAR, despite negative blood cultures. Fibrinogen (FBG), D-dimer (D-d) and interleukin 6 (IL-6) were also determined. The clinical endpoints were all-cause mortality and a composite of major adverse events (MAEs such as aortic rupture, need for reintervention and all-cause mortality) at follow-up.

**RESULTS**: PIS was diagnosed in 15.8% of patients and was associated with higher peak values of WBC (17.0 ± 5.1 vs 10.6 ± 3.7/nl, $P = 0.002$), CRP (22.0 ± 5.4 vs 16.8 ± 8.2 mg/dl, $P = 0.03$), FBG (779 ± 246 vs 639 ± 225 mg/dl, $P = 0.046$), D-d (1675 ± 605 vs 1048 ± 639 µg/l, $P = 0.003$) and IL-6 (192 ± 101 vs 84 ± 34 pg/ml, $P = 0.03$) than non-PIS patients. All-cause mortality did not significantly differ between PIS and non-PIS patients during the index hospitalization (0.0 vs 6.3%; $P = 0.60$) and at follow-up (18.8 vs 4.9%; $P = 0.086$). MAEs were more frequent in the PIS than in the non-PIS group (62.5 vs 25.9%; $P = 0.004$). PIS (hazard ratio [HR] 3.26, $P = 0.022$), stroke (HR 3.41, $P = 0.004$), aortic enlargement (HR 6.88, $P = 0.001$) and partial thrombosis of the false lumen (HR 6.20, $P = 0.003$) were independent predictors of MAEs.

**CONCLUSIONS**: PIS occurred in 15.8% of patients with AASs without affecting in-hospital outcome. At follow-up, PIS was associated with increased rates of MAEs, but not mortality.

**Keywords:** Post-implantation syndrome • Acute aortic syndromes • Acute aortic dissection • Intramural haematoma • Penetrating aortic ulcer • Thoracic endovascular aortic repair

AORTIC SURGERY

## INTRODUCTION

Post-implantation syndrome (PIS) represents a systemic inflammatory response syndrome initially observed following endovascular aortic repair (EVAR) of infrarenal abdominal aortic aneurysms (AAAs) [1]. Key clinical features of PIS consist of postoperative fever despite negative blood cultures, leucocytosis and increased C-reactive protein (CRP) [1–4].

Acute aortic syndromes (AASs) represent a growing area of interest for endovascular treatment; currently, the recent European Society of Cardiology (ESC) guidelines on aortic diseases assigned a class I-C recommendation to thoracic endovascular aortic repair (TEVAR) as the therapy of complicated type B AASs [5].

The aim of our study was to investigate the incidence, the biomarker profile and the clinical impact of PIS among patients undergoing TEVAR for type B AASs.

[†] The first two authors contributed equally to the manuscript.

## MATERIALS AND METHODS

### Study design

This retrospective study included patients with type B AASs who underwent TEVAR at the West-German Heart and Vascular Centre, Essen, Germany between 2002 and 2014 along with biomarker measurements (white blood cells [WBCs] count, fibrinogen [FBG], D-dimer [D-d], CRP and interleukin 6 [IL-6] serum levels) daily from the day before up to 72 h after TEVAR and with at least five measurements thereafter.

Blood samples were taken from a peripheral vein. Body temperature was recorded within the first 72 h after TEVAR and later at the physician's discretion.

PIS was defined as fever >38°C, WBC >12.0/nl and CRP >10 mg/dl within 72 h after TEVAR despite negative blood culture results [3, 4].

Exclusion criteria were as follows: clinical or instrumental evidence of preoperative infection, previous implantation of an endoprosthesis, autoimmune disorders, any type of malignancy, preoperative use of corticosteroids and incomplete laboratory data.

Among 146 patients, 1 was excluded due to the presence of a preoperative pulmonary infection, 2 were due to the diagnosis of bronchial carcinoma and 10 due to incomplete laboratory data. The remaining 133 patients were included in the study population.

All patients gave informed written consent for the procedure. Type B acute aortic dissection (AAD), intramural haematoma (IMH) and penetrating aortic ulcer (PAU) were defined according to the ESC guidelines on aortic diseases [5].

### Endovascular procedure

TEVAR was performed by an interdisciplinary team of interventional cardiologists, cardiothoracic surgeons and anaesthesiologists at the West-German Heart and Vascular Center Essen, Germany [6, 7]. The procedure has been described in detail elsewhere [7]. The stent-grafts implanted included 62 Relay (Bolton Medical, Sunrise, FL, USA), 60 Valiant (Medtronic Vascular, Santa Rosa, CA, USA), 22 Talent (Medtronic Vascular) and 13 TAG grafts (W. L. Gore & Associates, Flagstaff, AZ, USA). All patients received single-shot antibiotic treatment (cefazoline 2 g) intravenously at the beginning of the procedure; the postoperative use of antibiotics was left to the discretion of the attending ward physician. After TEVAR, patients were subjected to a follow-up protocol, including clinical assessment and imaging of the aorta prior to discharge, as well as at 3 and 6 months, 1 year and then annually thereafter.

### Biomarker analysis

The following systems were used to test biomarker serum levels: an immunoturbidometric assay (Scil Diagnostics, Martinsried, Germany) on an automated Advia 1650 clinical chemistry analyser (Bayer HealthCare, Diagnostic Division, Tarrytown, NY, USA) for CRP, a Gen-s haematology analyser (Beckman Coulter, Fullerton, CA, USA) for the WBC count, the Multifibren U test (Dade Behring, Marburg, Germany) on a BCS coagulation analyser (Dade Behring) for plasma FBG, a latex-enhanced turbidometric test (D-dimer Plus; Dade Behring) on a BCS coagulation analyser for D-d, an Immulite 2000 system analyser (Siemens Healthcare Diagnostics, Duisburg, Germany) for IL-6.

### Imaging modalities

Computed tomography (CT) angiography scans were performed on a 16-row multidetector scanner (2002–08; Somatom Sensation 16; Siemens Medical Solutions, Erlangen, Germany) and on a 64-row multidetector scanner (2009–14; Somatom Definition; Siemens Healthcare, Forchheim, Germany).

Transoesophageal echocardiography (TOE) was performed with a conventional TOE probe (2002–07) and a 3D TOE probe (X7-2t matrix transducer) (2008–14) on a Philips iE33 ultrasound unit (Philips Electronics N.V., Best, Netherlands).

MRI of the aorta was performed with a 1.5-T whole-body scanner (2002–14) (MAGNETOM Avanto, Siemens AG, Erlangen, Germany).

Intravascular ultrasound (IVUS) was performed using a catheter (Visions® PV 0.035, Volcano, San Diego, CA, USA) with a maximum imaging diameter of 60 mm and a 10-MHz frequency ultrasound. Specific protocols for each imaging modality have been already described previously [8–11].

### Clinical endpoints

The primary clinical endpoint of the study was in-hospital and long-term mortality from any cause. The secondary clinical endpoint was a composite of major adverse events (MAEs), including death from any cause, aortic rupture and need for reintervention during follow-up.

### Statistical analysis

Preliminary analyses were performed to verify linearity and normality. The Shapiro–Wilk test was used to determine whether each parameter followed a Gaussian distribution.

Continuous variables are presented as mean ± standard deviation; categorical variables are presented as frequencies and percentages. Comparison of categorical variables was made with the two-sided $\chi^2$ or, when appropriate, the two-sided Fisher's exact test. Comparison of continuous variables between groups was made using the unpaired two-sided Student's *t*-test for normally distributed variables and a Mann–Whitney *U*-test for non-normally distributed variables. Differences in study parameters between baseline and postoperative values within the same group were analysed using the paired-sample *T*-test for normally distributed variables or the Wilcoxon's rank test for non-normally distributed variables.

Demographic, clinical, instrumental and TEVAR-related variables were included in a Cox proportional hazard regression analysis to determine the univariate predictors of MAEs; those variables with $P < 0.10$ were then included into a multivariable Cox forward stepwise model adjusted for age and gender to determine the independent predictors. Survival analysis was performed using the Kaplan–Meier method; comparison of Kaplan–Meier curves was made with log-rank testing.

A value of $P < 0.05$ was considered statistically significant. All statistical analyses were made using the SPSS software (version 21.0; SPSS, Chicago, IL, USA).

## RESULTS

### Incidence and biomarker profile of post-implantation syndrome

PIS was diagnosed in 21 (15.8%) of 133 patients with no difference among the different type B AAS types (13.9% for AAD, 14.7% for IMH and 11.5% for PAU; $P = 0.86$).

After TEVAR, an inflammatory response was observed in all patients. More precisely, there was a significant increase compared with the baseline values, in both the PIS and the non-PIS group, of WBC, CRP, FBG and D-d (Fig. 1A–D). Interestingly, IL-6 significantly increased in the PIS group only (Fig. 1E). Different kinetics were evident as well: D-d and IL-6 peaked 24 h after TEVAR, WBC and CRP at 48 h, FBG at 72 h (Fig. 2). Moreover, by comparing biomarker peak and mean values during hospitalization between the two groups, we found that patients with PIS developed a systemic inflammatory response more striking and prolonged across the hospitalization (Table 1).

### Clinical characteristics of post-implantation syndrome versus non-post-implantation syndrome patients

***In-hospital outcome.*** Clinical data of the two groups are reported in Table 2.

Demographics and risk factors were similar between PIS and non-PIS patients.

Indications for TEVAR were not significantly different between the two groups; refractory pain and hypertension were observed slightly more frequently in the PIS group, whereas malperfusion syndrome was more frequent in the non-PIS group.

CT was performed prior to TEVAR in 95.5% of the study population; in the remaining cases, the procedure was planned according to MRI or IVUS findings.

Total stent lengths, oversizing ratios and the number of patients requiring coverage of the left subclavian artery were similar between the groups. Five patients in the non-PIS group underwent transposition of the left subclavian artery before TEVAR.

In patients with AAD, CT a few days after TEVAR showed no significant differences between the false lumen statuses of the PIS and non-PIS groups, even though an active false lumen (patent or partially thrombosed) was observed more frequently in PIS patients.

All-cause mortality occurred in 7 (6.3%) of 112 patients of the non-PIS group and in 0 (0.0%) of 21 patients of the PIS group ($P = 0.60$). One death was related to severe enduring malperfusion syndrome, 2 deaths were due to multiorgan failure, 2 to aortic rupture and 2 to cardiac complications. Length of hospitalization was similar between the PIS and non-PIS group (respectively, 26.2 ± 15.2 vs 26.2 ± 19.7 days; $P = 1.00$). The rate of in-hospital complications did not significantly differ between the groups, as well.

***Biomarker levels and malperfusion syndrome.*** Biomarker levels according to the presence of malperfusion syndrome at presentation are presented in Table 3. At baseline, patients without malperfusion showed higher FBG values than those with malperfusion ($P = 0.03$). Early after TEVAR, there were no significant

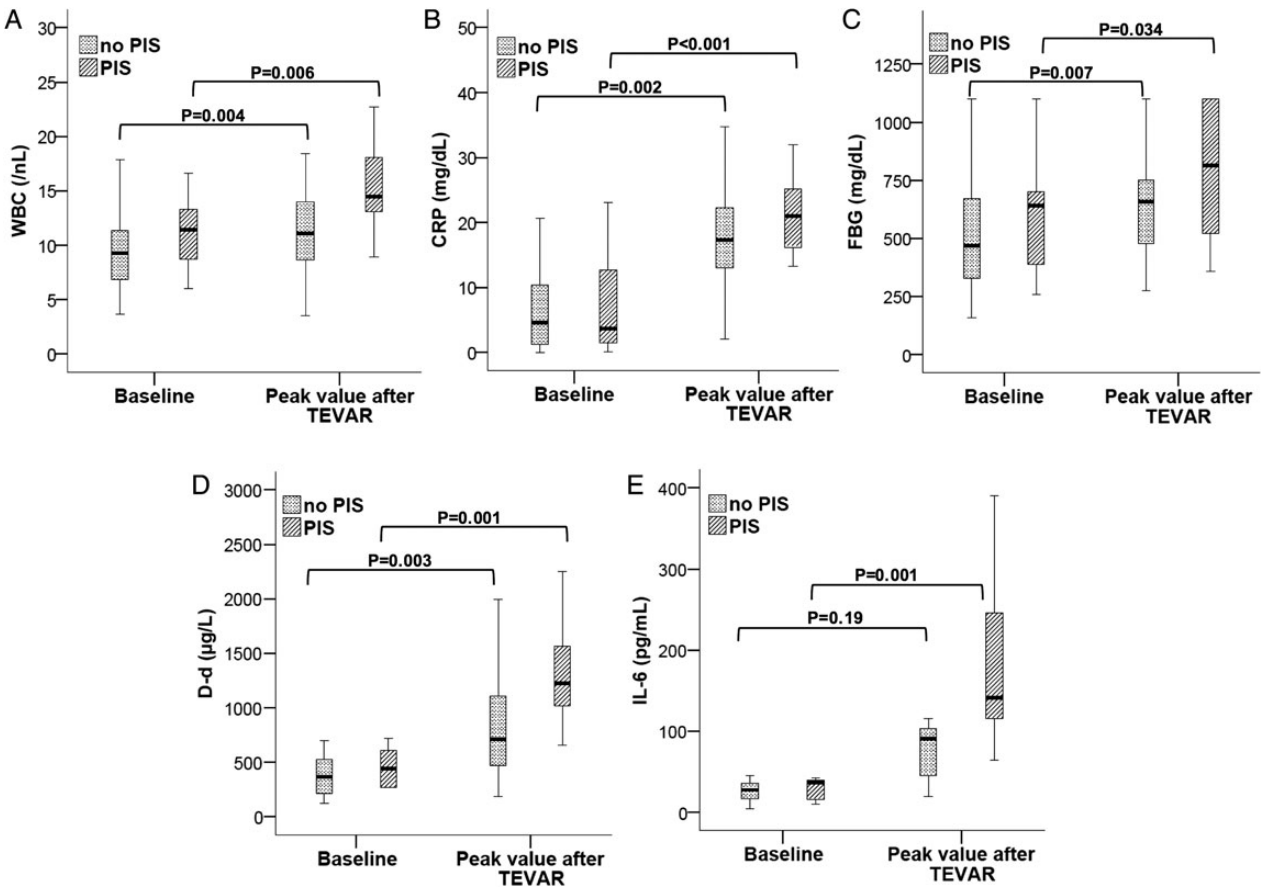


**Figure 1:** Baseline and peak values of white blood cells (WBCs; **A**), C-reactive protein (CRP; **B**), fibrinogen (FBG; **C**), D-dimer (D-d; **D**) and interleukin 6 (IL-6; **E**) within 3 days after thoracic endovascular aortic repair (TEVAR). PIS: post-implantation syndrome.

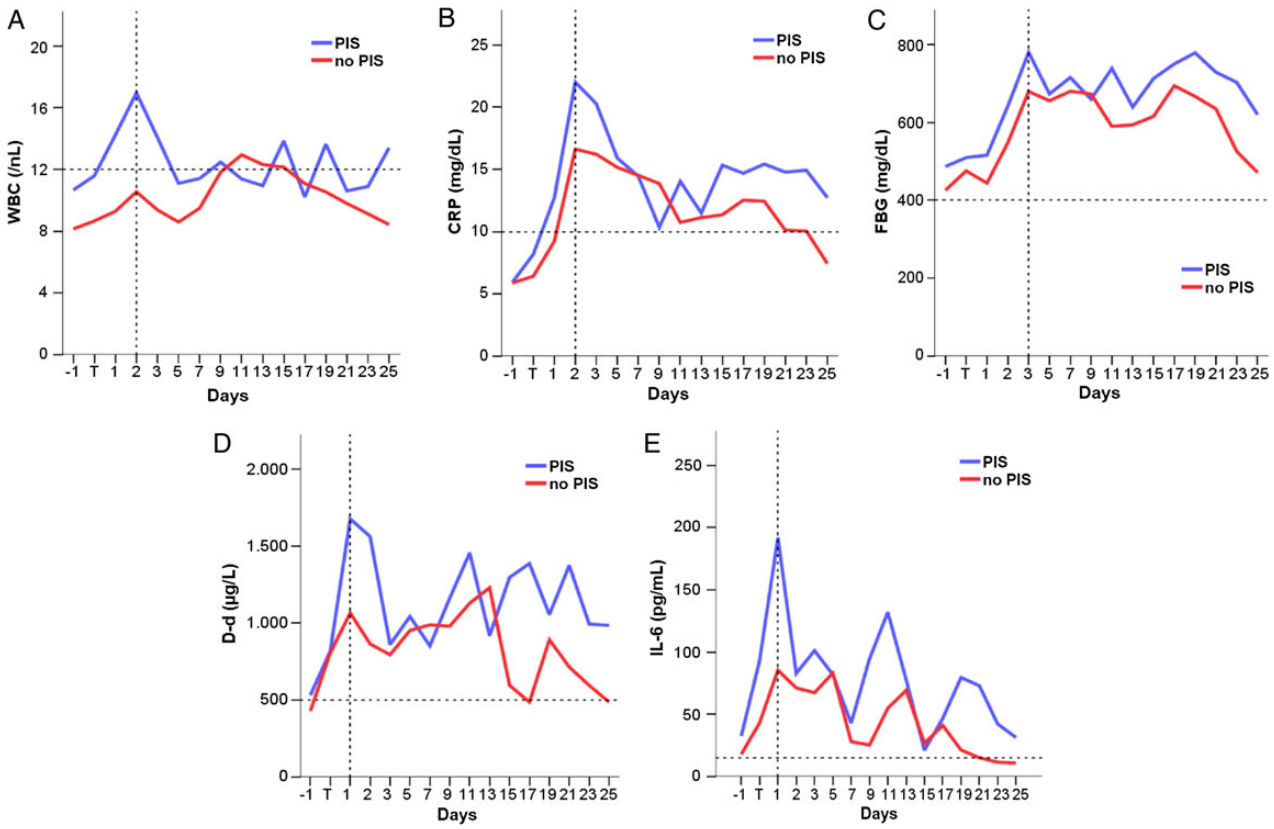


**Figure 2:** Time course of serum levels of white blood cells (WBCs; **A**), C-reactive protein (CRP; **B**), fibrinogen (FBG; **C**), D-dimer (D-d; **D**) and interleukin 6 (IL-6; **E**) during hospitalization. T: thoracic endovascular aortic repair; PIS: post-implantation syndrome.

**Table 1:** Biomarker levels at baseline, peak and mean value during hospitalization in patients with and without post-implantation syndrome

| Biomarkers | Overall | PIS (–) | PIS (+) | *P*-value (–) vs (+) |
|---|---|---|---|---|
| Baseline | | | | |
| WBC (/nl; nv < 9.2) | 9.7 ± 3.6 | 8.3 ± 3.2 | 10.6 ± 3.4 | 0.26 |
| CRP (mg/dl; nv < 0.5) | 7.0 ± 6.9 | 6.8 ± 6.8 | 7.1 ± 7.3 | 0.34 |
| FBG (mg/dl; nv < 400) | 532 ± 244 | 522 ± 246 | 573 ± 156 | 0.27 |
| D-d (µg/l; nv < 250) | 500 ± 312 | 429 ± 296 | 531 ± 235 | 0.41 |
| IL-6 (pg/ml; nv < 15) | 26 ± 18 | 17 ± 16 | 32 ± 15 | 0.13 |
| Peak value within 72 h after TEVAR | | | | |
| WBC (/nl; nv < 9.2) | 12.2 ± 4.1 | 10.6 ± 3.7 | 17.0 ± 5.1 | 0.002 |
| CRP (mg/dl; nv < 0.5) | 18.4 ± 8.1 | 16.8 ± 8.2 | 22.0 ± 5.4 | 0.03 |
| FBG (mg/dl; nv < 400) | 722 ± 224 | 639 ± 225 | 779 ± 246 | 0.046 |
| D-d (µg/l; nv < 250) | 1091 ± 578 | 1048 ± 639 | 1675 ± 605 | 0.003 |
| IL-6 (pg/ml; nv < 15) | 118 ± 91 | 84 ± 34 | 192 ± 101 | 0.03 |
| Mean value during hospitalization | | | | |
| WBC (/nl; nv < 9.2) | 10.9 ± 4.4 | 10.6 ± 4.2 | 13.0 ± 5.8 | 0.001 |
| CRP (mg/dl; nv < 0.5) | 11.9 ± 7.3 | 10.1 ± 7.1 | 13.9 ± 6.5 | 0.02 |
| FBG (mg/dl; nv < 400) | 617 ± 195 | 595 ± 202 | 660 ± 186 | <0.001 |
| D-d (µg/l; nv < 250) | 1032 ± 485 | 911 ± 421 | 1193 ± 673 | 0.001 |
| IL-6 (pg/ml; nv < 15) | 80 ± 64 | 43 ± 35 | 118 ± 86 | <0.001 |

PIS: post-implantation syndrome; WBCs: white blood cells; CRP: C-reactive protein; FBG: fibrinogen; D-d: D-dimer; IL-6: interleukin 6; nv: normal value; TEVAR: thoracic endovascular aortic repair.

differences in biomarker peak levels between patients with and without malperfusion syndrome. Biomarker mean levels across the hospitalization were similar as well, although WBC tended to be higher in the malperfusion group (11.2 ± 3.1/nl) compared with the non-malperfusion group (10.0 ± 2.9/nl, $P = 0.063$).

***Follow up.*** The mean length of follow-up was 4.0 ± 2.9 years with no significant differences between the PIS (3.5 ± 2.8 years) and the non-PIS group (4.1 ± 3.0 years; $P = 0.56$). In patients with AAD, a partially thrombosed false lumen was observed more frequently in the PIS group when compared with the non-PIS group (72.7 vs 35.6%, respectively; $P = 0.046$). In addition, a partially thrombosed false lumen was associated with aortic enlargement and secondary endoleaks during follow-up ($P = 0.008$ and 0.021, respectively).

All-cause mortality occurred overall in 7 (7.2%) of 97 patients with a mean survival of 3.1 years, whereas, according to the presence of PIS, in 3 (18.8%, mean survival 1.6 years) of 16 patients in the PIS group and in 4 (4.9%, mean survival 4.2 years) of 81 patients in the non-PIS group ($P = 0.086$; Table 4). Two deaths were related to non-cardiac causes, 2 to multiorgan failure and 3 to aortic rupture. On Kaplan–Meier analysis, a significant trend towards poorer survival for patients with PIS was evident: the unadjusted survival rate for PIS versus non-PIS was, respectively, 87.5 ± 8.3 and 97.2 ± 2.0% at 1 year, 70.0 ± 17.0 and 93.8 ± 3.8% at 4 years (log-rank $P = 0.014$; Fig. 3A).

MAEs occurred in 10 (62.5%) of 16 patients with PIS and in 21 (25.9%) of 81 patients without it ($P = 0.004$; Table 4).

**Table 2:** Clinical data of the study population divided according to the presence of post-implantation syndrome

| Variables | Overall | PIS (−) | PIS (+) | *P*-value (−) vs (+) |
|---|---|---|---|---|
| *N* (%) | 133 (100) | 112 (84.2) | 21 (15.8) | N/A |
| Age (years) | 71.3 ± 12.0 | 71.8 ± 12.2 | 68.1 ± 10.4 | 0.81 |
| Age >70 years old, *n* (%) | 67 (50.4) | 59 (52.7) | 8 (38.1) | 0.22 |
| Male sex, *n* (%) | 86 (64.7) | 74 (66.1) | 12 (57.1) | 0.66 |
| Risk factors, *n* (%) | | | | |
| Hypertension | 109 (82.0) | 92 (82.1) | 17 (81.0) | 1.00 |
| Diabetes | 19 (14.3) | 17 (15.2) | 2 (9.5) | 0.74 |
| Current smoke | 32 (24.1) | 24 (21.4) | 8 (38.1) | 0.10 |
| Known aortic aneurysm | 17 (12.8) | 15 (13.4) | 2 (9.5) | 1.00 |
| Imaging pre-procedure, *n* (%) | | | | |
| Computed tomography | 127 (95.5) | 107 (95.5) | 20 (95.2) | 1.00 |
| Intravascular ultrasound | 74 (55.6) | 59 (52.7) | 15 (71.4) | 0.11 |
| Transoesophageal echo | 35 (26.3) | 31 (27.7) | 4 (19.0) | 0.78 |
| Magnetic resonance imaging | 3 (2.3) | 2 (1.8) | 1 (4.8) | 0.40 |
| Indications for TEVAR, *n* (%) | | | | |
| Refractory pain/hypertension | 40 (30.1) | 30 (26.8) | 10 (47.6) | 0.06 |
| Signs of malperfusion | 36 (27.1) | 32 (28.6) | 4 (19.0) | 0.37 |
| Limb ischaemia | 18 (13.5) | 16 (14.3) | 2 (9.5) | 0.74 |
| Mesenteric ischaemia | 18 (13.5) | 16 (14.3) | 2 (9.5) | 0.74 |
| Renal ischaemia | 16 (12.0) | 15 (13.4) | 1 (4.8) | 0.47 |
| Signs of aortic rupture | 33 (24.8) | 27 (24.1) | 6 (28.6) | 0.66 |
| Maximum aortic diameter >50 mm | 24 (18.0) | 23 (20.5) | 1 (4.8) | 0.12 |
| Procedure | | | | |
| >1 stent-graft placed, *n* (%) | 24 (18.0) | 20 (17.9) | 4 (19.0) | 1.00 |
| Total stent length (mm) | 199 ± 78 | 197 ± 76 | 204 ± 91 | 0.73 |
| Proximal oversizing ratio[a] | 1.09 ± 0.09 | 1.08 ± 0.10 | 1.10 ± 0.09 | 0.54 |
| Distal oversizing ratio[a] | 1.58 ± 0.40 | 1.59 ± 0.43 | 1.57 ± 0.34 | 0.84 |
| Additional treatments, *n* (%) | | | | |
| Uncovered aortic stent | 12 (9.0) | 9 (8.0) | 3 (14.3) | 0.40 |
| Celiac artery stent | 1 (7.5) | 1 (0.9) | 0 (0.0) | 1.00 |
| SMA stent | 1 (7.5) | 1 (0.9) | 0 (0.0) | 1.00 |
| Renal artery stent | 6 (4.5) | 4 (3.8) | 2 (9.5) | 0.24 |
| Iliac artery stent | 5 (3.8) | 5 (4.5) | 0 (0.0) | 1.00 |
| Coverage of the LSA | 14 (10.5) | 11 (9.8) | 3 (14.3) | 0.54 |
| Transposition of arch vessels | 5 (3.8) | 5 (4.5) | 0 (0.0) | 1.00 |
| Imaging post procedure, *n* (%) | | | | |
| Computed tomography | 103 (77.4) | 85 (75.9) | 18 (85.7) | 0.41 |
| False lumen status[b], *n* (%) | | | | |
| Patent | 3 (3.9) | 2 (3.2) | 1 (7.7) | 0.44 |
| Partial thrombosis | 43 (56.6) | 34 (54.0) | 9 (69.2) | 0.31 |
| Complete thrombosis | 30 (39.5) | 27 (42.8) | 3 (23.1) | 0.18 |
| Transoesophageal echo | 13 (9.8) | 12 (10.7) | 1 (4.8) | 0.69 |
| Primary clinical endpoint, *n* (%) | | | | |
| All-cause mortality | 7 (5.3) | 7 (6.3) | 0 (0.0) | 0.60 |
| Specific complications, *n* (%) | | | | |
| Infection | 15 (11.3) | 14 (12.5) | 1 (4.8) | 0.46 |
| T > 38° within 72 h post TEVAR | 35 (26.3) | 14 (12.5) | 21 (100) | <0.001 |
| Stroke | 11 (8.3) | 9 (8.0) | 2 (9.5) | 0.69 |
| Primary endoleak[c] | 15 (11.3) | 10 (8.9) | 5 (23.8) | 0.062 |
| Type Ia | 11 (8.3) | 8 (7.1) | 3 (14.3) | 0.38 |

PIS: post-implantation syndrome; TEVAR: thoracic endovascular aortic repair; LSA: left subclavian artery; SMA: superior mesenteric artery.
[a]Defined as the ratio between the known stent-graft diameter and the diameter of the presumed proximal and distal landing zones, measured before implantation [12].
[b]Percentages are referred to patients with AAD.
[c]First observed during the perioperative (≤30 days) period.

The Kaplan–Meier curve for survival free from MAE is presented in Fig. 3B. The survival free from MAE was, respectively, 51.9 ± 13.5 and 85.0 ± 4.2% in the PIS and non-PIS group at 1 year, with further separation of the curves at 2 years with survival rates of 32.5 ± 13.9 and 74.1 ± 5.6% (log-rank $P < 0.001$).

The rate of specific complications such as aortic rupture, secondary type Ia endoleak, aorta-related rehospitalization and need for reintervention, were significantly higher in the PIS group than in the non-PIS group (Table 4).

Age- and gender-adjusted Cox proportional hazard regression analysis identified PIS (hazard ratio [HR] 3.26, confidence interval

**Table 3:** Biomarker levels at baseline, peak and mean value during hospitalization in patients with and without malperfusion syndrome at presentation

| Biomarkers | Overall | Malperfusion (–) | Malperfusion (+) | *P*-value (–) vs (+) |
|---|---|---|---|---|
| Baseline | | | | |
| WBC (/nl; nv < 9.2) | 9.7 ± 3.6 | 9.2 ± 3.2 | 10.0 ± 3.7 | 0.34 |
| CRP (mg/dl; nv < 0.5) | 7.0 ± 6.9 | 7.4 ± 6.9 | 6.2 ± 5.3 | 0.18 |
| FBG (mg/dl; nv < 400) | 532 ± 244 | 576 ± 261 | 427 ± 155 | 0.03 |
| D-d (µg/l; nv < 250) | 500 ± 312 | 639 ± 360 | 395 ± 256 | 0.55 |
| IL-6 (pg/ml; nv < 15) | 26 ± 18 | 24 ± 18 | 42 ± 8 | 0.08 |
| Peak value within 72 h after TEVAR | | | | |
| WBC (/nl; nv < 9.2) | 12.2 ± 4.1 | 11.9 ± 4.5 | 13.5 ± 3.6 | 0.25 |
| CRP (mg/dl; nv < 0.5) | 18.4 ± 8.1 | 18.2 ± 9.1 | 20.3 ± 8.2 | 0.54 |
| FBG (mg/dl; nv < 400) | 722 ± 224 | 747 ± 254 | 674 ± 209 | 0.79 |
| D-d (µg/l; nv < 250) | 1091 ± 578 | 1021 ± 684 | 1246 ± 563 | 0.75 |
| IL-6 (pg/ml; nv < 15) | 118 ± 91 | 120 ± 108 | 113 ± 62 | 0.85 |
| Mean value during hospitalization | | | | |
| WBC (/nl; nv < 9.2) | 10.9 ± 4.4 | 10.0 ± 2.9 | 11.2 ± 3.1 | 0.063 |
| CRP (mg/dl; nv < 0.5) | 11.9 ± 7.3 | 11.2 ± 5.9 | 12.2 ± 4.2 | 0.65 |
| FBG (mg/dl; nv < 400) | 617 ± 195 | 625 ± 199 | 595 ± 152 | 0.80 |
| D-d (µg/l; nv < 250) | 1032 ± 485 | 912 ± 672 | 1091 ± 888 | 0.52 |
| IL-6 (pg/ml; nv < 15) | 80 ± 64 | 72 ± 56 | 83 ± 41 | 0.57 |

WBCs: white blood cells; CRP: C-reactive protein; FBG: fibrinogen; D-d: D-dimer; IL-6: interleukin 6; nv: normal value; TEVAR: thoracic endovascular aortic repair.

**Table 4:** Follow-up data of the study population

| Variables | Overall | PIS (–) | PIS (+) | *P*-value (–) vs (+) |
|---|---|---|---|---|
| Follow-up available | 97/126 (77.0%) | 81/105 (77.1%) | 16/21 (76.2%) | 1.00 |
| Length of follow-up (years) | 4.0 ± 2.9 | 4.1 ± 3.0 | 3.5 ± 2.8 | 0.56 |
| Imaging, *n* (%) | | | | |
| Computed tomography | 66 (68.0) | 54 (66.7) | 12 (75.0) | 0.51 |
| Transoesophageal echo | 9 (9.3) | 7 (8.6) | 2 (12.5) | 0.64 |
| Magnetic resonance imaging | 16 (16.5) | 15 (18.5) | 1 (6.3) | 0.46 |
| Aortic enlargement[a] | 12 (12.4) | 10 (12.3) | 2 (12.5) | 1.00 |
| False lumen status[b], *n* (%) | | | | |
| Patent | 1 (1.4) | 1 (1.7) | 0 (0.0) | 1.00 |
| Partial thrombosis | 29 (41.4) | 21 (35.6) | 8 (72.7) | 0.046 |
| Complete thrombosis | 40 (57.2) | 37 (62.7) | 3 (27.3) | 0.046 |
| Primary clinical endpoint, *n* (%) | | | | |
| All-cause mortality | 7 (7.2) | 4 (4.9) | 3 (18.8) | 0.086 |
| Secondary clinical endpoint, *n* (%) | | | | |
| Major adverse events[c] | 31 (32.0) | 21 (25.9) | 10 (62.5) | 0.004 |
| Specific complications, *n* (%) | | | | |
| New dissection | 7 (7.2) | 6 (7.4) | 1 (6.3) | 1.00 |
| Extension of dissection/IMH | 3 (3.1) | 3 (3.7) | 0 (0.0) | 1.00 |
| Aortic rupture[d] | 5 (5.2) | 2 (2.5) | 3 (18.8) | 0.031 |
| Secondary endoleak[e] | 14 (14.4) | 6 (7.4) | 8 (50.0) | <0.001 |
| Type Ia | 10 (10.3) | 4 (4.9) | 6 (37.5) | 0.001 |
| Aorta-related rehospitalization | 36 (37.1) | 24 (29.6) | 12 (75.0) | 0.001 |
| Reintervention | 26 (26.8) | 17 (21.0) | 9 (56.3) | 0.01 |
| Secondary endoleak | 11 (11.3) | 5 (6.2) | 6 (37.5) | 0.002 |
| Aortic rupture | 2 (2.1) | 1 (1.2) | 1 (6.3) | 0.30 |
| Extension of dissection/IMH | 3 (3.1) | 3 (3.7) | 0 (0.0) | 1.00 |
| Aortic enlargement | 6 (6.2) | 5 (6.2) | 1 (6.3) | 1.00 |
| New dissection | 4 (4.1) | 3 (3.7) | 1 (6.3) | 0.52 |

PIS: post-implantation syndrome; IMH: intramural haematoma.
[a]Defined as an increase in total aortic diameter ≥5 mm/6 months or 1 cm/12 months [8].
[b]Percentages are referred to patients with AAD and available follow-up.
[c]Include all-cause mortality, aortic rupture and need for reintervention.
[d]Included open, contained and aortoesophageal fistula [5].
[e]Detection >30 days after intervention.

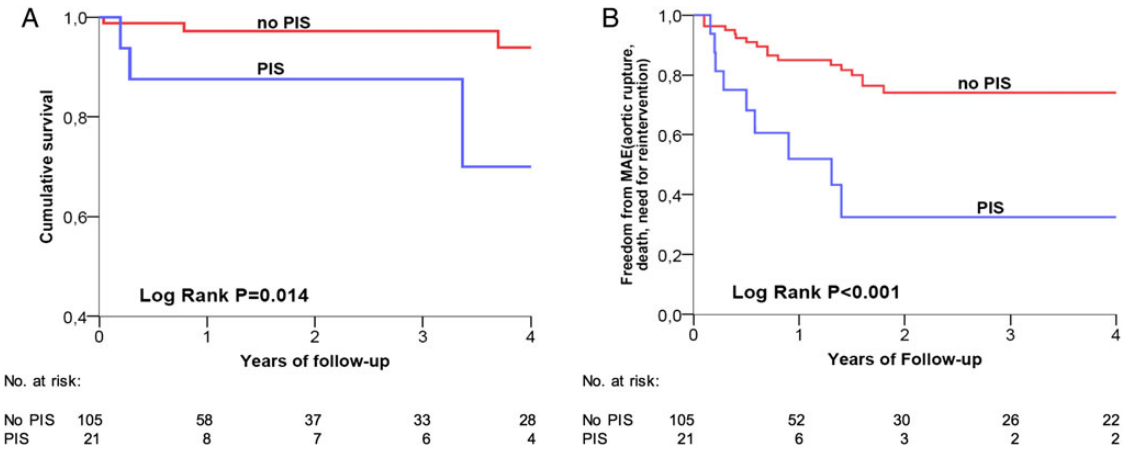


**Figure 3:** Kaplan–Meier curves showing the relationship between post-implantation syndrome (PIS) and survival (**A**) and between PIS and freedom from major adverse events (MAEs) (**B**).

**Table 5:** Uni- and multivariate predictors of major adverse events during follow-up ($P < 0.10$)

| | Hazard ratio | 95% CI | *P*-value |
|---|---|---|---|
| Univariate predictors | | | |
| Age ≥70 years old | 0.53 | 0.25–1.10 | 0.09 |
| Male sex | 0.50 | 0.24–1.00 | 0.05 |
| Acute aortic syndrome type | 0.79 | 0.64–0.99 | 0.04 |
| >1 stent-graft placed | 2.40 | 1.04–5.52 | 0.04 |
| Stent type | 0.69 | 0.47–1.01 | 0.06 |
| Stroke | 4.03 | 1.39–11.69 | 0.01 |
| Post-implantation syndrome | 3.90 | 1.81–8.42 | 0.001 |
| Aortic enlargement | 4.32 | 2.03–9.19 | <0.001 |
| Partial thrombosis of the false lumen | 6.32 | 2.07–19.33 | 0.001 |
| Multivariate predictors adjusted for age and gender | | | |
| Post-implantation syndrome | 3.26 | 1.19–8.95 | 0.022 |
| Aortic enlargement | 6.88 | 2.24–21.11 | 0.001 |
| Stroke | 3.41 | 1.18–11.25 | 0.004 |
| Partial thrombosis of the false lumen | 6.20 | 1.83–21.04 | 0.003 |

CI: confidence interval.

[CI] 1.19–8.95; $P = 0.022$), stroke (HR 3.41, CI 1.18–11.25; $P = 0.004$), aortic enlargement (HR 6.88, CI 2.24–21.11; $P = 0.001$) and partial thrombosis of the false lumen (HR 6.20, CI 1.83–21.04; $P = 0.003$) as the only independent predictors of MAEs during follow-up (Table 5).

## DISCUSSION

In our study, PIS occurred in the setting of AAS after TEVAR with an incidence of 15.8% and was characterized by a striking systemic inflammatory response that involved several inflammatory and coagulative biomarkers. Among these, IL-6 significantly increased within 24 h only in patients who developed PIS. However, the most important finding of our study was that PIS after TEVAR was an independent predictor of MAE during follow-up together with stroke, aortic enlargement and partial thrombosis of the false lumen. TEVAR was associated in all cases with an increase in all investigated biomarkers, albeit with different kinetics: D-d and IL-6 peaked at 24 h, CRP and WBC at 48 h and FBG at 72 h. This finding is consistent with other reports in the literature. Moulakakis *et al.* [13], in a recent study involving 30 patients submitted to EVAR, observed a significant increase in WBC, CRP, IL-10 and IL-6 levels postoperatively at 24–48 h with kinetics similar to those of our study; conversely, IL-8 and tumour necrosis factor α (TNF-α) did not significantly increase after EVAR. Similar findings were shown also by Eggebrecht *et al.* [14], Gabriel *et al.* [15] and Arnaoutoglou *et al.* [16]. However, two important concepts need to be pointed out: first, patients with PIS showed a more striking and prolonged inflammatory response during hospital stay, compared with patients without PIS; second, IL-6 levels increased significantly within the first 24 h after TEVAR only in patients who developed PIS. IL-6 has been described as the main pyrogenic cytokine and an early promoter of the inflammatory response [17]; during the implantation process, IL-6 is released by the vascular endothelium in the blood torrent and stimulates the liver to produce acute phase proteins such as FBG and CRP [17]. Swartbol *et al.* [18] observed in a small *in vitro* study involving 22 patients that after EVAR, the inflammatory cascade is initiated by an IL-6 release from aneurysmal thrombus formation, resulting in the synthesis of TNF-α. Our data seem to support this finding. Thus, IL-6 could play a pivotal role in the pathogenesis of PIS: the early peak observed within 24 h in patients with PIS seems to induce a release of CRP and FBG that culminates at 48–72 h after TEVAR. The resulting increase in the body temperature is the leading clinical feature of PIS and has to be differentiated from fever induced by a bacterial infection, which is typically characterized by positive blood cultures and high values of procalcitonin [19].

Additionally, organ malperfusion may be another potential confounding factor inducing a cytokine release, which may lead to overdiagnosis of PIS. Given that it is not possible to differentiate CRP or WBC increase due to PIS rather than organ malperfusion, our study showed that patients with malperfusion tended to show slightly increased biomarker levels than others, although not significantly. This finding is of particular interest considering biomarker peak levels in the first 72 h after TEVAR. Since PIS generally occurs within this time interval, the absence of significant differences in biomarker levels makes an overdiagnosis of PIS unlikely in our study population. Still, we believe that malperfusion syndrome should be also taken into account as differential diagnosis in case of PIS suspicion. In this regard, assessment of additional biomarkers indicating organ-ischaemia (such as troponin, lactate,

creatine kinase and aspartate transaminase/alanine aminotransferase) may be helpful to discriminate between these two conditions [5].

Few reports investigated the potential clinical implications of PIS. Arnaoutoglou *et al*. [16] reported that in patients submitted to EVAR for AAA, the development of PIS was associated only with prolonged hospital stay. This finding was not confirmed in our study probably because patients with AAS are at higher risk of complications (such as cerebrovascular events and malperfusion), which have a greater impact than PIS on the length of hospitalization, when compared with patients with infrarenal AAA.

In our study, we could not demonstrate a clear impact of PIS on long-term mortality; however, on Kaplan–Meier analysis, different trends of survival between patients with and without PIS were observed, suggesting that the lack in statistical significance at the Fisher's exact test may be caused by the limited number of events (7 deaths) during follow-up.

On the other hand, PIS was found to be an independent predictor of MAE together with aortic enlargement, partial thrombosis of the false lumen and stroke. Moreover, the presence of a partially thrombosed false lumen was significantly associated with PIS, aortic enlargement and secondary endoleaks, thus suggesting a close relationship between these variables. The inflammatory processes affecting the aneurysm wall are promoted by T and B lymphocytes, natural killer cells and macrophages; this inflammatory infiltrate leads to rapid expansion and increases the risk of rupture by promoting inflammation, protease production and extracellular matrix degradation [20].

Among inflammatory mediators, matrix metalloproteinases have been shown to play a pivotal role in causing endoleaks in patients who undergo EVAR or TEVAR for aortic aneurysms [21, 22].

Furthermore, Tsai *et al*. [23] proposed that a partially thrombosed false lumen may persistently stimulate the inflammatory response by allowing contact between the blood stream and the subendothelial matrix, and lead to aortic enlargement and rupture because of increased internal pressure.

Therefore, we believe that PIS may not have a causal effect on worse outcomes. Rather, it should be interpreted as a clinical marker resulting from the combination of several proinflammatory factors (stent-graft coating, stent length, amount of thrombus, false lumen status and exposure of the subendothelial matrix), which put the patient at a higher risk of MAE during follow-up. On multivariate analysis, the HRs related to aortic enlargement and partial thrombosis of the false lumen were far greater than the HRs for PIS, thus supporting our hypothesis that PIS is an epiphenomenon.

There is no established therapy for PIS. During the first years of the study, since the clinical scenario mimicked an infective status, we employed antibiotics on an empiric basis, in order to avoid stent-graft infection, which is a highly dreaded complication. Still, the absence of clinical or radiological evidence of microbial infection in these patients has gradually shifted our practice towards a more restrictive use of antibiotics. At present, in our centre, fever, accompanied in some cases by thoracic or back pain, and increasing inflammatory biomarkers (with negative blood cultures) within the first days after TEVAR, are managed with symptomatic treatment only. In this setting, treatment with corticosteroids may be a valuable therapeutic option to limit the duration of the inflammatory response and should be investigated in randomized studies.

## Study limitations

Our study has several limitations. First, the incidence of PIS in our study may have been overestimated by the predominant use (92%) of woven polyester stent-grafts (Valiant, Relay and Talent). As reported by Moulakakis *et al*. [24], the use of such stent-grafts induced a more intense inflammatory response early after EVAR, when compared with that following implantation of polytetrafluoroethylene stent-grafts. This finding was shown also by Voûte *et al* [25]. Similarly, the presence of organ malperfusion at presentation in some patients may have altered the incidence of PIS due to the cytokine release. Still, the absence of significant differences in biomarker levels among the study population stratified by organ malperfusion strengthens the solidness of our data. Secondly, the clinical impact of PIS was investigated by comparing the two groups with different sample sizes (112 patients in the non-PIS group versus 21 patients in the PIS group); therefore, the higher rates of complications observed during the follow-up in the PIS group are driven by a small number of cases. By examining a composite endpoint of MAE, we were able to partially overcome this limitation and strengthen our findings. Thirdly, we had 23% of patients without follow-up and this could also have affected our results. Finally, although we have profiled the biochemical changes occurring in patients with and without PIS after TEVAR, we are not yet able to elucidate the pathogenetic mechanisms of this process.

## CONCLUSIONS

In summary, PIS occurs in the setting of AAS within 48–72 h after TEVAR with an incidence of 15.8%. Among several inflammatory and coagulative biomarkers involved in this process, IL-6 levels increase significantly within 24 h after TEVAR only in patients who will develop PIS. Regarding the clinical implications, our data indicate that PIS, at follow-up, was associated with a higher rate of adverse events and was an independent predictor of such events in addition to aortic enlargement, partial thrombosis of the false lumen and stroke. Further studies are needed to confirm the validity of our results and to investigate the role of corticosteroids as therapeutic agents to improve the prognosis of patients with PIS.

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**Conflict of interest:** none declared.

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**EDITORIAL COMMENT**



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# Inflammatory response following stent grafting for acute aortic syndrome

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**Keywords:** Postimplantation syndrome • Dissection • Acute aortic syndrome • Inflammatory response

Currently, patients with an uncomplicated acute type B aortic dissection (ABAD) are treated conservatively. Despite adequate antihypertensive treatment, delayed aortic dilatation will develop in 20–50% of patients with uncomplicated ABAD, which can lead to the catastrophic event of aortic rupture. In light of this, some randomized controlled trials have studied the importance of prophylactic thoracic endovascular aortic repair (TEVAR) in uncomplicated ABAD to prevent such complications [1]. These studies failed to show that TEVAR was beneficial in the short term. Recently, however, a more positive long-term outcome after TEVAR has been demonstrated. Therefore, several epidemiological, clinical or morphological predictors have been studied in recent years to identify ABAD patients at high risk of aortic enlargement, who may benefit from early surgical or endovascular