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ORIGINAL RESEARCH

Post-Implantation Syndrome Incidence After Secondary Endovascular Aortic Interventions

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Objective: Post-implantation syndrome (PIS), a systemic inflammatory response following endovascular aneurysm repair (EVAR) is estimated to occur in approximately 30% of patients. It has been hypothesised to resemble a hypersensitivity reaction. A secondary exposure after a priming event could result in an altered risk and severity of PIS. This study aimed to determine the incidence and short-term clinical consequences of PIS after secondary endovascular aortic aneurysm interventions.

Methods: Single centre retrospective observational study. Between 2011 and 2022, all consecutive patients who underwent secondary elective endovascular aortic interventions following a primary elective EVAR, thoracic endovascular aneurysm repair, or fenestrated and branched EVAR were considered. Re-interventions occurring within the first 30 post-operative days were excluded. PIS was defined as tympanic temperature $\geq$38°C and C-reactive protein (CRP) $>$ 75 mg/L. Primary outcome was PIS incidence within three days. Secondary outcomes were short-term (30 days) outcomes and risk factors for PIS. Logistic regression analysis was performed to correct for confounders.

Results: Seventy nine secondary interventions in 71 patients who underwent elective primary repair were analysed. During secondary repair, shorter stent graft combinations (median 305 *vs.* 171 mm, $p \leq 0.001$) were implanted. In addition, patients were older (70 *vs.* 73 years, $p = 0.043$) and more frequently taking statin (79.4 *vs.* 92.2%, $p = 0.026$) or antiplatelet agents (66.7 *vs.* 85.6 %, $p = 0.010$). Overall, PIS occurred in 24.0%, significantly lower following secondary repair (32.3% *vs.* 16.5%, $p = 0.022$, adjusted odds ratio 0.38, 95% confidence interval 0.16–0.89). There were no significant differences in highest recorded temperature ($p = 0.25$), days of fever ($p = 0.44$), CRP, or peak white blood cell count. CRP presented a more delayed elevation in secondary PIS.

Conclusion: After secondary endovascular aortic interventions, PIS incidence appears reduced compared with primary aortic repair. This should be interpreted with caution, in the context of procedural heterogeneity and limited number of cases. Further studies to confirm these findings and explore the underlying immunological mechanisms are required.

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INTRODUCTION

In 1999, Velazquez *et al.* first proposed the concept of post-implantation syndrome (PIS), a systemic inflammatory response characterised by constitutional symptoms, low fever, and elevated inflammatory biomarkers, occurring in the early post-operative period following endovascular aneurysm repair (EVAR).[1] Subsequently, this reaction has been associated with most endovascular aortic aneurysm devices and is estimated to occur in nearly 30% of patients.[2]

Some short-term consequences have been associated with PIS, such as longer hospitalisation, increased risk of early re-admission, and a possible increase in cardiovascular events in the short to medium term.[4–9] Also, factors such as procedural complexity (fenestrated and branched EVAR [FB-EVAR], iliac branched device [IBD]), stent graft components (polyester *vs.* polytetrafluoroethylene [PTFE]), and new onset post-procedural thrombus formation have been related to an increased incidence of this syndrome.[4,10,11] It has been hypothesised that PIS acts like a hypersensitivity reaction within the bloodstream following stent graft implantation. Its

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incidence, severity, and impact after secondary endovascular aortic interventions, which are increasingly observed, is mostly unknown. This study aimed to determine the incidence and short-term clinical consequences of PIS after secondary endovascular aortic aneurysm interventions compared with primary repair.

MATERIALS AND METHODS

A single-centre, retrospective observational comparative study following the principles outlined by the STROBE guidelines was designed.[12] Following institutional review board approval, informed consent was waived according to institutional policy in retrospective observational research.

Patient population

All consecutive patients who underwent secondary elective endovascular aortic repair following a primary elective endovascular aortic repair, occurring between January 2011 and December 2022, at a tertiary academic institution were considered.

Two interventional groups were created, secondary intervention (SI) and primary intervention (PI). Dichotomisation was performed according to the intervention status (SI *vs.* PI). Therefore, individual patients were included in both groups and the inflammation following the PI served as a comparator to SI. This was performed in order to reduce bias posed by the individual innate propensity to develop PIS, as the PI served as control for SI, matching for time invariant personal characteristics (sex, genetic background). SI was defined as every secondary endovascular aortic aneurysm intervention occurring past 30 days from primary repair, with the implantation of at least one stent graft. Procedures due to endoleak, proximal and or distal aortic and or iliac aneurysmal disease progression, short sealing, migration, or a metachronous aneurysm were included in SI. The PI group was defined as the implantation of a standard thoracic, fenestrated, and or branched or infrarenal aortic bifurcated or uni-iliac device with or without IBD for an intact thoracic, thoraco-abdominal, or abdominal aortic aneurysm. Patients with at least one urgent aneurysm related operation or presenting mycotic or inflammatory pathologies were excluded. Secondary endovascular aortic interventions occurring during the same hospital stay or within the first 30 post-operative days as well as those that occurred at a different institution after the primary endovascular procedure were excluded. According to a case control design matched for time invariant characteristics, aiming for a statistical power (1 − beta) of 80%, and admitting a statistical significance (alpha) $<$ 0.10, and expecting a proportion of 35% in primary procedures and 15% on secondary procedures, the estimated required sample size was 71 per group. Sizing was performed using the Cleveland Clinic Risk Calculator (available at https://riskcalc.org/samplesize).[13]

Definitions

PIS was defined as the occurrence of tympanic temperature $>$38°C and C reactive protein (CRP) $>$ 75 mg/L, after excluding complications with an effect on inflammatory markers, namely infective post-operative complications, based on previously published diagnostic criteria for PIS.[10] Tympanic temperature and CRP measurement routine, as well as definitions on baseline data and outcomes, have been described elsewhere.[10] Primary and secondary PIS were defined as PIS following primary and secondary interventions, respectively. Intra-operative complications, adjunctive procedures, and secondary interventions were defined according to the reporting standards for EVAR by Chaikof *et al.*[14] Thoracic, thoraco-abdominal, and abdominal aortic segments were defined as per Czerny *et al.*[15] Aortic aneurysm extent was defined according to guidelines on abdominal aorto-iliac aneurysms by Wanhainen *et al.*[16] Total graft length was defined as the sum of all graft lengths implanted.

Data collection

Institutional medical record review was performed and baseline characteristics, procedure-related data and post-operative course, including vital signs, laboratory results and post-operative complications were obtained. Data were obtained until 30 days or during hospital stay, in the case of hospitalisation over 30 days after the primary or secondary procedure.

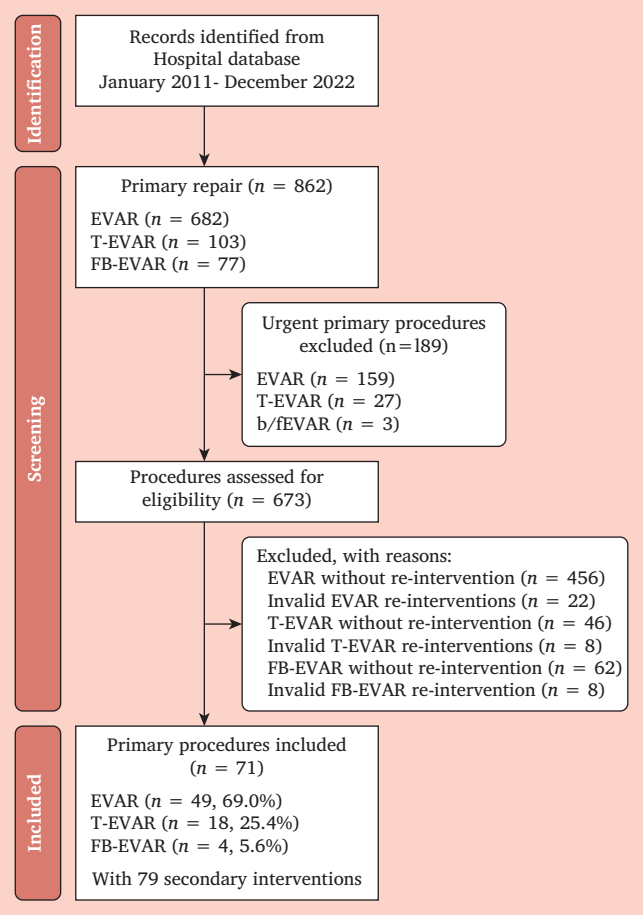

Figure 1. Patient selection study flowchart. The search strategy was based on all primary elective procedures for aortic aneurysm repair, followed by identification of those with a valid secondary intervention. EVAR = endovascular aneurysm repair; FB-EVAR = fenestrated and branched EVAR; T-EVAR = thoracic endovascular aneurysm repair.

Outcomes

The primary outcome was the occurrence of PIS (primary and secondary). Secondary outcomes were short-term (30 days) outcomes and risk factors for PIS.

Statistical analysis

Continuous data are presented as mean ± standard deviation for normally distributed data or median (interquartile range) for non-Gaussian distributed data and compared with Student's *t* test or Mann−Whitney *U* test, respectively. Dichotomous variables are expressed as counts (percentages), and differences in covariables between interventions was assessed using Pearson's χ^2 test or Fischer's exact test, as appropriate.

To account for potential confounding, PIS analyses were additionally adjusted for demographic data (age, medications), procedure (aortic segments covered, stent graft material, graft length, number of grafts implanted), and aneurysm diameter, performed as backward elimination logistic regression analysis of complete cases, using a stepwise alpha to remove >0.10. Data pertaining to this group of patients contained missing values. The method of multiple imputation was applied and to account for the variation in completing the dataset, ten imputed datasets were created.[17] Regression coefficients are presented as odds ratios (OR) with correspondent 95% CI. Statistics were considered significant if $p < 0.05$. Analysis was conducted using SPSS software version 26.0 (Chicago, IL, USA).

RESULTS

Between January 2011 and December 2022, 71 patients (71 primary and 79 elective secondary endovascular aortic procedures) met the inclusion criteria for the study (Fig. 1).

Baseline and procedure related characteristics

Other than significantly older (70 PI *vs.* 73 years SI, $p = 0.043$), a modest non-significant increase in comorbid conditions was noted when the secondary intervention occurred, Table 1. On secondary interventions, they were more frequently taking a statin (79.4 *vs.* 92.2%, $p = 0.026$) than antiplatelet therapy (66.7 *vs.* 85.6 %, $p = 0.010$) and the aneurysm diameter before the secondary intervention grew significantly larger (60 *vs.* 70 mm, $p \leq 0.001$) compared with the primary intervention.

The indications for primary repair were intact infrarenal (67.7%, $n = 48$), juxtarenal (4.2%, $n = 3$), thoracic (9.9%, $n = 7$), and thoraco-abdominal (18.3%, $n = 13$) aortic aneurysms. Forty nine (65.0%) were submitted to primary EVAR, 18 (25.4%) to thoracic endovascular aneurysm repair (T-EVAR), and four (9.6%) FB-EVAR. The most used stent

Table 1. Baseline characteristics of the 71 patients included in this cohort, before the primary (71 procedures) and secondary aortic aneurysm intervention (79 procedures).

Baseline characteristic	Missing data	Primary interventions ($n = 71$)	Secondary interventions ($n = 79$)	*p* value
Age - y	0 (0)	70.3 ± 9.1	73.3 ± 9.7	0.043
Male	0 (0)	66 (93.0)	74 (93.7)	0.86
Smoking	2 (1.3)	56 (78.9)	60 (77.9)	0.89
Hypertension	0 (0)	65 (91.5)	73 (92.4)	0.85
Diabetes mellitus	4 (2.7)	19 (27.5)	22 (28.6)	0.89
CKD	0 (0)	26 (36.6)	31 (39.2)	0.59
Heart disease	0 (0)	27 (38.0)	37 (46.8)	0.28
Neoplasm history	0 (0)	13 (18.3)	20 (25.3)	0.30
Cerebrovascular disease	2 (1.3)	15 (21.7)	22 (27.8)	0.39
Pulmonary disease	4 (2.9)	17 (24.6)	26 (33.8)	0.23
PAD	6 (4.0)	8 (11.6)	11 (14.7)	0.59
Beta blocker	4 (2.7)	31 (44.9)	37 (48.1)	0.71
Statin	5 (3.6)	54 (79.4)	71 (92.2)	0.026
Antiplatelet	5 (3.3)	46 (67.6)	66 (85.6)	0.010
Anticoagulant	4 (2.7)	7 (10.1)	11 (14.3)	0.45
Aneurysm diameter	7 (4.7)	60 (55, 70)	70 (59, 88)	≤0.001
Polyester stent graft	0 (0)	57 (80.3)	62 (78.5)	0.79
Aortic segments covered	0 (0)	3 (3, 4)	1 (1, 3)	≤0.001
Stent graft total length - mm	2 (1.3)	305 (222, 412)	171 (93, 294)	≤0.001
Number stent grafts implanted	0 (0)	3 (2, 4)	2 (1, 4)	0.033
Anaesthesia	0 (0)			0.99
Local		4 (5.6)	5 (6.3)	
Locoregional		7 (9.9)	8 (10.1)	
General		60 (84.5)	66 (83.5)	
Dexamethasone	23 (15.3)	16 (27.6)	29 (42.0)	0.090
Percutaneous	3 (2.2)	25 (35.2)	49 (62.0)	≤0.001
Operative time - min	0 (0)	138 ± 60	155 ± 95	0.20

Data are presented as *n* (%) or mean ± standard deviation, or median (interquartile range). CKD = chronic kidney disease; PAD = peripheral artery disease.

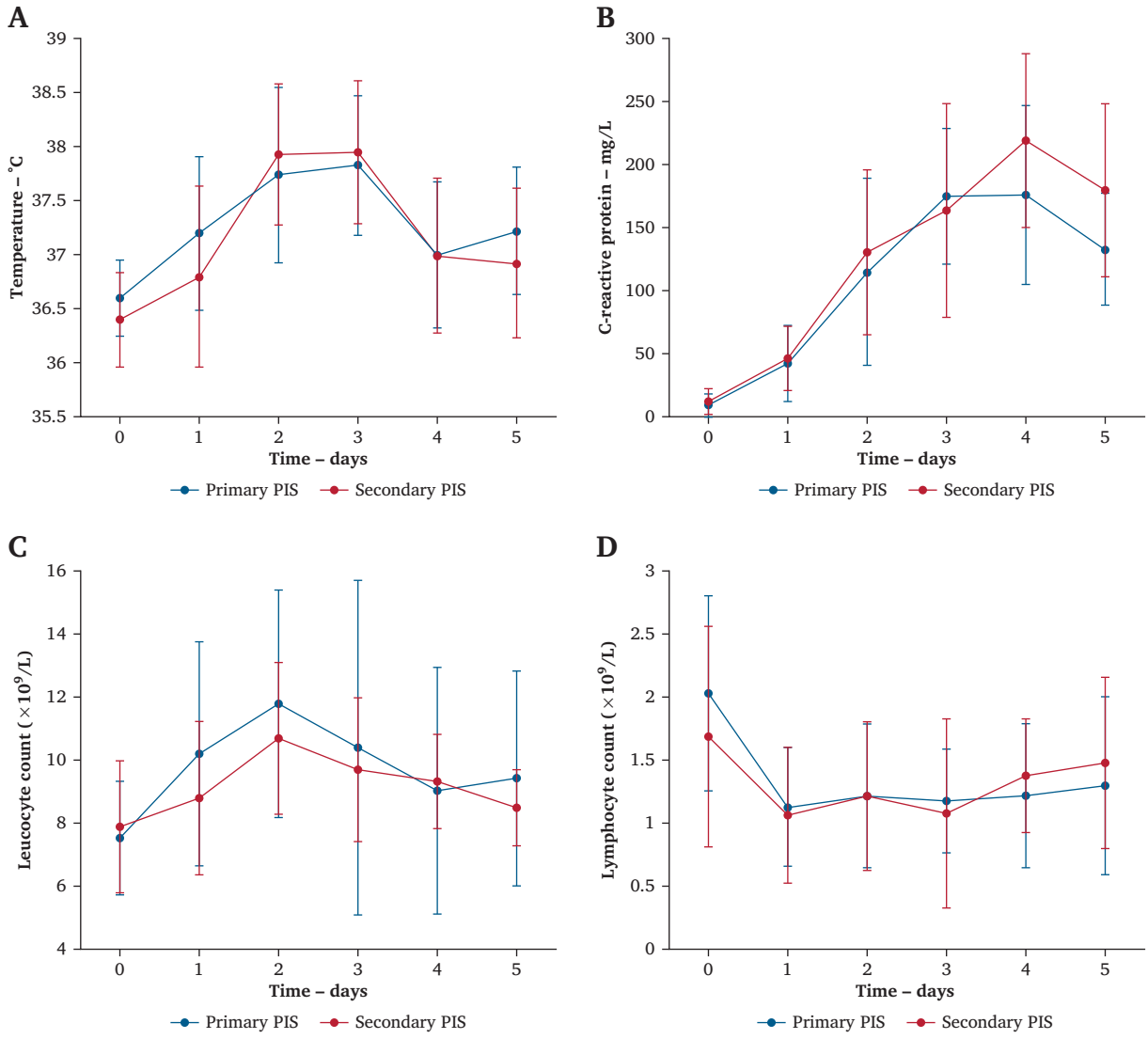

Figure 2. Primary vs secondary post-implantation syndrome (PIS) daily inflammatory response. (A) Highest tympanic temperature, (B) C reactive protein (CRP), (C) leucocyte count, (D) lymphocyte. Data are presented as mean ± standard deviation. Temperature (A) and leucocyte count (C) peaked on the second post-operative day. CRP (B) peaked on the third and fourth post-operative day in primary and secondary PIS, respectively (highest CRP recorded: 186 mg/L *vs*. 206 mg/L, $p = 0.27$, primary *vs*. secondary PIS, respectively).

grafts during primary intervention were Endurant II and IIs (25.4%), followed by Zenith Alpha/Flex (23.9%), and Zenith Alpha T-EVAR (16.9%) grafts.

Secondary interventions occurred over a median 1 104 (191—2 190) days, and 29.1% of secondary interventions occurred within the first year. The remaining 34.0% occurred between one and five years and 32.9% after five years. The indication was a metachronous aneurysm in 3.8%, staged aortic repair in 15.2%, short seal or graft kinking in 26.6%, and type 1—3 endoleak in the remaining 54.4%. T-EVAR extension was performed in 8.9%, FB-EVAR in 25.4%, chimney EVAR (Ch-EVAR) in 2.5%, aortobi-iliac EVAR in 3.8%, aortic cuff ± limb extension in 15.2%, limb extension ± hypogastric embolisation in 35.4%, and IBD distal extension in 8.8%.

During secondary procedures, shorter stent graft combinations (median 305 *vs.* 171 mm, $p \leq 0.001$) were implanted and fewer aortic segments were covered (median 3 *vs.* 2 segments, $p \leq 0.001$). Secondary interventions were more frequently performed percutaneously (62.0 *vs.* 35.2%, $p \leq 0.001$) (Table 1).

Post-implantation syndrome

Overall, the PIS incidence was 24% ($n = 36$, 95% CI 17—31%) and was significantly higher following PI (32.4%; 95% CI 21—44% PI *vs.* 16.5%; 95% CI 8—25% SI, $p = 0.022$). There were no significant differences in PIS incidence when depicting SI by time passed from the primary procedure, 27.8% *vs.* 9.1% *vs.* 18.5%, $p = 0.22$ (one month to one year *vs.* one to five years *vs.* after five years, respectively). In addition, there were no significant differences in highest recorded temperature (38.4°C SI *vs.* 38.2°C PI, $p = 0.25$), number of days of fever (1.5 days PI *vs.* 1.3 days SI, $p = 0.44$), nor in peak inflammatory markers (leucocyte,

Table 2. Regression analysis for the primary outcome: post-implantation syndrome occurrence.

Predictors	Univariable analysis aOR (95% CI)	Multivariable analysis aOR (95% CI)
Secondary intervention *vs.* primary repair	0.41 (0.19—0.89)*	**0.38 (0.16—0.89)***
Age	0.95 (0.92—0.99)*	0.93 (0.92—1.00)
Statin	0.45 (0.17—1.20)	—
Antiplatelet	1.03 (0.42—2.54)	—
Aneurysm diameter, per quartile increase	1.29 (0.92—1.82)	1.41 (0.96—2.08)
Polyester stent graft	3.58 (1.02—12.58)*	3.02 (0.88—11.74)
Aortic segments covered	1.39 (0.99—1.96)	—
Total stent graft length, per quartile increase	1.19 (0.99—1.03)	—
Number of stent grafts implanted	1.39 (0.99—1.94)	—
Percutaneous	2.19 (1.01—4.74)*	—

aOR = adjusted odds ratio; CI = confidence intervals.
* Statistically significant results.

Table 3. Short term (30 day) outcomes stratified by the occurrence of post-implantation syndrome in this interventional cohort.

Interventions	No PIS	PIS	*p* value
*Primary intervention**			
Hospital stay	5 (4, 8)	7 (4, 9)	0.16
Cardiac dysfunction	2 (4.2)	2 (8.7)	0.59
Acute kidney injury	4 (8.3)	5 (21.7)	0.25
Spinal cord ischaemia	0 (0)	0 (0)	—
Bowel ischaemia	0 (0)	0 (0)	—
Respiratory complications	2 (4.2)	2 (8.7)	0.59
Stroke	0 (0)	0 (0)	—
Acute limb ischaemia	0 (0.0)	1 (4.3)	0.32
Death	0 (0)	0 (0)	—
Secondary interventions†			
Hospital stay	7 (3, 10)	5 (3, 8)	0.76
Cardiac dysfunction	3 (4.5)	0 (0)	0.65
Acute kidney injury	13 (19.7)	1 (7.7)	0.44
Spinal cord ischaemia	2 (3.0)	0 (0)	—
Bowel ischaemia	3 (4.5)	0 (0)	0.65
Respiratory complications	4 (6.1)	0 (0)	0.48
Stroke	1 (1.5)	1 (7.7)	0.30
Acute limb ischaemia	0 (0)	0 (0)	—
Death	1 (1.5)	0 (0)	0.84

Data are presented as *n* (%), or median (interquartile range) Hospital stay is presented as days. PIS = post-implantation syndrome.
* No PIS, *n* = 48; PIS, *n* = 23.
† No PIS, *n* = 66; PIS, *n* = 13.

neutrophil, lymphocyte count) when comparing primary and secondary PIS, respectively. Leucocyte and neutrophil counts peaked on the second post-operative day in both PIS groups (11.75 × 10^9/L PI *vs.* 10.69 × 10^9/L SI, $p = 0.47$ and 9.41 × 10^9/L PI *vs.* 8.27 × 10^9/L SI, $p = 0.44$, respectively) (Fig. 2). Following a sudden decrease on the first post-operative day (1.13 PI *vs.* 1.07 × 10^9/L SI, $p = 0.74$), the lymphocyte count steadily increased over the following days in both interventional groups. In contrast, CRP presented a more delayed peak elevation in secondary PIS. The CRP peak was observed on the third post-operative day in primary PIS and the fourth post-operative day in secondary PIS (Fig. 2). Of those who developed PIS on the first re-intervention (*n* = 8), 12.5% (*n* = 1) developed this syndrome on further interventions. On univariable analysis, secondary procedure status (OR 0.41, 95% CI 0.19—0.89), age (OR 0.95, 95% CI 0.92—0.99, per year increase), polyester stent graft (OR 3.58, 95% CI 1.02—12.58), and the use of percutaneous vascular access (OR 2.19, 95% CI 1.01—4.74) were significantly associated with the odds of developing PIS (Table 2). For secondary interventions, this association was maintained following adjustment for confounders (adjusted OR 0.38, 95% CI 0.16—0.89).

Table 4. Short term (30 day) outcomes of patients who developed post-implantation syndrome in this interventional cohort, stratified as primary vs secondary repair.

PIS outcomes	Primary PIS (*n* = 23)	Secondary PIS (*n* = 13)	*p* value
Hospital stay - d	7 (4—9)	5 (3—8)	0.72
Cardiac dysfunction	2 (8.7)	0 (0)	0.53
Acute kidney injury	5 (21.7)	0 (0)	0.39
Spinal cord ischaemia	0 (0)	0 (0)	—
Bowel ischaemia	0 (0)	0 (0)	—
Respiratory complications	2 (8.7)	0 (0)	0.53
Stroke	0 (0)	1 (7.7)	0.36
Acute limb ischaemia	1 (4.3)	0 (0)	—
Death	0 (0)	0 (0)	—

Data are presented as *n* (%), median (interquartile range). PIS = post-implantation syndrome.

Short term (30 day) outcomes

Table 3 outlines short term outcomes stratified by intervention and PIS status. No significant differences between groups were noted, including when comparing primary *vs.* secondary PIS (Table 4).

DISCUSSION

In this cohort, PIS was a common finding (24.0%). In addition to its incidence seeming significantly reduced following secondary interventions (32.4% PI *vs.* 16.5% SI, $p = 0.022$; aOR 0.38), peak CRP elevation in secondary PIS appears slightly delayed. No significant differences in short-term outcomes were noted.

In the literature, and in studies with clearly defined criteria, PIS incidence after EVAR or TEVAR has reached up to 100%, and this reflects the lack of standardised diagnostic criteria.[4—6,8,9,18—22]

D'Oria *et al.* performed a systematic review on this topic, including 31 studies, including 2 847 patients. The authors

found an overall pooled PIS incidence of 25.3%, similar to the one found in the current cohort.[2]

In the present study, a combination of fever and elevated CRP, excluding infective complications, were chosen as the diagnostic criteria. These two markers are measured per protocol and have previously presented the most accurate combination of parameters at the institution.[10]

Also, no negative impact of PIS occurrence was found in peri-operative outcomes, irrespective of procedure status (PI *vs.* SI), suggesting the last might behave as a benign phenomenon, particularly after previous exposure to aortic stent grafts components. Of note, hospital stay was considerably long, reflecting a rather conservative practice. Nevertheless, it meant extended data on post-operative inflammation could be obtained. Similarly, no association between PIS incidence and time passed from the primary procedure was observed. The impact of previous exposure to an aortic stent graft and the development of PIS has rarely been addressed, and it is believed these findings might contribute to the existing literature on this topic. Previously, a retrospective analysis including 88 complex EVAR (c-EVAR) patients (30.6% secondary endovascular aortic interventions, redo c-EVAR) found that redo c-EVAR patients presented non-significant lower PIS rates than *de novo* c-EVAR (22.2 *vs*. 39.3%; $p = 0.12$). Although underpowered, this subanalysis suggested that a desensitisation process may occur after the primary exposure, among other possible factors, that may reduce the overall PIS risk downstream.[10]

There are some key factors directly implicated in the incidence of post-operative PIS, and these mostly reflect procedural and aneurysm related features. Polyester stent grafts (compared with PTFE) have been the most consistently feature associated with an increased PIS rate, with an up to five fold increase.[3–6,11] The latter was associated with a greater magnitude of CRP elevation and temperature, and some groups identified this as the sole predictor of PIS after infrarenal EVAR. Although this finding was not observed in the current analysis, this might have been due to the limited sample size. Also, the design was not intended to analyse this characteristic.

In addition, the increasing procedural complexity with branched, fenestrated or repair with parallel grafts, which include longer and more stent grafts, has been implicated in PIS incidence.[10,22] Recently, Wu *et al.*, in a retrospective analysis of 547 consecutive Stanford type B aortic dissections treated by T-EVAR, found that a number of trunk stents >1 and the use of at least one branch stent significantly predicted post-operative PIS.[22] In the current cohort, these specific data were accounted for; however, no significant impact was noted, which might also be due to the limited number of complex elective aortic repairs included.

An increased risk of PIS in c-EVAR patients can also result from a greater volume of new onset thrombus.[6,11] Since this study includes procedures for different surgical indications, several interventions did not result in significant new onset post-procedural thrombus. Also, standardised methodologies to measure new onset thrombus after procedures for relining, sealing improvement or endoleak are unavailable and probably unreliable. In the light of that, these data were not acquired. Also, occlusion of a patent IMA during EVAR has been related to transient bacterial translocation and an increased risk of developing PIS after EVAR or FB-EVAR. Since primary repairs not covering the IMA were also included, the specific data were not collected.[10,11]

An important feature of this study is the behavioural analysis of inflammatory markers. Previously, after standard EVAR, it was noted that inflammatory markers steadily increased during the first post-operative days with fever and CRP peaking on the second and third post-operative day, respectively.[4,23,24] Also, leucocytosis was dependent on neutrophilia, and a sudden decrease in lymphocyte count following stent graft implantation was expected. After secondary interventions, although temperature and leucocyte count appeared to exhibit a similar behaviour, it became apparent that CRP elevation was delayed, peaking after 96 hours, compared with 72 hours after primary repair. Interestingly, no differences in baseline inflammation were noted between groups. Moulakakis *et al.* studied the inflammatory response after 32 elective T-EVARs prospectively. The authors found significant increases in serum white blood cell, CRP, interleukin (IL)-10, and IL-6 levels 24 and 48 hours after the procedure. The number of endografts and the coverage of the coeliac or subclavian artery did not affect the magnitude of the inflammatory response.[25] Arnaoutoglou *et al.* prospectively enrolled 182 standard EVAR (35.7% PIS) and eloquently characterised these blood biomarkers up to twelve months. White blood cell count, CRP, and IL-6 were significantly higher in the PIS group during the post-operative period. At one month and thereafter, IL-6 levels attenuated towards non-PIS group levels.[9] Similar dynamics were observed in *in vitro* experiments.[26] These data suggest that specific inflammatory mediators' elevation might flatten early after EVAR, suggesting an early tolerance to stent graft components. Hypersensitivity to biomaterials is cell mediated (type IV hypersensitivity reaction), and typically occurs 24—48 hours after exposure, consistent with the typical symptom onset in PIS.[27] In the literature, the result of this cell mediated reaction has been better elucidated in orthopaedic, cardiac, and coronary implants, mostly regarding its metallic components. Nickel, a common component of vascular stents has been implicated in coronary stent re-stenosis.[27] Although nickel hypersensitivity usually presents as contact dermatitis (in up to 19% of the general population), following coronary stenting, cutaneous manifestations are scarce.[28] Polyester sensitivity also presents most often by contact dermatitis. In implants, this cell mediated hypersensitivity might ultimately lead to dysfunction with perivascular lymphocytic infiltrate, macrophage response, and granuloma formation with tissue necrosis.[29,30] The reduced incidence of PIS following secondary implantation might partly mimic the concept of allergen immunotherapy, the disease modifying treatment available for several hypersensitive reactions.[31] Skin sensitisation with contact

allergens (including nickel) has been shown to induce a strong, long lasting local memory.[32] Understandably, these hypotheses need to be addressed and clarified in purposely designed studies.

Limitations of the study are first, that it was a single centre retrospective study. Although statistical methods were applied to minimise potential design related bias, the small sample size may have underpowered analyses, particularly secondary outcomes. There is also heterogeneity concerning PIS diagnostic criteria, limiting comparisons with other literature. Significant heterogeneity across procedures and indications is the major limitation of this study. Although graft length, aortic segments covered and number of stent grafts implanted were accounted for, they might not completely eliminate this heterogeneity. Particularly, graft length might behave as a poorer surrogate than graft area or volume. The permissive sample sizing calculation strategy also allows for the risk of a type 1 statistical error. With uncertainty regarding the ideal design, there is the chance that comparing similar procedures performed as primary or secondary repair might be the optimal way to further evaluate this topic.

Despite the limitations above, this study is one of the largest on the subject of PIS after previous exposure to aortic stent grafts, which is commonly an exclusion criterion in PIS literature. The sole inclusion of patients with both interventions occurring in the same department limited potential bias generated by different laboratory methodologies between institutions, as well as significantly minimising the impact of the individual innate propensity to develop this syndrome.

Conclusion

For patients having elective secondary elective endovascular aortic repair, PIS incidence appears significantly reduced, compared with primary repair. Also, secondary PIS might present a slightly delayed inflammatory response, with reduced impact on peri-operative outcomes. This should be interpreted with caution, in the context of procedural heterogeneity and the limited number of cases included. Further studies to confirm these findings and explore the underlying immunological mechanisms will be beneficial.

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CONFLICTS OF INTEREST

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