Title

Clinical features and significance of leukopenia occurring immediately after endovascular surgery

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Abstract

Purpose: Inflammation after stent graft surgery is known as post-implantation syndrome (PIS) and it causes leukocytosis. However, we have experienced leukopenia in the very early postoperative phase of endovascular surgery at our institution. We investigated leukopenia, an under-recognized phenomenon that occurred after transcatheter aortic valve implantation (TAVI), endovascular aortic repair (EVAR), and thoracic endovascular aortic repair (TEVAR).

Methods: Records of patients who underwent TAVI, EVAR, and TEVAR between March 2018 and February 2019 were retrospectively reviewed. Primary outcomes were the decline rate of white blood cell count (DR-WBC) in the immediate postoperative period and its differences among surgical procedures. The secondary endpoint was the relationship between DR-WBC and infectious complications. Furthermore, the incidence of PIS and its differences among the procedures and associations with DR-WBC were evaluated.

Results: A total of 108 patients (TAVI 41, EVAR 37, TEVAR 30) were included. DR-WBC immediately after surgery was higher in the TAVI group compared with other groups (TAVI, 43.1 ± 22.6%; EVAR, 27.6 ± 17.3%; TEVAR, 25.4 ± 27.4%; $P < 0.01$). DR-WBC was not significantly different regardless of postoperative infection ($P = 0.45$)

or PIS (P = 0.62). The incidence rate of PIS was higher in the EVAR group compared with the TAVI group, and was not associated with DR-WBC.

Conclusions: Leukopenia was a common phenomenon immediately after endovascular surgery, especially TAVI. It resolved a day after surgery and was not associated with PIS or infectious complications. Therefore, it seems to be a transient abnormal hematological finding and a self-limiting condition.

Introduction

Fever and leukocytosis after endovascular aortic repair (EVAR), which is currently known as post-implantation syndrome (PIS), was first described in 1997 in Germany [1]. Subsequently, Velázquez et al. suggested that PIS was a reproducible phenomenon specific to the nature of this procedure rather than being related to postoperative infection [2]. Although PIS lacks definitive diagnostic criteria, it is usually characterized by fever and leukocytosis or elevation of C-reactive protein (CRP) level following endovascular procedures [3, 4].

On the other hand, we have experienced cases at our institution in which, compared to preoperative values, the number of leukocytes relatively decreased immediately after endovascular procedures. Although postoperative leukopenia has been reported in patients with lung cancer [5] and gastric cancer [6], to the best of our knowledge, no reports about leukopenia occurring after endovascular surgery have been published. There are various pathological conditions in which the number of leukocytes decreases and inflammatory reaction may cause not only leukocytosis but also leukopenia. In fact, the criteria of systemic inflammatory response syndrome (SIRS) once used to diagnose sepsis include leukopenia, as well as leukocytosis. In general, leukopenia is a risk factor for infection or a consequence of severe infection. Therefore, our concern was whether

postoperative change of white blood cell count (WBC) count, especially leukopenia, occurring immediately after endovascular surgery was harmful. We also considered that leukopenia might be correlated with the incidence of PIS if leukopenia indicated the severity of inflammation. The aim of this study was to characterize postoperative leukopenia after transcatheter aortic valve implantation (TAVI), EVAR, and thoracic endovascular aortic repair (TEVAR), and to evaluate the differences among the procedures and relationship of postoperative leukopenia with infectious complications and PIS.

Methods

This study was approved by the Institutional Ethical Review Board (IRB) of Teine Keijinkai Hospital (IRB No. 2-019105-01, approval date: October 26, 2020). Individual informed consent was obtained from the patients using an opt-out method of enrollment via the hospital's website. We retrospectively reviewed the electronic medical records of patients who underwent TAVI, EVAR, and TEVAR at Teine Keijinkai Hospital from March 2018 to February 2019. We excluded patients who were suspected of any infection prior to the procedure, who underwent other procedures simultaneously, and who underwent an emergency operation. We collected the following data: diagnosis; operation; height; weight; sex; comorbidities; medications; intraoperative information; intraoperative balance, which was defined as (infused volume + transfused volume) – (urine output + blood loss); perioperative laboratory tests, including WBC counts and CRP levels; and body temperature (within a week after surgery). Laboratory tests were performed before surgery, immediately after surgery, between the end of surgery and leaving the operation room, at postoperative day (POD)-1, and at least once within the following seven days.

Anesthesia and surgical procedures

All patients underwent surgery under general anesthesia. The choice of the anesthetic agent was left to the attending anesthesiologist. All patients were scheduled to be admitted to the intensive care unit (ICU). In most cases, extubation was performed in the operation room, but in some cases, it was performed in the ICU immediately after admission. EVAR for an abdominal aortic aneurysm (AAA) was performed using a stent graft system. Fenestrated stent grafting of the renal artery was performed for juxta-renal AAA, as necessary. Inferior mesenteric artery and internal iliac artery coiling and n-butyl-2-cyanoacrylate injection were performed for type 2 endoleak prevention in some cases. TEVAR was performed for thoracic aortic aneurysm and chronic type B aortic dissection. Fenestrated stent grafting of the left subclavian artery was performed as necessary. TAVI was performed using transfemoral, trans-subclavian, and transapical approaches with prosthetic valves. The stent graft system for EVAR and TEVAR and prosthetic valves for TAVI are described in Table 1.

Outcomes

We evaluated the severity of leukopenia using the decline rate of WBC count (DR-WBC), which was calculated as the number of leukocytes before surgery minus that

immediately after surgery, divided by that before surgery. We defined PIS as the condition satisfying all of the following: (1) fever (body temperature ≥ 38 °C), (2) leukocytosis (WBC ≥ 12,000/mm^3) or elevated CRP level (≥ 10 mg/dL), and (3) absence of infectious diseases, obvious noninfectious inflammatory diseases, and use of granulocyte colony-stimulating factor (G-CSF). This definition is in accordance with previous studies [3, 4]. Primary endpoints were DR-WBC and differences in DR-WBC among the surgical procedures. Additionally, the secondary endpoint was the relationship between DR-WBC and infectious complications. We determined cases with or without "postoperative infection" based on the descriptions of any infectious disease in the electronic medical records within a month after the surgeries. Furthermore, we evaluated the incidence of PIS, differences in the incidence of PIS among the surgical procedures, and the association with DR-WBC.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Each categorical variable is expressed as a number (percentage). Comparisons of continuous variables among procedures were performed using one-way analysis of variance (ANOVA) for normally distributed variables and using the Kruskal–

Wallis test for non-normally distributed variables. Test of normality was performed by Shapiro-Wilk test for all the variables. The change in WBC counts among procedures and time courses were compared using two-way repeated ANOVA. When the sphere was rejected by Mauchly's test, the statistic was calculated after adjusting the degrees of freedom by Greenhouse-Geyser's correction or Huynh-Feldt's correction as appropriate. Analysis of dichotomous variables was performed using Fisher's exact test and chi-squared test, as appropriate. Post hoc tests were performed using Bonferroni's multiple comparison test. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add frequently used statistical functions in biostatistics [7].

Results

A total of 116 patients were screened for eligibility from March 2018 to February 2019. Eight patients were excluded: one was excluded due to suspected aortic inflammatory syndrome, two were excluded due to undergoing simultaneous procedures (laparoscopic lymph node biopsy and artificial graft repair), and six were excluded as they underwent urgent surgery for acute aortic dissection. Finally, 108 patients were included in the analysis. Among these patients, 41, 37, and 30 received TAVI, EVAR, and TEVAR, respectively. In the TAVI group, 38 patients underwent surgery through a transfemoral approach, two through a transapical approach, and the remaining one through a trans-subclavian approach.

The baseline characteristics in each group are presented in Table 2. The mean age and percentage of females were higher in the TAVI group than in the other groups. There was no difference among the groups regarding oral administration of steroids and immunosuppressive agents such as cyclosporin for nephrotic syndrome. The intraoperative profiles in each group are presented in Table 3. Operation time in the TAVI group was shorter than those in the other groups (TAVI, 86.2 ± 23.7 min; EVAR, 146.3 ± 36.5 min; TEVAR, 124.9 ± 48.0 min; $P < 0.01$). Intraoperative fluid balance in the TAVI group was lower than those in the other groups (TAVI, 686 ± 451 mL; EVAR, 1271 ± 477

mL; TEVAR, 1326 ± 477 mL; $P < 0.01$).

For changes in WBC counts, two-way repeated ANOVA showed a statistical difference in both procedures ($P < 0.01$) and time courses ($P < 0.01$). No interaction was detected between procedures and time courses ($P = 0.12$). WBC counts among each time course point were statistically different in all procedures using Bonferroni's multiple comparison test. WBC counts just after operation were less than those of pre-operation ($P < 0.01$) and POD1 ($P < 0.01$). Baseline WBC counts in the TAVI group were lower than those in the other groups (TAVI, 5223 ± 1368/mm^3; EVAR, 6231 ± 1713/mm^3; TEVAR, 6239 ± 1527/mm^3; $P < 0.01$). Leukopenia in each group was resolved at POD-1. Therefore, we used DR-WBC for comparison of the severity of leukopenia immediately after surgery among procedures. One-way ANOVA showed DR-WBC was higher in TAVI than the other groups (TAVI, 43.2 ± 22.6%; EVAR, 27.6 ± 17.3%; TEVAR, 25.4 ± 27.4%; $P < 0.01$) (Figure 1). Furthermore, DR-WBC of TAVI was higher than that of EVAR ($P < 0.01$) and TEVAR ($P < 0.01$) using Bonferroni's multiple comparison test. Additionally, four patients in the TAVI group presented with aggressive leukopenia (WBC <1000/mm^3).

The details of PIS diagnosis are presented in Table 4. PIS was more common in the EVAR group compared with the TAVI group. Leukocytosis was more frequent in the EVAR group compared with the TAVI group. The incidence of postoperative infection

was not significantly different among the groups (TAVI, 4.9%; EVAR, 2.7%; TEVAR, 6.7%; P = 0.85). Two patients had urinary tract infections, and one had pneumonia, clostridium difficile enteritis, and bacteremia. Aggressive leukopenia in one patient in the TAVI group was treated with G-CSF on POD-0. Although PIS represents systemic inflammation after the procedure, the postoperative decline in WBC count occurred regardless of PIS (PIS, 30.8 ± 20.7%; no PIS, 33.5 ± 24.6%; P = 0.62). Furthermore, there was no significant difference in DR-WBC between patients with and without infection (infection, 25.0 ± 16.4%; no infection, 33.3 ± 24.0%; P = 0.45).

Discussion

In this study, patients who underwent TAVI, EVAR, and TEVAR were retrospectively evaluated for postoperative leukopenia and the occurrence of PIS. The main findings of this study were as follows: (1) leukopenia occurring immediately after surgery was common among these procedures, and DR-WBC was steeper in the TAVI group; (2) postoperative leukopenia was not related to subsequent infectious complications; and (3) although PIS was also common among these patients, especially in those who underwent aortic procedures, it was not associated with leukopenia occurring immediately after surgery.

To the best of our knowledge, leukopenia after endovascular surgery has not been reported yet. Generally, most patients undergoing endovascular surgery are older adults. Leukopenia is a consequence of increased consumption and decreased production of leukocytes. Both of these mechanisms can cause leukopenia, and its occurrence in older adults is possible as a result of systemic inflammation.

In older adults, compared with younger adults, excessive release of tumor necrosis factor alpha following lipopolysaccharide (LPS) administration has been reported, and such pro-inflammatory responses could cause leukopenia [8]. Kumagai et al. reported a higher reduction rate of peripheral blood leukocytes following LPS administration in

aging mice than in younger ones. Furthermore, they also demonstrated delayed recovery of leukocyte count following LPS administration in old mice and concluded that impaired myelopoiesis in aging mice caused this difference [9].

Fractionation of leukocytes provides important information on the presence of leukocytosis or leukopenia, while WBC count is fundamentally the sum of granulocytes and lymphocytes. While granulocytosis is a common phenomenon after surgery, lymphocytopenia has also been described as a postoperative change. Therefore, whether the total WBC count increases or decreases depends on the balance between granulocytosis and lymphocytopenia. In the abovementioned study [9], both granulocytosis and lymphocytopenia were observed in aging and young mice after LPS administration. Lymphocytopenia was dominant to granulocytosis, which resulted in leukopenia, and this phenomenon was remarkable in the early phase after LPS injection. We considered leukopenia after endovascular surgery an instant phenomenon, and therefore, the timing of blood sampling is an important consideration. In our hospital, postoperative blood samples are collected in the early period between the end of surgery and leaving the operation room. Therefore, the timing of blood sampling possibly affected our result. However, leukocyte fractionation was unfortunately not measured in our study.

In endovascular surgery, the causes of inflammation are diverse. Inflammation after

endovascular surgery has been reported to occur due to foreign body reactions [4], as well as postoperative thrombosis in the aneurysm sac after exclusion [10] and ischemia due to low cardiac output at the time of valve replacement [11]. In our study, leukopenia was severe in the TAVI group compared with the other groups. However, in the previous report, SIRS occurred with a high probability after TAVI [11]. Sexton et al. reported that the type of artificial valves used influenced the change in WBC count after TAVI and that the newer generation device induced less inflammatory response because of the valve design and a smaller delivery system [12]. In our study, the newer generation valves were implanted in all cases, and this may partly explain why leukocytosis was not observed in our study.

Furthermore, while continuous sedation was used for procedures in the previous study, general anesthesia with propofol was used in most of our cases. Costa et al. showed that propofol-anesthetized dogs presented with hematologic changes, including leukopenia, in the early postoperative period [13]. Therefore, one of the reasons for WBC count decrease in our study might be the use of general anesthesia. Like general anesthetics, narcotics can affect the perioperative inflammatory response. In our study, patients of the TAVI group received fentanyl-based anesthesia, while that of the aortic surgery groups received remifentanil-based anesthesia depending on the choice of the attending

anesthesiologist. The dose of fentanyl during surgery was higher in the TAVI group than in the aortic surgery groups. Inagaki et al. reported that remifentanil-based anesthesia attenuated postoperative leukocytosis more than fentanyl-based anesthesia via modulating surgical stress and inflammatory response [14]. Although the difference in narcotics might have partly affected the change of leukocyte count in our study, we cannot determine the effect of narcotics on postoperative leukopenia.

Acetaminophen has no anti-inflammatory effect [15]. There is a low probability that acetaminophen affects change in the WBC counts, while NSAIDs, such as flurbiprofen, can affect change in the WBC counts by modulating inflammatory response. However, these analgesics were administered immediately before the end of the surgery, and it was considered that they had little impact on our study.

In this study, the severity of leukopenia was evaluated using the DR-WBC. However, we use WBC count for this evaluation in clinical settings. Although there are no common diagnostic criteria for leukopenia, a WBC count < 4000/mm^3 is defined as leukopenia in SIRS [16]. A WBC count of < 4000/mm^3 immediately after surgery was more frequent in the TAVI group compared with the other groups (TAVI, 80.5%; EVAR, 43.2%; TEVAR, 43.3%; $P < 0.01$). However, we should consider that the WBC count at baseline in the TAVI group was lower than those in the other groups. McGrath et al. reported that the

mean WBC count decreased with age, and the mean WBC count for women was significantly lower than that for men in the elderly population [17]. Since the TAVI group had more females and older adults, the ages and sex of the patients possibly influenced the WBC count at baseline.

Generally, postoperative leukopenia is a risk factor for infectious complications. Leukopenia was found to be associated with mortality among patients who underwent urgent laparotomy [18]. Prolonged leukopenia and profound leukopenia have been reported to influence the occurrence of serious complications [19]. In our study, leukopenia occurring immediately after endovascular surgery was resolved promptly and was not associated with the risk of infectious complications. Therefore, leukopenia occurring immediately after endovascular surgery is self-limiting and observable.

We could consider that postoperative leukopenia and the low occurrence of PIS were due to a reduced inflammatory reaction after surgery. However, in our study, the decline in WBC count occurred regardless of PIS. Therefore, postoperative leukopenia and PIS were not considered as the consequences of the same mechanism.

This study has several limitations, mainly due to its retrospective nature and small sample size. Almost all surgeries were performed under general anesthesia with propofol. Thus, the influence of volatile anesthetics could not be evaluated. As mentioned above,

the choice of narcotics differed significantly between the TAVI group and the stent surgery groups. The timing of blood tests was not unified from POD-2 to POD-7; therefore, we might have underestimated the incidence of PIS. We researched postoperative infection using only electronic medical records; therefore, we might have underestimated its occurrence as well. We did not measure the leukocyte fraction and could not determine which fraction was susceptible to each endovascular procedure. There were no previous studies on leukopenia after endovascular surgery; therefore, we reviewed the cases during the period, as stated in the protocol. The incidence of postoperative infection was relatively rare. Therefore, the sample size for evaluating the risk of postoperative infection might have been inadequate. Additionally, our study focused only on the perioperative period; therefore, we could not determine whether transient leukopenia after endovascular surgery influenced long-term prognosis or not. Extension of the follow-up period, as well as a prospective study on a large scale, are required for further investigation. For further investigation, a large-scale prospective study with a longer follow-up period will be required.

In conclusion, leukopenia was a common phenomenon immediately after endovascular surgery, especially TAVI. However, leukopenia was resolved by the day after surgery and

was not associated with PIS or postoperative infectious complications. Therefore, postoperative leukopenia that occurs immediately after endovascular surgery is an observable transient abnormal hematological finding and a self-limiting condition.

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Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

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Figure Legends

Figure 1. Graph depicting changes in WBC counts between preoperative, immediate postoperative, and POD-1 values. DR-WBC is described in the table below the graph. *P*-value indicates between-group analysis.

†† $P < 0.01$ vs TAVI (adjustment for multiple comparison: Bonferroni)

DR-WBC = decline rate of white blood cell count, TAVI = transcatheter aortic valve implantation, EVAR = endovascular aortic repair, TEVAR = thoracic endovascular aortic repair, POD = post-operative day, ope = operation.

Tables

Table 1. List of devices used for EVAR, TEVAR, and TAVI

Product	Manufacturer (City, Country)	Number of cases
EVAR		
Aorfix®	Lombard Medical Ltd. (Oxford shire, United Kingdom)	8
AFX2®	Japan Lifeline Co., Ltd. (Tokyo, Japan)	7
ENDURANT®	Medtronic, Inc. (Minneapolis, United States)	13
EXCLUDER®	W. L. Gore & Associates, Inc. (Newark, United states)	9
ZENITH®	Cook Inc. (Bloomington, United States)	1
TEVAR		
cTAG®	W. L. Gore & Associates, Inc. (Newark, United states)	3
Najuta®	Kawasumi Laboratories, Inc. (Tokyo, Japan)	8
Relay®	Japan Lifeline Co., Ltd. (Tokyo, Japan)	7
Valiant®	Medtronic, Inc. (Minneapolis, United States)	10
Zenith alpha®	Cook Inc. (Bloomington, United States)	10
TAVI		
SAPIEN III®	Edwards Lifesciences LLC (Irvine, United states)	26
SAPIEN XT®	Edwards Lifesciences LLC (Irvine, United states)	14
Evolut R®	Medtronic, Inc. (Minneapolis, United States)	1

The total number of patients was not matched to the sum of patients for each device because in some cases two devices were used in the same patient.

EVAR = endovascular aortic repair, TEVAR = thoracic endovascular aortic repair, TAVI = transcatheter aortic valve implantation

Table 2. Baseline characteristics of the study patients

	TAVI N = 41	EVAR N = 37	TEVAR N = 30	*P*-value
Age (years)*	85 [83–87]	76 [71–83] ††	78 [70–85] ††	< 0.01
Height (cm)*	149 [145–159]	162 [154–166] ††	160 [156–169] ††	< 0.01
Weight (kg)*	51 [46–59]	60 [54–67] †	57 [52–69] †	< 0.01
Sex, male#	14 (34.1%)	30 (81.1%) ††	24 (80.0%) ††	< 0.01
BMI (kg/m^2)*	22.4 [19.3–26.2]	23.7 [21.3–25.7]	22.9 [21.0–25.9]	0.92
Hypertension#	37 (90.2%)	33 (89.2%)	27 (90.0%)	1.0
Dyslipidemia#	17 (41.5%)	24 (64.9%)	13 (43.3%)	0.08
Diabetes mellitus#	13 (31.7%)	2 (5.4%) †	4 (13.3%)	< 0.01
IHD#	15 (36.6%)	23 (62.2%)	15 (50.0%)	0.08
Arrythmia#	10 (24.4%)	9 (24.3%)	3 (10.0%)	0.25
COPD#	9 (22.0%)	7 (18.9%)	9 (30.0%)	0.55
CKD#	24 (58.5%)	22 (59.5%)	12 (40.0%)	0.21
Stroke#	7 (17.1%)	10 (27.0%)	8 (26.7%)	0.50
Steroid or immunosuppressant use#	4 (9.8%)	2 (5.4%)	1 (3.3%)	0.62

Data represented as * median [interquartile ranges] or as # number of patients (%)

P-value indicates between-group analysis.

† $P < 0.05$ vs TAVI, †† $P < 0.01$ vs TAVI (adjustment for multiple comparison: Bonferroni)

TAVI = transcatheter aortic valve implantation, EVAR = endovascular aortic repair, TEVAR = thoracic endovascular aortic repair, BMI = body mass index, IHD = ischemic heart disease, COPD = chronic obstructive lung disease, CKD = chronic kidney disease.

Table 3. Intraoperative data of all the study subjects

	TAVI N = 41	EVAR N = 37	TEVAR N = 30	*P*-value
Operation time (min)*	80 [69–99]	145 [123–175] ††	115 [85–162] ††	< 0.01
Administration of TIVA#	41 (100.0%)	31 (83.8%) †	26 (86.7%)	0.02
Remifentanil use#	0 (0.0%)	37 (100%)††	30 (100%)††	< 0.01
Fentanyl (μg)	293 ± 60	184 ± 73††	199 ± 80††	< 0.01
Bleeding (ml) #	30 (10–70)	50 (30–200) †	30 (20–79)	0.02
Performance of transfusion#	3 (7.3%)	5 (13.5%)	2 (6.7%)	0.59
Intraoperative fluid balance (ml)*	690 [336–965]	1372 [1027–1531] ††	1296 [1036-1681] ††	< 0.01
Steroid use#	0 (0.0%)	3 (8.1%)	3 (10.0%)	0.10
Acetaminophen use#	0 (0.0%)	35 (94.6%)††	26 (86.7%)††	< 0.01
Flurbiprofen use#	0 (0.0%)	0 (0.0%)	1 (3.3%)	0.28

Data are represented as * median [interquartile ranges] or as # number of patients (%).

P-value indicates between-group analysis.

† $P < 0.05$ vs TAVI, †† $P < 0.01$ vs TAVI (adjustment for multiple comparison: Bonferroni)

TAVI = transcatheter aortic valve implantation, EVAR = endovascular aortic repair, TEVAR = thoracic endovascular aortic repair, TIVA = total intravenous anesthesia.

Table 4. Post implantation syndrome

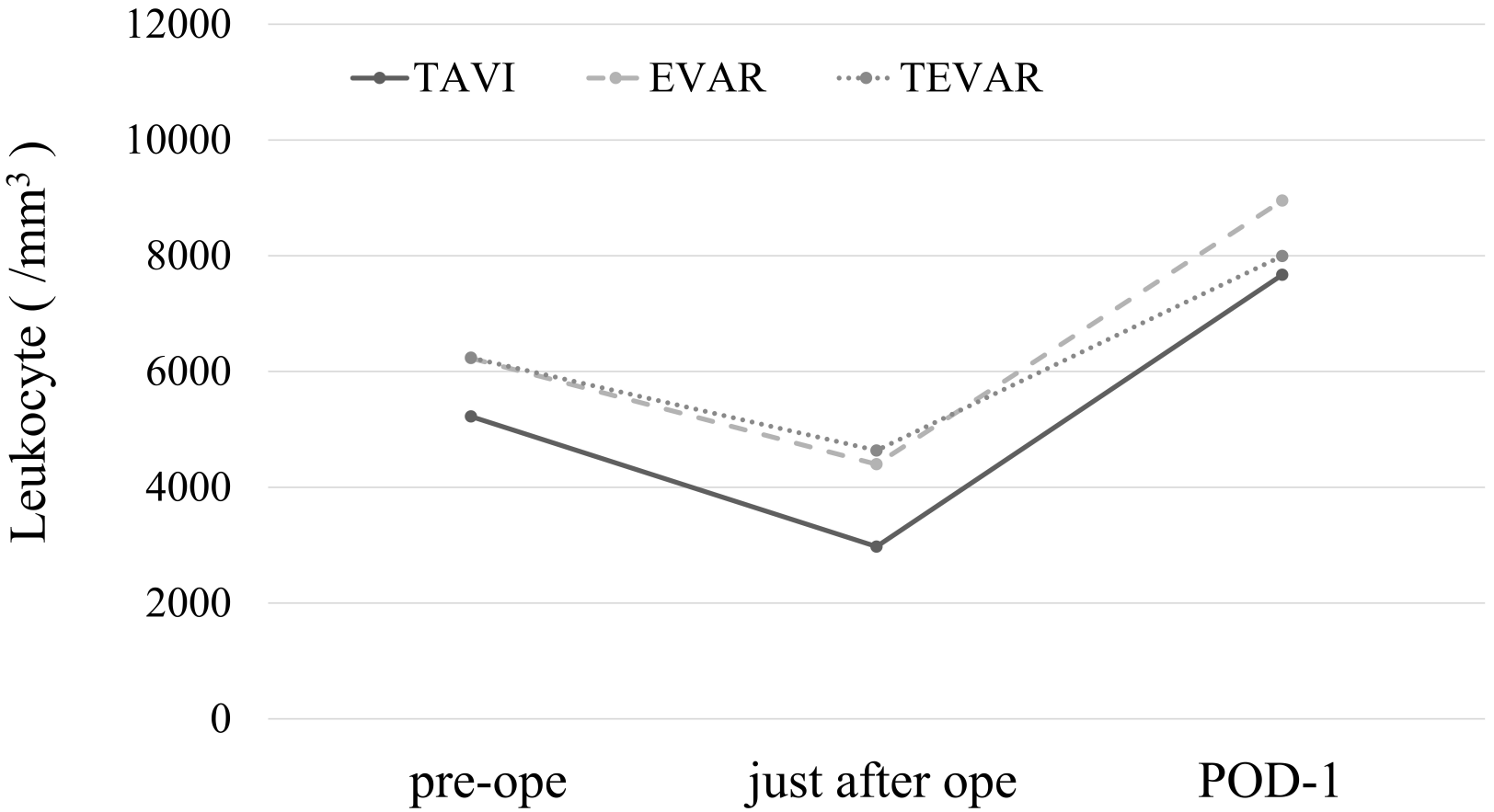
	TAVI N = 41	EVAR N = 37	TEVAR N = 30	*P*-value
Body temperature > 38℃	11 (26.8%)	16 (43.2%)	9 (30.0%)	0.28
WBC ≥ 12000 /mm^3	2 (4.9%)	13 (35.1%) ††	6 (20.0%)	< 0.01
CRP ≥ 10 mg/dl	8 (19.5%)	27 (73.0%) ††	18 (60.0%) ††	< 0.01
Postoperative infection	2 (4.9%)	1 (2.7%)	2 (6.7%)	0.85
Non-infectious inflammation	0 (0.0%)	2 (5.4%)	0 (0.0%)	0.19
Use of G-CSF	1 (2.4%)	0 (0.0%)	0 (0.0%)	1.00
PIS diagnosis	3 (7.3%)	14 (37.8%) ††	8 (26.7%)	< 0.01

Data are represented as number of patients (%).

P-value indicates between-group analysis.

† $P < 0.05$ vs TAVI, †† $P < 0.01$ vs TAVI (adjustment for multiple comparison: Bonferroni)

TAVI = transcatheter aortic valve implantation, EVAR = endovascular aortic repair, TEVAR = thoracic endovascular aortic repair, WBC = white blood cell, CRP = C-reactive protein, G-CSF = Granulocyte Colony Stimulating Factor, PIS = post implantation syndrome.



	TAVI	EVAR	TEVAR	*P*-value
DR-WBC	43.1 ± 22.6	27.6 ± 17.3 ††	25.4 ± 27.4 ††	< 0.01