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Original Article

Neutrophil–Lymphocyte Ratio as a Predictor of Persistent Type 2 Endoleak after Endovascular Aneurysm Repair

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Objectives: One of the important postoperative complications of endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA) is type 2 endoleak (T2EL). However, there is no well-established biomarker. We aimed to evaluate the validity of the neutrophil–lymphocyte ratio (NLR) as a predictor of T2EL.
Methods: Data were retrospectively collected from 146 patients who underwent EVAR for AAA at our institution between April 1, 2008 and March 31, 2021. Within 90 days before surgery, preoperative NLR was calculated from the same blood sample. The receiver operating characteristic curve (ROC) was used to determine the cutoff NLR values for persistent T2EL. Univariate and multivariate analyses were performed.
Results: Compared with patients without persistent T2EL, those who had persistent T2EL had lower preoperative NLR (P = 0.041), based on a cutoff value of 1.918, and the entire group was then divided into two groups based on these values for comparison. Univariate analysis showed significant differences in NLR, the white blood cell (WBC) count, the percentage of mural thrombus of aneurysm, history of the hypertension, follow-up term, and aneurysm diameter at final follow-up. Multivariate analysis showed that NLR and AAA diameter on the last follow-up were significantly associated with T2EL persistence.
Conclusions: Preoperative low NLR can be a useful predictor of postoperative persistent T2EL.

Keywords: neutrophil–lymphocyte ratio, abdominal aortic aneurysm, endovascular aneurysm repair, type 2 endoleak, complication

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Introduction

Type 2 endoleak (T2EL) is known to be one of the important postoperative complications of endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA).[1] Persistent cases have the risk of aneurysmal re-expansion and rupture that may require reintervention in some cases. Although persistent postoperative T2EL is known to be caused by several factors such as differences in diameter and number of lumbar arteries and models of stent grafts,[2] no useful biomarkers that can predict T2EL preoperatively are effective.[1,3,4]

The neutrophil–lymphocyte ratio (NLR) is a sensitive marker of reflecting infection and inflammation and has been shown to be influenced by various factors, such as chronic diseases, atherosclerosis, cancer, diabetes, and age.[5]

In particular, NLR has been used as a risk predictor for thrombus formation and embolization.[6,7] The aim of this study was to evaluate the value of NLR as a predictor of persistent postoperative T2EL after EVAR for AAA.

Materials and Methods

A total of 267 patients who underwent EVAR for AAA at Tokyo Medical and Dental University Hospital between April 1, 2008 and March 31, 2021 were included in this retrospective study. Measurement of the white blood cell (WBC) fractions was validated using cases that had normal WBC counts (leukocyte count, 3.0–8.6 × 10^3/mL), which were considered to be at steady state on blood tests. Patients who had factors that could be expected to influence a sudden increase or decrease in WBC count or percentage change in blood cell fractions from a steady state with obvious infections such as pneumonia or sepsis, active hematologic diseases such as myelodysplastic syndrome or leukemia, or inflammatory and infected AAA and those who had undergone rupture surgery were excluded. Patients without blood cell fractionation data within 90 days preoperatively were also excluded.

Preoperative NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count of the same blood sample that was subjected to leukocyte

fractionation within 90 days before surgery. For patients who had more than one blood sample, the most recent preoperative data that included complete blood count within the normal range were used. Preoperative coagulation and fibrinolytic system values were obtained from the same blood sample. Postoperative coagulation and fibrinolytic system values were calculated from the same blood samples taken within 1–3 days postoperatively. The diameter of the AAA was assessed using 0.5- to 5-mm-slice computed tomography (CT) images that were taken within 90 days before surgery; the maximum short-axis diameter was recorded as the AAA diameter. Simultaneously, the percentage of walled thrombus area in the cross-section with the maximum short-axis diameter was calculated. The other variables evaluated were number of patent lumbar arteries, diameter of the lumbar artery, inferior mesenteric artery (IMA) patency, and diameter of the IMA. The patient characteristics, comorbidities, and medications were extracted from the medical records. Information on the devices used during surgery, operative time, embolized arteries, and intraoperative complications were obtained from the operative records.

The patients were follow-up until death, censoring, or the end of the study period. Persistent T2EL was defined as cases without spontaneous resolution of the T2EL after six months or until the time of death within 6 months. The presence of T2EL was confirmed by the presence of blood flow into the aneurysm sac from branching vessels by angiography at the time of surgery and by contrast CT scan and vascular echo postoperatively. The diameter of the aneurysm on the last follow-up was determined using the latest imaging data.

For statistical analysis, continuous data were presented as mean (standard deviation [SD]). Categorical data were presented as counts and percentages. The receiver operating characteristic (ROC) curve and Youden's index were used to determine the ideal cutoff NLR value for persistent T2EL. Using the determined cutoff values, the patients were divided into the low NLR and high NLR groups, which were compared in terms of age, mass diameter, comorbidities, smoking history, operative time, lumbar artery diameter, number of lumbar arteries, stent graft model, and presence of emboli considered relevant to T2EL. The two-group comparison analysis was performed using the Mann–Whitney U test for continuous variables and Fisher's exact probability test for categorical variables. For T2EL risk factors, univariate and multivariate analyses were performed by logistic regression adjusted for multicollinearity. Univariate and multivariate analyses of continuous variables were statistically analyzed using single and multiple regression analyses.

For the univariate and multivariate analyses, two-tailed P values <0.05 were considered statistically significant. The variables with P values <0.20 in the univariate analysis were included in the multivariate analysis. Statistical analyses were performed using EZR (Easy R) analysis software version 1.61 (Department of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan).[8] The experimental protocol and informed consent for this study were approved by the Ethical Review Committee of Tokyo Medical and Dental University Hospital (M2021-279), and written informed consent was obtained from all patients.

Results

Of the 267 eligible patients, 121 were excluded based on the aforementioned criteria. The excluded cases included 4 ruptured cases, 6 cases of inflammatory/infected aneurysms, 4 cases with definitive infection, 2 cases of hematologic disease including leukemia, and 105 cases in which blood cell fractionation studies were not performed within 90 days before surgery. Of the 146 cases analyzed, 34 cases had persistent T2EL. **Figure 1** summarizes the inclusion and distribution of the study population. The mean (SD) age at surgery was 77.16 ± 6.81 years (range, 54–96 years). Majority of the patients were men (n = 123, 84.2%), and 23 (15.8%) were women. The percentage of mural thrombus of aneurysm in the section with the maximum short-axis diameter was 41.08 ± 22.23%. The mean (SD) follow-up period was 42.00 ± 33.99 months (range, 0–158 months). The overall patient demographics and baseline comorbidities, as well as the device used at the time of surgery, duration of surgery, and use of coil embolization, are detailed in **Table 1**.

The overall mean NLR was 2.99 (2.99 ± 1.52; median, 2.6; interquartile range [IQR], 2.03–3.50). The ROC analysis showed that a preoperative NLR of ≤1.918 was associated with T2EL persistence (**Fig. 2**), with the area under the curve of 0.616, a specificity of 82.1%, and a sensitivity of 41.2%. The low NLR group (≤1.918) comprised 33 patients, whereas the high NLR group (>1.918) comprised 113 patients. The NLR was significantly lower in patients with persistent T2EL than in those without persistent T2EL (2.63 ± 1.38; median, 2.42 [IQR, 1.62–3.19] vs. 3.16 ± 1.60; median, 2.74 [IQR, 2.15–3.57]; P = 0.041).

As detailed in **Table 2**, the baseline characteristics were similar between the two groups that were divided according to the cutoff NLR of 1.918. Univariate analysis showed that the low NLR and high NLR groups had significant differences in the NLR (1.49 ± 0.26; median, 1.56 [IQR, 1.33–1.64] vs. 3.49 ± 1.50; median, 3.02 [IQR, 2.52–3.85], P <0.001), WBC count (5.46 ± 1.21 × 10^3/mL; median, 5.50 × 10^3/mL [IQR, 4.60–6.20 × 10^3/mL] vs.

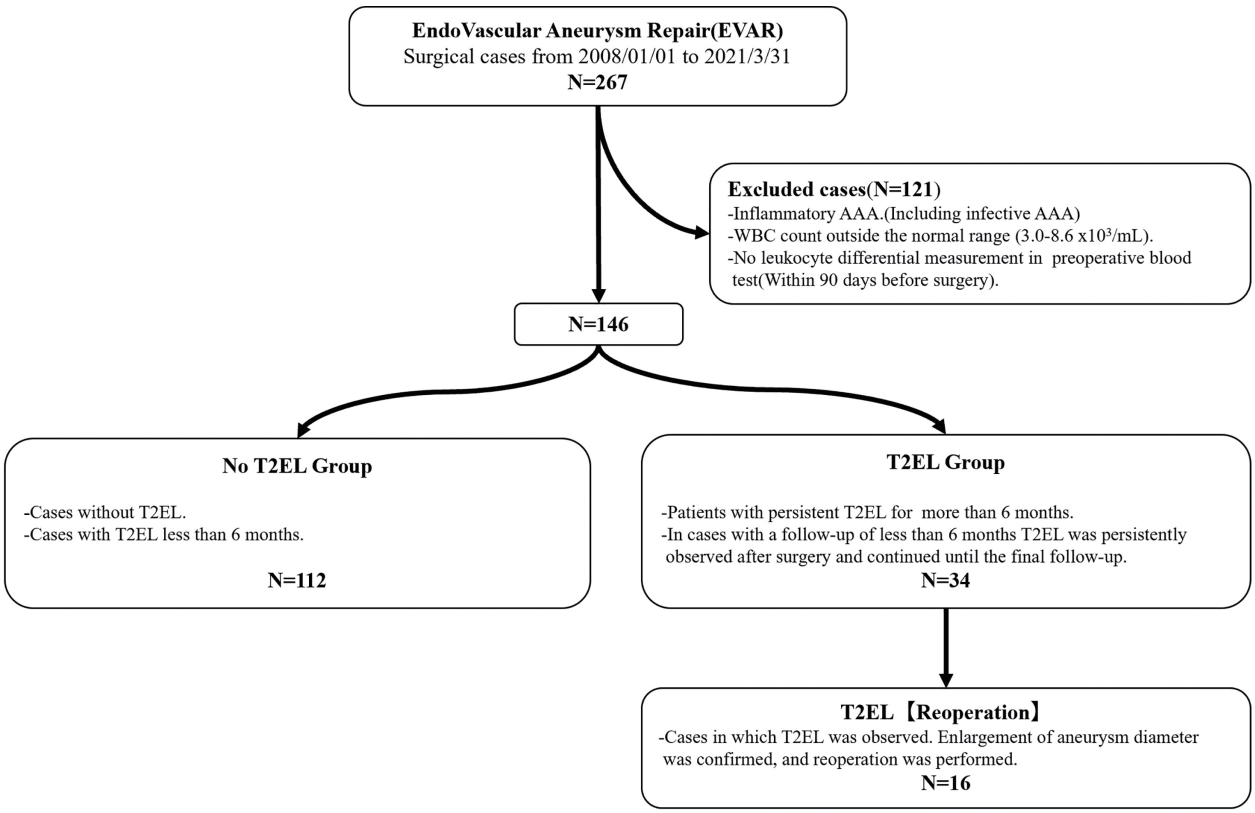

Fig. 1 Classification of the study population.
AAA: abdominal aortic aneurysm; WBC: white blood cell; T2EL: type 2 endoleak

6.01 ± 1.21 × 10^3/mL; median, 6.10 × 10^3/mL [IQR, 5.20–6.80 × 10^3/mL], P = 0.030), neutrophil count (2.94 ± 0.80 × 10^3/mL; median, 2.88 × 10^3/mL [IQR, 2.56–3.26 × 10^3/mL] vs. 4.11 ± 0.98 × 10^3/mL; median, 4.05 × 10^3/mL [IQR, 3.42–4.68 × 10^3/mL], P <0.001), lymphocyte count (2.03 ± 0.76 × 10^3/mL; median, 1.91 × 10^3/mL [IQR, 1.68–2.18 × 10^3/mL] vs. 1.30 ± 0.41 × 10^3/mL; median, 1.25 × 10^3/mL [IQR, 1.00–1.59 × 10^3/mL], P <0.001), aneurysm diameter (mm) (46.71 ± 8.65 mm; median, 50.00 mm [IQR, 43.0–52.0 mm] vs. 50.81 ± 8.72 mm; median, 50.70 mm [IQR, 47.0–56.0 mm], P = 0.040), percentage of mural thrombus of aneurysm (%) (33.29 ± 20.95%; median, 33.13% [IQR, 14.56–51.74%] vs. 43.12 ± 20.06%; median, 44.67% [IQR, 25.03–62.24%], P = 0.046), number of current smokers (9 [23.7%] vs. 12 [10.1%], P = 0.024), and number of persistent T2EL (14 [42.4%] vs. 20 [17.7%], P = 0.009). The two groups had no differences in the preoperative maximum short-axis diameter, number of patent lumbar arteries and lumbar artery diameter, IMA diameter, presence of coil embolization, and stent graft model, which are considered risk factors for T2EL.[2)]

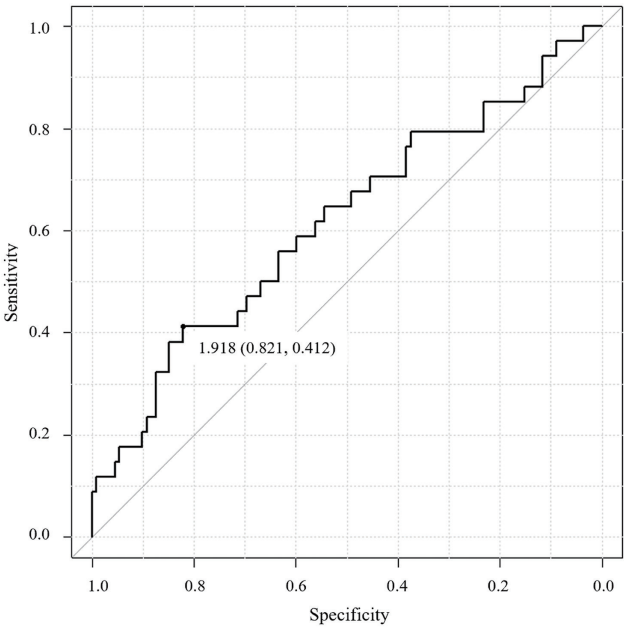

Fig. 2 Receiver operating characteristic curve for neutrophil–lymphocyte ratio as a predictor of persistent T2EL.
T2EL: type 2 endoleak

Table 3 shows preoperative and postoperative blood coagulation/fibrinolytic data. In the high NLR group, there was a slight postoperative shortening of the activated partial thromboplastin time (APTT) and a decrease in fibrinogen (Fbg), but there were no significant differences in coagulation and fibrinolytic data between the low and high NLR groups.

Table 1 Characteristics of all cases analyzed

Variable	Patient (N = 146)
NLR	2.99 ± 1.52
Absolute WBC count (×10³/mL)	5.86 ± 1.24
Absolute neutrophil count (×10³/mL)	3.81 ± 1.05
Absolute lymphocyte count (×10³/mL)	1.47 ± 0.60
Age, years	77.16 ± 6.81
Men	123 (84.2%)
Body mass index	23.62 ± 4.11
Percentage of mural thrombus of aneurysm (%)	41.08 ± 22.23
Aneurysm diameter (mm)	49.87 ± 8.88
Diabetes mellitus	26 (17.8%)
Hypertension	103 (70.5%)
Hyperlipidemia	58 (39.7%)
Cardiovascular disease	62 (42.5%)
Respiratory disease	31 (21.2%)
Smoking history	92 (63.0%)
Current smoker	21 (14.4%)
Prior smoker	71 (48.6%)
Number of lumbar arteries	5.00 ± 1.07
Maximum diameter of lumbar artery (mm)	2.40±0.38
Patency of the IMA	135 (92.5%)
Diameter of IMA (mm)	2.83 ± 0.91
Operation time (min)	189.36 ± 77.09
Stent graft type	
GORE EXCLUDER	78 (53.4%)
Aorfix	19 (13.0%)
AFX	16 (11.0%)
Endurant	11 (7.5%)
Zenith	10 (6.8%)
Endologix Powerlink (EPL)	8 (5.4%)
Other	4 (2.7%)
Arterial embolism	57 (39.0%)
Right internal iliac artery	29 (19.9%)
Left internal iliac artery	10 (6.8%)
Bilateral internal iliac artery	10 (6.8%)
IMA only	5 (3.4%)
IMA + internal iliac artery	3 (2.1%)
Complications (excluding T2EL)	15 (10.3%)
T2EL	34 (23.3%)
Follow-up term (month)	42.00 ± 33.99
Aneurysm diameter at final follow-up (mm)	47.15 ± 13.46
Patients who died during the follow-up period	31 (21.2%)
Secondary intervention for T2EL	16 (11.0%)

Continuous data are presented as mean ± standard deviation; categorical data are presented as numerical values (%).
NLR: neutrophil–lymphocyte ratio; T2EL: type 2 endoleak; IMA: inferior mesenteric artery; WBC: white blood cell

Table 4 shows the results of univariate logistic regression analysis. Persistence of T2EL was associated with NLR (OR, 0.31; 95% CI, 0.13–0.71; P = 0.006), hypertension (OR, 2.90; 95% CI, 1.04–8.12; P = 0.043), follow-up term (OR, 1.01; 95% CI, 1.00–1.02; P = 0.042), and aneurysm diameter at last follow-up (OR, 1.11; 95% CI, 1.06–1.16; P <0.001).

By multivariate logistic regression analysis, the persistence of T2EL was significantly associated with NLR (OR, 0.19; 95% CI, 0.06–0.57; P = 0.003) and aneurysm diameter at the last follow-up (OR, 1.11; 95% CI, 1.06–1.16; P <0.001) (**Table 5**).

Univariate analysis by single regression and multivariate analysis by multiple regression analysis were performed to examine factors affecting aneurysm diameter at the last follow-up, which was significantly different in multivariate analysis. Aneurysm diameter at the last follow-up was significantly associated with T2EL (P <0.001) and low NLR (P <0.001) in univariate analysis. In multivariate analysis, it was significantly associated with both T2EL (t-value 6.02; 95% CI: 9.99–19.76; P <0.001) and low NLR (t-value 2.33; 95% CI: 0.86–10.83; P = 0.021).

Discussion

This study suggested that low preoperative NLR is a valid predictor of T2EL persistence after EVAR for AAA. In cardiovascular disease, high NLR has been reported to be a predictor of prognosis for patients with acute coronary syndromes[9] and peripheral arterial disease.[10] Similarly, the association with mortality after EVAR[11,12] and the association between high NLR and thrombotic disease have been reported previously.[4,5] However, our literature search did not identify any study on the association between preoperative low NLR and T2EL persistence, which is a complication of EVAR.

NLR is one of the blood markers that have been studied in recent years and reflects both innate (neutrophils) and acquired (lymphocytes) immune responses. It is influenced by several factors, such as age, sex, chronic diseases, such as coronary heart disease, stroke, diabetes, obesity, and cancer; lifestyle habits; and stress. The etiology of cardiovascular disease has been closely related to inflammation. An association between chronic inflammatory diseases and cardiovascular disease has been reported.[13,14] Normal NLR values are influenced by the above factors, but several studies have reported the mean NLR values in healthy populations.[5,15–17] According to these studies, an NLR of 1–2 is generally considered normal.

We have not found any reports directly evaluating the relationship between low NLR status and vascular diseases such as thrombosis or blood coagulation. However, the relationship between neutrophils and thrombosis is important, and it is known that an increased neutrophil response, especially during inflammation, can contribute

Table 2 Patient characteristics in the two groups using NLR 1.918 as the cutoff

Variable	Low NLR (≤1.918) (N = 33)	High NLR (>1.918) (N = 113)	P value
NLR	1.49 ± 0.26	3.49 ± 1.50	**<0.001**
Absolute WBC count (×10³/mL)	5.46 ± 1.21	6.01 ± 1.21	**0.03**
Absolute neutrophil count (×10³/mL)	2.94 ± 0.80	4.11 ± 0.98	**<0.001**
Absolute lymphocyte count (×10³/mL)	2.03 ± 0.76	1.30 ± 0.41	**<0.001**
Age, years	76.85 ± 6.85	77.35 ± 6.73	0.916
Men	28 (84.8%)	95 (84.1%)	>0.99
Body mass index	24.36 ± 3.51	23.30 ± 4.24	0.122
Aneurysm diameter (mm)	46.71 ± 8.65	50.81 ± 8.72	**0.04**
Percentage of mural thrombus of aneurysm (%)	33.29 ± 20.95	43.12 ± 20.06	**0.046**
Diabetes mellitus	6 (18.2%)	20 (17.7%)	>0.99
Hypertension	21 (63.6%)	82 (72.6%)	0.386
Dyslipidemia	15 (45.5%)	43 (38.1%)	0.545
Cardiovascular disease	17 (51.5%)	45 (39.8%)	0.238
Respiratory disease	3 (27.3%)	28 (24.8%)	0.056
Smoking history	21 (63.6%)	71 (63.7%)	>0.99
Current smoker	9 (27.3%)	12 (10.1%)	**0.024**
Prior smoker	12 (36.4%)	59 (52.2%)	0.118
Number of lumbar arteries	4.88 ± 1.15	5.01 ± 1.04	0.669
Maximum diameter of lumbar artery (mm)	2.33 ± 0.26	2.42 ± 0.41	0.284
Patency of the IMA	33 (100.0%)	102 (90.3%)	0.198
Diameter of IMA (mm)	2.99 ± 0.61	2.78 ± 0.98	0.724
Operation time (min)	185.39 ± 90.40	189.21 ± 73.22	0.736
Stent graft type			0.076
GORE EXCLUDER	17 (51.5%)	61 (54.0%)	0.845
Aorfix	2 (6.1%)	17 (15.0%)	0.245
AFX	1 (3.0%)	15 (13.3%)	0.121
Endurant	4 (12.1%)	7 (6.2%)	0.269
Zenith	4 (12.1%)	6 (5.3%)	0.234
Endologix Powerlink (EPL)	3 (9.1%)	5 (4.5%)	0.381
Others	2 (6.1%)	2 (1.8%)	0.220
Arterial embolization	11 (33.3%)	46 (40.7%)	0.544
Right internal iliac artery	7 (21.2%)	22 (19.5%)	0.808
Left internal iliac artery	2 (6.1%)	8 (7.1%)	>0.99
Bilateral internal iliac artery	1 (3.0%)	9 (8.0%)	0.457
Inferior mesenteric artery only	0 (0%)	5 (4.4%)	0.588
Inferior mesenteric artery + internal iliac artery	1 (3.0%)	2 (1.8%)	0.539
Complication (excluding T2EL)	3 (9.1%)	12 (10.6%)	>0.99
T2EL	14 (42.4%)	20 (17.7%)	**0.009**
Follow-up term (month)	44.49 ± 30.59	40.56 ± 34.66	0.297
Aneurysm diameter at final follow-up (mm)	45.22 ± 13.12	47.53 ± 13.31	0.766
Patients who died during the follow-up period	6 (18.2%)	25 (22.1%)	0.809
Secondary intervention by T2EL	5 (15.6%)	11 (9.7%)	0.359

Continuous data are presented as mean ± standard deviation; categorical data are presented as number (%).
Bold values indicate items with significant differences at P <0.05.
NLR: neutrophil–lymphocyte ratio; T2EL: type 2 endoleak; IMA: inferior mesenteric artery; WBC: white blood cell

to thrombosis. A sustained neutrophil response induces increased synthesis of enzymes such as myeloperoxidase and neutrophil elastase, which, in turn, induces enzymatic reactions. Activation of enzymatic reactions inactivates and degrades proteins (such as antithrombin, thrombomodulin, and protein C) that play an important role in inhibiting blood coagulation.[18–20] In addition, this neutrophil count is also affected by granulocyte colony-stimulating factor, interleukin (IL)6, IL8, IL3, and IL17.[12,21–24] Thus, an increased neutrophil count and neutrophil response can be considered a high NLR state. In other words, patients with high NLR are more likely to have

Table 3 preoperative and postoperative coagulation/fibrinolytic blood data in the two groups using NLR 1.918 as the cutoff

Variable	Low NLR (≤1.918) (N = 33)	High NLR (>1.918) (N = 113)	P value
Pre-PT (sec.)	10.71 ± 1.70	10.72 ± 4.09	0.674
Pre-APPT (sec.)	29.15 ± 3.55	28.63 ± 8.33	0.552
Pre-Fbg (mg/dl)	296.34 ± 104.28	273.84 ± 123.69	0.611
Pre-D-dimer (μg/ml)	3.92 ± 4.68	4.91 ± 8.26	0.946
Post-PT (sec.)	11.52 ± 0.90	10.51 ± 3.71	0.435
Post-APPT (sec.)	30.33 ± 4.18	28.61 ± 10.43	0.289
Post-Fbg (mg/dl)	306.19 ± 112.26	259.58 ± 146.73	0.251
Post-D-dimer (μg/ml)	9.85 ± 9.77	8.52 ± 11.14	0.425

Continuous data are presented as mean ± standard deviation.
NLR: neutrophil–lymphocyte ratio; PT: prothrombin time; APTT: activated partial thromboplastin time; Fbg: fibrinogen

Table 4 Univariate logistic regression analysis of factors associated with T2EL persistence

Variable	Odds ratio	95% CI	P value
NLR	0.31	0.13–0.71	**0.006**
Absolute WBC count (×10^3/mL)	0.75	0.54–1.04	0.084
Age, years	0.97	0.92–1.03	0.335
Men	1.49	0.56–4.00	0.428
Body mass index	1.01	0.92–1.11	0.770
Aneurysm diameter (mm)	1.02	0.98–1.06	0.405
Percentage of mural thrombus of aneurysm (%)	1.00	0.98–1.02	0.878
Diabetes mellitus	1.00	0.37–2.76	0.994
Hypertension	2.9	1.04–8.12	**0.043**
Dyslipidemia	1.63	0.75–3.55	0.215
Cardiovascular disease	1.57	0.72–3.41	0.253
Respiratory disease	0.31	0.09–1.08	0.065
Smoking history			0.978
Current smoker	1.03	0.31–3.37	0.967
Prior smoker	0.93	0.40–2.15	0.863
Number of lumbar arteries	0.9	0.63–1.29	0.576
Maximum diameter of lumbar artery (mm)	1.16	0.43–3.18	0.768
Patency of the IMA	0.44	0.05–3.69	0.447
Diameter of IMA (mm)	1.07	0.70–1.65	0.756
Operation time (min)	0.99	0.99–1.00	0.682
Stent graft type	1.25	0.99–1.59	0.800
Arterial embolization	0.77	0.44–1.34	0.914
Complications (excluding T2EL)	0.46	0.09–2.13	0.319
Follow-up term (month)	1.01	1.00–1.02	**0.042**
Aneurysm diameter at final follow-up (mm)	1.11	1.06–1.16	**<0.001**

Bold values indicate items with significant differences at P <0.05.
NLR: neutrophil–lymphocyte ratio; T2EL: type 2 endoleak; IMA: inferior mesenteric artery; WBC: white blood cell

Table 5 Multivariate logistic regression analysis of factors associated with T2EL persistence

Variable	Odds ratio	95% CI	P value
NLR (≤1.916)	0.19	0.06–0.57	**0.003**
Absolute WBC count (×10^3/mL)	0.94	0.61–1.43	0.760
Hypertension	1.99	0.57–6.99	0.281
Respiratory disease	0.46	0.11–1.91	0.287
Follow-up term (month)	1.00	0.99–1.01	0.755
Aneurysm diameter at final follow-up (mm)	1.11	1.06–1.16	**<0.001**

Bold values indicate items with significant differences at P <0.05.
NLR: neutrophil–lymphocyte ratio; T2EL: type 2 endoleak; WBC: white blood cell

a chronic inflammatory disease, with increased blood coagulation secondary to enhanced neutrophil activity. Conversely, if the NLR is within the normal range, blood coagulation is unlikely to occur as a result of the neutrophil hyperactivity described above.

Meanwhile, T2EL after EVAR was reported in 16% to 50% of patients and accounted for about half of the endoleak cases, with 80% resolving spontaneously.[1,3,4] However, its detailed natural history is not reported.[6,7] T2EL had been mainly attributed to differences in the models of stent grafts, the presence of arterial emboli, the number of patent lumbar arteries, lumbar artery diameter, and IMA diameter.[1,3,25] T2EL is thought to be caused by sustained blood flow into the aneurysm from the lumbar artery and IMA, and resolution of T2EL is thought to be caused by loss of blood flow due to occlusion or thrombosis of these branch vessels. In this study, 23.3% of the population had persistent T2EL after EVAR.

In this study, lower preoperative NLR was significantly associated with T2EL persistence and aneurysm diameter at the final follow-up. It is suggested that the persistence of T2EL may have influenced the increase in aneurysm diameter at the final follow-up. The cutoff NLR value of 1.918 was within the normal range. This implied that the group with preoperative NLR within the normal range had a relatively high rate of T2EL persistence after more than 6 months of the EVAR.

Previous reports have shown that high NLR is associated with atherosclerosis[26,27] and more recently with DVT and VTE.[6,7,28] As a cause of AAAs, arteriosclerosis is considered the primary factor, as it is associated with the fragility of the arterial wall.[29] On the other hand, there are some reports that there is little association between AAA and arteriosclerosis obliterans,[30] diabetes,[31] and hyperlipidemia,[32] so it is thought that it is not caused by arteriosclerosis alone. Similarly, the report shows a low correlation between NLR and smoking, which is believed to be closely related to atherosclerosis.[33] These reports suggest that high NLR may indeed reflect atherosclerotic changes, but NLR itself may reflect not only an increased blood clotting response associated with atherosclerosis but also a combined increase in blood clotting response against the background of various factors. Therefore, it is likely that AAA was observed in the group with low NLR in this study and that low NLR was also observed in smokers.

These results suggested that compared with patients with normal NLR, those with high preoperative NLR were more likely to have chronic inflammation due to a combination of factors before surgery and enhanced intravascular coagulation. In this study, we could not find a significant association between preoperative and postoperative values of NLR in blood test data of coagulation and fibrinolysis systems. This is because, unlike acute inflammation, chronic inflammatory responses are characterized by persistent inflammation in the microenvironment and do not present with the characteristic symptoms of acute inflammation.[34] This may explain why, unlike acute inflammation, abnormalities in the coagulation and fibrinolytic systems may not be reflected in blood test data. On the other hand, in contrast-enhanced CT scan, it was observed that the percentage of mural thrombus in the aortic aneurysm arterial wall was significantly lower in patients with low preoperative NLR than in those with high NLR, as shown in **Table 2**. Univariate analysis showed no significant association between aneurysm wall thrombosis and NLR (**Table 3**), suggesting that factors such as aneurysm shape and size may also influence thrombosis.

Stent grafting in AAAs may lead to a relatively rapid decrease in blood flow in the arterial branches that are primarily involved in the T2EL (e.g., lumbar artery and IMA); therefore, thrombotic occlusion of such branch vessels may likely occur in case of enhanced intravascular coagulation in a short period of time postoperatively. Contrarily, T2EL may be prolonged in patients with normal coagulation states who were represented as preoperative NLR within the normal range because of the low likelihood of neutrophil-induced intravascular coagulation and postoperative thrombotic occlusion of the branch vessels.

This may be the reason why the preoperative low NLR was useful in predicting persistent T2EL after EVAR in this study.

Our study had several limitations. There may have been selection bias due to the inclusion of excluded cases because only 54.8% of the patients treated during the study period were analyzed. The retrospective study design precluded preoperative leukocyte fraction measurements in all patients, albeit preferable, and limited the generalizability of our results. In addition, the specificity of the cutoff value obtained from the ROC curve was low. Although the number of cases exceeded the minimum statistically valid sample size required, the small number of T2EL cases did not allow us to detect significant differences in the number and diameter of lumbar arteries and IMA diameter or IMA patency, which are known predictors of T2EL. Similarly, with regard to chronic inflammation and thrombosis, inflammatory mediators such as ILs caused by chronic inflammation were not measured in most cases, making it difficult to directly support the results of this study.

Nevertheless, the NLR, which can be easily measured by a blood test, was found to be valuable in predicting persistent postoperative T2EL. If the persistence of postoperative T2EL can be predicted using a blood cell fractionation test, it would be very effective in clinical practice, allowing preoperative countermeasures to be considered. Although there are limitations to this study and further research is needed to generalize it, it is clinically very

useful in that it can predict the possibility of future T2EL at an early stage. Early prediction of T2EL is likely to be useful in determining the procedure, including additional embolization of the inflow vessel causing T2EL but more cases need to be accumulated to draw this conclusion. Low preoperative NLR is a good predictor of postoperative T2EL persistence, an important finding in our study. Further evaluation through prospective studies will help to support this validity.

Conclusion

The group with low preoperative NLR had a significantly high rate of persistent postoperative T2EL. These findings suggest that preoperative leukocyte fractionation and calculation of the NLR can be valid tools for predicting T2EL persistence after EVAR for AAA.

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Analysis: T Kikuchi
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