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ORIGINAL RESEARCH

Predictive Value of the Platelet-to-Lymphocyte Ratio in Cancer Patients Undergoing Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES The purpose of this study is to investigate the predictive value of the platelet-to-lymphocyte ratio (PLR) in cancer patients undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND The PLR is a promising marker to predict clinical outcomes in various cancer types as well as in cardiovascular disease.

METHODS Consecutive TAVR patients were enrolled in the study. We stratified patients into 2 groups: cancer and noncancer. Baseline complete blood counts with a differential hemogram were collected before TAVR. The primary outcome was all-cause death within a 3-year follow-up.

RESULTS In total, 240 of 1,204 patients (19.9%) had a cancer history. Cancer patients had a significantly higher baseline PLR than noncancer patients (median [interquartile range], 159.8 [109.6 to 244.6] vs. 150.3 [108.7 to 209.0]; $p = 0.024$). Kaplan-Meier analysis revealed that cancer patients had worse outcomes than noncancer patients (log-rank $p < 0.001$). Patients who died had a significantly higher baseline PLR than those who survived both in the cancer ($p = 0.009$) and noncancer ($p = 0.027$) groups. Multivariable analyses showed that the PLR (by 100 increase) was an independent predictor of adverse outcomes in both cancer (hazard ratio: 1.07; 95% confidence interval: 1.02 to 1.13; $p = 0.006$) and noncancer (hazard ratio: 1.20; 95% confidence interval: 1.06 to 1.36; $p = 0.004$). The highest mortality was observed for patients with cancer and increased PLR (above the median) (log-rank $p < 0.001$).

CONCLUSIONS Cancer patients undergoing TAVR had a significantly higher PLR than those without cancer. Higher PLR was associated with a worse outcome following TAVR. (J Am Coll Cardiol CardioOnc 2019;1:159–69)

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CBC = complete blood count

EuroSCORE = European System for Cardiac Operative Risk Evaluation Score

HR = hazard ratio

IQR = interquartile ratio

PLR = platelet-to-lymphocyte ratio

STS = Society of Thoracic Surgery score

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative to surgical aortic valve replacement for symptomatic severe aortic stenosis (AS) patients at increased surgical risk, and TAVR has shown favorable 5-year results in appropriately selected patients (1). The indication for TAVR is now expanding toward lower surgical risk patients (2,3) as well as younger patients (4).

With an aging patient population and an improvement in treatment outcomes for cancer, the number of coexistent cases of cardiovascular disease and cancer is steadily increasing (5), and attention is being given to the study of their combination within the field of cardio-oncology. A recent publication reported that TAVR patients with cancer had a worse 1-year prognosis than noncancer patients (6). However, cancer patients have largely been excluded from most TAVR studies (7), and little is known about the outcomes after TAVR in patients with cancer.

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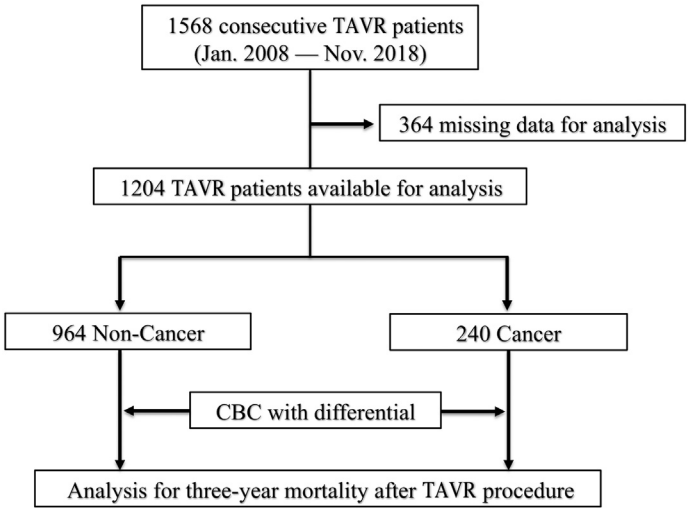
Chronic inflammation is a driver of both cardiovascular disease, including atherosclerosis and valvular calcification (8,9), and cancer (10). The platelet-to-lymphocyte ratio (PLR), calculated from a peripheral complete blood cell count with differential, is a promising marker of inflammation that has been widely studied over the past decade in atherosclerotic disease (11), aortic stenosis (12,13), and various cancers (14,15). However, the relevance of the PLR in cancer patients undergoing TAVR is unknown. The purpose of the present study is to investigate the predictive value of the PLR in cancer patients undergoing TAVR.

FIGURE 1 Flowchart of the Present Study



From 1,568 consecutive TAVR patients at the University Hospital Bonn between January 2008 and November 2018, we excluded 364 patients that were missing a white blood cell count and differential. A total of 1,204 patients with complete data were available for analysis. Among them, 240 patients (19.9%) had a history of cancer.
TAVR = transcatheter aortic valve replacement.

METHODS

STUDY POPULATION AND CLINICAL DATA. This is a single-center, observational cohort study. All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. Consecutive patients, undergoing TAVR between January 2008 and November 2018, were included in this study. Baseline demographic data, medical histories, laboratory parameters before TAVR, periprocedural characteristics including computed tomography analyses, implanted valve types, complications within 30 days, and other valvular diseases upon discharge were documented via interview and/or by examining medical records. The European System for Cardiac Operative Risk Evaluation Score (EuroSCORE) calculator and the Society of Thoracic Surgery Score (STS) calculator were used to calculate the surgical risk of each patient.

DEFINITION OF THE CANCER GROUP. We divided subjects into 2 groups according to the presence or absence of cancer in their medical history: a cancer cohort and a noncancer cohort. A history of cancer was defined as having a present or history of malignant diseases, as previously reported (16). These malignant diseases included: 1) cancers originating from the hematopoietic organs, including leukemia, malignant lymphoma, myeloma; and 2) cancers originating from epithelial cells. Representative cancers generated from epithelial cells included: lung cancer, breast cancer, stomach cancer, colorectal cancer, uterine cancer, ovarian cancer, and head and neck cancers (laryngeal cancer, pharyngeal cancer, tongue cancer); and 3) sarcomas originating from non-epithelial cells. Representative sarcomas included: osteosarcoma, chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, liposarcoma, and angiosarcoma.

A history of cancer included current cancer, which was defined as patients currently undergoing cancer treatments and/or with plans to undergo cancer treatment after the TAVR procedure, and past cancer, defined as having had cancer treatment before TAVR

TABLE 1 Clinical Parameters of the Study Participants at Baseline

	Total (N = 1,204)	Cancer (n = 240)	Noncancer (n = 964)	p Value
Male, %	618 (51.3)	150 (62.5)	468 (48.5)	<0.001
Age, yrs	80.9 ± 6.2	80.5 ± 5.9	81.0 ± 6.3	0.28
BMI, kg/m^2	26.9 ± 6.4	26.4 ± 5.1	27.0 ± 6.7	0.22
Diabetes, %	335 (27.8)	61 (25.4)	274 (28.4)	0.38
Hypertension, %	1,034 (86.0)	202 (84.2)	832 (86.5)	0.35
Dyslipidemia, %	857 (71.3)	181 (75.4)	676 (70.3)	0.13
eGFR, ml/min/1.73 m^2	52.7 ± 18.7	54.1 ± 17.7	52.4 ± 18.9	0.21
Hemodialysis, %	42 (3.5)	11 (4.6)	31 (3.2)	0.33
Atrial fibrillation, %	528 (43.9)	120 (50.0)	408 (42.3)	0.035
CAD, %	758 (63.0)	147 (61.3)	611 (63.4)	0.55
Prior PCI, %	463 (38.5)	81 (33.8)	382 (39.6)	0.10
Previous MI, %	154 (12.8)	34 (14.2)	120 (12.4)	0.52
Prior CABG, %	152 (12.6)	28 (11.7)	124 (12.9)	0.67
Prior valve surgery, %	45 (3.7)	10 (4.2)	35 (3.6)	0.70
Prior pacemaker, %	151 (12.5)	30 (12.5)	121 (12.6)	1.00
Previous stroke, %	140 (11.6)	26 (10.8)	114 (11.8)	0.74
PAD, %	413 (34.3)	79 (32.9)	334 (34.6)	0.65
Ejection fraction, %	54.2 ± 13.4	53.8 ± 13.4	54.3 ± 13.4	0.60
Pulmonary artery pressure, mm Hg	36.0 ± 17.2	34.5 ± 17.3	36.4 ± 17.2	0.16
Logistic EuroSCORE, %	20.0 ± 14.4	18.7 ± 13.8	20.3 ± 14.6	0.13
EuroSCORE II, %	6.7 ± 5.7	6.2 ± 5.7	6.8 ± 6.5	0.17
STS, %	5.5 ± 5.0	5.1 ± 4.1	5.6 ± 5.2	0.18
NYHA functional class III or IV, %	1,102 (91.9)	214 (90.3)	888 (92.3)	0.35
COPD, %	218 (18.1)	42 (17.5)	176 (18.3)	0.85
MR ≥2, %	593 (50.9)	123 (53.0)	470 (50.4)	0.51
TR ≥2, %	296 (27.5)	63 (28.8)	233 (27.2)	0.67
AVA, cm^2	0.73 ± 0.17	0.73 ± 0.16	0.72 ± 0.17	0.43
Annulus area by CT, mm	452.8 ± 102.2	464.9 ± 110.0	449.8 ± 100.1	0.095
Annulus perimeter by CT, mm	75.8 ± 10.7	77.3 ± 10.2	75.4 ± 10.8	0.049
Residual PVL ≥2 after TAVR, %	48 (4.5)	6 (2.9)	42 (4.8)	0.26
Complications at 30 days, %				
Pacemaker implantation	161 (13.4)	38 (15.8)	123 (12.8)	0.21
Stroke	27 (2.2)	4 (1.7)	23 (2.4)	0.63
Major vascular	45 (3.7)	12 (5.0)	33 (3.4)	0.25
Major bleeding	45 (3.7)	12 (5.0)	33 (3.4)	0.25
Antithrombotic drugs at discharge, %				
Warfarin	192 (16.3)	33 (14.3)	159 (16.7)	0.43
DOAC	346 (29.3)	73 (31.6)	273 (28.7)	0.42
Aspirin	834 (70.6)	161 (69.7)	673 (70.8)	0.75
Clopidogrel	975 (82.6)	188 (81.4)	787 (82.8)	0.63
Ticagrelor	14 (1.2)	2 (0.9)	12 (1.3)	1.00

Values are n (%) or mean ± SD.

AVA = aortic valve area; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CT = computed tomography; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; PVL = paravalvular leak; STS score = Society of Thoracic Surgery Risk Score; TAVR = transcatheter aortic valve replacement; TR = tricuspid regurgitation.

with remission and without any further plans for cancer treatment.

COMPLETE BLOOD COUNTS WITH DIFFERENTIAL. Baseline complete blood counts (CBCs) with differential analysis were collected from a peripheral blood sample obtained before the TAVR procedure. The CBC parameters collected were a platelet count and a white blood cell count, which includes 3 types of leukocytes (neutrophils, lymphocytes, and monocytes). We calculated the ratios between platelets and lymphocytes, platelets and neutrophils, lymphocytes and monocytes, neutrophils and lymphocytes, and neutrophils and monocytes.

CLINICAL OUTCOMES. After the TAVR procedure, patients were followed at the outpatient clinic of the University Hospital Bonn. The primary end point of

TABLE 2 Distribution and Ratios of Differential Blood Counts and Platelet Between Cancer and Noncancer Patients

	Total (N = 1,204)	Cancer (n = 240)	Noncancer (n = 964)	p Value
Timing of the CBC (days before TAVR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.24
White blood cells ($\times 10^3$)	7.3 (6.0–8.9)	7.2 (6.0–9.0)	7.3 (6.0–8.9)	0.77
Neutrophil	4.8 (3.8–6.3)	4.8 (3.8–6.4)	4.8 (3.8–6.2)	0.87
Lymphocyte	1.4 (1.0–1.8)	1.3 (0.9–1.8)	1.4 (1.0–1.8)	0.011
Monocyte	0.7 (0.5–0.8)	0.7 (0.5–0.8)	0.7 (0.5–0.8)	0.54
Platelets ($\times 10^3$)	211 (170–258)	206 (170–262)	213 (170–258)	0.65
Ratios				
Platelet to lymphocyte	152.5 (108.8–218.3)	159.8 (109.6–244.6)	150.3 (108.7–209.0)	0.024
Platelet to neutrophil	43.6 (33.0–56.6)	42.9 (32.2–56.1)	43.8 (33.1–56.7)	0.49
Lymphocyte to monocyte	2.1 (1.5–2.9)	1.9 (1.3–2.9)	2.1 (1.5–2.9)	0.051
Neutrophil to lymphocyte	3.4 (2.4–5.2)	3.7 (2.6–6.3)	3.4 (2.4–5.1)	0.030
Neutrophil to monocyte	7.2 (5.7–9.3)	7.2 (6.0–9.3)	7.1 (5.7–9.3)	0.18

Values are median (interquartile range).
CBC = complete blood count; TAVR = transcatheter aortic valve replacement.

the present study was all-cause death. Investigators blinded to this study performed the observations and the information for death was ascertained by reviewing the medical records and/or was confirmed by direct contact with the families or physicians. In the present study, we analyzed the clinical outcome within a 3-year follow-up period.

STATISTICAL ANALYSIS. Statistical analyses were performed using SPSS version 25 (IBM Inc., Armonk, New York). Continuous variables with a normal distribution are expressed as the mean ± SD, whereas those with skewed distributions are expressed as median (interquartile range [IQR]). Categorical data are presented as numbers (proportions). Differences between the 2 groups were tested using Fisher exact test or a chi-square test for categorical variables, as appropriate. Differences in continuous variables were analyzed with an analysis of variance. Relationships between the PLR ratio and other clinical parameters were analyzed using a linear regression analysis. We performed a stepwise multivariable analysis to identify independent factors that were associated with a higher PLR ratio (variables needed to have $p < 0.05$ to enter the multivariable model and then $p < 0.10$ to remain in the model; all candidate variables were re-evaluated when a new variable was added). Linearity was tested evaluating through evaluation of a histogram and the normal P-P plot. The Kaplan-Meier method was used to estimate the probability of mortality after 3 years, with patients censored at the time of last follow-up, and a log-rank test was performed to compare the distribution of survival times across groups. Cox proportional hazard analyses were used to calculate the hazard ratio (HR) for clinical outcomes, and the proportional hazards assumption was tested for all models. We performed a stepwise multivariable analyses (variables needed to have $p < 0.05$ to enter the multivariable model and then $p < 0.10$ to remain in the model; all candidate variables were re-evaluated when a new variable was added) and also used focused inclusion models (select variables that were significant in univariable analyses were included and colinear variables were excluded). PLR values were divided into high and low values according to the median value. Spline curve analysis was performed to determine the cutoff value of the PLR for all-cause mortality within a 3-year follow-up. A p value < 0.05 was considered to denote statistical significance.

RESULTS

CLINICAL PARAMETERS IN STUDY COHORTS. Of 1,568 consecutive TAVR patients between January 2008 and November 2018, we excluded 364 that were missing a differential white blood cell count. For 1,204 patients, complete data were available for analysis (**Figure 1**). Among these, 240 patients (19.9%) had a history of cancer (**Figure 1**). Supplemental Table 1 shows the prevalence of different cancers diseases, with prostate, breast, colorectal, bladder cancers, and leukemia showing the highest prevalence (Supplemental Table 1). Current or past cancer treatments are summarized in Supplemental Table 2A.

Table 1 is a comparison of the clinical characteristics between the cancer and noncancer groups. Clinical parameters at baseline were similar between the 2 groups, except for male sex (62.5% in cancer vs 48.5% in noncancer; $p < 0.001$), atrial fibrillation (50.0% in cancer vs 42.3% in noncancer; $p = 0.035$), and annulus perimeter assessed by computed tomography (77.3 ± 10.2 mm in cancer vs. 75.4 ± 10.8 mm; in noncancer

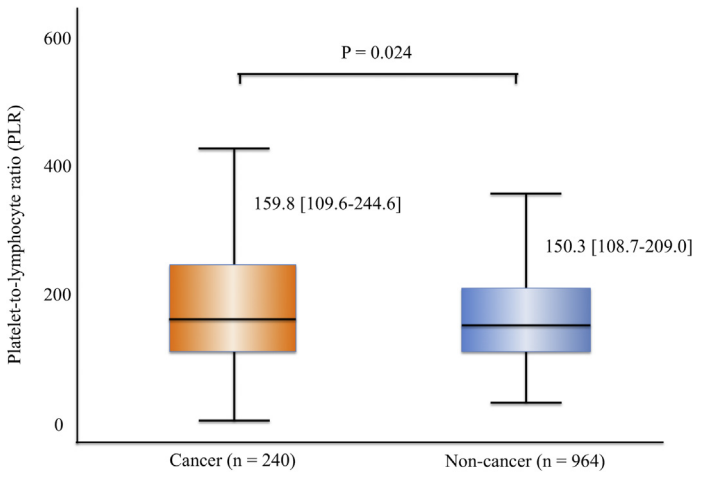
p = 0.049), respectively. Other parameters were similar between the 2 groups, including surgical risk scores, complications at 30 days, and antithrombotic drugs at discharge.

PLR BETWEEN CANCER AND NONCANCER PATIENTS. Table 2 shows the distribution of platelets and differential white blood cell counts between cancer and noncancer patients. Cancer patients had a significantly higher PLR than noncancer patients (median [IQR]: 159.8 [109.6 to 244.6] vs 150.3 [108.7 to 209.0]; p = 0.024) (Table 2, Figure 2). A stepwise multivariable regression analysis was performed to identify independent clinical factors associated with the PLR in the cancer and noncancer groups (Table 3). In the cancer group, the surgical risk score (logistic EuroSCORE) was found to be an independent factor associated with the PLR (Table 3), whereas in the noncancer group, male sex, age, body mass index, and the logistic EuroSCORE were independently associated with the PLR value (Table 3). Additional correlation analyses between the PLR and surgical risk scores are described in Figure 3. We found the PLR to be positively associated with the logistic EuroSCORE (R = 0.15; p < 0.001), EuroSCORE II (R = 0.11; p < 0.001), and STS score (R = 0.14; p < 0.001).

CLINICAL OUTCOMES WITHIN THE 3-YEAR FOLLOW-UP. Data from 1,204 patients were available for determining the clinical outcomes; a total of 305 patients (25.3%) were deceased within the 3-year follow-up. The median (IQR) time to event for all-cause mortality in the cancer and noncancer group was 177 (65 to 385) and 235 (51 to 567) days, respectively (p = 0.20). A Kaplan-Meier analysis revealed that cancer patients had a significantly worse prognosis than noncancer patients (estimated mortality rate at 3-year follow-up, 49.2% vs. 36.8%; log-rank p < 0.001) (Central Illustration, upper panel). The baseline PLR between survivors and nonsurvivors were additionally compared using those subjects that were known to be alive or deceased at 3-year follow-up. Patients who died within the follow-up period had a significantly higher baseline PLR than patients who lived both in the cancer (median [IQR]: 203.6 [143.3 to 281.7] vs. 154.7 [107.7 to 223.3]; p = 0.009) and noncancer (median [IQR]: 178.9 [127.5 to 264.0] vs. 166.1 [118.0 to 229.6]; p = 0.027) group (Central Illustration, lower panel). Details of cardiac or noncardiac mortality according to cancer status are summarized in Supplemental Table 2B.

Table 4 show the results of univariable and multivariable Cox proportional hazard regression analyses for the prediction of all-cause mortality after TAVR in the cancer and noncancer group, respectively. In the cancer group, the PLR (by each 100-U increase) was found to be an independent predictor of all-cause mortality both by a stepwise backward model (HR: 1.07; 95% CI: 1.02 to 1.13; p = 0.006) and a forced inclusion model (HR: 1.07; 95% CI: 1.02 to 1.12; p = 0.005) (Table 4). Similarly, in the noncancer group, the PLR (by each 100-unit increase) predicted all-cause mortality within 3 years both by a stepwise backward model (HR: 1.20; 95% CI: 1.06 to 1.36; p = 0.004) and a forced inclusion model (HR: 1.17; 95% CI: 1.07 to 1.28; p = 0.001) (Table 4). We further divided our cohort into 4 groups according to cancer

FIGURE 2 Baseline PLR in Cancer and Noncancer Patients



Cancer patients had a significantly higher PLR than noncancer patients (median [interquartile range]: 159.8 [109.6 to 244.6] vs. 150.3 [108.7 to 209.0]; p = 0.024). PLR = platelet-to-lymphocyte ratio.

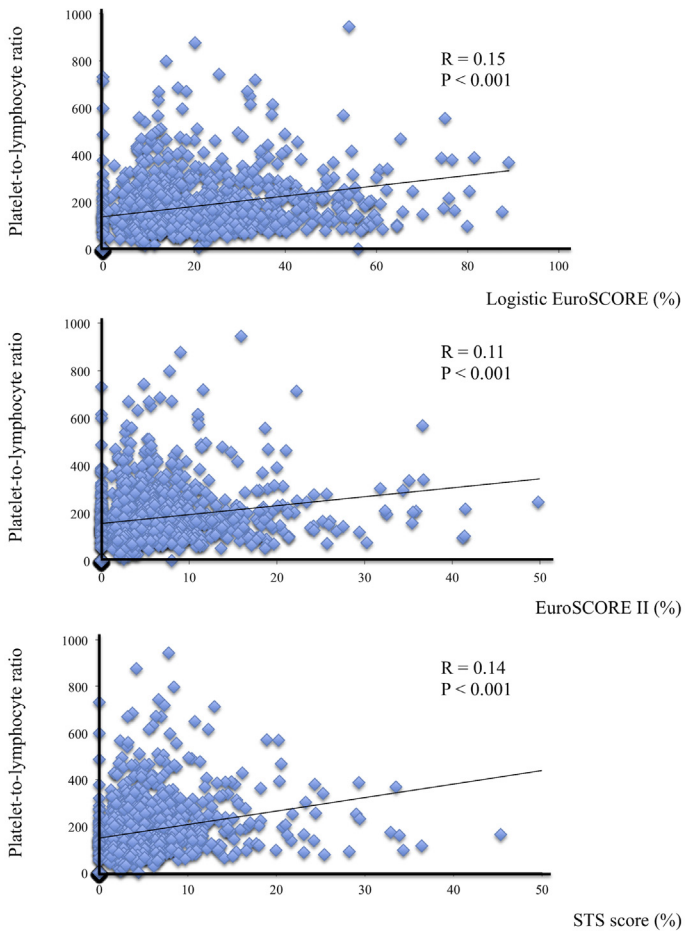
TABLE 3 Stepwise Multivariable Regression Analysis for PLR Value in Cancer and Noncancer Cohorts

	Regression Coefficient	p Value
PLR value in cancer cohort		
Logistic EuroSCORE	4.58 ± 1.46	0.002
Intercept term	131.36 ± 33.75	<0.001
PLR value in noncancer cohort		
Male	−20.78 ± 6.89	0.003
Age	−1.20 ± 0.59	0.040
Body mass index	−1.42 ± 0.51	0.006
Logistic EuroSCORE	1.30 ± 0.23	<0.001
Intercept term	295.66 ± 52.15	<0.001

Values are regression coefficient ± SEM. Factors included in the stepwise multivariable regression model were age, male sex, body mass index, logistic EuroSCORE, diabetes, hypertension, dyslipidemia, previous stroke, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease.

Abbreviation as in Table 1.

FIGURE 3 Correlation Analyses Between PLR and Surgical Risk Scores



The PLR was positively correlated with logistic EuroSCORE ($r = 0.15$; $p < 0.001$), EuroSCORE II ($r = 0.11$; $p < 0.001$), and STS score ($r = 0.14$; $p < 0.001$). EuroSCORE = European System for Cardiac Operative Risk Evaluation; PLR = platelet-to-lymphocyte ratio; STS = Society of Thoracic Surgery Risk Score.

history and a high or low PLR (according to the median value of 152.5); as a result, we found the highest mortality rate in TAVR patients with a history of cancer and an increased PLR, above the median (**Figure 4**, log-rank test; $p < 0.001$).

The spline curve analysis suggested that the cutoff value of the PLR for the all-cause mortality within a 3-year follow-up was 216.2 (Supplemental Figure 1). In multivariable analyses across the entire cohort, a high PLR greater than this cutoff was found to be independently associated with all-cause mortality both by a stepwise backward model (HR: 1.60; 95% CI: 1.21 to 2.10; $p = 0.001$) and a forced inclusion model (HR: 1.56; 95% CI: 1.20 to2.04; $p = 0.001$) (Supplemental Table 3).

DISCUSSION

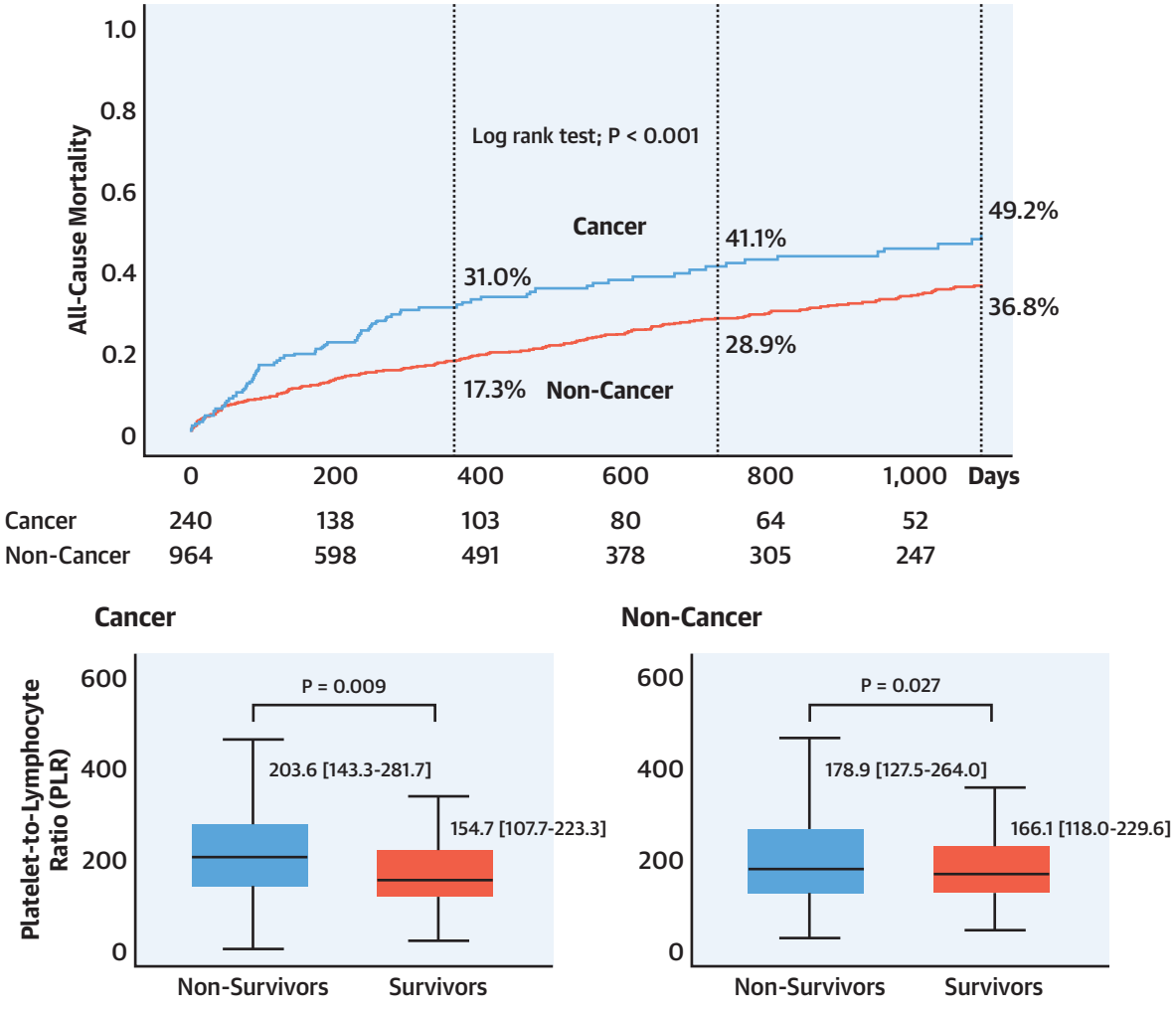
FINDINGS OF THE PRESENT STUDY. In the present study, we assessed the prognostic value of the PLR in TAVR patients stratified according to the history of cancer for the prediction of mortality. The main findings of the present study were as follows: 1) cancer patients had a significantly higher PLR than noncancer patients; 2) in the cancer group, the surgical risk score (logistic EuroSCORE) was found to be an independent factor associated with the PLR, whereas in the noncancer group, male sex, age, body mass index, and logistic EuroSCORE were independently associated with the PLR; 3) patients with cancer had a significantly worse prognosis than those without cancer, and patients who died within 3 years had a significantly higher baseline PLR than patients who lived; and 4) both in the cancer and noncancer groups, a higher PLR had a negative association on the prognosis.

PLR AND SEVERE AORTIC STENOSIS. Platelets produce cytokines and chemokines, which act as mediators of vascular inflammation (17). Platelets also have an important role in the transportation of progenitor cells and leukocytes in vascular injury and inflammation; they release anti-inflammatory factors, pro-inflammatory factors, angiogenic factors, as well as microparticles into the systemic circulation (18). An increased platelet count has been reported to be correlated with the severity of atherosclerosis (19). On the other hand, a decreased lymphocyte count has been shown to be a useful tool for predicting worse prognosis in patients with atherosclerotic coronary artery disease (20).

Using the PLR as a predictive marker is a promising method of combining these 2 parameters. A number of previous studies have reported that PLR is associated with systemic inflammation (21), severity of coronary artery disease (11), and the severity of calcific aortic stenosis (12). Akdag et al. (12) recently reported that PLR is also associated with the transaortic mean pressure gradient in patients with AS and that the PLR was significantly higher in severe AS than in mild-to-moderate AS or control patients (mean PLR: 151, 138, and 126, respectively). Our study confirms these results and also shows that patients with severe AS undergoing TAVR had a high baseline PLR (median, 152.5), which is comparable with the prior study.

COEXISTENCE OF CANCER IN TAVR PATIENTS AND PLR. TAVR is generally performed in elderly patients, as shown in our cohort (mean age, 80.9 years). The coexistence of cardiovascular and cancer diseases is predicted to increase in older subjects (5), and in the

CENTRAL ILLUSTRATION **Platelet-to-Lymphocyte Ratio in Cancer Patients Undergoing TAVR**



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Clinical outcomes within the 3-year follow-up and baseline PLR according to survival in the cancer and noncancer groups. A Kaplan-Meier analysis revealed that cancer patients had a significantly worse prognosis than noncancer patients (estimated mortality rate at 3-year follow-up, 49.2% vs. 36.8%; log-rank $p < 0.001$) **(top)**. Patients who died within 3 years had a significantly higher baseline PLR than patients who lived both in the cancer (median [IQR]: 203.6 [143.3 to 281.7] vs. 154.7 [107.7 to 223.3]; $p = 0.009$) and noncancer (median [IQR]: 178.9 [127.5 to 264.0] vs. 166.1 [118.0 to 229.6]; $p = 0.027$) groups **(bottom)**. PLR = platelet-to-lymphocyte ratio; TAVR = transcatheter aortic valve replacement.

present study, 240 of 1,204 patients (19.9%) had a history of cancer. A previous survey in the United States reported that 25% of individuals with cardiovascular diseases also had cancer, whereas 19% of all cancer survivors had cardiovascular diseases, and the coexistence of cardiovascular and cancer diseases was more prevalent in older subjects (5). Therefore, the high frequency of cancer diseases in TAVR patients as seen in our cohort likely reflects the clinical population.

Previous studies have shown that the systemic inflammatory response is a critical component of cancer progression (10,22). Among various inflammatory parameters, PLR has been proposed as a reliable marker to predict various cancer prognosis (14,15,23–25). However, data regarding the significance of the PLR in the field of cardio-oncology are sparse. In the present study, cancer patients undergoing TAVR had a significantly higher PLR than noncancer patients. Moreover, a multivariable

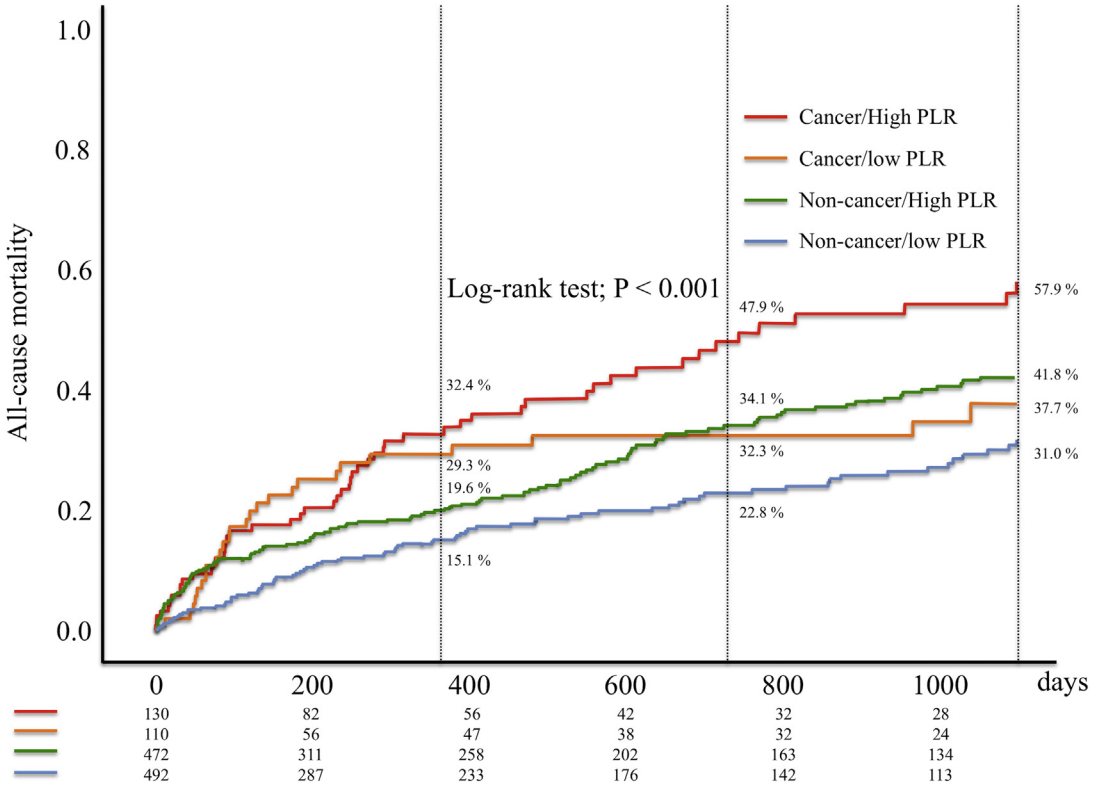
TABLE 4 Cox Proportional Hazards Regression Analyses for All-Cause Mortality in Cancer and Noncancer Cohorts

	Univariable Regression			Multivariable Regression Stepwise Backward			Multivariable Regression Forced Inclusion Model		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Cancer cohorts									
PLR value (by 100 increase)	1.07	1.03-1.11	0.002	1.07	1.02-1.13	0.006	1.07	1.02-1.12	0.005
Age, yrs	1.01	0.97-1.06	0.57						
Male	1.47	0.92-2.35	0.10	2.27	1.24-4.14	0.008			
Logistic EuroSCORE	1.02	1.01-1.04	0.003				1.01	1.00-1.03	0.079
EuroSCORE II	1.01	0.98-1.05	0.50						
STS score	1.04	1.00-1.09	0.076						
BMI	0.97	0.92-1.02	0.20	0.95	0.90-1.01	0.095			
Diabetes	1.16	0.71-1.90	0.54						
Hypertension	0.89	0.51-1.56	0.68						
Dyslipidemia	1.36	0.80-2.33	0.26						
eGFR	0.99	0.98-1.00	0.032	0.98	0.97-1.00	0.009	0.99	0.98-1.00	0.090
Dialysis	1.72	0.69-4.25	0.24						
Previous stroke	1.47	0.80-2.72	0.22						
CAD	1.29	0.80-.07	0.29						
Previous MI	1.20	0.64-2.27	0.57						
Previous PCI	1.13	0.72-1.78	0.60						
Prior CABG	1.14	0.55-2.37	0.73						
Prior valve surgery	1.14	0.42-3.12	0.80						
Atrial fibrillation	1.29	0.83-2.00	0.26						
Prior pacemaker	0.56	0.26-1.21	0.14						
NYHA functional class III or IV	0.72	0.22-2.29	0.58						
COPD	0.99	0.54-1.79	0.97						
EF	0.99	0.98-1.01	0.21						
PAP	1.01	0.99-1.02	0.28						
PVL post TAVR ≥2	4.43	1.76-11.17	0.002	3.68	1.25-10.84	0.018	4.50	1.78-11.41	0.002
Noncancer cohorts									
PLR value (by 100 increase)	1.21	1.13-1.30	<0.001	1.20	1.06-1.36	0.004	1.17	1.07-1.28	0.001
Age, yrs	0.99	0.97-1.01	0.35						
Male	1.19	0.92-1.55	0.18						
Logistic EuroSCORE	1.03	1.02-1.03	<0.001	1.02	1.01-1.03	<0.001	1.01	1.00-1.02	0.098
EuroSCORE II	1.05	1.03-1.06	<0.001						
STS score	1.07	1.06-1.09	<0.001						
BMI	0.99	0.97-1.02	0.59						
Diabetes	1.31	0.99-1.74	0.059						
Hypertension	0.94	0.65-1.38	0.76						
Dyslipidemia	1.01	0.75-1.34	0.98						
eGFR	0.98	0.97-0.98	<0.001	0.98	0.97-0.99	<0.001	0.98	0.97-0.99	<0.001
Dialysis	1.79	1.02-3.14	0.041						
Previous stroke	1.28	0.90-1.83	0.18						
CAD	1.65	1.23-2.21	0.001				1.31	0.93-1.85	0.12
Previous MI	1.32	0.92-1.89	0.13						
Previous PCI	1.27	0.98-1.65	0.076						
Prior CABG	1.27	0.90-1.79	0.18						
Prior valve surgery	0.96	0.49-1.87	0.90						
Atrial fibrillation	1.20	0.92-1.56	0.18						
Prior pacemaker	1.35	0.96-1.89	0.083						
NYHA functional class III or IV	1.92	0.79-4.66	0.15						
COPD	1.67	1.24-2.24	0.001				1.28	0.91-1.81	0.16
EF	0.95	0.93-0.97	<0.001				1.00	0.99-1.01	0.73
PAP	0.98	0.97-0.99	<0.001				1.01	1.00-1.01	0.28
PVL after TAVR ≥2	1.01	1.01-1.02	0.001	2.46	1.49-4.09	<0.001	2.29	1.41-3.73	0.001

Factors included in the stepwise multivariable regression model were PLR (by 100 increase), age, male sex, BMI, logistic EuroSCORE, diabetes, hypertension, dyslipidemia, eGFR, previous stroke, CAD, prior valve surgery, atrial fibrillation, prior pacemaker, NYHA functional class III or IV, COPD, EF, PAP, and PVL after TAVR ≥ 2.

CI = confidence interval; EF = ejection fraction; HR = hazard ratio; PAP = pulmonary artery pressure; PLR = platelet-lymphocyte ratio; other abbreviations as in Table 1.

FIGURE 4 Kaplan-Meier Curve According to Cancer History and High or Low PLR Level



The highest mortality rate was observed in TAVR patients with a history of cancer and an elevated PLR (log-rank test; $p < 0.001$). Abbreviations as in Figures 1 and 2.

analysis revealed that having a history of cancer independently correlated with a higher PLR. As stated previously, it has been reported that both severe AS and cancer status are associated with higher values of the PLR. Accordingly, we can assume that the PLR increases additively in patients with both of these diseases. To the best of our knowledge, this is the first report to determine the differences in PLR between cancer and noncancer patients with severe AS undergoing TAVR.

MORTALITY AND THE PLATELET-TO-LYMPHOCYTE RATIO. Condado et al. (13) recently reported that an elevated PLR was associated with a higher surgical risk score and adverse short-term outcomes for TAVR. Also, in the present study, a higher PLR value correlated with surgical risk scores, such as logistic EuroSCORE, EuroSCORE II, and STS scores. Moreover, our results suggest that a higher PLR value was associated with a worse survival following TAVR. These findings altogether suggest an evaluation of underlying systemic inflammation could potentially be used to stratify patients that are more likely to survive following TAVR. In the present study, PLR >216.2 was independently associated with all-cause mortality following TAVR. In clinical practice, CBC with a differential hemogram may be routinely evaluated before the TAVR procedure, and PLR is easy to calculate. Results of the present study suggested that assessing this ratio might be useful in risk stratification and provide physicians with important prognostic information following the procedure.

As shown in the results of the Cox multivariable analyses, a higher PLR was a predictor of mortality in both cancer and noncancer patients. The poor prognosis for cancer as well as noncancer patients with a higher PLR undergoing TAVR might be partly caused by a higher degree of inflammation. Thus, the PLR value might be useful in evaluating the baseline inflammatory status of patients and may be a promising surrogate marker for clinical outcomes. Assessment of the PLR could help to stratify post-procedural mortality risk both in cancer and noncancer patients, as shown in Figure 4.

Of note, we observed some nonproportional hazards between the higher and lower PLR cancer groups within 1 year after the TAVR procedure. There is no clear explanation for this observation; however, clinical outcomes in cancer patients might be affected by many factors, such as cancer type, cancer stage, current cancer treatments, and the frailty of the patient. These other factors might have overcome the effect of the PLR value within 1 year in cancer patients. The greater effect size in noncancer than in cancer patients (Table 4) might also be reflected by these specific factors in cancer patients. Nonetheless, our results suggest that the PLR could be useful for predicting long-term survival in TAVR patients both in cancer and noncancer patients. Although further investigations are needed to confirm our results, we propose PLR as a potential promising marker to assess the underlying inflammatory status of patients and to predict the benefits of undergoing the TAVR procedure both in cancer and noncancer patients.

STUDY LIMITATIONS. First, this is a single-center, observational cohort study. Second, we included consecutive TAVR patients but excluded patients that were missing data from differential white blood cell counts, which could cause some bias. Third, we included many types of cancers, but PLR might have substantial variability based on cancer types, previous therapeutic regimens, and cancer stages. Thus, further studies are needed to investigate the effect of the PLR in each type of cancer and cancer stage. Fourth, the present study evaluated only the PLR value and did not evaluate other inflammatory markers such as cytokines and chemokines. Thus, additional pathophysiological and molecular physiological data are still needed. Fifth, the rate of cardiac death was relatively low and the relationship between PLR and cardiac death could not be fully evaluated. Sixth, the PLR values between survivors and nonsurvivors could only be compared using those of subjects known alive or deceased at 3-year follow-up. Moreover, we did not investigate other functional assessments, such as frailty, nutrition, mobility, and gait speed, which would aid in determining surgical risk in the present study. The addition of the PLR value as a factor associated with mortality to 1 of these scales may be helpful in determining the usefulness of the PLR.

CONCLUSIONS

Cancer patients undergoing TAVR had a significantly higher PLR, which was associated with a worse overall survival.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Little is known about the prediction of adverse outcomes after TAVR in patients who have cancer. In this study, we derived the platelet-to-lymphocyte ratio (PLR), derived from a complete blood count with differential. Cancer patients undergoing TAVR had a significantly higher PLR than noncancer patients, and worse overall survival. An elevated PLR was associated with an increased risk of mortality, in both cancer and non-cancer patients. The highest mortality rate was observed in TAVR patients with a history of cancer and an elevated PLR.

TRANSLATIONAL OUTLOOK: The PLR, calculated from a differential complete blood cell count, might be a promising marker to assess the underlying inflammatory status of patients and to predict the benefits of undergoing the TAVR procedure both in cancer and noncancer patients. Additional studies are needed to further validate these findings.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.