Original Study

ANNALS OF SURGERY

OPEN

Pan-immune-inflammation Value and Prognosis in Patients With Esophageal Cancer

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Objective: To examine the relationship between the pan-immune-inflammation value (PIV), tumor immunity, and clinical outcomes in 866 patients with esophageal cancer.

Background: The PIV, calculated from all immune-inflammatory cells in the peripheral blood count, is a recently proposed marker for clinical outcomes in some types of cancers. Nonetheless, the prognostic significance of PIV in esophageal cancer remains unclear.

Methods: In the derivation cohort (n = 433), we set the optimal cutoff value using a time-dependent receiver operating characteristic (ROC) curve. In the validation cohort (n = 433), the relationships between the PIV, tumor-infiltrating lymphocytes (TILs), CD8 expression by immunohistochemical staining, and patient prognosis were examined.

Results: The area under the ROC curve for the PIV at 5 years was 0.631 in the derivation cohort. The validation cohort, divided into PIV-low cases (n = 223) and PIV-high cases (n = 210), showed significantly worse overall survival (log-rank $P = 0.0065$; hazard ratio [HR]: 1.48; 95% confidence interval [CI]: 1.12–1.98; $P < 0.001$; multivariate HR: 1.41; 95% CI: 1.05–1.90; $P = 0.023$). The prognostic effect of the PIV was not significantly modified by any clinical characteristics (P for interaction > 0.05). The PIV-high cases were significantly associated with a low TIL status ($P < 0.001$) and low CD8-positive cell counts ($P = 0.011$).

Conclusions: The PIV was associated with clinical outcomes in esophageal cancer, supporting its role as a prognostic biomarker. Considering the relationship between the PIV and TILs, systemic immune competence may influence patient prognosis through a local immune response.

Keywords: pan-immune-inflammation value, tumor-infiltrating lymphocytes, prognosis, esophageal cancer, tumor immunity

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related deaths and the seventh most common carcinoma worldwide.[1] Despite the development of multimodal therapies, which include surgery, radiotherapy, chemotherapy, and chemoradiotherapy, the prognoses of patients with esophageal cancer remains unfavorable.[2–6] The limited improvement in the treatment outcome by conventional therapies has prompted the search for innovative approaches for the treatment of esophageal cancer, especially immunotherapeutically targeted treatments.[7] Recently, the development of immune checkpoint inhibitors (ICIs), such as programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors, have led to remarkable therapeutic responses among multiple malignancies, including esophageal cancer.[8–12] Therefore, a good understanding of systemic and tumor immune status in cancer patients is clinically important.[13–15]

The identification of new biomarkers for good prognostic stratification and prediction of therapeutic outcomes for esophageal cancer is desperately needed in the clinical setting.[16–18] In particular, simple blood-based biomarkers derived from complete blood count, are readily available and inexpensive markers that can reflect the host immune system.[19] The pan-immune-inflammation value (PIV) is a recently proposed scoring system that includes all immune-inflammatory cells in the peripheral blood count (neutrophil count × platelet count × monocyte count)/lymphocyte count).[20] The PIV proved to be a useful prognostic biomarker in some types of malignancies, such as colon and breast cancers.[20–23] In addition, the PIV has been reported to be a strong predictor of outcomes in microsatellite instability-high metastatic colorectal cancer patients receiving ICIs.[24] Nonetheless, the prognostic significance of the PIV in esophageal cancer is yet to be revealed. Additionally, the relationship between PIV and local tumor immunity, such as tumor-infiltrating lymphocytes (TILs), is yet to be examined in any type of human cancer.

In this study, the correlations between the PIV, TILs, and clinical outcomes were examined using a nonbiased database of 866 resected esophageal cancers. We evaluated TILs using

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Disclosure: The authors declare that they have nothing to disclose.

This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (grant numbers 20H03755 and 17KK0195 [to Y.B.]).

SDC *Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).*

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Annals of Surgery Open (2022) 1:e113

Received: 20 September 2021; Accepted 11 November 2021

Published online 22 December 2021

DOI: 10.1097/AS9.0000000000000113

pathological findings (morphological lymphocytic reaction) and CD8 immunostaining. To the best of our knowledge, this is the first study to comprehensively evaluate the relationship between the PIV, TILs, and patient prognosis in human cancers.

METHODS

Patients

A total of 932 consecutive patients with esophageal cancer, who underwent surgical resection at Kumamoto University Hospital between April 2005 and August 2020 were enrolled in this study. Fifty-one patients who lacked assessable cancer cells, and 15 patients without clinical and epidemiological data, were excluded. Thus, 866 esophageal cancer patients were included in this study. These 866 patients were randomly assigned to the derivation cohort (n = 433) and validation cohort (n = 433). There was no significant difference in the clinical and pathological characteristics between the derivation and validation cohorts (Supplemental Table 1, http://links.lww.com/AOSO/A88). Blood samples were obtained and analyzed within 7 days before surgery. The PIV was calculated as previously described: (neutrophil count (10^3/mm^3) × platelet count (10^3/mm^3) × monocyte count (10^3/mm^3))/lymphocyte count (10^3/mm^3).[20] This study has been approved by the Institutional Review Board of Kumamoto University.

TIL Evaluation and CD8 Immunohistochemical Staining

Hematoxylin and eosin-stained tissue sections were reviewed for location and density of TILs by a pathologist (Y.B.), who was unaware of other data previously reported.[25] Lymphocyte infiltration in the tumor invasive margin was scored as weak, moderate, or strong.[25] Immunostainings for CD8 and PD-1 was performed as previously described.[19,26]

Statistical Analysis

Statistical analyses were performed using JMP version 13 software (SAS Institute, Cary, NC). Categorical data were compared with Fisher's exact or χ^2 test, when appropriate, and continuous data using two-tailed paired t tests. The Kaplan-Meier method was used to evaluate overall survival (OS) and cancer-specific survival (CSS). Log-rank *P* values were used to assess OS and CSS differences among groups. Cox proportional hazard models were fitted to obtain estimates of hazard ratios (HRs) in univariable and multivariable models. The sensitivity and specificity of the prognosis prediction of the PIV were evaluated using a time-dependent receiver operating characteristic (ROC) curve in R software.

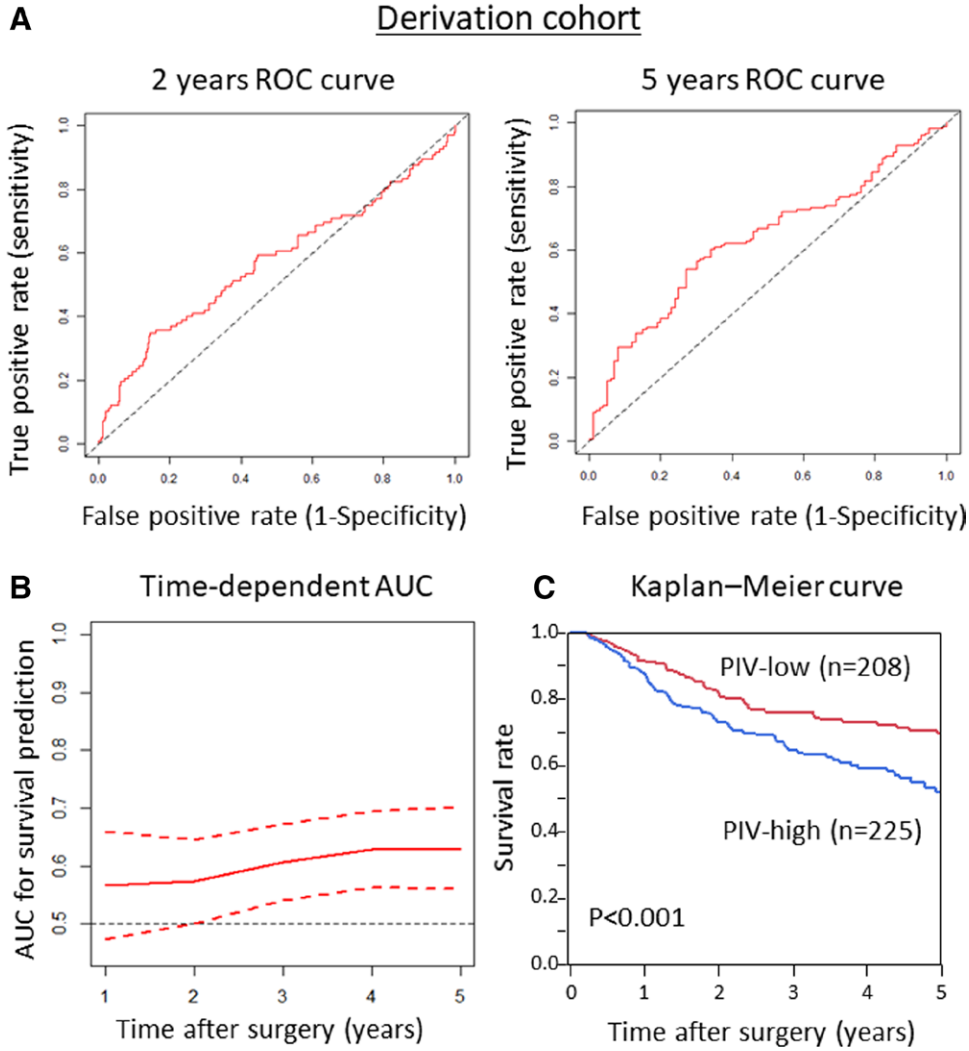


FIGURE 1. (A) A ROC curve for the PIV at 2 years (B) a ROC curve for the PIV at 5 years (C) Area under the ROC curve values during follow-up from the time-dependent ROC curve (D) Kaplan-Meier curves for overall survival according to the PIV in the derivation cohort. PIV indicates pan-immune-inflammation value; ROC, receiver operator characteristic.

RESULTS

The PIV in the Derivation Cohort

In the derivation cohort, the distribution of the PIV was as follows: mean, 251.4; median, 169.6; standard deviation (SD), 264.1; range, 6.22–2263.7; and interquartile range, 104.8–296.7. First, the prognostic accuracy of the PIV was evaluated using a time-dependent ROC analysis in the derivation cohort. The area under the ROC curve for the PIV at 1, 2, 3, 4, and 5 years was 0.567, 0.573, 0.607, 0.629, and 0.631, respectively (Figure 1A). Area under the ROC curve values during follow-up from the time-dependent ROC curve analysis are shown in Figure 1B. According to the time-dependent ROC curve to predict 5-year OS, a PIV score of 164.6, was defined as the optimal cutoff value. In the Kaplan-Meier analysis, the PIV-high group (PIV ≥ 164.6; n = 225) showed a significantly shorter OS (log rank $P < 0.001$) than the PIV-low group (PIV < 164.6; n = 208) (Figure 1C).

PIV and Clinical Features

In the validation cohort (n = 433), the distribution of PIV was as follows: mean, 264.1; median, 161.4; SD, 336.9; range, 6.34–3814.1; interquartile range, 94.3–300.1. There was no significant difference between the PIV in the derivation and validation cohorts ($P = 0.54$) (Supplemental Figure 1, http://links.lww.com/AOSO/A88).

Based on the results of the derivation cohort, we divided the patients in the validation cohort into two groups: the PIV-low group (PIV < 164.6; n = 223) and PIV-high group (PIV ≥164.6; n = 210). Table 1 summarizes the clinicopathological features of the validation cohort. The PIV was significantly associated with body mass index ($P < 0.001$) and pathological stage ($P = 0.001$). There were no significant differences in the age, sex, alcohol use status, tobacco use status, history of comorbidities, histological type, location, preoperative therapy, or postoperative therapy between the two groups.

PIV and Patient Survival

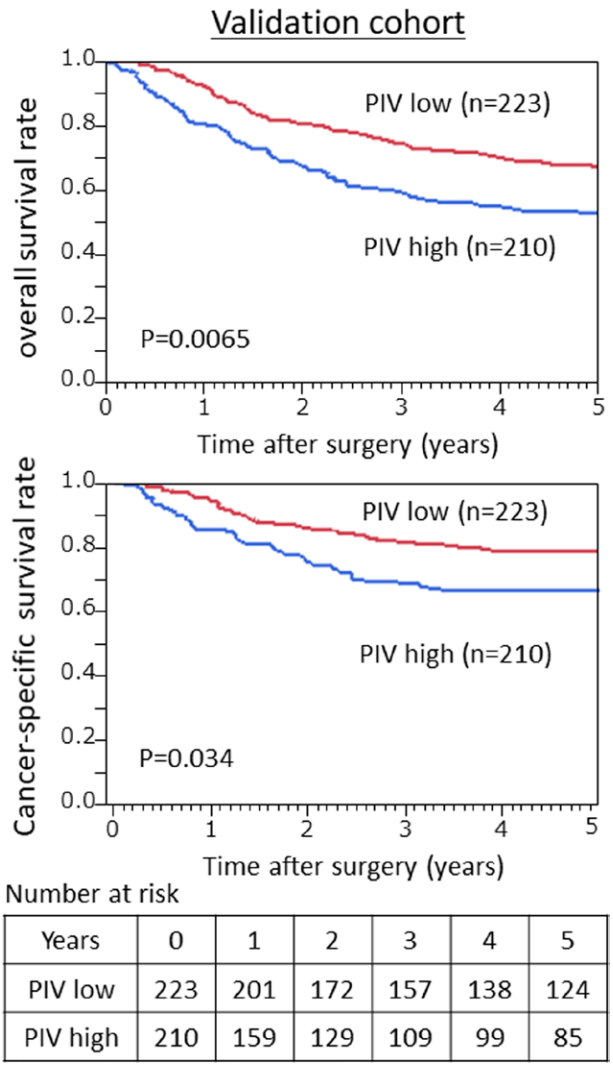
A total of 189 deaths occurred among the 433 esophageal cancer patients, this included 109 esophageal cancer-specific deaths. The median follow-up time of censored patients was 4.9 years. In the Kaplan-Meier analysis, the PIV-high group showed a significantly shorter OS (log rank $P = 0.0065$) and CSS (log rank $P = 0.034$) than the PIV-low group (Figure 2). In the univariate Cox regression analyses, patients in the PIV-low group showed significantly lower overall mortality than those in the PIV-high group (HR: 1.48; 95% confidence interval (CI): 1.12–1.98; $P < 0.001$). Adjusting for clinical, epidemiological, and pathological features in the multivariate Cox model, the PIV was associated with significantly higher overall mortality (multivariate HR, 1.37; 95% CI, 1.02–1.85; $P = 0.035$) (Table 2). We also performed Cox regression analysis using

TABLE 1.

Patient Characteristics (Validation Cohort)

		PIV		
	Total Patients	Low (<164.6)	High (≥164.6)	
Variables	N = 433	N = 223	N = 210	*P*
Age (y), mean ± SD	66.3 ± 8.9	66.6 ± 8.5	66.0 ± 9.4	0.5
Sex				0.14
Male	384 (88.7)	193 (86.6)	191 (91.0)	
Female	49 (11.3)	30 (13.4)	19 (9.1)	
Body mass index, mean ± SD	21.7 ± 3.1	22.1 ± 2.9	21.3 ± 3.2	<0.001
Alcohol use				0.82
Yes	384 (88.7)	197 (88.3)	187 (89.1)	
No	49 (11.3)	26 (11.7)	23 (11.0)	
Tobacco use				0.12
Yes	363 (83.8)	181 (81.2)	182 (86.7)	
No	70 (16.2)	42 (18.8)	28 (13.3)	
Comorbidity				0.41
Present	316 (73.0)	159 (71.3)	157 (74.8)	
Absent	117 (27.0)	64 (28.7)	53 (25.2)	
Histological type				0.52
Squamous cell carcinoma	375 (86.6)	197 (88.3)	178 (84.8)	
Adenocarcinoma	37 (8.5)	16 (7.2)	21 (10.0)	
Others	21 (4.9)	10 (4.5)	11 (5.2)	
Location				0.49
Upper	67 (15.5)	36 (16.1)	31 (14.8)	
Middle	203 (46.9)	109 (48.9)	94 (44.8)	
Lower	163 (37.6)	78 (35.0)	85 (40.5)	
Preoperative therapy				0.2
Present	158 (36.5)	75 (33.6)	83 (39.5)	
Absent	275 (63.5)	148 (66.4)	127 (60.5)	
Pathological stage				0.041
0	6 (1.4)	5 (2.2)	1 (0.48)	
I	150 (34.6)	94 (42.2)	56 (26.7)	
II	111 (25.6)	49 (22.0)	62 (29.5)	
III	97 (22.4)	44 (19.7)	53 (25.2)	
IV	69 (15.9)	31 (13.9)	38 (18.1)	
Postoperative therapy				0.43
Present	88 (20.3)	42 (18.8)	46 (21.9)	
Absent	345 (79.7)	181 (81.2)	164 (78.1)	

PIV indicates pan-immune inflammation value.



Years	0	1	2	3	4	5
PIV low	223	201	172	157	138	124
PIV high	210	159	129	109	99	85

FIGURE 2. Kaplan-Meier curves for overall survival and cancer-specific survival according to the pan-immune-inflammation value in the validation cohort.

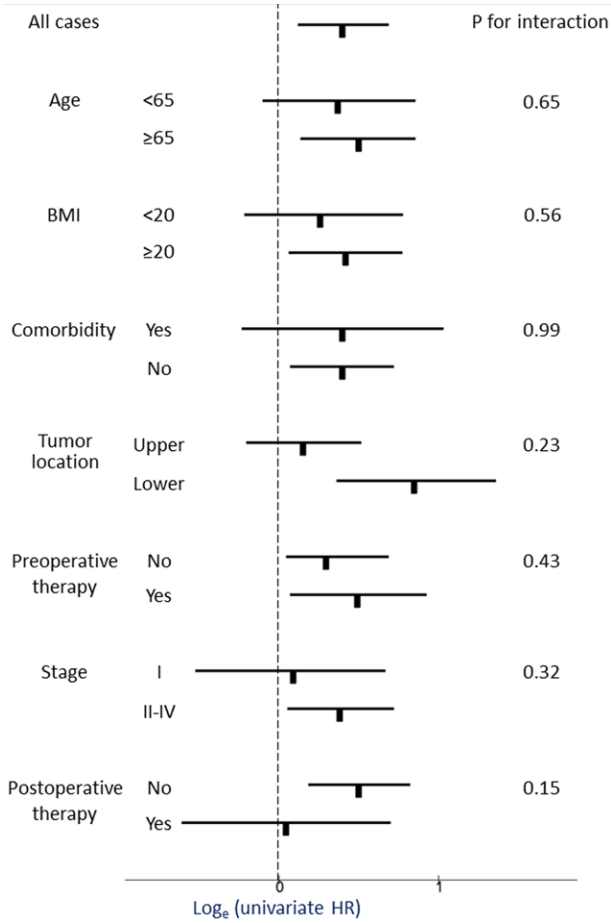


FIGURE 3. Relationship between the PIV and overall survival. Loge (HR) plots of overall survival rate in the PIV-high and -low groups are shown. PIV indicates pan-immune-inflammation value.

the PIV as a continuous variable. A decrease in the PIV was associated with a statistically significant decrease in OS. The univariate HR for OS rate associated with a 100 unit decrease in PIV was 1.13 (95% CI = 1.09 to 1.17). In addition, we performed the Kaplan-Meier analysis using the entire cohort (derivation and validation cohort). The PIV-high group showed a significantly shorter OS (log rank $P < 0.001$) and CSS (log rank $P < 0.001$), than the PIV-low group (Supplemental Figure 2, http://links.lww.com/AOSO/A88).

Survival Analyses of Interactions Between the PIV and Other Variables

We further determined whether the influence of the PIV on OS was affected by any of the clinical, pathological, or epidemiological variables. The effect of PIV was not significantly modified

TABLE 2.

Univariate and Multivariate Analysis of Overall Survival

	Univariate Analysis		Multivariate Analysis	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (≥65 vs <65)	1.45 (1.08–1.96)	0.014		
Sex (male vs female)	1.31 (0.82–2.23)	0.27		
BMI (≥20 vs <20)	0.64 (0.47–0.86)	0.0041		
Alcohol use (yes vs no)	0.77 (0.51–1.20)	0.23		
Tobacco use (yes vs no)	0.91 (0.63–1.34)	0.61		
Comorbidity (present vs absent)	1.55 (1.10–2.24)	0.011		
Location (upper vs middle, lower)	1.12 (0.76–1.60)	0.56		
Preoperative therapy (present vs absent)	2.02 (1.51–2.70)	<0.001	1.78 (1.31–2.40)	<0.001
Pathological stage (II- vs I)	2.20 (1.59–3.08)	<0.001	1.72 (1.23–2.46)	0.0016
Postoperative therapy (present vs absent)	0.86 (0.59–1.22)	0.39		
PIV (high vs low)	1.48 (1.12–1.98)	<0.001	1.37 (1.02–1.85)	0.035

CI indicates confidence interval; HR, hazard ratio; PIV, Pan-Immune Inflammation Value.

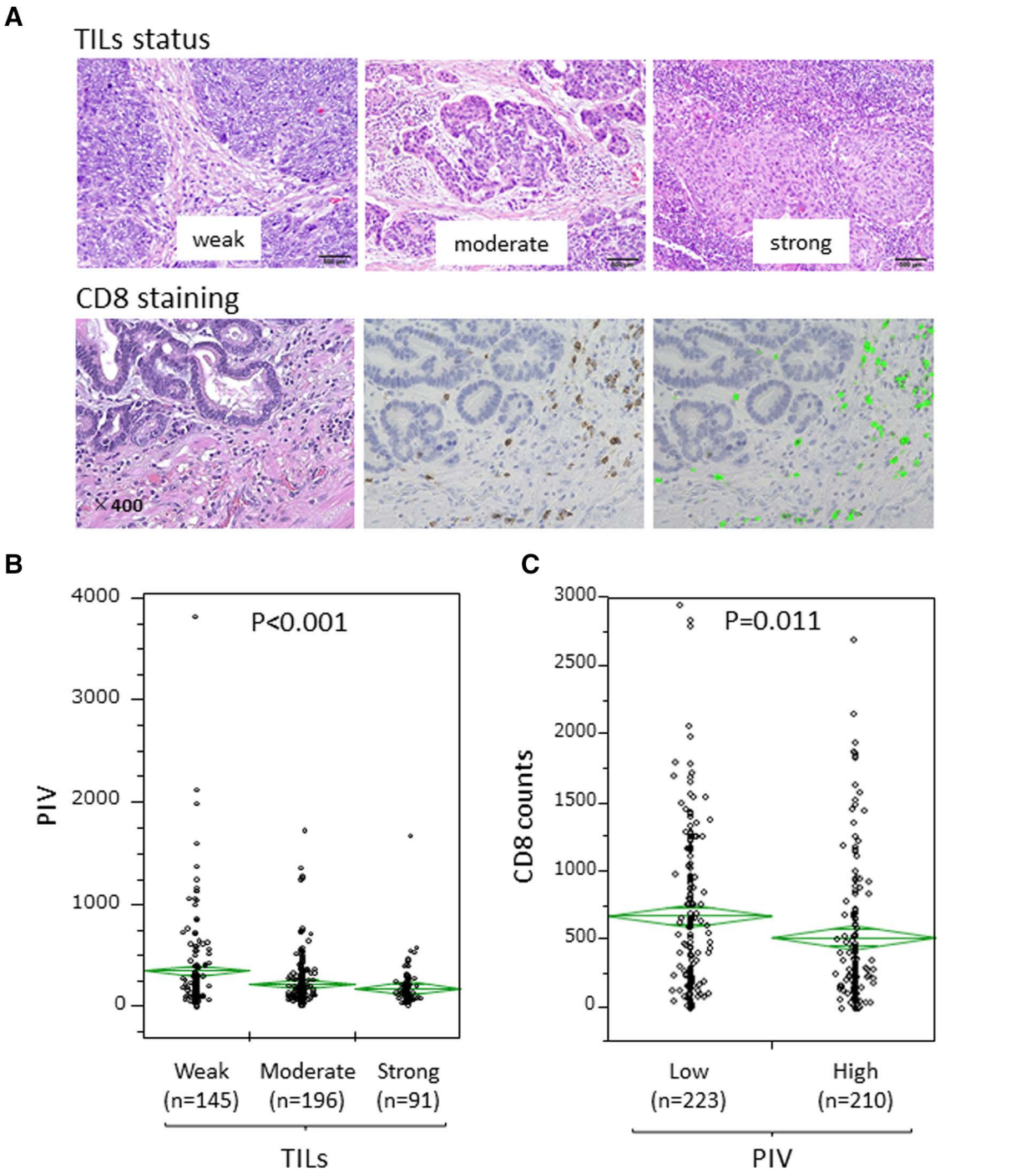


FIGURE 4. (A) The TIL status was evaluated at the tumor invasive margin and divided into three status groups: weak (upper left), moderate (upper center), and strong (upper right). CD8 staining (lower center) and cell counting (lower right) are presented. (B) Association between the TIL status and the pan-immune-inflammation value (PIV). (C) Association between the PIV and CD8-positive cell count. PIV indicates pan-immune-inflammation value; TIL, tumor-infiltrating lymphocytes.

by the age, body mass index, alcohol use status, tobacco use status, history of comorbidities, location, preoperative therapy, or pathological stage ($P > 0.15$ for all interactions) (Figure 3).

The Relationship Between PIV and TILs Status

We hypothesized that the systemic immunological status (namely, the PIV) in patients might be associated with local tumor immunity thus, the relationship between the PIV and TIL status were evaluated. The PIV was significantly associated with the TIL status, with significantly lower PIV observed in patients with TIL-strong tumors than in those with TIL-weak or moderate tumors ($P < 0.001$) (Figure 4A). The evaluation of tumor immunity using CD8 immunohistochemical staining showed that CD8 counts were significantly higher in PIV-low patients than in PIV-high patients ($P = 0.012$) (Figure 4A). There was no significant relationship between PIV and PD-1 counts ($P = 0.63$).

DISCUSSION

We conducted this study to examine the relationship between the PIV, tumor immunity, and clinical outcomes in 866 patients

who had undergone esophageal cancer resection. We found that the PIV-high group was significantly associated with a poor prognosis, suggesting that the PIV could be used as a marker to identify patients who are likely to experience an unfavorable clinical outcome. Interestingly, the PIV-high cases had tumors with few TILs. Taken together, we propose that the systemic immunological status of patients might affect their prognosis through local tumor immunity.

The PIV is a new and potent marker of clinical outcomes in patients with cancer. A pooled analysis of the Valentino and TRIBE first-line trials showed that, the PIV was significantly associated with progression-free survival, and OS in patients with metastatic colorectal cancer receiving first-line therapy.[20] Interestingly, the prognostic value of the PIV was stronger than that of other well-established immune-inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio. Ligorio et al. reported that the PIV was a useful predictor of OS in HER2+ advanced breast cancer patients treated with first-line trastuzumab-pertuzumab-containing biochemotherapy.[21] Fucà et al revealed that a high PIV was independently associated with poor OS in patients with metastatic melanoma receiving first-line therapy.[22] No study has examined the prognostic impact of the PIV in esophageal cancer patients. In line with these previously published data for other types of cancers, we found that a high PIV was independently associated with worse patient OS and CSS, utilizing a nonbiased cohort with 866 esophageal cancer cases. Importantly, the PIV is a simple blood-based biomarker derived from complete blood count. In this respect, our findings may have clinical implications, although we acknowledge that they should be confirmed in independent cohorts.

ICIs have increasingly gained attention as a novel treatment strategy for esophageal cancer.[7,27] The therapy uses the patient's own immune system to fight malignant cells by suppressing the immune checkpoint pathway.[28,29] Recently, it has been proposed that the density of TILs at the invasive tumor margin might predict the therapeutic response to ICIs.[30,31] TILs are a specific histological feature of human cancers, reflecting an individual's immunological tumor response. Standardized methods for evaluating the TIL status have not been established. In a previous article on esophageal cancer, we evaluated four morphological components of lymphocytic reactions (peritumoral, intra-nest, lymphoid, and stromal reactions) and found that only a peritumoral reaction among the four components was associated with patient prognosis.[25] In the current study, the PIV was significantly associated with the TIL status (peritumoral reaction). In addition, we examined the presence of CD8+ lymphocytes in TILs. CD8 positive lymphocytes are cytotoxic T cells that recognize and kill cancer, infected, and damaged cells.[32,33] We found that the PIV-high group was significantly associated with low CD8 counts in tumors. Our findings regarding the strong relationship between the PIV and TILs, may support the idea of the association between systemic immunological status and local immune competence. Given that the PIV could be a surrogate marker for tumor local immunity, it is likely that the PIV might predict the therapeutic response to ICIs in human cancers. We of course acknowledge that future studies are needed to confirm our findings, and also to examine other potential mechanism(s) by which PIV affects clinical outcome in cancer patients.

This study has several limitations. First, this was a single institutional retrospective study. Second, the patients were included from just our institution. The significance of PIV needs to be validated using other cohorts. However, despite these limitations, we demonstrated the potential of a simple scoring system derived from the complete blood count data and basic clinical variables for the first time in patients with esophageal cancer.

In conclusion, to the best of our knowledge, this is the first study to comprehensively assess the interrelation between the PIV, TIL status, and clinical outcomes in human cancers. The PIV was associated with clinical outcomes in patients with esophageal cancer, supporting its role as a prognostic biomarker. In addition, it was significantly associated with the TIL status and CD8-positive cell count. Collectively, systemic immune competence may influence patient prognosis through the local immune response.

ACKNOWLEDGMENTS

We thank Editage from www.editage.com for editing the draft of this manuscript.

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