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Predictive Impact of Prognostic Nutritional Index on Pembrolizumab for Metastatic Urothelial Carcinoma Resistant to Platinum-based Chemotherapy

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Abstract. *Background/Aim: We investigated the prognostic nutritional index (PNI), comprised of lymphocytes and albumin, as a potential prognosticator of metastatic urothelial carcinoma (mUC) patients receiving pembrolizumab. Patients and Methods: Sixty-five patients were retrospectively enrolled and classified as low (<40) and high (≥40) based on pretreatment PNI. Progression-free survival (PFS), overall survival (OS) and response rates were evaluated. Results: In the low PNI group, significantly shorter PFS and OS were observed. PNI was shown to be an independent predictor of PFS and OS in the multivariate analysis. C-index for both PFS and OS improved with the addition of PNI to the model described in the KEYNOTE-045 study. Significantly more patients experienced initial disease progression in the low PNI group. Conclusion: PNI is a useful predictor of prognosis and disease progression in mUC patients receiving pembrolizumab.*

Management of metastatic urothelial carcinoma (mUC) has been challenging because of the high mortality of mUC and limited treatment options (1). For many years, the only internationally recognized standard of care was a chemotherapy regimen based on platinum agents, such as methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin (2). The recent introduction of pembrolizumab, an immune-checkpoint inhibitor (ICI) targeting programmed cell death protein-1, as a second line regimen has resulted in a paradigm shift in this field, with pembrolizumab demonstrating superior efficacy to chemotherapy with docetaxel, paclitaxel, or vinflunine (3). However, pembrolizumab treatment is only beneficial for a minority of mUC patients. In the KEYNOTE-045 study, the objective response rate was only 21.1% in the pembrolizumab group; thus, almost 80% of patients receiving this regimen experienced initial treatment failure. Considering this high failure rate, a method to stratify treatment outcomes to exclude patients with a high risk of failure is essential. Although previous studies have revealed several biomarkers that may successfully predict pembrolizumab treatment outcome for urothelial carcinoma, these biomarkers have not been validated, and the level of evidence remains low (4-7). Therefore, there is still an urgent clinical need for biomarkers capable of accurately predicting treatment outcomes.

The relationship between systemic inflammatory response and malignant tumors has garnered a great deal of attention, especially since the advent of ICI treatments. The usefulness of the prognostic nutritional index (PNI), a prognostic model comprising serum lymphocyte counts and albumin, has been demonstrated for various types of cancers, including urothelial carcinomas (8-14). Although Hsieh *et al.* reported the usefulness of PNI for the prediction of outcomes in mUC patients undergoing systemic chemotherapy, the impact of PNI on mUC patients undergoing pembrolizumab treatment remains unclear (8).

Therefore, the aim of the present study was to investigate the prognostic value of PNI on pembrolizumab treatment outcomes in mUC patients.

Patients and Methods

Patients. This retrospective observational study recruited 67 consecutive patients with mUC or relapsed urothelial carcinoma receiving pembrolizumab after the failure of at least one platinum-

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based chemotherapy at three tertiary institutions between January 2018 and June 2020. After excluding patients whose serum blood samples were not measured prior to pembrolizumab initiation (n=1) and those administered with another ICI prior to pembrolizumab treatment (n=1), 65 patients were finally included.

Study design and data collection. All clinical and laboratory data were obtained from an electronic database and from patient medical records. PNI was calculated using the formula:

PNI=10× serum albumin value (g/dl) + 0.005× lymphocyte count (per mm^3) (15).

Although several different cut-off values for PNI have been reported, we used the cut-off value originally suggested by Onodera *et al*. (PNI=40), because this cut-off value can be used to stratify patients with a very low nutritional status (15). The PNI values of all patients were determined within a 2-week period prior to pembrolizumab initiation, and the patients were classified into low PNI (<40) and high PNI (≥40) groups on the basis of baseline PNI values. We then compared progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR) after pembrolizumab initiation between the low PNI and high PNI groups. In addition, the following survival-associated factors suggested in the KEYNOTE-045 study were analyzed: sex, age (≥65 years), Eastern Cooperative Oncology Group performance status (ECOG-PS) score (≥1), smoking status, histologic type (pure UC), primary tumor lesion (lower urinary tract), visceral metastasis, liver metastasis, hemoglobin concentration (<10 g/dl), number of prior systemic therapies (two or more), time since most recent chemotherapy (≥3 months), low PNI, and neutrophil-lymphocyte ratio (NLR).

Protocol for pembrolizumab therapy. In all institutions, pembrolizumab was administered at a fixed dose (200 mg) every 3 weeks, in accordance with the protocol of the KEYNOTE-045 study and without any dose modification (3). A prolongation of the 3-week interval was permitted when the condition of the patient was poor or in cases of adverse events. No patient received any other ICI therapies during sequential pembrolizumab therapy. Follow-up computed tomographic or magnetic resonance imaging of the chest, abdomen, and pelvis were performed every 2 months, and additional scanning was performed depending on the patients' condition. The radiologic treatment response was evaluated by an independent radiologist in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1. Pembrolizumab treatment was terminated when either radiographic or clinical disease progression or intolerable adverse events were observed.

Ethics approval. This study was approved by the Internal Ethics Review Board of the Tokyo Women's Medical University and Saiseikai Kawaguchi General Hospital, and was performed in accordance with the tenets of the Declaration of Helsinki. Informed consent was waived by both Internal Ethics Review Board owing to the retrospective nature of the study.

Statistical analyses. Continuous variables were analyzed using the Mann–Whitney *U*-test, and categorical variables were analyzed using Chi-square test or Fisher's exact test with 95% confidence intervals (CI). PFS and OS were determined using the Kaplan–Meier method and compared using log-rank test. PFS was defined as the time from pembrolizumab treatment initiation until disease progression or death, whichever occurred first. Patients with no disease progression during the final follow-up were censored. OS was defined as the time from pembrolizumab treatment initiation until death due to any reason. Patients lost to follow-up were censored at the time of last confirmed survival. To identify factors associated with PFS and OS, univariate and multivariate analyses using Cox proportional hazard regression models were performed. The risks were expressed as hazard ratios (HRs) and 95%CIs. Accuracy of predicting survivals was calculated using Harrell's concordance index (C-index). In line with the studies by Bellmunt *et al*., we first calculated the C-index for four predictive factors [ECOG-PS ≥1, liver metastasis, hemoglobin concentration (<10 g/dl), and time since most recent chemotherapy (≥3 months)] and subsequently for five predictive factors, including PNI (3, 16). All analyses were performed using JMP software (version 14.0; SAS Institute, Cary, NC, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria). Differences were considered statistically significant at *p*-values <0.05.

Results

Patient characteristics. Patient baseline characteristics are summarized in Table I. In total, 20 (31.0%) patients had primary UC of the lower tract, whereas 45 (69.7%) patients had primary UC of the upper urinary tract. Further, 13 (20.0%) patients were segregated into the low PNI group, and 52 (80.0%) patients were segregated into the high PNI group. The ECOG-PS score distribution differed between the two groups. However, although ECOG-PS scores in the low PNI group were worse, the difference was not statistically significant (p=0.274). Patients in the low PNI group were more likely to demonstrate pure UC histology (84.6% *vs*. 80.8%) and to have received pembrolizumab in the third or later line of mUC treatment than those in the high PNI group (30.8% *vs*. 21.2%), although the differences were not significant (both, non-specific). Follow-up period was significantly shorter for the low PNI group than the high PNI group [median: 2.3 (95%CI=1.2-6.7) *vs*. 8.8 (95%CI=4.2-14.0) months; p=0.004]. Other features including sex, age, history of smoking, location of primary tumor, history of radical surgery for primary cancer, metastatic sites, and time since most recent chemotherapy, were all comparable between the groups (all, non-specific).

Survival after pembrolizumab treatment based on PNI. During the study period, 43 (66.2%) and 32 (49.2%) patients showed disease progression and died due to any cause, respectively. PFS was significantly shorter in the low PNI group than in the high PNI group [median: 1.4 (95%CI=0.7-5.6) *vs*. 7.2 (95%CI=4.7-14.8) months; p=0.010]. Furthermore, OS was significantly shorter in the high PNI group than in the low PNI group [median: 2.3 (95%CI=1.1-6.2) *vs*. 19.5 (95%CI=10.0-N.R.); p<0.001] (Figure 1).

Risk factors for survival after pembrolizumab initiation. From univariate analysis, ECOG-PS (1/2, HR=5.19; p<0.001), location of the primary tumor (lower tract, HR=0.49;

Table I. *Baseline characteristics*.

	All patients N=65	Low PNI (<40) N=13 (20.0%)	High PNI (≥40) N=52 (80.0%)	*p*-Value
Gender, Male (%)	44 (67.7)	11 (84.6)	33 (63.5)	0.125
Age, median (IQR)	73 (65.0-78.9)	69.5 (62.6-77.5)	73.1 (65.3-79.0)	0.451
>65 years old, N (%)	50 (76.5)	9 (69.2)	41 (78.8)	0.473
ECOG performance status (%)				0.274
0	25 (38.7)	3 (23.1)	22 (42.3)	
1	25 (38.7)	5 (38.5)	20 (38.5)	
2	15 (23.2)	5 (38.5)	10 (19.2)	
History of smoking, yes (%)	21 (32.5)	5 (38.5)	16 (30.8)	0.600
Location of the primary tumor (%)		0 (0.0)	0 (0.0)	0.158
Lower tract	20 (31.0)	2 (15.4)	18 (34.6)	
Upper tract	45 (69.7)	11 (84.6)	34 (65.4)	
Histology (%)				0.745
UC, pure	53 (82.1)	11 (84.6)	42 (80.8)	
UC with atypical variants	12 (18.6)	2 (15.4)	10 (19.2)	
Radical surgery for primary lesion, yes (%)	41 (63.5)	8 (61.5)	33 (63.5)	0.898
Metastatic sites (%)				
Lymph nodes	45 (69.7)	9 (69.2)	36 (69.2)	>0.999
Bone	6 (9.3)	2 (15.4)	4 (7.7)	0.419
Any visceral organs	43 (66.6)	12 (92.3)	31 (59.6)	0.014
Lung	24 (37.2)	7 (53.8)	17 (32.7)	0.164
Liver	18 (27.9)	5 (38.5)	13 (25.0)	0.344
Pembrolizumab treatment line (%)				0.473
2	50 (77.4)	9 (69.2)	41 (78.8)	
3 or later	15 (23.2)	4 (30.8)	11 (21.2)	
Time since most recent chemotherapy (%)				0.198
<3 months	46 (70.6)	11 (84.6)	35 (67.3)	
≥3 months	19 (29.4)	2 (15.4)	17 (32.7)	
NLR (≥3.35)	26 (39.8)	9 (69.2)	17 (32.7)	0.017
Follow up duration in months, median (IQR)	7.2 (2.7-12.6)	2.3 (1.2-6.7)	8.8 (4.2-14.0)	0.004

ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; PNI: prognostic nutritional index; UC: urothelial carcinoma.

p=0.037), and low PNI (HR=2.24; p=0.042) were revealed to be significant factors associated with PFS. From multivariate analysis using the aforementioned factors, all ECOG-PS (1/2, HR=5.57; p<0.001), location of the primary tumor (lower tract, HR=0.49; p=0.048), and low PNI (HR=2.46; p=0.028) were independently associated with PFS (Table II). The C-index for the previously reported model of Bellmunt *et al*. (ECOG-PS, liver metastasis, hemoglobin concentration, and time since most recent chemotherapy) was 0.756, which increased to 0.781 with the addition of PNI.

Univariate analysis for OS revealed that ECOG-PS (1/2, HR=32.19; p<0.001), location of the primary tumor (lower tract, HR=0.37; p=0.017), visceral metastasis (HR=2.68; p=0.018), liver metastasis (HR=3.77; p<0.001), and low PNI (HR=3.82; p=0.002) were significant factors associated with OS. Because the number of events (death due to any cause) was 32, we included the three factors with the most significant association (*i.e*., smaller p-value) in the multivariate analysis. Here, ECOG-PS (1/2, HR=33.78; p<0.001), liver metastasis (HR=2.42; p=0.025), and low PNI (HR=5.35; p<0.001) were independently associated with OS (Table III). C-index increased from 0.816 for the Bellmunt model to 0.870 with the addition of PNI.

Association between the best response and PNI. Optimal treatment responses based on high PNI and low PNI groups are shown in Figure 2. In the high PNI group, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were achieved in 4 (7.7%), 13 (25.0%), 11 (21.2%), and 24 (46.2%) patients, respectively. In the low PNI group, CR, PR, SD, and PD were achieved in 2 (15.4%), 0 (0.0%), 1 (7.7%), and 11 (76.9%) patients, respectively. Overall, the high PNI group achieved a higher ORR (CR + PR), but without significance (32.7% *vs*. 15.4%; p=0.198), and a higher DCR (CR + PR + SD) than those of the low PNI group (53.9% *vs*. 23.1%; p=0.042).

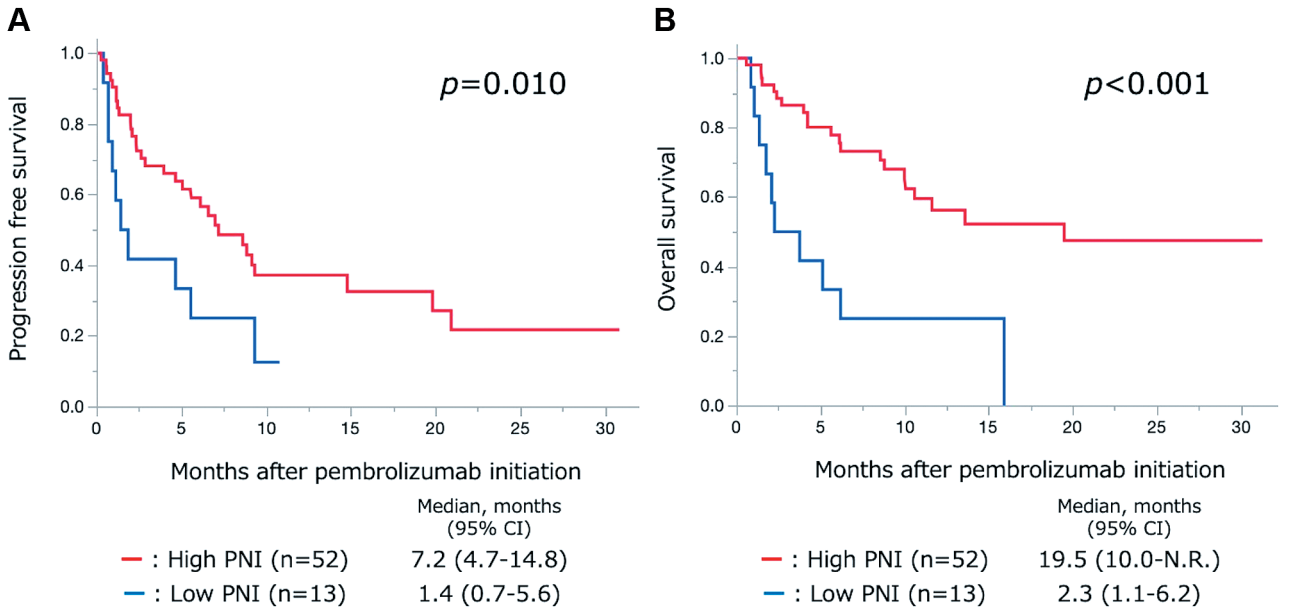

Figure 1. *Association between pretreatment PNI and survival. (A) Progression-free survival. (B) Overall survival. CI: Confidence interval; N.R.: not reached; PNI: prognostic nutritional index.*

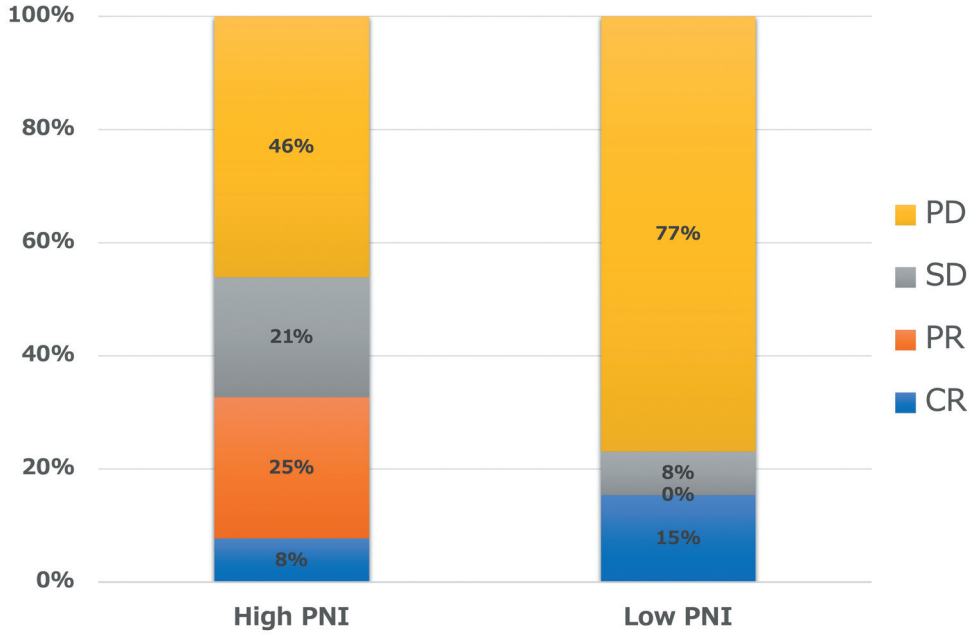

Figure 2. *Association between treatment response with pretreatment PNI. CR: Complete response; DCR: disease control rate; ORR: objective response rate; PNI: prognostic nutritional index; PD: progressive disease; PR: partial response; SD: stable disease.*

Discussion

This study demonstrates that a low PNI (<40) prior to pembrolizumab treatment initiation is a significant factor predicting both shorter PFS and shorter OS in mUC patients. Moreover, multivariate analysis revealed high PNI to be an independent predictor for both PFS and OS. Models including both PNI and previously reported survival-related

Table II. *Analysis of factors associated with progression-free survival.*

	Univariate		Multivariate	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (≥65)	0.94 (0.47-2.03)	0.893		
Gender (male)	0.95 (0.52-1.84)	0.899		
ECOG performance status (1 or 2)	5.19 (2.53-11.74)	<0.001	5.57 (2.66-12.87)	<0.001
History of smoking (yes)	1.25 (0.63-2.38)	0.509		
Histology (pure UC)	0.75 (0.36-1.75)	0.478		
Primary tumor (lower tract)	0.49 (0.23-0.96)	0.037	0.49 (0.22-0.99)	0.048
Visceral metastasis (yes)	1.47 (0.77-2.99)	0.255		
Liver metastasis (yes)	1.96 (0.98-3.72)	0.058		
Hemoglobin (<10 mg/l)	1.08 (0.56-2.02)	0.805		
Pembrolizumab treatment line (≥3)	0.90 (0.39-1.85)	0.793		
Time since most recent chemotherapy (<3 months)	0.66 (0.32-1.28)	0.228		
Low PNI (<40)	2.24 (1.03-4.48)	0.042	2.46 (1.11-5.06)	0.028
NLR (≥3.35)	1.18 (0.63-2.18)	0.595		

ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; PNI: prognostic nutritional index; UC: urothelial carcinoma.

Table III. *Analysis of factors associated with overall survival.*

	Univariate		Multivariate	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age (≥65)	0.86 (0.40-2.05)	0.710		
Gender (male)	1.69 (0.80-3.88)	0.176		
ECOG performance status (1 or 2)	32.19 (6.86-574.02)	<0.001	33.78 (6.96-609.20)	<0.001
History of smoking (yes)	1.82 (0.85-3.75)	0.119		
Histology (pure UC)	0.51 (0.24-1.22)	0.125		
Primary tumor (lower tract)	0.37 (0.14-0.85)	0.017		
Visceral metastasis (yes)	2.68 (1.17-7.23)	0.018		
Liver metastasis (yes)	3.77 (1.79-7.74)	<0.001	2.42 (1.12-5.09)	0.025
Hemoglobin (<10 mg/l)	1.65 (0.79-3.37)	0.177		
Pembrolizumab treatment line (≥3)	1.07 (0.43-2.36)	0.875		
Time since most recent chemotherapy (<3 months)	0.54 (0.21-1.19)	0.133		
Low PNI (<40)	3.82 (1.70-8.07)	0.002	5.35 (2.21-12.60)	<0.001
NLR (≥3.35)	1.59 (0.78-3.23)			

CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IQR: interquartile range; PNI: prognostic nutritional index; UC: urothelial carcinoma.

factors provided a c-index of 0.781 for PFS and 0.870 for OS, demonstrating the clinical relevance of these models for the prediction of survival outcomes. Thus, patients with a high PNI are less likely to achieve a response (CR + PR) or disease control (CR + PR + SD).

PNI is a score comprising serum lymphocyte count and albumin values, reflecting two cancer host statuses that have been gaining attention, the inflammatory status and nutritional status. This model was first introduced to assess immune-nutritional status and thus, the risk of surgery for patients undergoing gastrointestinal operations (15). Lymphocytes are an important mediator of the immune response to malignant cells (lymphocyte count is also a component of NLR), demonstrating both cytotoxic potential and the ability to induce other inflammatory immune cells for the inhibition of cancer cell activities such as proliferation and invasion (17, 18). Therefore, reduced lymphocyte counts may serve as a surrogate marker of reduced host anti-tumor response. Serum albumin has long been utilized as a marker of malnutrition (19).

Because serum lymphocyte counts and albumin values are easily measured parameters used in everyday tests, PNI can

also be easily calculated without too much time or effort. In addition to reports on gastrointestinal malignancies, several previous studies have reported a relationship between PNI and UC, including between PNI and tumor stage, between PNI and prognosis after radical surgery or radiotherapy, and between PNI and perioperative complications (9, 20-26). To date, only the study by Hsieh *et al*. has focused on the relationship between PNI and the metastatic stage of UC (8). Thus, Hsieh *et al*. found that PNI can predict OS after first-line chemotherapy. Several other studies have investigated the usefulness of PNI as a prognosticator for patients undergoing ICI treatments in other malignancies, including gastric, esophageal, lung, and salivary gland cancers (10, 12, 23, 27). We have shown in the present study that PNI can also be utilized as a prognosticator in pembrolizumab treatment for mUC patients refractory to platinum-based chemotherapy.

The correlation between inflammation and malignant potential is widely known, and the prognostic value of inflammatory markers, including NLR and CRP kinetics, for pembrolizumab treatment of mUC has already been reported (6, 7, 28). Regarding nutritional status, Fukushima *et al*. suggested that sarcopenia may be a predictor for the efficacy of pembrolizumab treatment in mUC patients (4). Because PNI reflects both the inflammation status and nutritional status, it was reasonable to assume that PNI may also be a predictor for ICI treatment, and we verified this in the present study.

There are several concrete advantages of predicting treatment responses to pembrolizumab, some of which are unique to mUC patients. First and foremost, mUC is a malignancy with a rapid-progressive nature; hence, any delay in appropriate decision making would potentially harm the patients' overall benefit. According to our study, patients in the low PNI group had a substantially poorer prognosis, with a median OS of approximately 3 months. Because of the lack of a control arm in our study, it is not known whether these patients would benefit from alternative systemic treatments. However, it can be assumed that patients with an aggressive malignancy profile would not benefit from ICI. As ICIs have been associated with potential life-threatening adverse events, pembrolizumab treatment may unnecessarily put these patients at risk and consequently disbenefit them (29). Furthermore, because pembrolizumab treatment is costly, some reports argue that the quality-adjusted survival benefits are low (30). Accordingly, the results reported in this study suggest that PNI may both predict survival and serve as a predictor of initial treatment failure, making it possible to identify poor candidates for this treatment.

There are several limitations to our study. First, this was a retrospective study with a small patient cohort, conducted at tertiary-care institutions, which may have introduced potential biases in patient selection. Second, the intervals of radiographic examination were not uniform, possibly resulting in a bias in survival analysis. Third, our cohort differed from that of the KEYNOTE-045 trial because more patients with UC of the upper tract (renal pelvis and ureter) were included (69.7%). This may reflect the profile of our institutions that have a high interest in and thus a high referral rate for tumors detected in kidneys from primary/secondary care centers. Therefore, it is possible that our study population affected the results to some extent. Fourth, we did not perform a comparative analysis against known inflammatory or nutrition-related markers, such as CRP kinetics, owing to missing laboratory data in some patients. Future prospective studies with larger patient cohorts are needed to confirm our results.

Conclusion

PNI before pembrolizumab initiation is a significant and independent prognostic factor for survival in mUC patients. PNI also served to identify patients who did not respond to pembrolizumab. Further analyses are needed to confirm our results.

Conflicts of Interest

Tsunenori Kondo received honoraria from Pfizer, Novartis, and Ono Pharmaceutical. Toshio Takagi received honoraria from Ono Pharmaceutical. All other Authors have no conflicts of interest to declare.

Authors' Contributions

Yudai Ishiyama: study concepts and designs, acquisition, analysis and interpretation of the data, manuscript preparation. Tsunenori Kondo: study concepts and design, analysis and interpretation of the data, manuscript editing. Yuki Nemoto: data acquisition. Yuki Kobari: data acquisition. Hiroki Ishihara: manuscript review. Hidekazu Tachibana: manuscript review. Kazuhiko Yoshida: manuscript review. Yasunobu Hashimoto: manuscript review. Toshio Takagi: manuscript editing and review. Junpei Iizuka: manuscript review. Kazunari Tanabe: manuscript review.

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2020. CA Cancer J Clin *70(1)*: 7-30, 2020. PMID: 31912902. DOI: 10.3322/caac.21590

2 von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A and Arning M: Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol *23(21)*: 4602-4608, 2005. PMID: 16034041. DOI: 10.1200/JCO.2005.07.757

3 Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK, Necchi A, Gerritsen W, Gurney H, Quinn DI, Culine S, Sternberg CN, Mai Y, Poehlein CH, Perini RF, Bajorin DF and KEYNOTE-045 Investigators: Pembrolizumab as second-line therapy for

advanced urothelial carcinoma. N Engl J Med *376(11)*: 1015-1026, 2017. PMID: 28212060. DOI: 10.1056/NEJMoa1613683

4 Fukushima H, Fukuda S, Moriyama S, Uehara S, Yasuda Y, Tanaka H, Yoshida S, Yokoyama M, Matsuoka Y and Fujii Y: Impact of sarcopenia on the efficacy of pembrolizumab in patients with advanced urothelial carcinoma: A preliminary report. Anticancer Drugs *31(8)*: 866-871, 2020. PMID: 32740015. DOI: 10.1097/CAD.0000000000000982

5 Fukushima H, Kijima T, Fukuda S, Moriyama S, Uehara S, Yasuda Y, Tanaka H, Yoshida S, Yokoyama M, Matsuoka Y, Saito K, Matsubara N, Numao N, Sakai Y, Yuasa T, Masuda H, Yonese J, Kageyama Y and Fujii Y: Impact of radiotherapy to the primary tumor on the efficacy of pembrolizumab for patients with advanced urothelial cancer: A preliminary study. Cancer Med *9(22)*: 8355-8363, 2020. PMID: 32886446. DOI: 10.1002/cam4.3445

6 Kijima T, Yamamoto H, Saito K, Kusuhara S, Yoshida S, Yokoyama M, Matsuoka Y, Numao N, Sakai Y, Matsubara N, Yuasa T, Masuda H, Yonese J, Kageyama Y and Fujii Y: Early C-reactive protein kinetics predict survival of patients with advanced urothelial cancer treated with pembrolizumab. Cancer Immunol Immunother: 2020. PMID: 32876736. DOI: 10.1007/s00262-020-02709-2

7 Ogihara K, Kikuchi E, Shigeta K, Okabe T, Hattori S, Yamashita R, Yoshimine S, Shirotake S, Nakazawa R, Matsumoto K, Mizuno R, Hara S, Oyama M, Masuda T, Niwakawa M and Oya M: The pretreatment neutrophil-to-lymphocyte ratio is a novel biomarker for predicting clinical responses to pembrolizumab in platinum-resistant metastatic urothelial carcinoma patients. Urol Oncol *38(6)*: 602.e1-602.e10, 2020. PMID: 32139290. DOI: 10.1016/j.urolonc.2020.02.005

8 Hsieh MC, Rau KM, Chiang PH, Sung MT, Lan J, Luo HL, Huang CC, Huang CH and Su HY: Impact of prognostic nutritional index on overall survival for patients with metastatic urothelial carcinoma. J Cancer *9(14)*: 2466-2471, 2018. PMID: 30026844. DOI: 10.7150/jca.25061

9 Huang J, Yuan Y, Wang Y, Chen Y, Kong W, Xue W, Chen H, Zhang J and Huang Y: Preoperative prognostic nutritional index is a significant predictor of survival in patients with localized upper tract urothelial carcinoma after radical nephroureterectomy. Urol Oncol *35(12)*: 671.e1-671.e9, 2017. PMID: 28826702. DOI: 10.1016/j.urolonc.2017.07.028

10 Qi F, Zhou X, Wang Y, Wang Y, Wang Y, Zhang Q, Cong R, Yang J and Song N: Pre-treatment prognostic nutritional index may serve as a potential biomarker in urinary cancers: A systematic review and meta-analysis. Cancer Cell Int *18*: 207, 2018. PMID: 30564063. DOI: 10.1186/s12935-018-0708-7

11 Qi F, Xu Y, Zheng Y, Li X and Gao Y: Pre-treatment Glasgow prognostic score and modified Glasgow prognostic score may be potential prognostic biomarkers in urological cancers: A systematic review and meta-analysis. Ann Transl Med *7(20)*: 531, 2019. PMID: 31807513. DOI: 10.21037/atm.2019.09.160

12 Shoji F, Takeoka H, Kozuma Y, Toyokawa G, Yamazaki K, Ichiki M and Takeo S: Pretreatment prognostic nutritional index as a novel biomarker in non-small cell lung cancer patients treated with immune checkpoint inhibitors. Lung Cancer *136*: 45-51, 2019. PMID: 31437663. DOI: 10.1016/j.lungcan.2019.08.006

13 Namikawa T, Yokota K, Tanioka N, Fukudome I, Iwabu J, Munekage M, Uemura S, Maeda H, Kitagawa H, Kobayashi M and Hanazaki K: Systemic inflammatory response and nutritional biomarkers as predictors of nivolumab efficacy for gastric cancer. Surg Today *50(11)*: 1486-1495, 2020. PMID: 32542414. DOI: 10.1007/s00595-020-02048-w

14 Ogura Y, Kataoka N, Kunimatsu Y, Tachibana Y, Sugimoto T, Tani N, Sato I, Hirose K, Kato D and Takeda T: Predictors of survival among Japanese patients receiving first-line chemoimmunotherapy for advanced non-small cell lung cancer. Thorac Cancer *12(1)*: 97-105, 2021. PMID: 33124197. DOI: 10.1111/1759-7714.13720

15 Onodera T, Goseki N and Kosaki G: [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi *85(9)*: 1001-1005, 1984. PMID: 6438478.

16 Bellmunt J, De wit R, Vaughn D, Fradet Y, Lee J, Fong L, Vogelzang N, Climent M, Petrylak D, Choueiri T, Necchi A, Gerritsen W, Gurney H, Quinn D, Culine S, Sternberg C, Jensen E, Frenkl T, Perini R and Bajorin D: Impact of prognostic factors and risk groups on overall survival (OS) in patients treated with pembrolizumab vs investigator's choice chemotherapy for advanced urothelial cancer (UC): Post hoc analysis of KEYNOTE-045. Annals of Oncology *29*: viii320-viii321, 2020. DOI: 10.1093/annonc/mdy283.110

17 Coussens LM and Werb Z: Inflammation and cancer. Nature *420(6917)*: 860-867, 2002. PMID: 12490959. DOI: 10.1038/nature01322

18 Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. Nature *454(7203)*: 436-444, 2008. PMID: 18650914. DOI: 10.1038/nature07205

19 Keller U: Nutritional Laboratory Markers in Malnutrition. J Clin Med *8(6)*: 2019. PMID: 31159248. DOI: 10.3390/jcm8060775

20 Peng D, Gong YQ, Hao H, He ZS, Li XS, Zhang CJ and Zhou LQ: Preoperative prognostic nutritional index is a significant predictor of survival with bladder cancer after radical cystectomy: A retrospective study. BMC Cancer *17(1)*: 391, 2017. PMID: 28578683. DOI: 10.1186/s12885-017-3372-8

21 Stangl-Kremser J, D'Andrea D, Vartolomei M, Abufaraj M, Goldner G, Baltzer P, Shariat SF and Tamandl D: Prognostic value of nutritional indices and body composition parameters including sarcopenia in patients treated with radiotherapy for urothelial carcinoma of the bladder. Urol Oncol *37(6)*: 372-379, 2019. PMID: 30578161. DOI: 10.1016/j.urolonc.2018.11.001

22 Karsiyakali N, Karabay E and Yucetas U: Predictive value of prognostic nutritional index on tumor stage in patients with primary bladder cancer. Arch Esp Urol *73(2)*: 132-139, 2020. PMID: 32124844.

23 Yu J, Hong B, Park JY, Hwang JH and Kim YK: Impact of prognostic nutritional index on postoperative pulmonary complications in radical cystectomy: a propensity score-matched analysis. Ann Surg Oncol : 2020. PMID: 32776190. DOI: 10.1245/s10434-020-08994-6

24 Kosuga T, Konishi T, Kubota T, Shoda K, Konishi H, Shiozaki A, Okamoto K, Fujiwara H, Kudou M, Arita T, Morimura R, Murayama Y, Kuriu Y, Ikoma H, Nakanishi M and Otsuji E: Value of prognostic nutritional index as a predictor of lymph node metastasis in gastric cancer. Anticancer Res *39(12)*: 6843-6849, 2019. PMID: 31810951. DOI: 10.21873/anticanres.13901

25 Shimizu T, Taniguchi K, Asakuma M, Tomioka A, Inoue Y, Komeda K, Hirokawa F and Uchiyama K: Lymphocyte-to-monocyte ratio and prognostic nutritional index predict poor prognosis in patients on chemotherapy for unresectable

pancreatic cancer. Anticancer Res *39(4)*: 2169-2176, 2019. PMID: 30952764. DOI: 10.21873/anticanres.13331

26 Takao K, Konishi H, Fujiwara H, Shiozaki A, Shoda K, Kosuga T, Kubota T, Arita T, Morimura R, Murayama Y, Kuriu Y, Ikoma H, Nakanishi M, Okamoto K and Otsuji E: Clinical significance of prognostic nutritional index in the treatment of esophageal squamous cell carcinoma. In Vivo *34(6)*: 3451-3457, 2020. PMID: 33144453. DOI: 10.21873/invivo.12184

27 Watanabe H, Yamada T, Komori K, Hara K, Kano K, Takahashi K, Kumazu Y, Fujikawa H, Numata M, Aoyama T, Tamagawa H, Inokuchi Y, Machida N, Shiozawa M, Yukawa N, Morinaga S, Rino Y, Masuda M, Ogata T and Oshima T: Effect of prognostic nutrition index in gastric or gastro-oesophageal junction cancer patients undergoing nivolumab monotherapy. In Vivo *35(1)*: 563-569, 2021. PMID: 33402510. DOI: 10.21873/invivo.12292

28 Yamamoto Y, Yatsuda J, Shimokawa M, Fuji N, Aoki A, Sakano S, Yamamoto M, Suga A, Tei Y, Yoshihiro S, Kitahara S, Nagao K, Takai K, Kamiryo Y, Akao J, Yamaguchi S, Oba K, Shimabukuro T, Matsumoto H, Kamba T and Matsuyama H: Prognostic value of pre-treatment risk stratification and post-treatment neutrophil/lymphocyte ratio change for pembrolizumab in patients with advanced urothelial carcinoma. Int J Clin Oncol *26(1)*: 169-177, 2021. PMID: 32948925. DOI: 10.1007/s10147-020-01784-w

29 Baxi S, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L and Korenstein D: Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: Systematic review and meta-analysis. BMJ *360*: k793, 2018. PMID: 29540345. DOI: 10.1136/bmj.k793

30 Criss SD, Weaver DT, Sheehan DF, Lee RJ, Pandharipande PV and Kong CY: Effect of PD-L1 testing on the cost-effectiveness and budget impact of pembrolizumab for advanced urothelial carcinoma of the bladder in the United States. Urol Oncol *37(3)*: 180.e11-180.e18, 2019. PMID: 30528699. DOI: 10.1016/j.urolonc.2018.11.016

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