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ORIGINAL ARTICLE **CME**

Pembrolizumab with or without Concurrent Chemotherapy in Metastatic Non–Small-Cell Lung Cancer with High Programmed Death Ligand 1 Expression

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ABSTRACT

Introduction: *We evaluated overall survival (OS), time on treatment (ToT), and prognostic factors in patients with metastatic non–small-cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) expression of ≥50% receiving first-line pembrolizumab with or without chemotherapy.*

Methods: *Patients receiving at least one cycle of pembrolizumab in a single tertiary oncology centre in Hong Kong from January 2018 to December 2022 were included. OS and ToT were assessed by Kaplan-Meier curves. Prognostic factors, including clinical-biochemical prognostic indices (PIs) at selected cut-offs, were assessed. The sensitivities and specificities of neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), platelet-to-lymphocyte ratio (PLR), and advanced lung cancer inflammation index (ALI) were evaluated.*

Results: *A total of 133 consecutive cases were included, with 112 receiving pembrolizumab alone and 21 receiving pembrolizumab in combination with chemotherapy. The median OS and ToT were 17.8 months (95% confidence interval [CI] = 13.4-23.5) and 8.0 months (95% CI = 5.5-12.0), respectively, with no significant difference between the two groups. ALI outperformed other PIs in 6-month, 1-year, and 2-year OS predictions. For 1-year OS prediction, ALI had an area under the curve of 0.813 (95% CI = 0.731-0.895), and 85.7% sensitivity and 71.9% specificity for ALI values ≤17.4. All PIs, low body weight, Eastern Cooperative Oncology Group performance status score of 2, and presence of liver metastasis were significant independent poor prognostic factors in multivariable regression analyses.*

Conclusion: *In patients with metastatic NSCLC with high PD-L1 expression receiving first-line pembrolizumab, OS and ToT were similar independent of chemotherapy use. ALI served as a simple effective index with the highest hazard ratio in stratifying prognosis.*

Key Words: *Carcinoma, non–small-cell lung; Lung neoplasms; Prognosis; Survival*

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中文摘要

使用帕博利珠單抗或帕博利珠單抗聯合化療治療高表達程序性死亡配體1轉移性非小細胞肺癌

呂活證、余洛汶、林美瑩

引言：我們的研究對象是接受第一線帕博利珠單抗或帕博利珠單抗聯合化療的程序性死亡配體1（PD-L1）水平≥50%的轉移性非小細胞肺癌患者，找出他們的整體存活期、治療時間及預後因素。

方法：本研究納入於2018年1月至2022年12月期間曾在香港一所三級腫瘤科中心接受最少一個帕博利珠單抗療程的患者。我們使用Kaplan-Meier曲線評估整體存活期及治療時間，並分析了預後因素（包括於不同選定截斷點的臨床生化學預後指數）。我們找出以下四個指數的敏感度和特異度：嗜中性白血球與淋巴性白血球比例（NLR）、衍生的嗜中性白血球與淋巴性白血球比例（dNLR）、血小板與淋巴性白血球比例（PLR）及晚期肺癌炎症指數（ALI）。

結果：本研究共包括133個連續個案，當中112名患者只接受帕博利珠單抗治療，21名患者則同時接受化療。整體存活期及治療時間中位數分別為17.8個月（95%置信區間 = 13.4-23.5）及8.0個月（95%置信區間 = 5.5-12.0）；兩組患者在統計學上沒有顯著差別。ALI在6個月、1年及兩年整體存活期預測的表現較其他三個指數佳。在1年整體存活期預測方面，ALI的曲線下面積為0.813（95%置信區間 = 0.731-0.895），而ALI數值≤17.4的敏感度和特異度則分別為85.7%及71.9%。所有預後指數、體重輕、美國東岸癌症臨床研究合作組織體能狀態為2分及有肝轉移在多變項迴歸分析中是重要的獨立不佳預後因素。

結論：在接受第一線帕博利珠單抗治療的高表達PD-L1轉移性非小細胞肺癌患者中，不論是否有同時接受化療，他們的整體存活期及治療時間均相若。ALI是簡單而有效的指數，在為預後進行分層方面的風險比最高。

INTRODUCTION

Lung cancer is the leading cancer in Hong Kong.[1] Although epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) translocation are especially common in the Asian population, approximately half of lung cancer patients suffer from disease without an actionable driver mutation.[2,3]

Since the release of the KEYNOTE-024 (KN-024) study, first-line pembrolizumab monotherapy has become one of the standards of care for metastatic non–small-cell lung cancer (NSCLC) with high expression of programmed death ligand 1 (PD-L1), defined as having a tumour proportion score ≥50%.[4,5] Subsequently, the KEYNOTE-189 (KN-189) and KEYNOTE-407 (KN-407) trials found that a pembrolizumab-chemotherapy combination was effective regardless of the level of PD-L1 expression.[6-10]

For those with PD-L1 expression of ≥50%, pembrolizumab alone has a response rate of approximately 45% (44.8% in the KN-024 trial).[4] The KN-189 and KN-407 trials found that adding chemotherapy to pembrolizumab increased the response rates to >60% in both non-squamous (62.1% in the KN-189 trial)[7] and squamous cell carcinoma (64.4% in the KN-407 trial),[10] although the survival outcomes were comparable. From the latest 5-year update report,[8] the median overall survival (OS) and 5-year OS rates were similar with pembrolizumab monotherapy (26.3 months and 31.9%),[5] combined with pemetrexed and carboplatin in non-squamous carcinoma (27.7 months and 29.6%),[8] and combined with paclitaxel/nab-paclitaxel and carboplatin (19.9 months and 23.3%).[10] Therefore, the optimal choice of first-line treatment remains unsettled.

There is an unmet need to identify those who will be durable responders, as well as those who are expected to have futile and non-sustained responses to pembrolizumab treatment. Early combination with chemotherapy as an intensified treatment may benefit

some patients, whereas early symptomatic care may be more appropriate. Careful selection and prudent decisions should be made together with patients after considering all available factors.

Clinical, biochemical, pathological, and radiological parameters are assessed for their predictive value as well as their adverse effects. Consensus on the preferred markers is difficult to arrive at in many tumours due to the complex interplay between tumour microenvironment and host immune system.[11,12] The proinflammatory status of the patient may promote cancer cell progression and immune resistance.[13] Clinical-biochemical parameters have been proposed and some are commonly used to reflect a dysfunctional host immune state, such as a neutrophil-to-lymphocyte ratio (NLR) ≥5, a derived neutrophil-to-lymphocyte ratio (dNLR) ≥3, a platelet-to-lymphocyte ratio (PLR) ≥200, and an advanced lung cancer inflammation index (ALI) ≤18. Utilisation of such indices can serve as a simple but effective tool to assist clinical decision.[14-20]

We aimed to review the clinical outcomes of patients with metastatic NSCLC with high PD-L1 expression receiving first-line pembrolizumab with or without concurrent chemotherapy and to evaluate the utility of several commonly used clinical-biochemical prognostic indices.

METHODS

Study Population

This was a retrospective cohort study conducted in a single tertiary oncology centre in Hong Kong, which provides cluster-based oncology services to the most densely populated districts in the city. The cases of patients aged ≥18 years with pathologically confirmed metastatic NSCLC, without sensitising EGFR mutation or ALK translocation, and with ≥50% PD-L1 expression, who had received at least one cycle of pembrolizumab with or without concurrent chemotherapy in a first-line setting between January 2018 and December 2022 were included. Cases with Eastern Cooperative Oncology Group (ECOG) performance status score of ≥3, and baseline blood results, body weight, or height not recorded within 28 days from the first cycle of pembrolizumab were excluded. The case list was generated from the Clinical Data Analysis and Reporting System of the Hospital Authority.

Assessment

Both electronic and physical records were reviewed. Relevant demographic, clinical, laboratory, treatment, and outcome data were extracted. The tumour proportion scores of PD-L1 were analysed by immunohistochemistry using 22C3 or SP263 antibodies. Response evaluation was performed as per the physician's assessment and investigator's review based on clinical symptoms, physical examination, chest radiography, computed tomography, and carcinoembryonic antigen levels.

The data cut-off date was 30 April 2023. The duration of follow-up was calculated from the date of initiating the first cycle of pembrolizumab to the date of death or the date of the last follow-up if the date of death was unavailable.

Study Endpoints

The primary endpoint was OS, which was defined as the time from the beginning of the first cycle of pembrolizumab to the date of death from any cause or the last date of follow-up if the date of death was unavailable. Only one patient was lost to follow-up.

The key secondary endpoints included the following: (1) time on treatment (ToT), which was defined as the time of the initiation of the first cycle of pembrolizumab to the last efficacious date after discontinuation (date of last pembrolizumab injection plus 21 or 42 days for every 3- or 6-week regimen, respectively) for any reason or death, whichever was earlier; (2) reasons for treatment discontinuation; (3) calculation of the four prognostic indices, namely NLR, dNLR, PLR and ALI, where baseline blood results within 28 days of pembrolizumab were used for analysis (online supplementary Table); and (4) negative prognostic factors for OS, including concurrent chemotherapy, male sex, age ≥70 years, ever-smoker, ECOG performance status score of 2, histology of squamous cell carcinoma, baseline brain metastasis, baseline pleural metastasis or pleural effusion, baseline liver metastasis, previous radiotherapy treatment, and NLR, dNLR, PLR and ALI at their respective cut-offs.

Statistical Analysis

Differences in baseline characteristics between the pembrolizumab alone (immunotherapy [IO]-alone) group and concurrent platinum-based chemotherapy (IO-combination) group were compared with the Pearson's Chi squared test or Fisher's exact test for categorical variables and an independent *t* test or the Mann-Whitney *U* test for continuous variables. OS and ToT were calculated using the Kaplan-Meier method and compared with the log-rank test.

Time-dependent receiver operating characteristic (ROC) curves were used to evaluate the discriminative ability of the four prognostic indices on OS. The time-dependent area under the curve (AUC), sensitivity, and specificity with 95% confidence interval (95% CI) were calculated at 6 months, 1 year, and 2 years after therapy initiation. The cut-off of the prognostic indices was determined by the highest achievable sensitivity and specificity based on stepwise testing of incremental improvement. Sensitivity ≥70% for 6-month and 1-year OS prediction was required, and specificity ≥60% for 6-month and 1-year OS prediction was attempted. Escalation of sensitivity and specificity testing at 5% increments were attempted alternately to achieve the best cut-off. After achieving a minimum sensitivity of ≥75% and specificity of ≥65% for 6-month and 1-year OS prediction, further increments focused on 1-year OS prediction to attain the highest achievable combination of sensitivity and specificity when selecting the representative cut-off.

Univariate Cox proportional hazards regression analyses were performed to identify potential prognostic factors associated with OS. The association of OS with each prognostic index was examined using a multivariable Cox regression model adjusting for chemotherapy and other factors with p value < 0.1 in the univariate analyses. The variance inflation factor was used to check multicollinearity among independent variables in the regression model, and the Akaike information criterion was used to compare the performance of different regression models.

All statistical analyses were carried out using RStudio version 4.3.1 with packages 'survival', 'timeROC', and 'performance'. A p value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

After excluding 9 cases with ECOG performance status score ≥3, and 31 cases without baseline blood results, body weight, or height recorded within 28 days from the first cycle of treatment, a total of 133 cases of pathologically confirmed metastatic NSCLC with ≥50% PD-L1 expression, and no sensitising EGFR mutation or *ALK* translocation, who had received at least one cycle of pembrolizumab with or without concurrent chemotherapy in a first-line setting were included. Molecular tests on *EGFR* and *ALK* were routinely performed for all adenocarcinoma and NSCLC but not squamous cell carcinoma as per institutional practice. Additional molecular tests were arranged based on the individual physician's decisions. All tested patients were negative for EGFR exon 19 deletion, EGFR exon 21 L858R mutation, and *ALK* translocation. Fifteen patients had rare mutations detected, including *ROS1* translocation (n = 1), EGFR exon 20 insertion (n = 3), human epidermal growth factor receptor 2 exon 20 insertion (n = 1), rearranged during transfection rearrangement (n = 1), *KRAS* (Kirsten rat sarcoma virus) mutation (G12C, G12D/S, and G12X; n = 3), MET (mesenchymal epithelial transition receptor) exon 14 skipping (n = 5), and co-mutation of *KRAS* G12C mutation and MET exon 14 skipping (n = 1).

Among the 133 consecutive cases, 112 received pembrolizumab alone and 21 received pembrolizumab with chemotherapy. Baseline characteristics are summarised in Table 1. Both groups were balanced except for age and radiotherapy treatment prior to pembrolizumab. The combination group was younger (mean age, 64.9 ± 6.1 years; p < 0.001) and had less radiotherapy before pembrolizumab (n = 2, 9.5%; p = 0.003).

Treatment

Pembrolizumab with or without Chemotherapy

The dosing and frequency of pembrolizumab varied and depended on financial and funding issues. A total of 78.9% (n = 105) of patients started one of two standard fixed-dose regimens (94 at 200 mg every 3 weeks and 11 at 400 mg every 6 weeks), while the remaining 21.1% (n = 28) received a weight-based regimen (three at 80 mg, 24 at 100 mg, and one at 120 mg every 3 weeks). Twenty-eight patients had a change of dose and frequency during the treatment course. Most patients changed from every 3 weeks to every 6 weeks regimen for easier logistics and less frequent hospital visits.

Twenty-one patients received concurrent chemotherapy with the choice of agents depending on histological subtypes, where 18 of them received concurrent pemetrexed and carboplatin (16 had adenocarcinoma, one had large cell carcinoma, and one had NSCLC not otherwise specified) with a median number of five cycles (range, 1-10). The remaining three patients received concurrent paclitaxel and carboplatin (one had squamous cell carcinoma, one had lymphoepithelial-like carcinoma, and one had NSCLC not otherwise specified) with a median number of five cycles (range, 3-5).

Table 1. Baseline characteristics by treatment groups.*

	All (n = 133)	IO-alone (n = 112)	IO-combination (n = 21)	p Value
Male sex	108 (81.2%)	91 (81.3%)	17 (81.0%)	1.000
Age, y	70.8 ± 9.7	71.9 ± 9.9	64.9 ± 6.1	< 0.001
≥70	74 (55.6%)	70 (62.5%)	4 (19.0%)	< 0.001
Body mass index				0.320
Underweight (<18.5 kg/m^2)	24 (18.0%)	22 (19.6%)	2 (9.5%)	
Normal	64 (48.1%)	55 (49.1%)	9 (42.9%)	
Overweight/obese (≥23 kg/m^2)	45 (33.8%)	35 (31.3%)	10 (47.6%)	
Smoking status				0.565
Never	33 (24.8%)	26 (23.2%)	7 (33.3%)	
Ex-smoker	59 (44.4%)	50 (44.6%)	9 (42.9%)	
Smoker	41 (30.8%)	36 (32.1%)	5 (23.8%)	
ECOG performance status score				0.765
0	31 (23.3%)	25 (22.3%)	6 (28.6%)	
1	76 (57.1%)	65 (58.0%)	11 (52.4%)	
2	26 (19.5%)	22 (19.6%)	4 (19.0%)	
Histology				0.096
Non–squamous cell carcinoma†	86 (64.7%)	68 (60.7%)	18 (85.7%)	
Squamous cell carcinoma	26 (19.5%)	25 (22.3%)	1 (4.8%)	
NSCLC not otherwise specified	21 (15.8%)	19 (17.0%)	2 (9.5%)	
Baseline brain metastasis	17 (12.8%)	16 (14.3%)	1 (4.8%)	0.308
Baseline pleural metastasis or effusion	54 (40.6%)	46 (41.1%)	8 (38.1%)	0.799
Baseline liver metastasis	26 (19.5%)	20 (17.9%)	6 (28.6%)	0.247
Radiotherapy before pembrolizumab	51 (38.3%)	49 (43.8%)	2 (9.5%)	0.003
No. of sites for radiotherapy				1.000
1	44 (86.3%)	42 (85.7%)	2 (100%)	
2	6 (11.8%)	6 (12.2%)	0	
3	1 (2.0%)	1 (2.0%)	0	
Sites for radiotherapy				N/A
Brain	8	8	0	
Lung	27	27	0	
Spine	11	11	0	
Bone	4	3	1	
Neck lymph node	6	5	1	
Other	3	3	0	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IO = immunotherapy; N/A = not applicable; NSCLC = non–small-cell lung cancer.

* Data are shown as No., No. (%) or mean ± standard deviation, unless otherwise specified.

† Includes adenocarcinomas (n = 84), large-cell carcinoma (n = 1), and lymphoepithelial-like carcinoma (LELC) [n = 1], of which large-cell carcinoma and LELC were in the IO-combination group.

Clinical Outcomes

The median follow-up time was 10.2 months (range, 0.2-75). One patient was lost to follow-up. At the time of analysis, 69 deaths had occurred, and 88 patients had discontinued pembrolizumab. Median OS and ToT of the entire cohort were 17.8 months (95% CI = 13.4-23.5) [Figure 1a] and 8.0 months (95% CI = 5.5-12.0) [Figure 1b], respectively. No significant difference was observed between IO-alone and IO-combination groups (median OS = 18.2 months [95% CI = 12.6-38.9] vs. 17.8 months [95% CI = 5.2 to not applicable], p = 0.792; median ToT = 8.1 months [95% CI = 5.0-12.4] vs. 7.4 months [95% CI = 3.2-14.8], p = 0.863) [Figure 1c and 1d].

Reasons for discontinuation of pembrolizumab included death (n = 30); disease progression (n = 45); disease remission (n = 2); severe immune-related adverse events (n = 9) including four with pneumonitis, two with hepatitis, two with skin reactions, and one with flareup of stable autoimmune disease; deteriorated performance status (n = 2); second malignancies (n = 2; one hepatocellular carcinoma and one liposarcoma); and one case switching to capmatinib after receipt of additional molecular results. Seven patients stopped pembrolizumab due to financial reasons.

Performance of Clinical-Biochemical Prognostic Indices

The time-dependent ROC curves, sensitivities, and specificities of various prognostic indices are shown in

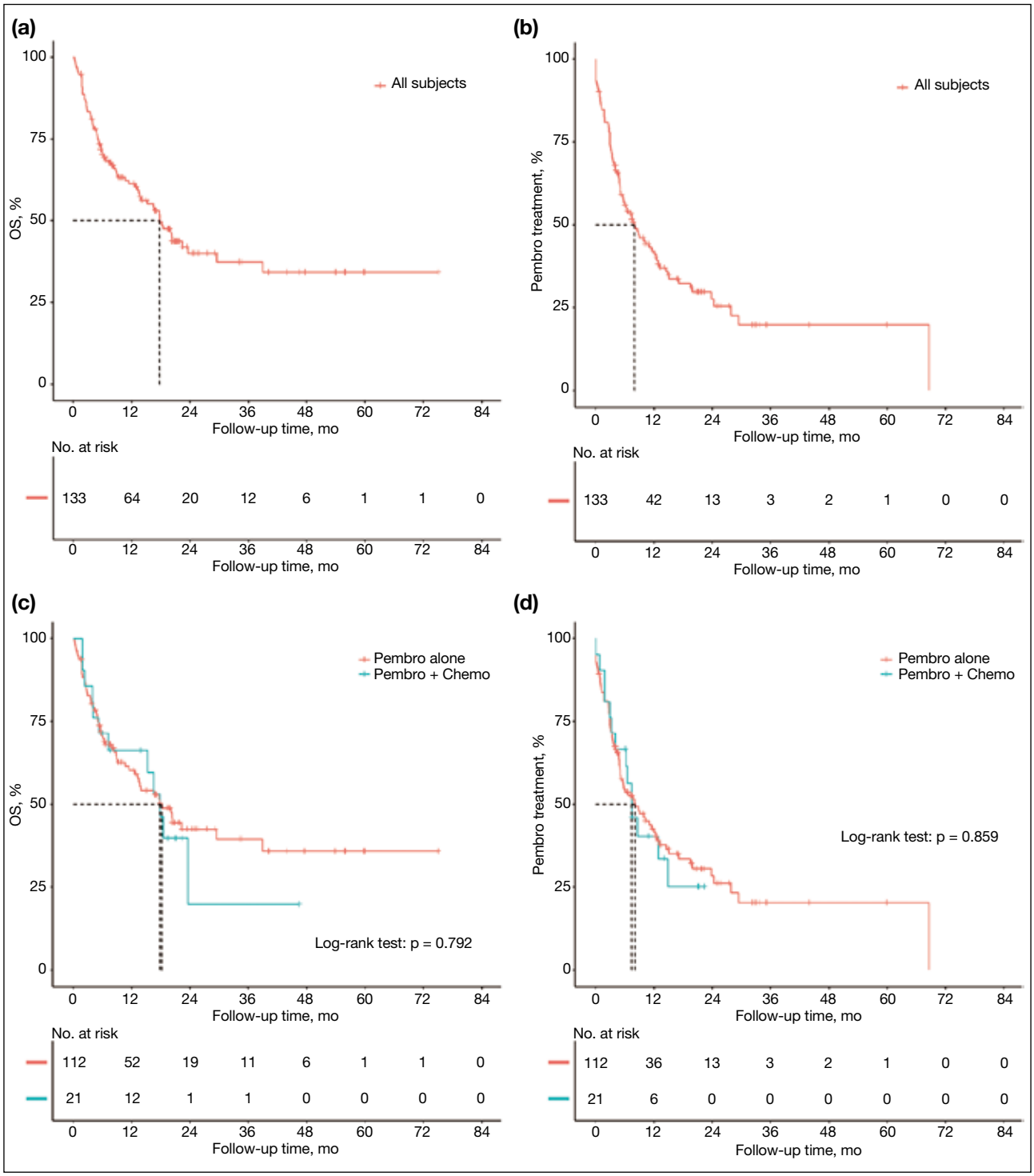

Figure 1. Kaplan–Meier estimates of overall survival (OS) and time-on-treatment (ToT) of all subjects and by treatment groups. (a) OS of all subjects. (b) ToT of all subjects. (c) OS by treatment group. (d) ToT by treatment group. No difference was observed between treatment groups. Tick marks indicate censoring of data at the last time the patient was known to be alive.
Abbreviations: chemo = chemotherapy; pembro = pembrolizumab.

Figure 2. The ALI outperformed the other prognostic indices, with the highest AUCs of 0.797, 0.813 and 0.815 for 6-month, 1-year and 2-year OS predictions, respectively. An ALI ≤17.4 had sensitivities and specificities in 6-month (84.2% and 60.9%), 1-year (85.7% and 71.9%), and 2-year (73.1% and 95.0%) OS

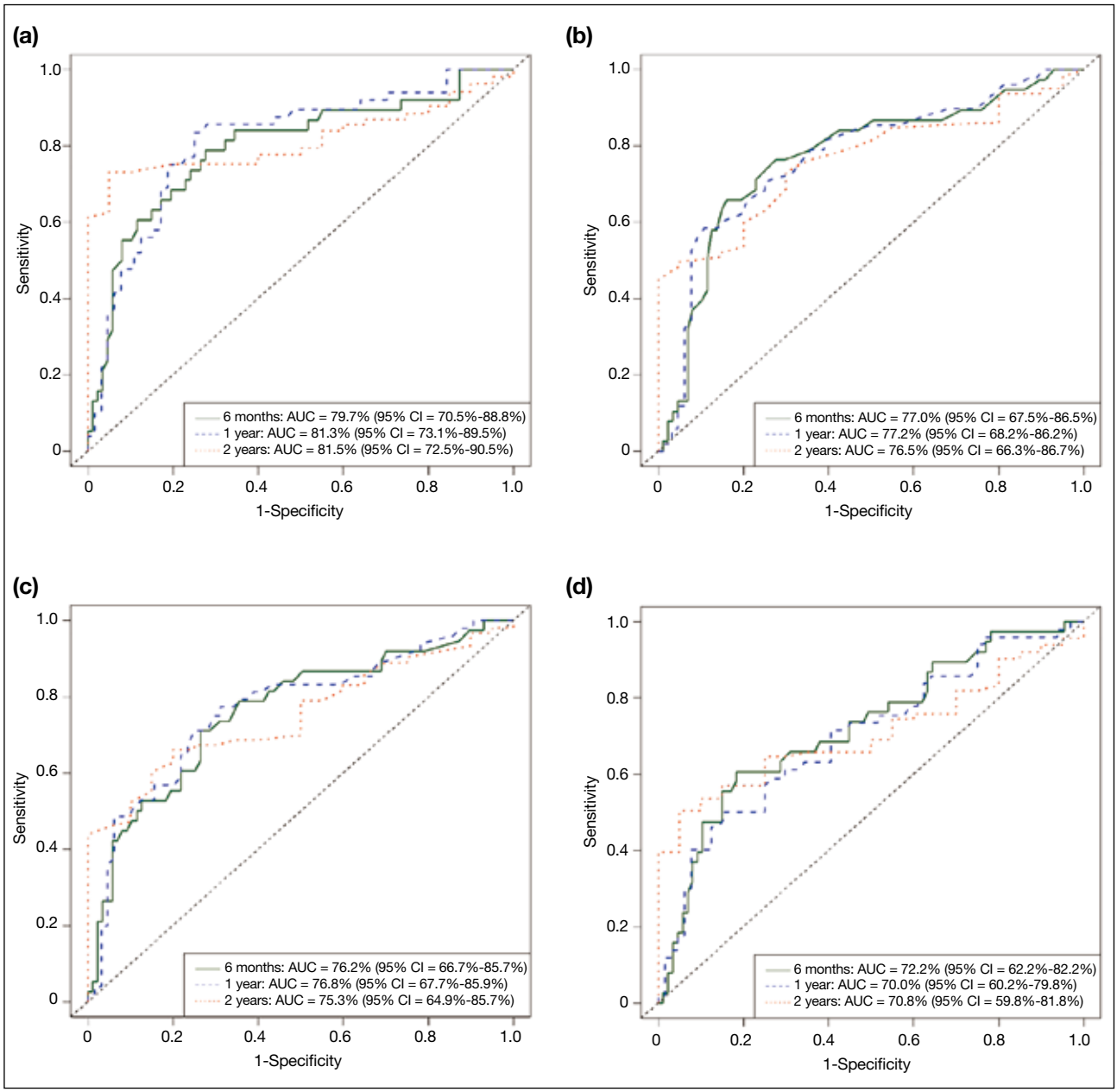

Figure 2. Time-dependent receiver operating characteristic curves on overall survival predictions according to prognostic indices. (a) Advanced lung cancer inflammation index. (b) Derived neutrophil-to-lymphocyte ratio. (c) Neutrophil-to-lymphocyte ratio. (d) Platelet-to-lymphocyte ratio.
Abbreviations: 95% CI = 95% confidence interval; AUC = area under the curve.

predictions. Cut-off values of ALI (≤17.4), dNLR (≥2.6), NLR (≥4.8), and PLR (≥232) were comparable to those identified in the literature (Table 2).[13-20]

Other Prognostic Factors Compared with the Advanced Lung Cancer Inflammation Index

The variables included in the univariate and multivariable regression analyses are shown in Table 3. Low body weight (body mass index [BMI] <18.5 kg/m^2), ECOG performance status score of 2, baseline liver metastasis, and all prognostic indices at their respective cut-offs were identified as independent poor prognostic factors in multivariable regression analyses. Adjusted hazard ratios were 4.43 for ALI ≤17.4 ($p < 0.001$), 2.21 for dNLR ≥2.6 ($p = 0.006$), 2.08 for NLR ≥4.8 ($p = 0.010$),

Table 2. Sensitivities and specificities for overall survival predictions of the prognostic indices at respective cut-off values.

Cut-off value		Sensitivity (95% CI)			Specificity (95% CI)		
		6 months	1 year	2 years	6 months	1 year	2 years
ALI	≤18	84.6% (73.2%-96.0%)	85.7% (75.8%-95.6%)	73.1% (61.8%-84.5%)	59.1% (48.8%-69.4%)	68.8% (57.4%-80.1%)	90.0% (76.8%-100%)
	≤17.4	84.2% (72.5%-95.8%)	85.7% (75.8%-95.6%)	73.1% (61.8%-84.5%)	60.9% (50.6%-71.2%)	71.9% (60.8%-82.9%)	95.0% (85.4%-100%)
dNLR	≥3	69.3% (54.8%-83.8%)	62.4% (48.7%-76.2%)	50.9% (38.6%-63.2%)	77.3% (68.5%-86.1%)	79.7% (69.8%-89.6%)	85.0% (69.3%-100%)
	≥2.6	76.3% (62.8%-89.9%)	70.7% (57.7%-83.6%)	59.8% (47.6%-72.0%)	70.1% (60.5%-79.8%)	75.0% (64.4%-85.6%)	80.0% (62.4%-97.6%)
NLR	≥5	74.4% (60.7%-88.1%)	71.2% (58.4%-84.0%)	58.5% (46.2%-70.8%)	68.2% (58.4%-78.0%)	73.4% (62.6%-84.3%)	85.0% (69.3%-100%)
	≥4.8	78.9% (65.9%-91.9%)	75.1% (62.8%-87.3%)	62.8% (50.7%-74.9%)	64.4% (54.3%-74.5%)	70.3% (59.1%-81.5%)	80.0% (62.4%-97.6%)
PLR	≥200	76.8% (63.5%-90.1%)	75.4% (63.3%-87.6%)	69.2% (57.3%-81.0%)	42.0% (31.7%-52.4%)	42.2% (30.0%-54.3%)	45.0% (23.1%-66.9%)
	≥232	73.7% (59.7%-87.8%)	71.5% (58.8%-84.2%)	62.4% (50.2%-74.7%)	54.0% (43.5%-64.5%)	59.4% (47.3%-71.5%)	75.0% (56.0%-94.0%)

Abbreviations: 95% CI = 95% confidence interval; ALI = advanced lung cancer inflammation index; dNLR = derived neutrophil-to-lymphocyte ratio; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio.

and 1.75 for PLR ≥232 (p = 0.037). OS curves showed clear separation with each prognostic index in which ALI performed the best (Figure 3).

DISCUSSION

The choice of the optimal first-line treatment for metastatic NSCLC with PD-L1 expression of ≥50% remains challenging. The level of PD-L1 expression appears to be indicative and was suggested as part of routine testing in non–oncogene-addicted metastatic NSCLC by international guidelines such as those from the European Society for Medical Oncology[21] and the National Comprehensive Cancer Network.[22] However, high PD-L1 expression alone was known to have limited predictive value of IO benefit, given a significant proportion of patients remained resistant to pembrolizumab treatment. Emerging biomarkers such as tumour mutation burden and tumour microenvironment appeared promising, but the best clinical criteria and biomarkers for patient selection and outcome prediction remain unsettled.[23] To our knowledge, this is the largest review in our locality of pembrolizumab with or without chemotherapy for metastatic NSCLC with high PD-L1 expression along with the comparison of four prognostic indices for OS prediction.

OS is a less ambiguous endpoint in the real-world setting where the timing imaging is variable, and response evaluation is not standardised. Yet, the exact treatment effectiveness could still be difficult to interpret due to susceptibility to post-baseline events. Conversely, treatment-based endpoints such as ToT are considered an approximation of progression-free survival. It can serve as a pragmatic endpoint for the evaluation of treatment benefit, especially in the context of IO or targeted therapy, by taking into consideration some other clinically relevant reasons for treatment discontinuation (such as worsened performance status, patient preference, and immune-related toxicities) or treatment continuation (such as for pseudo-progression during the early treatment phase, treatment beyond progression in the context of continued clinical benefits, and limited further treatment choices).[24] However, its interpretation should be cautioned as reasons including financial constraints and second malignancy were also included. Response rate analysis was not performed due to the lack of protocol and inconsistency in response evaluation and follow-up imaging.

We observed that a higher proportion of individuals in the IO-combination group were younger, required less radiotherapy, had more non-squamous histology, fewer underweight, and fewer brain metastases compared to the IO-alone group. However, only the former two factors were statistically significant (Table 1). These characteristics signified better prognosis at baseline and were compatible with the usual clinical selection criteria for combination treatment in which these patients were

Table 3. Univariate and multivariable analyses for prognostic factors on overall survival prediction.

	Univariate		Multivariable							
	Model 0		Model 1		Model 2		Model 3		Model 4	
	HR_{unadj} (95% CI)	p Value	HR_{adj} (95% CI)	p Value	HR_{adj} (95% CI)	p Value	HR_{adj} (95% CI)	p Value	HR_{adj} (95% CI)	p Value
IO-combination vs. IO-alone	1.09 (0.58-2.04)	0.785	1.12 (0.57-2.18)	0.742	1.08 (0.56-2.10)	0.819	1.06 (0.54-2.06)	0.875	0.84 (0.42-1.65)	0.605
Male sex	0.88 (0.49-1.58)	0.668								
Age ≥70 y	0.92 (0.57-1.48)	0.732								
Underweight (BMI <18.5 kg/m^2)	2.74 (1.60-4.66)	< 0.001	2.29 (1.28-4.07)	0.005	2.28 (1.27-4.11)	0.006	2.28 (1.28-4.07)	0.005		
Ever-smoker	0.75 (0.45-1.25)	0.263								
ECOG performance status score 2 vs. 0 or 1	2.92 (1.70-5.03)	< 0.001	1.93 (1.07-3.47)	0.030	1.97 (1.10-3.53)	0.023	2.53 (1.43-4.48)	0.001	1.56 (0.88-2.77)	0.125
Histology										
Non–squamous cell carcinoma	1	N/A	1	N/A	1	N/A	1	N/A	1	N/A
Squamous cell carcinoma	1.60 (0.91-2.80)	0.101	1.05 (0.57-1.97)	0.867	0.98 (0.52-1.85)	0.955	1.11 (0.59-2.08)	0.755	1.05 (0.57-1.93)	0.885
NSCLC not otherwise specified	0.43 (0.18-1.01)	0.054	0.51 (0.21-1.25)	0.142	0.46 (0.19-1.13)	0.092	0.56 (0.23-1.35)	0.197	0.45 (0.19-1.10)	0.081
Baseline brain metastasis	0.99 (0.49-1.99)	0.975								
Baseline pleural metastasis or effusion	2.13 (1.33-3.44)	0.002	1.55 (0.94-2.56)	0.085	1.46 (0.87-2.43)	0.148	1.62 (0.99-2.66)	0.055	1.41 (0.86-2.34)	0.177
Baseline liver metastasis	1.94 (1.13-3.33)	0.016	1.63 (0.90-2.94)	0.108	1.54 (0.85-2.78)	0.154	1.67 (0.92-3.02)	0.091	1.88 (1.06-3.36)	0.032
Radiotherapy before pembrolizumab	0.87 (0.53-1.42)	0.564								
NLR ≥4.8	3.10 (1.88-5.11)	< 0.001	2.08 (1.19-3.63)	0.010						
dNLR ≥2.6	3.20 (1.94-5.27)	< 0.001			2.21 (1.25-3.92)	0.006				
PLR ≥232	2.22 (1.35-3.66)	0.002					1.75 (1.04-2.97)	0.037		
ALI ≤17.4	5.07 (2.89-8.89)	< 0.001							4.43 (2.37-8.30)	< 0.001

Abbreviations: 95% CI = 95% confidence interval; ALI = advanced lung cancer inflammation index; BMI = body mass index; dNLR = derived neutrophil-to-lymphocyte ratio; ECOG = Eastern Cooperative Oncology Group; HR_{adj} = adjusted hazard ratio; HR_{unadj} = unadjusted hazard ratio; IO = immunotherapy; N/A = not applicable; NLR = neutrophil-to-lymphocyte ratio; NSCLC = non–small-cell lung cancer; PLR = platelet-to-lymphocyte ratio.

deemed fit enough to endure intensive combination treatment. However, despite treatment escalation, both the IO-alone and IO-combination groups showed similar median OS. Slightly longer ToT was noted in the IO-combination group, although the difference was not statistically significant. This illustrates the unmet need for optimal selection to receive IO-alone versus IO-combination treatment in metastatic NSCLC with high PD-L1 expression. There is no reason to expose patients to chemotherapy early if there is no potential benefit. There is no trial result directly comparing pembrolizumab alone and combination treatment in first-line setting for patients with metastatic NSCLC with high PD-L1 expression.

Unsurprisingly, our real-world OS and ToT were shorter than those in the trial setting, which is consistent with prior real-world study.[25] Inclusion of patients with ECOG performance status score of ≥2 for treatment in real-world practice (19.6% in the IO-alone group and 19.0% in the IO-combination group) [Table 1] compared with none in the three landmark trials (KN-024,[5] KN-189,[8] and

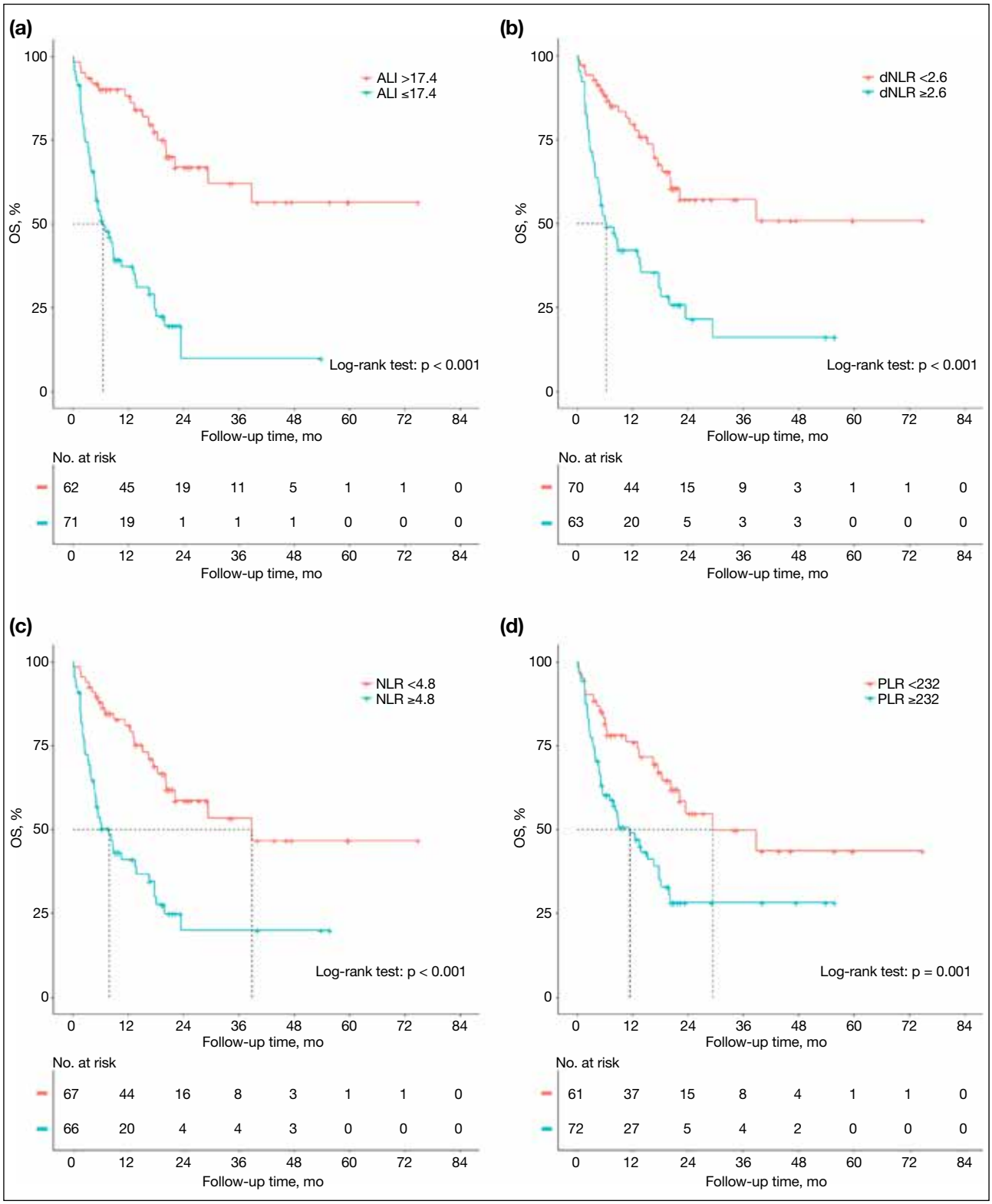

Figure 3. Kaplan–Meier estimates of overall survival (OS) according to prognostic indices at respective cut-offs of (a) advanced lung cancer inflammation index (ALI), (b) derived neutrophil-to-lymphocyte ratio (dNLR), (c) neutrophil-to-lymphocyte ratio (NLR), and (d) platelet-to-lymphocyte ratio (PLR). ALI ≤17.4 has the greatest ability to stratify the prognosis. Tick marks indicate data censoring at the last time the patient was known to be alive.

KN-407[10]) is one of the explanations. Poor performance status is a well-established factor associated with poor survival and increased toxicities in the chemotherapy era, which also holds true for IO, as demonstrated in prior retrospective studies.[26-28]

Prior studies have shown that various prognostic indices were effective at their respective cut-off values.[13-20] Still, there were no local data to compare and demonstrate their applicability in our locality. In our study, we performed ROC analyses to determine the optimal cut-off values based on local survival data. Given the prognostic nature of these indices, preference was given to sensitivity rather than specificity. We emphasised their ability to identify patients with poor prognoses and at higher risk of deterioration, in which clinicians could intensify treatment at an early stage for a suitable population or maintain closer monitoring of the patient's condition during treatment.

All four prognostic indices, namely ALI, dNLR, NLR, and PLR in descending order of their prognostic abilities, effectively stratified patients' prognoses at respective cut-off values. The identified cut-off values in our study were comparable to the results from the literature.[14-20] This served as a validation of these prognostic indices and acted as the indicative reference for local practice. ALI ≤17.4 had the largest AUCs, highest sensitivities, and specificities (Table 2). This is likely explained by the composition of ALI, which included the host's general well-being as reflected by nutritional status (BMI and serum albumin level) and an inflammation-based marker alone (dNLR) that might have a synergistic relationship with IO.[19] Furthermore, our multivariable regression analyses also demonstrated that BMI <18.5 kg/m^2, ECOG performance status score of 2, and baseline liver metastases were statistically significant poor prognostic factors (Table 3). This is consistent with prior studies showing liver metastasis being an indicator of poor prognosis and poor response to IO, which may favour the use of combination treatment.[7,29]

Given its prognostic value and easily collected variables in daily practice, ALI is an appealing marker to be incorporated into the treatment algorithm. However, the interpretation and application of ALI in a clinical context are important. Poor prognosis, despite pembrolizumab treatment, may result from poor baseline condition, limited treatment response, or both. For patients with high disease load and turnover rate, intensifying the treatment with an early chemotherapy combination allows a rapid cytotoxic effect on fast-growing cells and provides a synergistic immune-modulating effect, hence improving the efficacy of pembrolizumab.[30,31] However, patients who are deemed to be poor candidates for any form of anti-cancer treatment, early introduction of best supportive care instead of proceeding with pembrolizumab and/or chemotherapy would be more appropriate. ALI can predict a patient's prognosis with pembrolizumab, but the exercise of clinical judgement is needed to formulate a patient's management plan.

Limitations

Several limitations were identified in our study. First, our study was retrospective and therefore prone to biases. Other commonly utilised prognostic indices, including inflammatory markers (such as the C-reactive protein/erythrocyte sedimentation rate) and lactate dehydrogenase (LDH)–related markers (such as LDH level and the lung immune prognostic index), were unavailable in our study because they are not routine baseline blood tests. It is believed that the C-reactive protein/erythrocyte sedimentation rate may indicate host inflammation status, and LDH level may indicate tumour metabolism.[32]

Secondly, our sample size was relatively small, and patients receiving IO-combination represent only a minority within our cohort. This was explained by the different approval timelines of pembrolizumab alone in 2016[33] and combination treatment in 2017 (for non–squamous cell carcinoma)[34] and 2018 (for squamous cell carcinoma)[35] by the United States Food and Drug Administration and the time needed for the local working group in Hong Kong to adopt their regular uses in public health sectors. It was difficult to objectively compare disease burden and tumour turnover among these two groups, although the proportion of patients with baseline brain, pleural, and liver metastases appeared comparable among the two cohorts.

Thirdly, there is limited generalisability of our result to NSCLC with driver mutations other than common ones of *EGFR* and *ALK* due to small patient numbers. Variable responses to IO had been observed in different studies, especially concerning those harbouring rarer driver mutations.[36,37] However, the exact interplay between biology and immunology is yet to be determined.

Lastly, other emerging biomarkers related to tumour genome (e.g., tumour mutation burden, microsatellite instability, and DNA repair gene) and immune

microenvironment were not available for current analysis. However, these newer biomarkers are much more technology-demanding and research-based, and are not readily available in day-to-day practice for clinicians to quickly identify patients who are expected to have poor prognoses and limited benefit from pembrolizumab.

Despite these limitations, our results validated and suggested that patients with ALI ≤17.4 and the presence of baseline liver metastasis are at higher risk of shorter OS and earlier disease progression. Evaluation of ALI and detection of liver metastasis may guide clinicians' decisions in formulating management plans with patients.

CONCLUSION

Judicious evaluation of the reasons for low ALI attributed to poor baseline general condition where little gain from any anti-cancer treatment is expected, or aggressive disease with high tumour burden and rapid tumour turnover where treatment intensification with combination treatment may be considered as essential.

REFERENCES

1. Hong Kong Cancer Registry, Hospital Authority. Leading cancer sites in Hong Kong in 2020. 2022. Available from: https://www3.ha.org.hk/cancereg/pdf/top10/rank_2020.pdf. Accessed 10 Oct 2023.
2. Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non–small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol. 2014;9:154-62.
3. Pan Y, Zhang Y, Li Y, Hu H, Wang L, Li H, et al. *ALK*, *ROS1* and *RET* fusions in 1139 lung adenocarcinomas: a comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. Lung Cancer. 2014;84:121-6.
4. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med. 2016;375:1823-33.
5. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non–small-cell lung cancer with PD-L1 tumor proportion score ≥50. J Clin Oncol. 2021;39:2339-49.
6. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. N Engl J Med. 2018;378:2078-92.
7. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non–small-cell lung cancer. J Clin Oncol. 2020;38:1505-17.
8. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non–small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. J Clin Oncol. 2023;41:1992-8.
9. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer. N Engl J Med. 2018;379:2040-51.
10. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, et al. Pembrolizumab plus chemotherapy in squamous non–small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 study. J Clin Oncol. 2023;41;1999-2006.
11. Pitt JM, Marabelle A, Eggermont A, Soria JC, Kroemer G, Zitvogel L. Targeting the tumor microenvironment: removing obstruction to anticancer immune responses and immunotherapy. Ann Oncol. 2016;27:1482-92.
12. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A. 2002;99:12293-7.
13. Banna GL, Friedlaender A, Tagliamento M, Mollica V, Cortellini A, Rebuzzi SE, et al. Biological rationale for peripheral blood cell–derived inflammatory indices and related prognostic scores in patients with advanced non–small-cell lung cancer. Curr Oncol Rep. 2022;24:1851-62.
14. Sacdalan DB, Lucero JA, Sacdalan DL. Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: a review and meta-analysis. Onco Targets Ther. 2018;11:955-65.
15. Russo A, Russano M, Franchina T, Migliorino MR, Aprile G, Mansueto G, et al. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and outcomes with nivolumab in pretreated non–small cell lung cancer (NSCLC): a large retrospective multicenter study. Adv Ther. 2020;37:1145-55.
16. Platini H, Ferdinand E, Kohar K, Prayogo SA, Amirah S, Komariah M, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as prognostic markers for advanced non–small-cell lung cancer treated with immunotherapy: a systematic review and meta-analysis. Medicina (Kaunas). 2022;58:1069.
17. Zhang Q, Gong X, Sun L, Miao L, Zhou Y. The predictive value of pretreatment lactate dehydrogenase and derived neutrophil-to-lymphocyte ratio in advanced non–small cell lung cancer patients treated with PD-1/PD-L1 inhibitors: a meta-analysis. Front Oncol. 2022;12:791496.
18. Zhou K, Cao J, Lin H, Liang L, Shen Z, Wang L, et al. Prognostic role of the platelet to lymphocyte ratio (PLR) in the clinical outcomes of patients with advanced lung cancer receiving immunotherapy: a systematic review and meta-analysis. Front Oncol. 2022;12:962173.
19. Jafri SH, Shi R, Mills G. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non–small cell lung cancer (NSCLC): a retrospective review. BMC Cancer. 2013;13:158.
20. Mountzios G, Samantas E, Senghas K, Zervas E, Krisam J, Samitas K, et al. Association of the advanced lung cancer inflammation index (ALI) with immune checkpoint inhibitor efficacy in patients with advanced non–small-cell lung cancer. ESMO Open. 2021;6:100254.
21. Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, et al. Non–oncogene-addicted metastatic non–small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34:358-76.
22. National Comprehensive Cancer Network. NCCN Guidelines. Non–Small Cell Lung Cancer. 2023. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450. Accessed 10 Oct 2023.
23. Bai R, Lv Z, Xu D, Cui J. Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors. Biomark Res. 2020;8:34.
24. Blumenthal GM, Gong Y, Kehl K, Mishra-Kalyani P, Goldberg KB,

Khozin S, et al. Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non–small-cell lung cancer. Ann Oncol. 2019;30:830-8.
25. Waterhouse D, Lam J, Betts KA, Yin L, Gao S, Yuan Y, et al. Real-world outcomes of immunotherapy-based regimens in first-line advanced non–small cell lung cancer. Lung Cancer. 2021;156:41-9.
26. Sehgal K, Gill RR, Widick P, Bindal P, McDonald DC, Shea M, et al. Association of performance status with survival in patients with advanced non–small cell lung cancer treated with pembrolizumab monotherapy. JAMA Netw Open. 2021;4:e2037120.
27. Middleton G, Brock K, Savage J, Mant R, Summers Y, Connibear J, et al. Pembrolizumab in patients with non–small-cell lung cancer of performance status 2 (PePS2): a single arm, phase 2 trial. Lancet Respir Med. 2020;8:895-904.
28. Billingham LJ, Cullen MH. The benefits of chemotherapy in patient subgroups with unresectable non–small-cell lung cancer. Ann Oncol. 2001;12:1671-5.
29. Tumeh PC, Hellmann MD, Hamid O, Tsai KK, Loo KL, Gubens MA, et al. Liver metastasis and treatment outcome with anti–PD-1 monoclonal antibody in patients with melanoma and NSCLC. Cancer Immunol Res. 2017;5:417-24.
30. Galluzzi L, Humeau J, Buqué A, Zitvogel L, Kroemer G. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. Nat Rev Clin Oncol. 2020;17:725-41.
31. Liu W, Zhang L, Xiu Z, Guo J, Wang L, Zhou Y, et al. Combination of immune checkpoint inhibitors with chemotherapy in lung cancer. Onco Targets Ther. 2020;13:7229-41.
32. Mezquita L, Auclin E, Ferrara R, Charrier M, Remon J, Planchard D, et al. Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non–small cell lung cancer. JAMA Oncol. 2018;4:351-7.
33. United States Food and Drug Administration. Pembrolizumab (Keytruda) checkpoint inhibitor. 2016 Oct 24. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/pembrolizumab-keytruda-checkpoint-inhibitor. Accessed 25 Oct 2024.
34. United States Food and Drug Administration. Pembrolizumab (Keytruda) 5-10-2017. 2017 May 10. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/pembrolizumab-keytruda-5-10-2017. Accessed 25 Oct 2024.
35. United States Food and Drug Administration. FDA approves pembrolizumab in combination with chemotherapy for first-line treatment of metastatic squamous NSCLC. 2018 Oct 30. Available from: https://www.fda.gov/drugs/fda-approves-pembrolizumab-combination-chemotherapy-first-line-treatment-metastatic-squamous-nsclc. Accessed 25 Oct 2024.
36. Addeo A, Passaro A, Malapelle U, Banna GL, Subbiah V, Friedlaender A. Immunotherapy in non–small cell lung cancer harbouring driver mutations. Cancer Treat Rev. 2021;96:102179.
37. Vokes NI, Pan K, Le X. Efficacy of immunotherapy in oncogene-driven non–small-cell lung cancer. Ther Adv Med Oncol. 2023;15:17588359231161409.