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Novel Preoperative Immune Prognostic Index for Predicting Outcomes in Patients Undergoing Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

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Abstract

Background/Aim: The lung immune prognostic index (LIPI), which is determined by assessing the derived neutrophil-to-lymphocyte ratio in conjunction with the level of lactate dehydrogenase, predicts outcomes in various cancers. Its utility as a preoperative biomarker in upper tract urothelial carcinoma (UTUC) patients remains unexplored.

Patients and Methods: This is a retrospective study of UTUC patients who underwent radical nephroureterectomy. Patients were stratified into favorable, intermediate, and poor LIPI groups. Non-urothelial tract recurrence-free survival (NUTRFS) was evaluated using Kaplan-Meier analysis, and Cox regression analyses were performed to identify risk factors for NUTRFS.

Results: A total of 567 UTUC patients were included, with 46.4% in the favorable, 44.6% in the intermediate, and 9.0% in the poor (9.0%) LIPI groups. The median participant age was 74 years, with a median follow-up of 26 months. Kaplan-Meier curves demonstrated that NUTRFS was significantly worse in patients with poor and intermediate LIPI scores than in those with favorable LIPI scores. Furthermore, combining LIPI status with pathological stages (pT3-4/ypT2-4) and lymph node metastasis status improved postoperative non-urothelial tract recurrence prognosis assessment.

Conclusion: The preoperative LIPI is a prognostic indicator for patients with UTUC undergoing nephroureterectomy. Its predictive accuracy improves when combined with advanced pathological stages and lymph node metastasis status.

Keywords: Upper tract urothelial carcinoma, lung immune prognostic index, LIPI, preoperative biomarker, multicenter study.

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Introduction

Upper tract urothelial carcinoma (UTUC) is an uncommon malignancy, constituting about 10% of renal and 5% of urothelial tumors, with a growing incidence over recent years (1, 2). Typically, UTUC is more prevalent in the renal pelvis than in the ureter at the time of diagnosis (3). The standard approach for managing this disease, aimed at long-term control, involves radical nephroureterectomy together with excision of the bladder cuff. Despite this aggressive treatment strategy, there remains a significant risk, approximately 30%, of recurrence or mortality post-surgery (4-6). Therefore, better preoperative prognostic biomarkers for patients treated with nephroureterectomy are required.

In search of improved prognostic indicators for those undergoing nephroureterectomy, recent research has shed light on the potential role of inflammatory markers (7-9). The neutrophil-to-lymphocyte, derived neutrophil-to-lymphocyte (dNLR), lymphocyte-to-monocyte, and platelet-to-lymphocyte ratios have been scrutinized for their connections to surgical outcomes in UTUC cases (7-9). However, findings have been varied, leaving the definitive value of these markers under question.

In other oncological contexts, such as advanced non-small cell lung cancer and renal cell carcinoma (RCC), the lung immune prognostic index (LIPI), which encompasses both the dNLR and lactate dehydrogenase (LDH) level, has been recognized for its ability to predict outcomes, particularly in response to immune checkpoint inhibitors (ICIs) (10-12). Similarly, it has been proposed as a prognostic biomarker for patients with RCC and melanoma treated with ICIs (12). We recently reported the potential of the LIPI as a prognostic tool in bladder cancer scenarios (13). Despite these developments, the applicability of the LIPI for UTUC patients has not been explored. Given this backdrop, our study was designed to fill the gap in current research by examining the prognostic implications of the LIPI in the context of UTUC, particularly focusing on the risk of disease recurrence post-nephroureterectomy.

Patients and Methods

Patients. This investigation included individuals who underwent radical nephroureterectomy from January 2012 to December 2021, conducted at The Jikei University Hospital and its 16 collaborating institutions, under the consortium known as the JIKEI-YAYOI Collaborative Group. Of the initial 724 patients with complete hematological profiles obtained within one month preceding their surgeries, several were excluded due to various reasons: incomplete clinical records (n=35), non-malignant pathology (pathological T0 stage, n=2), indeterminate pathological findings (n=2), diagnosis other than urothelial carcinoma (n=39), and treatment with adjuvant chemotherapy post-surgery (n=79). Ultimately, the study cohort comprised 567 participants.

Surgical procedure. Certified urologists performed all surgical interventions, choosing between open and laparoscopic techniques based on patient and surgeon preferences. The procedure typically involved complete nephroureterectomy along with bladder cuff removal. Lymph node dissection was conducted based on the surgical team's judgement. The Jikei University Institutional Review Board granted ethical approval for this study (approval number 33-260[10878]).

Data collection. Data including patient demographics, clinicopathological features, surgical details, treatment management, and follow-up outcomes, were collected. Tumor staging was in accordance with the American Joint Committee on Cancer's 8th edition criteria, 2017. The presence of lymphovascular invasion (LVI) was confirmed when tumor cells were identified within the endothelium of blood or lymph vessels. Tumor grading and subtype analyses adhered to the 2016 World Health Organization's standards (14).

The LIPI was determined using preoperative values of the dNLR and LDH level, with the dNLR derived using the formula (neutrophils)/[(leucocytes-neutrophils) ratio], with the threshold set at 2.75 as indicated by time-

dependent receiver operating characteristic (ROC) analysis at 36 months. LDH levels were compared against the upper limit of normal (222 IU/l) with reference to existing literature (10, 12, 13, 15). Patients were classified into three LIPI score categories: favorable (0), intermediate (1), and poor (2). Non-urothelial tract recurrence-free survival (NUTRFS), cancer-specific survival, and overall survival (OS) were compared among these groups.

Outcome measures. Recurrence was identified as the emergence of disease beyond the urinary tract or bladder following surgery. Follow-up assessments included blood tests, liver and kidney function evaluations, chest radiography, urinary cytology, cystoscopy, and abdominal computed tomography scans, scheduled bi-annually for the initial two years and biennially thereafter.

Statistical analysis. The chi-squared and Kruskal-Wallis tests were utilized to assess the relationship between histological types and clinical-pathological variables. The study's primary endpoint was NUTRFS, calculated from the date of surgery to the occurrence of local or distant recurrence, metastasis, or death. The secondary endpoints were CSS and OS. The Kaplan-Meier method was employed for survival analysis, with log-rank tests for comparison. Cox proportional hazards models were applied to identify variables impacting recurrence-free survival (RFS). The predictive capability of the LIPI was assessed by integrating it into the CheckMate 274 risk criteria (16) and comparing the Harrell's concordance index values (17) between the baseline and LIPI-augmented models in the context of UTUC. Statistical significance was set at $p<0.05$. All analyses were conducted using Stata software (version 13.1, Stata Corp., TX, USA).

Results

Patient demographics. The study encompassed 567 individuals, divided into three prognostic categories according to the LIPI score: favorable (46.4%, n=263), intermediate (44.6%, n=253), and poor (9.0%, n=51) (Table I). The median participant age was 74 years (range=38-94 years), with a median follow-up of 26 months (range=1-133 months). Lymph node dissection was performed in 27.0% of patients (n=153), of whom 5.8% (n=33) exhibited lymph node involvement. Prior to undergoing radical nephroureterectomy, 10.8% of patients (n=61) received neoadjuvant chemotherapy. Significant differences were observed between the LIPI categories in terms of positive lymph node status and LVI presence, with increasing positivity from favorable to poor categories ($p=0.002$ for both). Additionally, the analysis indicated significant variability in the distribution of pT stages among the three groups, with the prevalence of stages pT2-4 increasing from the favorable group, through the intermediate group, to the poor group, a trend that was statistically significant ($p=0.002$).

Oncological outcomes. Of the total patients, 23.3% (n=132) experienced recurrence outside the urothelial tract, with a cancer-specific mortality rate of 12.9% (n=73) and overall mortality of 18.7% (n=106). The recurrence rate was 14.4% in the favorable group, 29.2% in the intermediate group, and 39.2% in the poor group. The Kaplan-Meier curves revealed that NUTRFS, CSS, and OS were significantly worse in the poor group than in the favorable group ($p<0.01$, $p<0.01$, and $p<0.01$, respectively) (Figure 1). By contrast, although there were trends, NUTRFS, CSS, and OS did not significantly differ between the poor and intermediate groups ($p=0.17$, $p=0.45$, and $p=0.52$, respectively) (Figure 1). The 3-year RFS, CSS, and OS stratified by the LIPI criteria are summarized in Table II.

Factors associated with non-urothelial tract recurrence. Univariate analysis revealed that Eastern Cooperative Oncology Group performance status (ECOG-PS) (HR=2.07 for ≥2 in reference to 0-1; $p=0.017$), urinary cytology (HR=1.82 for positive in reference to negative; $p=0.001$), pT (HR=3.22 for T2; 6.11 for T3; and 17.68 for T4 in reference to Ta/is/T1; all $p<0.001$), pN (HR=7.01 for N1 in reference to N0/Nx; $p<0.001$), tumor grade (HR=2.55 for high grade in reference to low grade or not reported;

Table I. *Patients' characteristics.*

Variable	Overall n=567	Favorable LIPI=0 n=263 (46.4%)	Intermediate LIPI=1 n=253 (44.6%)	Poor LIPI=2 n=51 (9.0%)	*p*-Value
Age, year (range)	74 (38-94)	74 (40-94)	73 (38-91)	77 (53-92)	0.42
Follow-up, month (range)	26 (1-133)	29 (1-133)	23 (1-111)	22 (1-129)	0.092
Sex, n (%)					
Male	410 (72.3)	198 (75.3)	183 (72.3)	29 (56.9)	0.027
Female	157 (27.7)	65 (24.7)	70 (27.7)	22 (43.1)	
ECOG-PS, n (%)					
0	444 (78.3)	213 (81.0)	195 (77.1)	36 (70.6)	0.369
1	88 (15.5)	35 (13.3)	44 (17.4)	9 (17.6)	
>2	35 (6.2)	15 (56.3)	14 (5.5)	6 (11.8)	
Laterality, n (%)					
Right	265 (46.7)	115 (43.7)	126 (49.8)	24 (47.1)	0.384
Left	302 (53.3)	148 (56.3)	127 (50.2)	27 (52.9)	
Hydronephrosis, n (%)					
Absent	273 (48.1)	124 (47.1)	124 (49.0)	25 (49.0)	0.906
Present	294 (51.9)	139 (52.9)	129 (51.0)	26 (51.0)	
Operative method, n (%)					
Open	94 (16.6)	45 (17.1)	37 (14.6)	12 (23.5)	0.282
Laparoscopic	473 (83.4)	218 (82.9)	216 (85.4)	39 (76.5)	
Tumor location, n (%)					
Renal pelvis	282 (49.7)	141 (53.6)	116 (45.8)	25 (49.0)	0.289
Ureter	255 (45.0)	110 (41.8)	120 (47.4)	25 (49.0)	
Both	30 (5.3)	12 (4.6)	17 (6.7)	1 (2.0)	
Tumor grade, n (%)					
Low grade	100 (17.6)	51 (19.4)	43 (17.0)	6 (11.8)	0.605
High grade	431 (76.0)	196 (74.5)	195 (77.1)	40 (78.4)	
NR	36 (6.3)	16 (6.1)	15 (5.9)	5 (9.8)	
Urine cytology, n (%)					
Positive	350 (61.7)	169 (64.3)	147 (58.1)	34 (66.7)	0.266
Negative	217 (38.3)	94 (35.7)	106 (41.9)	17 (33.3)	
Histology, n (%)					
Pure UC	541 (95.4)	255 (97.0)	240 (94.9)	46 (90.2)	0.091
UC with variant histology	26 (4.6)	8 (3.0)	13 (5.1)	5 (9.8)	
Pathological T stage					
(y)pTis/a/1	293 (51.7)	158 (60.1)	117 (46.2)	18 (35.3)	0.002
(y)pT2	81 (14.3)	31 (11.8)	39 (15.4)	11 (21.6)	
(y)pT3	164 (28.9)	68 (25.9)	78 (30.8)	18 (35.3)	
(y)pT4	29 (5.1)	6 (2.3)	19 (7.5)	4 (7.8)	
Lymph node status, n (%)					
(y)pN0	180 (31.7)	91 (34.6)	69 (27.3)	20 (39.2)	0.002
(y)pN1-2	33 (5.8)	5 (1.9)	23 (9.1)	5 (9.8)	
(y)pNx	354 (62.4)	167 (63.5)	161 (63.6)	26 (51.0)	
Concomitant CIS, n (%)					
Absent	476 (84.0)	224 (85.2)	213 (84.2)	39 (76.5)	0.298
Present	91 (16.0)	39 (14.8)	40 (15.8)	12 (23.5)	
LVI, n (%)					
Absent	405 (71.4)	205 (77.9)	171 (67.6)	29 (56.9)	0.002
Present	162 (28.6)	58 (22.1)	82 (32.4)	22 (43.1)	
Neoadjuvant chemotherapy, n (%)					
Absent	506 (89.2)	237 (90.1)	225 (88.9)	44 (86.3)	0.704
Present	61 (10.8)	26 (9.9)	28 (11.1)	7 (13.7)	

CIS: Carcinoma in situ; ECOG-PS: Eastern Cooperative Oncology Group performance status; LIPI: lung immune prognostic index; LVI: lymphovascular invasion; UC: urothelial carcinoma.

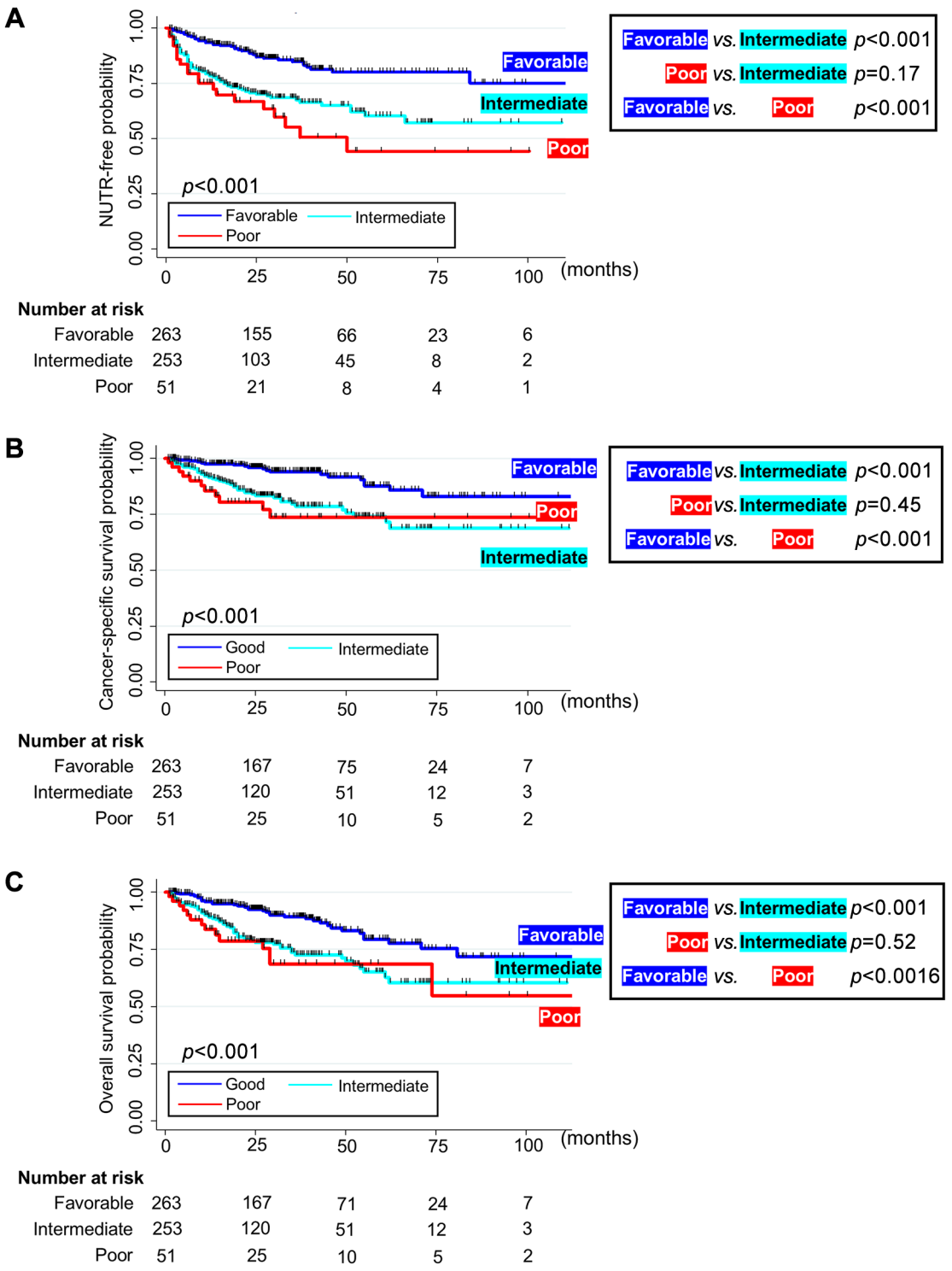

Figure 1. *Oncological outcomes stratified according to the lung immune prognostic index score. A) Non-urothelial tract recurrence-free survival (NUTRFS) in the three lung immune prognostic index (LIPI) score groups. B) Cancer-specific survival in the three LIPI score groups. C) Overall survival in the three LIPI score groups.*

Table II. *The 3-year survival rates of upper tract urothelial carcinoma patients.*

LIPI	Number of cases	3-year NUTRFS % (95%CI)	3-year CSS % (95%CI)	3-year OS % (95%CI)
Favorable	263	84.6 (78.8-89.0)	93.9 (89.4-96.6)	89.1 (83.7-92.8)
Intermediate	253	67.1 (59.9-73.3)	78.3 (70.9-84.0)	72.3 (64.7-78.5)
Poor	51	54.7 (36.6-69.7)	78.3 (70.9-84.0)	68.3 (50.9-80.7)

CI: Confidence interval; NUTRFS: non-urothelial recurrence-free survival; CSS: cancer specific survival; OS: overall survival; LIPI: lung immune prognostic index.

$p<0.001$), LVI (HR=5.9 for present in reference to absent; $p<0.001$), and LIPI score (HR=2.30 for intermediate and 2.78 for poor in reference to favorable; both $p<0.001$) were significantly associated with NUTRFS, whereas age, sex, tumor location, hydronephrosis, and variant histology were not (Table III).

In multivariate analysis, factors such as ECOG-PS, urinary cytology results, pathological T and N stages, LVI presence, and LIPI score independently predicted RFS outcomes (Table III). A decision curve analysis was conducted to assess the clinical utility of the LIPI score in patients qualifying for adjuvant therapy, as per the CheckMate 274 trial guidelines (16). This demonstrated that incorporating the LIPI score into the predictive model enhanced recurrence forecasting compared with using only the pathological T and N stages (Figure 2); the concordance indices for the models were 0.72 and 0.77, respectively.

Discussion

This research delves into the outcomes of UTUC patients stratified by LIPI scores following nephroureterectomy. We observed markedly reduced RFS in patients classified as high-risk based on LIPI scores. Through multivariate analysis, we established that variables such as advanced pathological T and N stages and LIPI status are independently associated with patient outcomes post-surgery. Our study contributes a novel perspective by being among the first to assess the prognostic importance of LIPI status in UTUC patients post-radical nephroureterectomy. Conducted retrospectively across multiple centers, this study aimed to reduce biases typically associated with individual clinician judgments and inconsistencies in patient assessments and treatments across different institutions.

Inflammatory mechanisms, involving various cellular components like neutrophils and lymphocytes, are pivotal in the carcinogenesis process (18-20). Increased neutrophil counts prompt the secretion of cytokines, such as interleukin (IL)-1β, tumor necrosis factor-α, and IL-12, to induce a chronic inflammatory state and release of arginase-1 to inhibit natural killer cells and effector T-cell-mediated antitumor immunity (21). Therefore, the dNLR is recognized as an indicator of systemic inflammation, potentially serving as a prognostic marker in cancer scenarios. Prior research, including studies by Dalpiaz *et al.,* has highlighted the prognostic significance of elevated dNLRs in UTUC outcomes post-nephroureterectomy (22). Moreover, other inflammatory markers like LDH, C-reactive protein, and serum albumin levels have been implicated in cancer prognosis, suggesting their potential as informative biomarkers for inflammation-related cancer progression (23-26). Indeed, Tan *et al.* showed that a preoperative serum LDH level >220 U/l is an independent prognostic biomarker for OS (HR=4.03, 95%CI=1.37-11.88) in patients with localized UTUC (26).

In this research, we present novel findings indicating that the LIPI score can predict outcomes of UTUC patients following surgery. Broader applications of the LIPI, apart from its use with ICIs, have not been well established. Our study, alongside limited existing research of radical cystectomy and radical nephrectomy, contributes new insights (13, 27). In these analyses, we were able to stratify

Table III. *Uni-and multi-variate analyses to identify clinicopathological characteristics related to relapse-free survival (n=52).*

		Univariate analysis			Multivariate analysis		
Covariant	Reference	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age, (continuous)		1.02	0.99-1.04	0.094	0.99	0.97-1.02	0.61
Sex							
Female	Male	1.42	0.99-2.04	0.056	1.36	0.94-1.96	0.11
ECOG-PS							
≥2	0-1	2.07	1.14-3.76	0.017	2.22	1.14-4.34	0.019
Tumor location							
Ureter	Pelvis	1.26	0.89-1.80	0.2	1.26	0.82-1.92	0.29
Both		1.52	0.75-3.08	0.24	1.63	0.77-3.41	0.2
Hydronephrosis							
Present	Absent	1.17	0.83-1.66	0.37	1	0.67-1.50	0.99
Urine cytology							
Positive	Negative	1.82	1.30-2.56	0.001	1.73	1.20-2.49	0.003
Pathological T stage							
pT2	pTa/is/1	3.22	1.82-5.70	<0.001	1.78	0.97-3.29	0.065
pT3		6.11	3.90-9.58	<0.001	3.56	2.14-5.93	<0.001
pT4		17.68	9.55-32.72	<0.001	4.22	1.94-9.17	<0.001
Lymph node status							
pN1	pN0 or pNx	7.01	4.38-11.19	<0.001	2.52	1.39-4.55	0.002
Histology							
UC with variant histology	pure UC	1.74	0.85-3.57	0.13	0.89	0.42-1.91	0.77
Pathological grade							
High	Low or NR	2.55	1.53-4.24	<0.001	1.03	0.59-1.78	0.93
Concomitant CIS							
Present	Absent	1.24	0.80-1.92	0.33	0.66	0.42-1.06	0.083
LVI							
Present	Absent	5.9	4.15-8.40	<0.001	3.01	1.97-4.57	<0.001
LIPI							
Intermediate	Favorable	2.30	1.59-3.26	<0.001	1.96	1.32-2.89	0.001
Poor		2.78	1.70-4.55	<0.001	2.59	1.52-4.39	<0.001

CI: Confidence interval; CIS: carcinoma in situ; ECOG-PS: Eastern Cooperative Oncology Group performance status; LIPI: lung immune prognostic index; LVI: lymphovascular invasion.

post-surgical recurrence risk into three levels: favorable, intermediate, and poor.

Consequently, we suggest that individuals meeting any one of the criteria, be it the dNLR or LDH levels, might benefit from supplementary adjuvant therapies or enhanced surveillance. The feasibility of incorporating the LIPI alongside other prognostic indices or predictive models for clinical use was demonstrated, highlighting the accessibility and utility of the LIPI in a clinical setting. Routine measurements of the dNLR and LDH level in clinical practices underscore their critical roles in advanced cases (28, 29). Incorporating the LIPI status has enriched the evaluative framework of the CheckMate 274

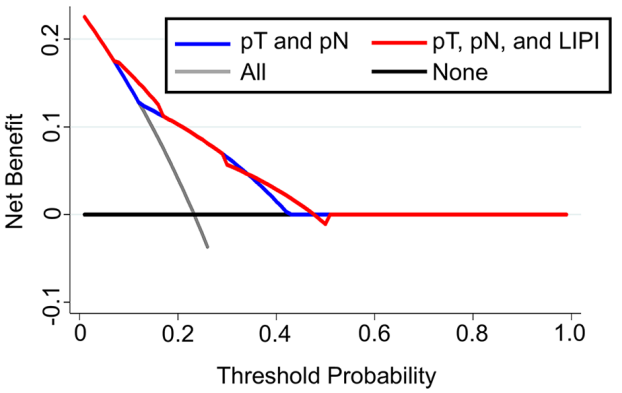

Figure 2. *Recurrence predictions based on decision curve analyses. Basic model: pT3-4 and pN+ (ypT2-4 and pN+) status. New model: basic model with the addition of lung immune prognostic index (LIPI) status.*

trial (16). Future research could explore the capability of the LIPI to identify patients who may benefit from ICIs as adjuvant therapy. This investigation would be grounded in the previously discussed notion that the LIPI score may have specific relevance in certain conditions, which could include scenarios involving the use of ICIs (10). Ongoing research will explore the role of the LIPI in identifying patients who could benefit from adjuvant ICI therapy, especially considering the potential specificity of the LIPI in certain clinical scenarios. Moreover, the ability to determine LIPI status before surgery offers a promising avenue to enhance preoperative assessments, particularly when combined with imaging studies. This approach could improve how clinicians communicate risks and treatment strategies to patients before surgery.

The determination of cutoff values for the dNLR and LDH level presents notable challenges due to inconsistencies across studies. In our analysis, we adhered to the original dNLR cutoff value of 2.75, as determined by ROC curve analysis of our patient cohort. This decision aligns closely with the findings of previous research, thereby ensuring comparability with existing literature (13, 30-32). For the LDH level, it is generally considered that using the upper limit of the normal range as the cutoff value is the most common practice (33). This discrepancy highlights the need for ongoing research and standardization to establish a universally accepted benchmark that can be effectively applied in clinical practice.

Study limitations. Firstly, despite the multicenter approach, the study's retrospective nature and relatively brief duration of follow-up may limit the generalizability of the findings. Secondly, there was a lack of standardization in follow-up procedures, with variations in the nature and frequency of postoperative examinations among patients. This inconsistency could affect the reliability of outcome assessments. Thirdly, the pathological data were collected from different institutions without undergoing a centralized pathology review, potentially leading to variability in the histopathological interpretation. Fourthly, the neoadjuvant chemotherapy regimens administered were not uniform across all participants, which could have impacted the oncological outcomes of patients with UTUC undergoing nephroureterectomy. Lastly, our study did not include any patients who received adjuvant nivolumab following nephroureterectomy, diverging from current clinical practices. This omission could limit the applicability of our results in the context of emerging treatment modalities.

Conclusion

The LIPI has demonstrated potential as a significant prognostic biomarker for predicting recurrence of UTUC. Implementing the LIPI in clinical practice may enhance decision-making processes related to the administration of adjuvant therapy and the implementation of rigorous surveillance strategies.

Conflicts of Interest

The Authors declare that there are no conflicts of interest in relation to this study.

Authors' Contributions

Conception and design: Ken Shibata, Fumihiko Urabe; Administrative support: Ken Shibata, Fumihiko Urabe, Yu Imai; Provision of study materials or patients: Ken Shibata, Fumihiko Urabe; Collection and assembly of data: All Authors; Data analysis and interpretation: Ken Shibata, Fumihiko Urabe, Kosuke Iwatani; Manuscript writing: All Authors; Final approval of manuscript: All Authors.

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