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Article

Increased Pre-Operative Lung Immune Prognostic Index Score Is a Prognostic Factor in Cases of Pathological T3 Renal Cell Carcinoma

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Abstract: We examined the efficacy of the lung immune prognostic index (LIPI) for predicting the progression of pathological T3 renal cell carcinoma (RCC). The LIPI scores of patients with pathological T3 RCC were calculated in the pre-operative and post-operative phases. Patients were divided into the zero-points, one-point, and two-points groups according to their LIPI score and into the upstage and non-upstage groups according to the pre- and post-operative increase in LIPI score. Overall survival (OS) was evaluated using Kaplan–Meier curves stratified by group. Univariate and multivariate analyses of OS was performed via Cox proportional hazard regression analysis. LIPI scores were calculated in 80 patients for whom blood sampling data were available. The upstage and non-upstage groups comprised 8 and 72 patients, respectively. Kaplan–Meier curves showed a significant difference in the pre- to post-operative LIPI score upstage group. LIPI score change was a poor prognostic factor in univariate analysis (OS: hazard ratio [HR] = 4.10, 95% confidence interval [CI] = 1.07–15.61, $P = 0.038$) and multivariate analysis (OS: HR = 4.38, 95% CI = 1.13–16.89, $P = 0.031$). An increase in LIPI score in the pre-operative phase is a poor prognostic factor in pathological T3 RCC.

Keywords: lung immune prognostic index; prognostic factor; renal cell carcinoma; T3; immune biomarkers

1. Introduction

The advent of immune checkpoint inhibitors (ICIs) for cancer treatment represents a major shift in the chemotherapy era. They have resulted in significant changes in treatment regimens since the early days of chemotherapy. ICIs have been used to treat a wide range of cancers, and numerous studies have been conducted to identify the factors that predict their efficacy in different cancer types. The Lung Immune Prognostic Index (LIPI) has been studied as a predictor of patient responses to ICIs in non-small cell lung cancer [1]. LIPI studies have also been conducted for other cancer types, including renal cell carcinoma (RCC), to assess the predictive value of ICI in terms of response, overall survival (OS), and recurrence-free survival.

Adjuvant treatment is now available for patients with RCC who are considered at a high risk of recurrence, as indicated by the KEYNOTE 564 trial [2–4]. Patients with diagnoses of pathological T3 (pT3) have worse prognoses than those with T1 and T2, thus requiring more careful monitoring. However, there are currently no tumor markers that reflect the disease status of RCC. Therefore, we investigated whether changes in LIPI scores could be used to predict the progression of pT3 RCC.

In this study, we evaluated the pre- and post-operative LIPI scores in patients with pT3 RCC as well as the changes in LIPI scores between the two periods. We also examined whether LIPI scores and their degree of change were associated with disease progression.

2. Methods

2.1. Patients

This retrospective, single-center study included 80 patients out of 85 patients diagnosed with pT3 who were treated surgically for whom blood samples were appropriately obtained (39 who underwent open total nephrectomy, 30 who underwent laparoscopic total nephrectomy, 6 who underwent robot-assisted partial nephrectomy, and 5 who underwent robot-assisted total nephrectomy) at Jichi Medical University Hospital between January 2014 and July 2024.

2.2. Ethical Considerations

This study was approved by the institutional review board of Jichi Medical University Hospital (approval no.: A22-023). Written informed consent was obtained from all of the participants prior to their inclusion in the study.

2.3. Endpoints

The primary outcome was OS divided by the pre- and post-operative LIPI score and the changes in LIPI scores between the two periods. OS was defined as the time from surgery until death.

2.4. Calculation of LIPI Score

LIPI score was calculated on the basis of the results of the patients' blood tests. It was assigned on the basis of a derived neutrophil-to-leukocyte ratio (dNLR; neutrophils / [leukocytes – neutrophils]) of >3 according to the cutoff used in the largest study published to date on ICI use in patients with cancer. The upper limit for lactate dehydrogenase (LDH) was 222 IU/L [1,5]. This LDH cutoff value has been adopted by our institution, and is similar to what has been used in previous studies [6,7]. The LIPI score stratified the patients into three groups: the zero-points, one-point, and two-points groups.

2.5. Data Collection

The LIPI score calculated from each patient's pre-operative blood sample (taken within one month preoperatively) was defined as the pre-operative score, whereas the score calculated using the patient's post-operative blood sample (taken within three months postoperatively) was defined as the post-operative score (Figure 1). The group was divided into two groups on the basis of the LIPI score, one with zero points and the other with one or two points. Changes in LIPI scores between the pre- to post-operative scores were calculated and classified into two groups: upstage and non-upstage.

Figure 1. Timing of blood sampling used to calculate the patients' LIPI scores. LIPI, lung immune prognostic index.

2.6. Statistical Analysis

The OS between pre- and post-operative LIPI scores and between the upstage and non-upstage groups were assessed using the Kaplan–Meier method and compared via the log-rank test. The associations of OS with clinical parameters, including pathology results and LIPI score changes, were assessed using Cox's proportional hazard regression analysis. The parameters included pre- and post-operative LIPI scores, as well as the changes thereof. The Fuhrman and WHO/International Society of Urological Pathology (ISUP) classifications were divided into grades 3/4 and others. Pre- and post-operative levels of serum C-reactive protein (CRP), which is considered a prognostic predictor of RCC, were also included with a cutoff of 0.5[8–10]. In our univariate comparisons, categorical data were compared using the Chi-squared test, and continuous data were compared

using the Mann–Whitney U test. All statistical analyses were performed using JMP Pro, version 17 (SAS Institute, Cary, NC, USA). Statistical significance was set at $P < 0.05$.

3. Results

The background characteristics of the patients are presented in Table 1 (n = 80). None were treated with pre-operative chemotherapy, and nine cases were treated with pembrolizumab as a post-operative adjuvant therapy.

Table 1. Characteristics of the overall patient population (n = 80).

Parameter	Value (%) or median [IQR]
Age, years	68 [60–75]
Sex:	
Male	59 (73.8)
Female	21 (26.2)
Surgical Technique:	
Open	39 (48.8)
Laparoscopic	30 (37.5)
RAPN	6 (7.5)
RARN	5 (6.2)
Tumor side, left	47 (58.8)
Pathological stage:	
pT3a	78 (97.5)
pT3b	2 (2.5)
Pathology:	
Clear cell	74 (92.5)
Non-clear cell	6 (7.5)
Fuhrman, or WHO/ISUP grade:	
1	7 (8.8)
2	43 (53.8)
3	19 (23.7)
4	8 (10)
Unclassified	3 (3.7)
Lymphatic vessel invasion	66 (82.5)
Sarcomatoid change	8 (10)
Pre-operative metastasis	9 (11.3)
CRP > 0.5	
Pre-operative	25 (31.3)
Post-operative	15 (18.8)

RAPN, Robot-assisted partial nephrectomy; RARN, Robot-assisted radical nephrectomy; ISUP, International Society of Urological Pathology; CRP, C-reactive protein; IQR, Interquartile range.

The LIPI scores and cases at the pre-operative and post-operative phases are shown in Figure 2. The pre-operative LIPI scores were 0 points in 60 cases, 1 point in 16 cases, and 2 points in 4 cases. The post-operative LIPI scores were 0 points in 67 cases, 1 point in 11 cases, and 2 points in 2 cases.

Figure 2. Number of scores and cases at each of the pre-operative phase and post-operative phase.

The OS was assessed using the Kaplan–Meier method, and the pre- and post-operative LIPI scores as well as the change in LIPI score from pre- to post-operative in two groups were compared using the log-rank test. The median OS for the pre-operative LIPI score was not reached in the 0-points group (95% confidence interval [CI] = 104–not reached [NR]) and the 1-point and 2-points groups (95% CI = 47–NR). (Figure 3A). The median OS was also not reached in the 0-points group (95% CI = 104–NR) and the 1-point and 2-points groups (95% CI = 12–NR) in terms of post-operative LIPI score (Figure 3B). For the pre- to post-operative period, there were 8 cases in the upstage group and 72 in the non-upstage group in terms of LIPI score change. The median OS was not reached in the upstage group (95% CI = 104–NR) and non-upstage group (95% CI = 12–NR) (Figure 3C).

Figure 3. Kaplan–Meier curves depicting (A) OS in the pre-operative LIPI score, (B) OS in the post-operative LIPI score, and (C) OS in the change of LIPI score from pre- to post-operative. OS, overall survival; LIPI, lung immune prognostic index.

The log-rank test was used to evaluate the difference in OS between the two groups, and no significant difference was found in pre-operative LIPI (zero points vs. one and two points) ($p = 0.725$), nor was a significant difference found in post-operative LIPI (zero points vs. one and two points) ($p = 0.402$). On the other hand, there was a statistically significant difference in the change in LIPI score from pre- to post-surgery (upstage group vs. non-upstage group) ($p = 0.024$).

Univariate and multivariate analyses were performed for OS by using Cox proportional hazards regression (Table 2). For OS, our univariate analysis identified sarcomatoid change and LIPI score change (pre- to post-operative) as poor prognostic factors. Our multivariate analysis of these factors identified both LIPI score change (pre- to post-operative) (hazard ratio [HR] = 4.38, 95% CI = 1.13–16.89, $P = 0.031$) and Sarcomatoid change (HR = 8.71, 95% CI = 1.64–46.19, $P = 0.010$) as independent factors related to poor prognosis.

Table 2. Univariate and multivariate Cox proportional hazard regression analyses of OS in the overall study population ($n = 80$).

Parameter	Cutoff	Univariable		Multivariable	
		HR (95% CI)	p	HR (95% CI)	p
Sex	Male	2.78 (0.35–21.59)	0.328	Reference	
	Female	Reference			
Age	>70 years	1.51 (0.46–5.00)	0.492	Reference	
	≤70	Reference			
Fuhrman·WHO/ISUP	Grades 3/4	1.15 (0.33–3.99)	0.814	Reference	
	Grade 1/2/unclassified	Reference			
Sarcomatoid change	Yes	7.81 (1.56–39.12)	0.012*	8.71 (1.64–46.19)	0.010*
	No	Reference			
Lymphatic vessel invasion	Yes	1.03 (0.22–4.70)	0.969	Reference	
	No	Reference			
Pre-operative LIPI	1 or 2 points	1.23 (0.37–4.13)	0.728	Reference	
	0 points	Reference			
Post-operative LIPI	1 or 2 points	1.73 (0.46–6.40)	0.411	Reference	
	0 points	Reference			
Pre-operative CRP	>0.5	1.29 (0.40–4.14)	0.662	Reference	
	≤0.5	Reference			
Post-operative CRP	>0.5	1.26 (0.34–4.71)	0.722	Reference	
	≤0.5	Reference			
LIPI score change (pre- to post-operative)	Upstage	4.10 (1.07–15.61)	0.038*	4.38 (1.13–16.89)	0.031*
	Non-upstage	Reference			

OS, Overall survival; CI, Confidence interval; HR, Hazard ratio; ISUP, International Society of Urological Pathology; CRP, C-reactive protein; LIPI, Lung immune prognostic index. *Statistically significant.

4. Discussion

In this study, we investigated whether pre- and post-operative LIPI scores and the changes in these scores correlated with OS in patients with pT3 RCC. It was found that the change in LIPI score from pre- to post-operative was highly correlated with OS.

LIPI was first reported to represent a predictor of patient responses to ICIs, mainly in non-small-cell lung cancer [1]. Its prognostic value in terms of ICIs has since been demonstrated in other cancers as well [6], including RCC [8,9]. Several studies have reported an association between LIPI score and both ICI and tyrosine kinase inhibitors in metastatic RCC [10–12]. The dNLR of LIPI has recently been studied in various ways. Although the neutrophil-to-leukocyte ratio (NLR) appears to represent a prognostic factor in non-small cell lung carcinoma, it may be even more relevant than NLR, because it includes monocytes and other granulocyte subpopulations [13,14]. High dNLR is associated with shorter survival times in patients with several tumor types—including melanoma, as well as pancreatic, bladder, and kidney cancer [5,15–17].

A number of studies have examined LIPI scores in blood tests at single points in time, such as before surgery or after ICI treatment. However, this study focused on how LIPI scores changed over the course of the RCC disease. This is because we hypothesized that blood test results do not necessarily reflect the tumor environment only at the particular time point of sampling. Infections, inflammation, hematologic disorders, and oral steroid use, for example, can also cause elevated white blood cell counts. We therefore believe that it is important to perform multiple tests to obtain more accurate diagnoses. In this study, we evaluated the association with OS using only pre- and post-operative LIPI scores, but found no significant results.

This study only investigated LIPI scores in pT3 RCC, but we recognize that other reports have evaluated this parameter in RCCs of the $\geq$ pT3, N1-2, and M0 classifications as well—all of which are considered high risk [18]. In the KEYNOTE 564 trial, pT3 RCC was considered appropriate for treatment via adjuvant therapy, owing to its high risk of recurrence [2–4]. Several reports have shown that RCC with a pathological diagnosis of T3 has a worse prognosis compared to the T1 and T2 types [19–21]. Considering that T4 RCC cases are exceedingly rare, this study only included cases of RCC with pathological diagnoses of T3 following surgical treatment.

The lack of suitable tumor markers makes it difficult to accurately monitor RCC progression. Several studies have reported that serum CRP level is associated with the progression and recurrence of RCC [22–24]. The present study also evaluated serum CRP level in terms of OS by using univariate analyses. In univariate analyses, pre- and post-operative CRP was not an independent predictor of poor prognosis. In clinical practice, CRP level can be influenced by a number of factors; therefore, it is not considered to accurately reflect early-stage tumor effects. Therefore, it is important to monitor disease progression using several prognostic markers over multiple time points.

This study has a few limitations that are worth noting. Selection bias may have occurred because the data were retrospectively obtained from a single center. In this study, the pathology of RCC was classified as clear cell type or other, and abnormal growth patterns such as rhabdoid changes and necrosis, which can impact prognosis, were not considered [25]. Both Fuhrman and ISUP grading systems were used for nuclear grading. Although one of these systems is standardized, the system used at the time of diagnosis was also considered, in order to reduce the burden on the pathologists [26].

5. Conclusion

In this study, we showed that patients with pT3 RCC whose LIPI scores rise from the pre-operative phase generally have poor disease prognoses. There are no specific tumor markers for RCC, making it difficult to accurately monitor the microenvironment of this tumor type. Monitoring changes in LIPI scores may therefore help to manage the treatment course for patients with this deadly malignancy and may also be useful in the selection of patients in whom more adjuvant therapy should be given.

Author Contributions: HH and TS contributed to the study conception and design, data analysis and interpretation, and drafting of the first version of the manuscript. MK, ET and SA contributed to the data acquisition and helped draft the manuscript. HK and TF supervised the study, helped draft the manuscript, and critically revised it for important intellectual content. All the authors have read and approved the final version of the manuscript.

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Informed Consent Statement: Written informed consent was obtained from all of the patients prior to their participation in the study.

Data Availability Statement: The dataset analyzed in this study is available from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ICIs	Immune checkpoint inhibitors
LIPI	Lung Immune Prognostic Index
RCC	Renal cell carcinoma
OS	Overall survival
pT3	Pathological T3
dNLR	Derived neutrophil-to-leukocyte ratio
NLR	Neutrophil-to-leukocyte ratio
LDH	Lactate dehydrogenase
ISUP	International Society of Urological Pathology
CRP	C-reactive protein
CI	Confidence interval
NR	Not reached
HR	Hazard ratio

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