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The CANLPH Score, an Integrative Model of Systemic Inflammation and Nutrition Status (SINS), Predicts Clinical Outcomes After Surgery in Renal Cell Carcinoma: Data From a Multicenter Cohort in Japan

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ABSTRACT

Background. A myriad of studies have demonstrated the clinical association of systemic inflammatory and nutrition status (SINS) including C-reactive protein/albumin ratio (CAR), the neutrophil/lymphocyte ratio (NLR), and the platelet/hemoglobin ratio (PHR). This study aimed to investigate the predictive value of the score integrating these variables (CANLPH) in patients with renal cell carcinoma (RCC).

Methods. Using cohort data from a multi-institutional study, 757 of 1109 patients were retrospectively analyzed. The optimal cutoff value for outcome prediction of continuous variables in CAR, NLR, and PHR was determined and the CANLPH score was then calculated as the sum score of 0 or 1 by the cutoff value in each ratio.

Results. The median follow-up time was 76 months for the patients who survived (n = 585) and 31 months for those who died (n = 172). The Youden Index offered an optimal cutoff of 1.5 for CAR and 2.8 for NLR, and a higher value from the cutoff was assigned as a score of 1. The cutoff value of the PHR was defined as 2.1 for males and 2.3 for females. The patients were assigned a CANLPH score of 0 (47.2%), 1 (31.3%), 2 (13.1%), or 3 (8.5%). In the multivariate analysis, the CANLPH score served as an independent predictor of cancer-specific mortality in both localized and metastatic RCC.

Conclusion. The score was well-correlated with clinical outcome for the RCC patients. Because this score can be concisely measured at the point of diagnosis, physicians may be encouraged to incorporate this model into the treatment for RCC.

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Renal cell carcinoma (RCC) is the most common kidney cancer, and the expected numbers in United States accounted for 65,340 of the new cases and 14,970 of the deaths in 2018.[1] Accumulating evidence shows that systemic inflammatory and nutrition status (SINS) is associated with clinical outcomes in the treatment for RCC.[2–5] For nutrition status, recent studies suggest that higher body mass index (BMI) seems to be correlated with

a favorable outcome for elderly patients with localized RCC who undergo nephrectomy[3] although obesity is an established risk factor for the development of RCC.[6,7] Furthermore, a large-scale study involving 1975 patients from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and an external validation cohort of 4657 patients showed improved survival for patients with a higher BMI who were treated with molecular targeted agents for metastatic RCC.[2] These results indicate that compromised nutrition status such as hypoalbuminemia is associated with a poor clinical outcome in RCC. In addition, substantial efforts to classify the risk prediction have been made using putative indicators for systemic inflammatory including C-reactive protein (CRP), neutrophil count, lymphocyte count, platelet count, and hemoglobin.[8–13] These indicators possess an advantage in providing objective findings at diagnosis, which potentially benefits patients and physicians for the treatment decision-making. On the other hand, every single variable might be affected by other factors such as liver and kidney function as well as infection. Therefore, it still is elusive how SINS should be practically evaluated in patients treated for cancer. In this report, we demonstrate an integrative scoring model using the CRP/albumin ratio (CAR), the neutrophil/lymphocyte ratio (NLR), and the platelet/hemoglobin ratio (PHR), which shows precise prediction of clinical outcomes in RCC.

MATERIALS AND METHODS

This multicenter study (Tokyo-Osaka Urologic Malignancy Cohort) was designed to analyze the prognostic factors of clinical outcomes of treatment with nephrectomy in RCC. The inclusion criteria for the study are shown in Fig. 1. Patients who did not undergo nephrectomy or had any missing clinicopathologic or laboratory information were excluded from the study. The study design was approved by the institutional review board (IRB approval no. RIN-750-2571).

The primary end point of the study was overall survival (OS) and cancer-specific survival (CSS) from the time of surgery, and the secondary end point was metastatic-free survival (MFS) for M0 patients. The study was performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.[14]

The clinical stage of each patient was evaluated by computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, chest x-ray, and other patient information including performance status (Eastern Cooperative Oncology Group [ECOG-PS]) and body mass index (BMI). All the clinical laboratory measurements in peripheral blood (CRP, albumin, neutrophils, lymphocytes, platelets, and hemoglobin) were preoperatively recorded within 1 month before surgery.

A pathologic review, including Fuhrman nuclear grade,[15] was examined for all the patients as well as the 7th tumor-node-metastasis (TNM) classification of the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) guidelines for renal tumors. A University of California, Los Angeles (UCLA) Integrated Staging System (UISS) risk score was assigned for each patient using their TNM classification, Fuhrman nuclear grade, and ECOG-PS.[16] The modified Glasgow Prognostic Score (mGPS) was calculated as previously described.[17] In short, the patients with both an elevated CRP (>10 mg/L) and hypoalbuminemia (< 3.5 g/dL) were assigned a score of 2. The patients with elevated CRP (>10 mg/L) and an albumin level higher than 3.5 g/dL were assigned a score of 1, and all the other patients were assigned a score of 0.

After discharge, follow-up CT and chest x-ray were performed to detect any findings of suspected disease progression every 3 months during the first year.

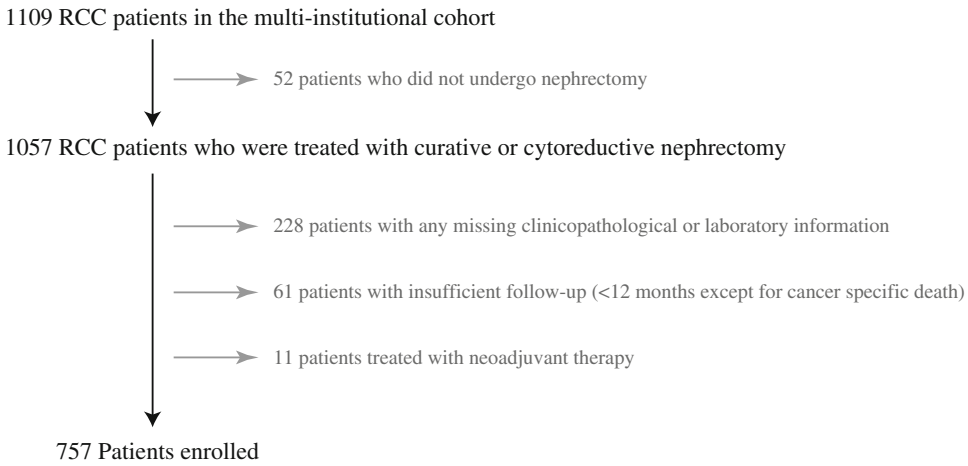

FIG. 1 Study design and inclusion criteria

Thereafter, the patients were followed up every 6 months. Both OS and CSS after nephrectomy were evaluated for all 757 patients. The follow-up period was calculated from the day of surgery to the day of death or last visit, and MFS was calculated from the date of surgery to the date of disease recurrence, metastasis, or last follow-up visit for localized RCC patients.

The clinicopathologic findings in the analysis included patient age, sex, affected side, BMI, ECOG-PS, TNM classification, histology type, tumor size, nuclear grade, and type of surgery (total or partial nephrectomy). The ability for outcome prediction of continuous variables by CAR, NLR, and the PHR was determined by receiver operating characteristic (ROC) curve analysis, and the optimal cutoff values were defined by the Youden Index as the point maximizing the difference between the true-positive and false-positive rates for all possible cut-point values.[18,19]

The distribution of each factor was assessed by contingency table with Chi square analysis. Kolmogorov–Smirnov normality was examined to check the normal distribution of continuous variables followed by performance of Student's t-test or one-way analysis of variance (ANOVA) to assess the difference between the variables. For variables with non-normal distribution, the Wilcoxon or Kruskal–Wallis test was performed to assess the difference. A Kaplan–Meier analysis was performed to estimate the survival-free ratio, and the log-rank test was performed to compare the difference between assigned patient groups.

In the uni- and multivariate analyses, Cox proportional-hazard regression models were used to estimate crude hazard ratios (HRs) followed by calculation of the covariate-adjusted HR. Harrell's C-index was used for discrimination of prediction models proposed in the study.[20] In general, a C-index value greater than 0.75 was considered to represent relatively good discrimination. All the statistical tests were two sided, with a P value lower than 0.05 considered to indicate statistical significance. All analyses were performed using JMP 13 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical Characteristics and Outcomes of the 757 RCC Patients After Nephrectomy

Table 1 shows all the clinicopathologic characteristics of all 757 patients. The mean age of the patients at diagnosis was 62.3 years. The predisposition to the disease was 71.5% for the 541 males and 28.5% for the 216 females. Distant metastasis, including multiple regional lymph

TABLE 1 Characteristics in all 757 RCC patients investigated

Age (mean ± SD)	62.3 ± 11.7
Sex	
Male (%)	541 (71.5%)
Female (%)	216 (28.5%)
BMI (mean ± SD)	23.5 ± 3.3
Side	
Right (%)	356 (47.0%)
Left (%)	401 (53.0%)
Pathological T stage	
pT1 (%)	538 (71.1%)
pT2 (%)	73 (9.6%)
pT3 (%)	138 (18.2%)
pT4 (%)	8 (1.1%)
Metastasis at diagnosis	
No (%)	662 (87.5%)
Yes (%)	95 (12.5%)
ECOG-PS	
0 (%)	655 (86.5%)
1 (%)	61 (8.1%)
2 (%)	29 (3.8%)
3 (%)	6 (0.8%)
4 (%)	6 (0.8%)
CRP (mg/L)	
Mean ± SD	12.8 ± 33.1
Median (quartile)	3.0 (0.9, 4.0)
Albumin (g/dL)	
Mean ± SD	4.2 ± 0.5
Median (quartile)	4.3 (4.0, 4.5)
Neutrophils (cells/uL)	
Mean ± SD	4026 ± 1492
Median (quartile)	3835 (3048, 4792)
Lymphocytes (cells/uL)	
Mean ± SD	1791 ± 1965
Median (quartile)	1591 (1200, 2000)
Platelet (cells × 10^4/uL)	
Mean ± SD	24.7 ± 8.2
Median (quartile)	23.4 (19.6, 28.3)
Hemoglobin (g/dL)	
Mean ± SD	13.4 ± 2.0
Median (quartile)	13.7 (12.3, 14.8)
Histology	
Clear cell (%)	669 (88.4%)
Papillary (%)	36 (4.8%)
Chromophobe (%)	19 (2.5%)
Other (%)	33 (4.4%)
Fuhrman classification	
1 (%)	126 (16.6%)
2 (%)	471 (62.2%)
≥ 3 (%)	158 (20.9%)
Unknown	2 (0.3%)

TABLE 1 continued

Tumor size (cm)	
Mean ± SD	4.8 + 2.7
Median (quartile)	4.1 (2.8, 6.2)
Operation	
TN (%)	626 (82.7%)
PN (%)	129 (17.0%)
Unknown (%)	2 (0.3%)

RCC renal cell carcinoma, *SD* standard deviation, *BMI* body mass index, *ECOG-PS* Eastern Cooperative Oncology Group—perfomance status, *CRP* C-reactive protein, *TN* total nephrectomy, *PN* partial nephrectomy

nodes, was present in 95 patients (12.5%), and localized RCC was diagnosed for 662 of these patients (87.5%) at surgery. The proportions for pathologic T stage were 71.1% for pT1, 9.6% for pT2, 18.2% for pT3, and 1.1% for pT4.

At surgery, the ECOG-PS was 0 for 655 (86.5%), 1 for 61 (8.1%), and 2 or more for 41 (5.4%) of the patients. Most of the resected tumors had a histologic diagnosis of clear cell carcinoma (669 patients, 88.4%), whereas the diagnosis was papillary RCC in 36 cases (4.8%) and chromophobe RCC in 19 cases (2.5%). The mean tumor size was 4.8 cm. Partial nephrectomy was performed in 129 cases (17%), and total nephrectomy was performed in 626 cases (82.7%).

The clinical outcomes for the cohort are summarized in Table 2. A mean follow-up time for all 757 patients was 80 months, with a median follow-up time of 76 months for the patients who survived and 31 months for those who died during their follow-up time. Of the 172 patients (22.7%) who were deceased, 127 (16.8%) had died of the disease. The 5-year OS and CSS rates were respectively 81.5% and 85.9%, and the 10-year OS and CSS rates were respectively 72.6% and 79.6%.

During the follow-up period, metastasis eventually developed in 124 (18.7%) of 662 patients. The median MFS for these 124 patients was 30 months. Of 95 patients who already had metastasis at cytoreductive surgery, 70 (73.7%) died during the follow-up period. with 2- and 5-year OS rates of 46.6% and 27.2%, respectively.

Development of the CANLPH Score for the Predication of Disease Lethality

First, we sought to verify that the CAR, NLR, and PHR ratios had prognostic value for cancer-specific death in the cohort. Due to the difference in the normal range of hemoglobin in peripheral blood between the sexes (lower limit: 13.5 g/dL for the men, and 12 g/dL for the women) and the fact that the prognosis for patients with RCC might be affected by sex[21,22] we assessed whether those ratios exhibited the difference between the sexes. We found no significant difference between the sexes in terms of the CAR ($p = 0.31$) or the NLR ($p = 0.75$), whereas the PHR for the women was significantly higher than for the men (mean of 2.14 for the women and 1.83 for the men; $p < 0.0001$) (Fig. 2).

Next, ROC curve analysis for the prediction of cancer-specific mortality was performed for each ratio (Fig. 3). For the PHR, the ROC curve was separately analyzed

TABLE 2 Follow up summary in all 757 patients

Median follow up time: months (quartile)	
Patients survived	76 (35–126)
Patients died	31 (11–77)
Number of deaths (cancer specific deaths)	172 (127)
5 yr OS rate	81.5%
10 yr OS rate	72.6%
5 yr CSS rate	85.9%
10 yr CSS rate	79.6%
In 662 of M0 patients at diagnosis	
Patients who did not develop metastasis	538
Patients who developed metastasis	124
Median MFS in 124 patietns who developed metastasis: months (quartile)	30 (10–76)
5 yr MFS rate in 662 of M0 patients at diagnosis	85.3%
10 yr MFS rate in 662 of M0 patients at diagnosis	75.9%
In 95 of M1 patients at diagnosis	
2 yr OS rate	46.6%
5 yr OS rate	27.2%

OS overall survival, *CSS* cancer-specific survival, *MFS* metastatis-free survival

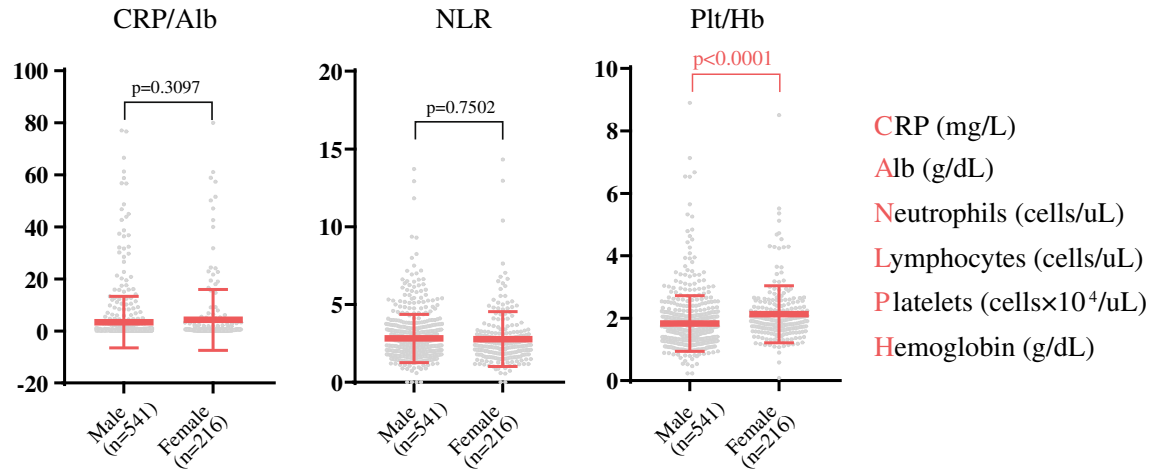

FIG. 2 Comparison of C-reactive protein/albumin, neutrophil/lymphocyte, and platelet/hemoglobin ratios between males (n = 541) and females (n = 216). Results are represented as mean ± SD

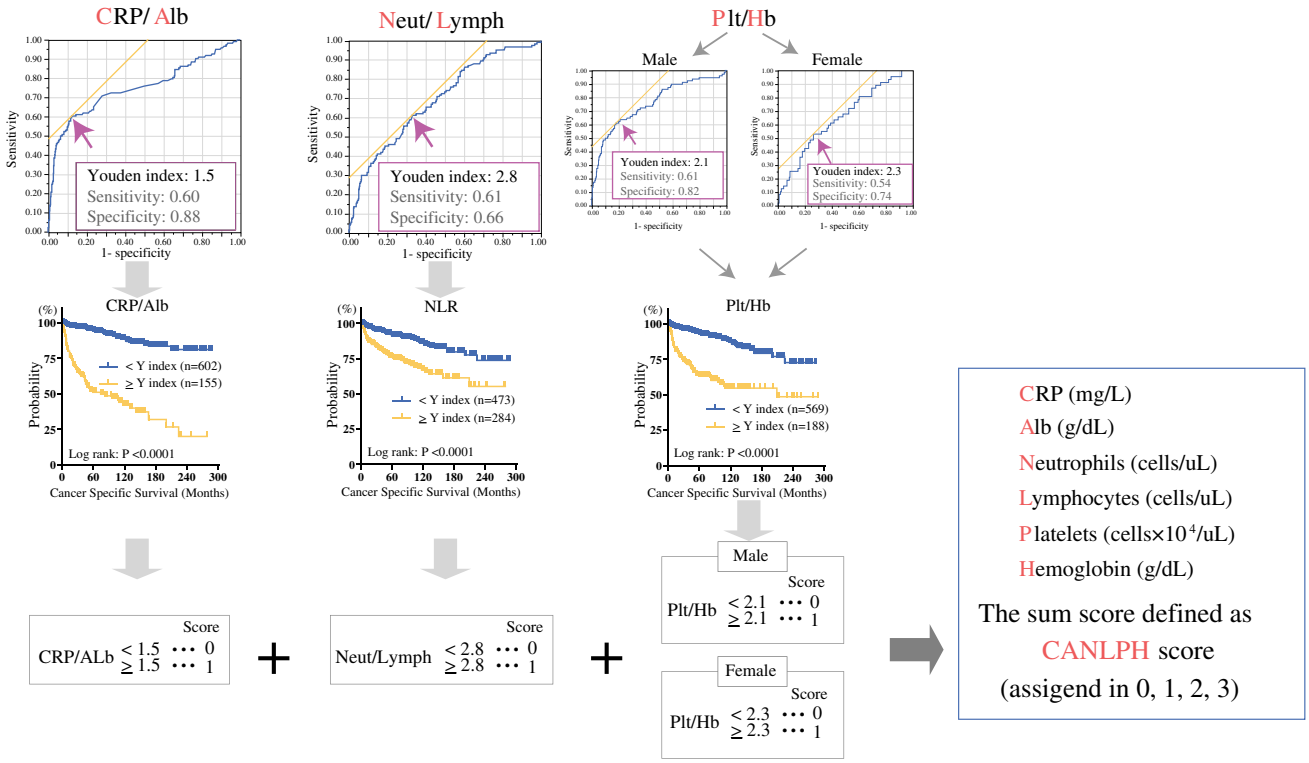

FIG. 3 Receiver operating characteristic (ROC) curves in C-reactive protein/albumin, neutrophil/lymphocyte, and platelet/hemoglobin ratios for the prediction of cancer-specific lethality. The Youden Index was determined as an optimal cut-off value in each ratio. Kaplan–Meier curves show significantly shorter cancer-specific survival (CSS), with higher values for all ratios. The CANLPH score was determined as the summed score of 0 or 1 according to each cutoff value

according to sex. The Youden Index, the point maximizing the difference between the true-positive and false-positive rates over all possible cut-point values, was determined for each ratio. The patients were divided into two groups according to the Index, and the Kaplan–Meier curves showed a significantly shorter CSS for the patients with a higher value of those ratios than for those with a lower value, suggesting the predictive value of these indicators for disease-specific mortality in RCC.

To develop the scoring system for prediction of mortality in RCC, each indicator (CAR, NLR, and PHR) were assigned to a score of 0 or 1 according to the Youden Index. The cutoff points were 1.5 for CAR and 2.8 for NLR, and a higher value from the cutoff was assigned a

TABLE 3 Patient characteristics according to the CANLPH score in all 757 patients

	CANLPH score				
	0 n = 357	1 n = 237	2 n = 99	3 n = 64	p value (ANOVA/Chi square)
Age (mean ± SD)	61.6 ± 12.3	63.6 ± 11.5	61.4 ± 11.3	63.5 ± 9.5	0.2103
Side					0.094
Right	180 (50.4%)	109 (46.0%)	36 (36.4%)	31 (48.4%)	
Left	177 (49.6%)	128 (54.0%)	63 (63.6%)	33 (51.6%)	
Sex					0.1316
Male	259 (72.6%)	176 (74.3%)	61 (61.6%)	45 (70.3%)	
Female	98 (27.4%)	61 (25.7%)	38 (38.9%)	19 (29.7%)	
BMI (mean ± SD)	24.1 ± 3.2	23.3 ± 3.4	22.3 ± 2.9	22.3 ± 2.6	< 0.0001*
pT stage					< 0.0001*
1	303 (84.9%)	171 (72.2%)	48 (48.5%)	16 (25.0%)	
2	23 (6.4%)	24 (10.1%)	13 (13.1%)	13 (20.3%)	
3	31 (8.7%)	40 (16.9%)	35 (35.4%)	32 (50.0%)	
4	0 (0%)	2 (0.8%)	3 (3.0%)	3 (4.7%)	
Mets at diagnosis					< 0.0001*
0	344 (96.4%)	213 (89.9%)	73 (73.7%)	32 (50.0)	
1	13 (3.6%)	24 (10.13%)	26 (26.3%)	32 (50.0)	
ECOG-PS					< 0.0001*
0	238 (94.7%)	206 (86.9%)	75 (75.8%)	36 (56.3%)	
1	12 (3.4%)	19 (8.0%)	16 (16.2%)	14 (21.9%)	
2	6 (1.7%)	9 (3.8%)	6 (6.1%)	8 (12.5%)	
3	0 (0.0%)	1 (0.4%)	2 (2.0%)	3 (4.7%)	
4	1 (0.3%)	2 (0.8%)	0 (0.0%)	3 (4.7%)	
Histology					0.0536
Clear cell	327 (91.6%)	206 (86.9%)	82 (82.8%)	54 (84.4%)	
Papillary	12 (3.4%)	13 (5.5%)	6 (6.1%)	5 (7.8%)	
Chromophobe	8 (2.2%)	9 (3.8%)	2 (2.0%)	0 (0.0%)	
Others	10 (2.8%)	9 (3.8%)	9 (9.1%)	5 (7.8%)	
Fuhrman nuclear grade					< 0.0001*
1	74 (23.4%)	29 (13.2%)	10 (10.1%)	1 (1.6%)	
2	207 (65.5%)	154 (70%)	53 (53.5%)	24 (37.5%)	
≥ 3	35 (11.1%)	37 (16.8%)	36 (36.4%)	39 (60.9%)	
Tumor Size (cm: mean ± SD)	4.1 ± 2.4	4.7 ± 2.6	6.0 ± 2.9	7.8 ± 2.7	< 0.0001*
Operation					< 0.0001*
TN	272 (76.2%)	200 (84.4%)	91 (91.9%)	63 (98.4%)	
PN	84 (23.5%)	36 (15.2%)	8 (8.1%)	1 (1.6%)	
Unknown	1 (0.3%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	
UISS risk group					< 0.0001*
Low	268 (75.1%)	140 (59.1%)	36 (36.4%)	10 (15.6%)	
Intermediate	88 (24.7%)	95 (40.1%)	58 (58.6%)	49 (76.6%)	
High	1 (0.32%)	2 (0.8%)	5 (5.1%)	5 (7.8%)	

BMI body mass index, *ECOG-PS* Eastern Cooperative Oncology Group—perfomance status, *TN* total nephrectomy, *PN* partial nephrectomy, *UISS* UCLA integrated staging system

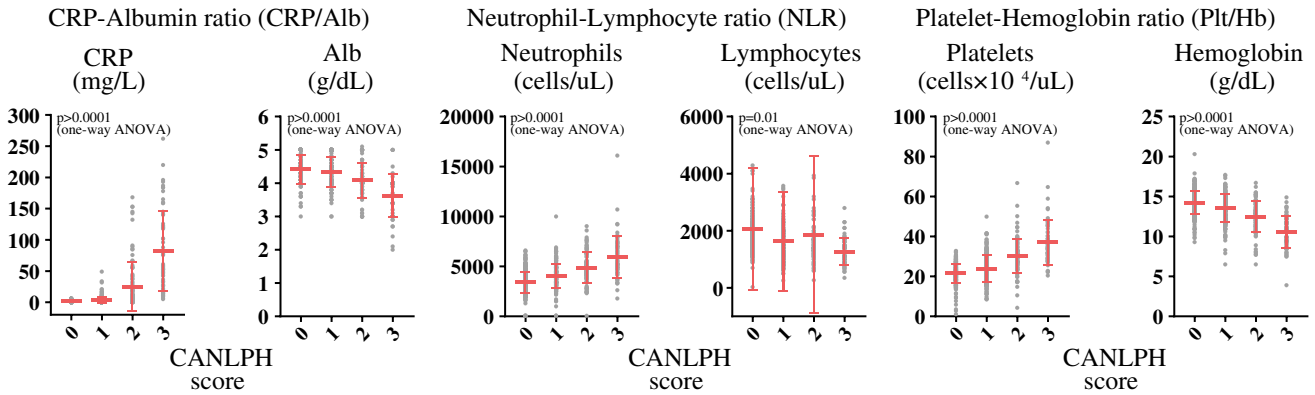

FIG. 4 The value of C-reactive protein, albumin, neutrophil counts, lymphocyte counts, platelet counts, and hemoglobin in peripheral blood according to the CANLPH score for the 757 patients with renal cell carcinoma (RCC). The results are represented as mean ± SD

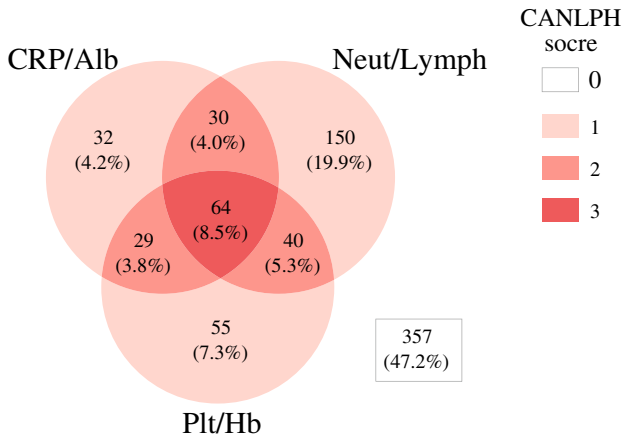

FIG. 5 Venn diagram of each population according to the CANLPH score for the 757 patients with renal cell carcinoma (RCC)

score of 1. As noted, the cutoff value of the PHR was defined as 2.1 for the men and 2.3 for the women. The CANLPH score then was calculated as the summed score of 0 or 1 in CAR, NLR, and PHR, which divided the whole cohort into four groups, namely, with CANLPH scores of 0 to 3.

Patient Characteristics and Clinical Outcomes According to the CANLPH Score

Table 3 summarizes the patient characteristics in all 757 patients according to the CANLPH score. The distributions of pathologic T stage, number of metastatic patients at surgery, ECOG-PS, Fuhrman nuclear grade, type of operation, and UISS risk group differed significantly between the scores. As expected, the mean value of CRP, neutrophils, and platelets was significantly elevated with the higher score, whereas albumin, lymphocytes, and hemoglobin inversely showed those that decreased (Fig. 4). A Venn diagram illustrated the patient number for each section, in which the proportion was 47.2% (n = 357) for a score of 0, 31.3% (n = 237) for a score of 1, 13.1% (n = 99) for a score of 2, and 8.5% (n = 64) for a score of 3 (Fig. 5). In the Kaplan–Meier curve analysis, the CANLPH score clearly discriminated clinical outcomes in terms of OS and CSS (Fig. 6). To analyze this predictive value of the CANLPH score further, we stratified the cohort according to the presence of metastasis at surgery. As shown in Table 4, the CANLPH score was well correlated with the clinical outcomes in both the M0 and M1 groups.

Cox Regression and Concordance Index Analysis for CSS

We next performed multivariate analysis including the major clinical variables for the prediction of CSS (Table 5). In the total cohort (n = 757), several variables were identified as independent predictors for CSS, including the presence of metastasis (HR, 5.288; 95% CI, 3.293–8.520; $p < 0.0001$), BMI (HR, 0.509; 95% CI, 0.308–0.807; $p = 0.035$), pT stage (HR, 2.717; 95% CI, 1.694–4.359; $p < 0.001$), Fuhrman nuclear grade (HR, 2.384; 95% CI, 1.579–3.611; $p = 0.0033$), ECOG-PS (HR, 2.687; 95% CI, 1.745–4.125; $p < 0.0001$), and the CANLPH score (HR, 2.402; 95% CI, 1.597–3.688; $p < 0.001$).

We also performed a multivariate analysis for the patients with and without metastasis at surgery. For the M0 patients, the independent prognostic factors for CSS were pT stage (HR, 4.758; 95% CI, 2.616–8.580; $p < 0.0001$), Fuhrman nuclear grade (HR, 4.459; 95% CI, 2.504–7.960; $p < 0.0001$), ECOG-PS (HR, 3.858; 95% CI, 1.987–7.088; $p < 0.0001$), and the CANLPH score (HR, 2.398; 95% CI, 1.369–4.361; $p < 0.0029$). Notably, the CANLPH score still remained as an independent predictor of CSS for the the M1 patients (HR, 2.097; 95% CI, 1.167–3.938;

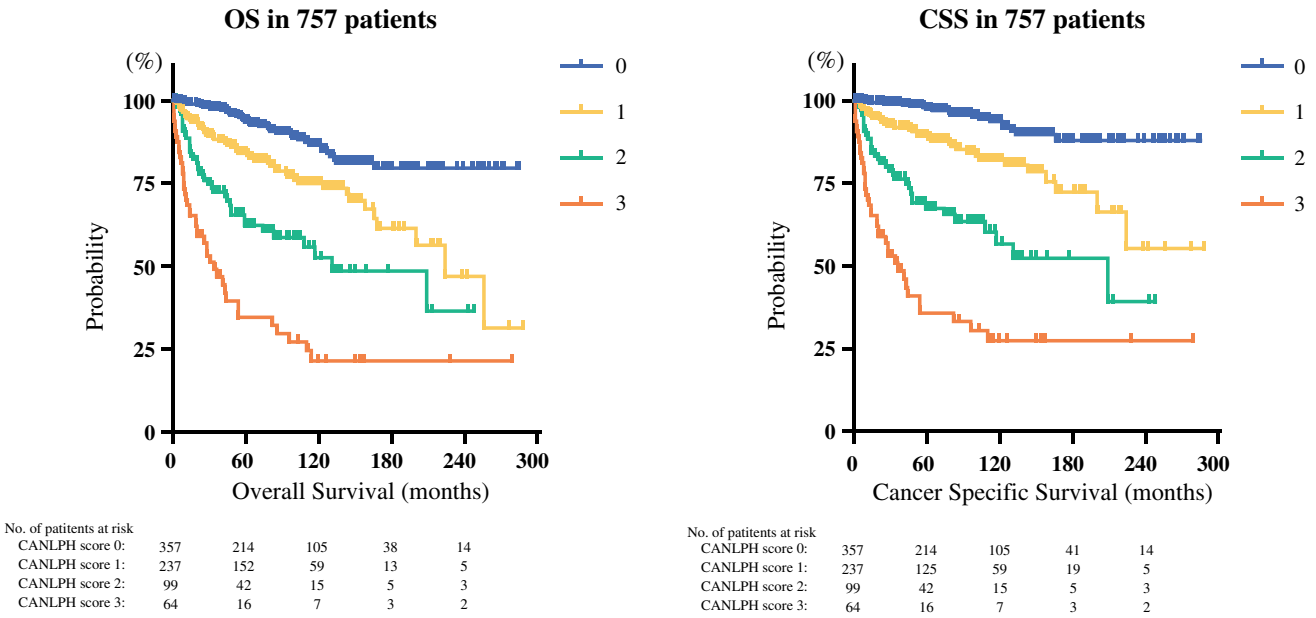

FIG. 6 Kaplan–Meier curve of overall survival (OS) and cancer-specific survival (CSS) for all 757 RCC patients according to the CANLPH score

TABLE 4 Clinical outcomes in the study according to the CANLPH score

CANLPH score	Total cohort (n = 757)		M0 patients (n = 662)			M1 patients (n = 95)	
	5 yrs CSS rate	10 yrs CSS rate	5 yrs CSS rate	10 yrs CSS rate	5 yrs MFS rate	2 yrs OS rate	5 yrs OS rate
0	97.4	93.6	97.9	94.8	91.7	73.9	63.3
1	89.3	82.1	96	89	87.7	53.6	31.3
2	67.4	56.7	82.2	69.9	66.5	41.7	19.7
3	35.8	27.4	61.9	49.9	42.1	24.5	4.9

CSS cancer specific survival, *OS* overall survival, *MFS* metastatic free survival

TABLE 5 Multivariate analysis adjusting with major clinical variables for the prediction of cancer-specific survival in patients with renal cell carcinoma

	All patients (n = 757)				M0 patients (n = 662)				M1 patients (n = 95)			
	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value
Mets at diagnosis (−vs +)	5.288	3.293	8.520	< 0001*	–	–	–	–	–	–	–	–
Age (< 65 vs ≥ 65)	0.987	0.677	1.431	0.944	0.879	0.489	1.558	0.6613	1.028	0.604	1.736	0.9178
Sex (Male vs Female)	0.957	0.655	1.383	0.818	1.025	0.567	1.781	0.9314	0.934	0.554	1.557	0.7941
BMI (< 25 vs ≥ 25)	0.509	0.308	0.807	0.0035*	0.722	0.323	1.456	0.3906	0.630	0.319	1.168	0.1597
pT stage (≤ 2 vs ≥ 3)	2.717	1.694	4.359	< .0001*	4.758	2.616	8.580	< 0001*	1.413	0.775	2.676	0.2713
Fuhrman grade ≤ 2 vs ≥ 3)	2.384	1.579	3.611	0.0033*	4.459	2.504	7.960	< .0001*	1.451	0.835	2.544	0.1893
Tumor size (≤ 4 cm vs > 4)	1.291	0.840	1.954	0.24	1.325	0.741	2.318	0.3307	1.536	0.812	2.779	0.1686
ECOG-PS (0 vs ≥ 1)	2.687	1.745	4.125	< .0001*	3.858	1.987	7.088	< .0001*	2.569	1.455	4.634	0.0013*
CANLPH score (0, 1 vs 2, 3)	2.402	1.597	3.688	< .0001*	2.398	1.369	4.361	0.0029*	2.097	1.167	3.938	0.0163*

HR hazard ratio, *CI*:confidential interval, *ECOG-PS* Eastern Cooperative Oncology Group—perfomance status

TABLE 6 Comparison of C-index between the models for the prediction of cancer-specific mortality

Models	c index	95% CI		p value
CANLPH score	0.788	0.740	0.829	ref
UISS	0.757	0.719	0.799	0.304
CRP-Alb ratio	0.753	0.693	0.805	0.146
Plt-Hb ratio	0.744	0.693	0.789	0.0074*
mGPS	0.717	0.670	0.761	0.0003*
Neut-Lymph ratio	0.691	0.638	0.740	< 0.0001*
ECOG-PS	0.671	0.624	0.714	< 0.0001*
BMI	0.592	0.537	0.645	< 0.0001*

UISS UCLA integrated staging system, *CRP* C-reactive protein, *Alb* albumin, *Plt* platelet, *Hb* hemoglobin, *mGPS* modified Glasgow prognostic score, *Neut* neutrophils, *Lymph* lymphocytes, *ECOG-PS* Eastern Cooperative Oncology Group—perfomance status, *BMI* body mass index

$p = 0.0163$), as well as ECOG-PS (HR, 2.569; 95% CI, 1.455–4.634; $p = 0.0013$).

To assess the predictive value of the CANLPH score for CSS, we compared the C-index with other putative candidates including the UISS score, CAR, NLR, PHR, mGPS, ECOG-PS, and BMI (Table 6). The C-index of 0.788 (95% CI, 0.740–0.829) in the CANLPH score was significantly higher than the PHR (C-index, 0,744; $p = 0.0074$), mGPS (C-index, 0,717; $p = 0.0003$), NLR (C-index, 0,691; $p < 0.0001$), ECOG-PS (C-index, 0.671; $p < 0.0001$), or BMI (C-index, 0,592; $p < 0.0001$). In addition, the Index demonstrated a higher value for the CANLPH score than for the UISS risk groups (C-index, 0.757), collectively suggesting the potential utility of the CANLPH score for disease outcome prediction in RCC.

DISCUSSION

The current study demonstrated an integrative scoring model of SINS to predict clinical outcome in RCC. We retrospectively analyzed the patient cohort that underwent curative or cytoreductive nephrectomy and were not treated with any neoadjuvant treatment, including molecular targeted drugs. This allowed us to assess the crude value of blood examination in CAR, NLR, and PHR without it being affected by treatment agents. The results exhibited a robust predictive value of the CANLPH score for the lethality in localized RCC patients who had undergone nephrectomy with curative intent, as well as in metastatic RCC, which generally is considered with the resection as cytoreductive therapy.

A myriad of studies have demonstrated the clinical association of SINS including CRP, albumin, NLR, platelet count, and hemoglobin. The scoring system (e.g., mGPS) that uses CRP and albumin is one of the most widely recognized tools for predicting clinical outcomes in various cancer types.[8,23–26] Recently, the CAR also has been studied as an alternative for predicting treatment outcome in genitourinary and gastrointestinal tumor cases.[27,28] In a number of studies, absolute neutrophil count by lymphocyte count (NLR) has been reported to serve as a valid prognostic factor for the patients with RCC.[9–11] In addition, some investigators have shown the combination use of NLR with other potential indicators including platelet count,[29–31] CA[32] regulatory T cell count,[33] and the platelet-lymphocyte ratio.[34] It has been suggested that a higher platelet count in blood is associated with a poor clinical outcome,[35,36] and anemia, the hallmark of deteriorated status by cancer progression, has been applied with platelet count, namely, the PHR.[37,38]

Several studies have demonstrated an integrative approach combining hemoglobin, albumin, lymphocyte, and platelet count as a continuous variable in gastric,[39] colorectal,[40] and urothelial[41] cancers. In the current study, we hypothesized that an integration of the variables, including the CAR, NLR, and PHR, whose elevation is associated with a poor clinical outcome, enhances the predictive ability by using the optimal cutoff value for each ratio. The CANLPH summed score evaluating these values has provided valid risk stratification in both localized and metastatic RCC.

With regard to a small RCC (< 4 cm), a study from Germany reported that 8% of all tumors smaller than 4 cm were pT3 stage, and that the 5-year CSS rate was 93.8% for stage pT1a versus 79.4% for stage pT ≥ pT3 disease ($p < 0.001$).[42] In our multicenter cohort, 4.1% of all the tumors smaller than 4 cm were pT3 stage disease, and the 5-year CSS rate was 96.6% for stage pT1a versus 81.5% for stage pT ≥ pT3 disease ($p = 0.0032$). These data indicate that despite the relatively indolent feature in most cases, some cases with aggressive and lethal potential in small RCC do exist. Intriguingly, logistic regression analysis in our cohort showed that a higher CANLPH score as a continuous variable could predict pT3 in small RCC (HR, 2.7; 95% CI, 1.44–5.05; $p = 0.003$), and we noted that the CANLPH score independently predicted MFS in patients who had a small RCC (376 patients), with an adjustment of pT stage (i.e., pT1 vs ≥ pT3) (HR, 1.716; 95% CI, 1.120–2.546; $p = 0.0096$).

For the treatment of metastatic RCC, the recent data from the CARMENA trial suggests that cytoreductive nephrectomy for metastatic RCC should be carefully considered by patient status.[43] Given that the CANLPH score preoperatively serves as an independent predictor of

cancer-specific mortality in both localized and metastatic RCC, it might be assumed that an incorporation of the CANLPH score enhances the assessment of risk stratification for the treatment decision-making.

The limitations in the current study include its retrospective design and relatively small sample size, which might have caused selection bias. Large-scale and prospective studies are warranted to set the optimal cutoff value and to confirm our preliminary findings.

In conclusion, we report the valid predictive ability of the CANLPH score, which comprehensively defines SINS using CAR, NLR, and PHR. The score was an independent predictor for CSS in RCC patients treated with curative or cytoreductive surgery. Because this score can be concisely measured at diagnosis, physicians may be encouraged to incorporate this model into the treatment for RCC.

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