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Deciphering the efficiency of preoperative systemic-immune inflammation related markers in predicting oncological outcomes of upper tract urothelial carcinoma patients after radical nephroureterectomy

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Purpose: To assess the prognostic value of the preoperative neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic immune-inflammation response index (SIRI) in patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy (RNU).

Materials and Methods: One hundred seven patients were retrospectively enrolled. Chi-square (χ^2) tests were adopted to assess the association of the inflammatory ratios and indexes to clinical risk factors. Overall survival (OS), metastasis-free survival (MFS), local, lymph node, and contralateral recurrence-free survival (RFS) were estimated by the Kaplan–Meier method and the corresponding curves were compared using log-rank test. Univariate and multivariate survival analysis were performed using general linear models to identify risk factors for prognosis.

Results: NLR, MLR, PLR, SII, and SIRI were predictive of OS (p=0.024, p=0.025, p=0.004, p=0.006, and p=0.03, respectively). Besides, PLR was predictive of local (p<0.001) and lymph node RFS (p=0.014) and SII was associated to lymph node and contralateral RFS prediction (p=0.034 and p=0.023, respectively). All candidate markers adding high NLR+high MLR+high PLR combination were independent risk factors of OS. PLR was an independent risk factor of local and lymph node RFS whereas the above cited combination and NLR were independent prognosticators of local and contralateral RFS respectively. All markers were correlated to poor postoperative clinical characteristics mainly pathological grade (p<0.05).

Conclusions: Preoperative NLR, MLR, PLR, SII, and SIRI were associated with higher pathologic features and worse oncological outcomes in patients treated with RNU for UTUC.

Keywords: Carcinoma; Inflammation; Lymphocytes; Neutrophils; Prognosis

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INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is an uncommon malignancy accounting for around 5% to 10% of all urothelial tumors [1,2]. Approximatively, two-thirds of patients diagnosed with UTUCs present with invasive disease at initial diagnosis with 9% of the them having metastasis.

The gold standard treatment for high-risk localized UTUC is radical nephroureterectomy (RNU) with or without adjuvant chemotherapy [3].

Despite its rareness, postoperative oncological outcomes remain unsatisfactory with nearly 50% of recurrence and 5 years cancer specific survival ranging from less than ten to 50% according to the tumor stage [4].

Different prognosis factors and models based on clinical data and imaging findings have been developed and can be used to risk-stratify patients and select the most appropriate treatment [5]. However, most of these factors are either identified postoperatively or have limited accuracy in risk stratification and treatment decision making [6]. It is therefore mandatory to identify preoperative markers potentially useful in selecting the most beneficial clinical care for UTUC patients undergoing RNU.

In this context, an imminent interest has been recently raised toward the potential assessment of preoperative hematological systemic inflammatory markers in patients with urothelial carcinomas [7-9]. Several reports pointed out the role of the inflammatory reaction in tumorigenesis and progression [10]. Considering that inflammation may trigger out the stimulation of leukocytosis, neutrophilia, and thrombocytosis in the tumor microenvironment, various hematological inflammatory markers, namely neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) have been interrogated as potential preoperative risk stratification tools and early outcome prognostic markers in UTUC [11-13]. Lately, the preoperative systemic immune-inflammation index (SII) and the systemic immune-inflammation response index (SIRI) based on neutrophile, monocyte, lymphocyte, and platelet counts have emerged with imminent potential clinic applicability and promising prognosis utility in UTCU [7-9,14,15]. In fact, multiple studies have advanced SIRI as a significant risk factor for various cancers, including pancreatic adenocarcinoma, renal cell and thyroid carcinomas [1-3]. Most importantly, these studies have shown that the predictive ability of SIRI is more powerful than that of other inflammatory factors, such as NLR, PLR, and MLR [16-18]. Additionally, preoperative SIRI has been shown to be a more effective predictor of bladder cancer survival outcomes compared to other inflammatory markers [19,20].

Yet, a little is known regarding the prognostic value of preoperative SIRI and the role of SII has not been thoroughly investigated in UTUC postoperative outcomes along with controversial data reported so far regarding the optimal clinical usefulness of the aforementioned serum inflammation makers in this context [14].

Hence, this study aimed to assess the prognostic value of NLR, PLR, MLR, SII, and SIRI, as well as the combined use of these inflammatory markers, in patients undergoing RNU for UTUC.

MATERIALS AND METHODS

1. Patients and data selection

The present retrospective study examined the records of patients who underwent RNU for non-metastatic UTUC at Urology Department of Charles Nicolle Hospital (Tunis, Tunisia) in the period between 1989 and December 2020. It was approved by the Charles Nicolle's local ethics committee (date of approval: 16/06/2020) and written informed consents were waived by the IRB due to the retrospective nature of the study.

Metastatic patients at first presentation or with concurrent bladder tumor, acute hematological or autoimmune disorders, presence of active infection or chronic inflammation or with preoperative chemotherapy were not included. Patients with less than 3 months of follow-up or with missing data were excluded (Fig. 1). Tumor stage was evaluated according to the 2002 American Joint Committee on Cancer TNM system. Histological grade of all cases was reviewed by two pathologists and re-classified as low- or high-grade using the 2004/2016 World Health Organization guidelines. Tumor size was defined by the largest tumor diameter on computed tomography. Multifocality was defined by the presence of tumor in both the ureter and the pelvic or the presence of two or more tumors.

All data was anonymized and maintained confidential. Clinical parameters including demographic characteristics, pathological features and oncologic follow-up are summarized in Table 1.

2. Definitions of the preoperatory inflammatory parameters and indexes

Neutrophils, lymphocytes, monocytes, and platelets counts were considered as measured in the preoperative complete blood count. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, MLR as the absolute monocyte count divided by the absolute lymphocyte count and PLR as the absolute platelet count divided by

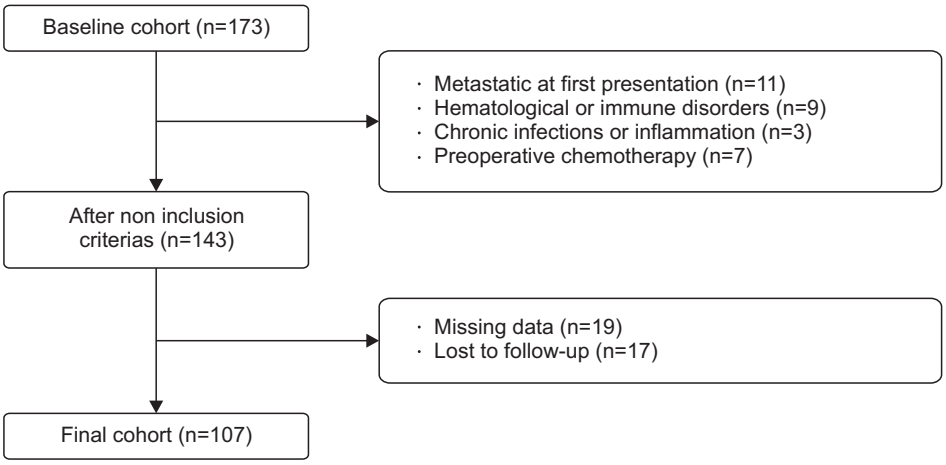

Fig. 1. Flowchart design of the present study.

the absolute lymphocyte count. Preoperative inflammatory indexes, SII, and SIRI were respectively calculated as follows: SII=platelet counts×neutrophil counts/lymphocyte counts; SIRI=neutrophil counts×monocyte counts/lymphocyte counts.

Threshold values of NLR, MLR, PLR, SII, and SIRI were obtained by creating a time-dependent receiver operating characteristic (ROC) curve plotting using the XLSTAT software, with confirmation via the Youden index (identified as the endpoint to yield the highest Youden index value [i.e., sensitivity+specificity − 1]).

3. Patient management and follow-up

Patients underwent RNU with bladder cuff removal. They were regularly monitored after surgery until December 2021. Follow-up was performed each quarter during the first year, semiannually for the next two years, and annually thereafter. It included physical examination, serum creatinine level evaluation, urinary cytology, endoscopy, and computed tomography.

During each follow-up, postoperative tumor recurrence and survival status of the patients were recorded. The endpoint of the follow-up was the time of the last follow-up or time of death.

The oncological outcomes investigated in our study were overall survival (OS), metastasis-free survival (MFS), local, lymph node, intravesical and contralateral recurrence-free survival (RFS).

Survival time was defined as the time between the date of surgery and the date of death or the last follow-up of the patients. OS was calculated from RNU to death. MFS was estimated as the time between surgical intervention and metastasis. Finally, recurrence was defined as the duration from RNU to disease recurrence (including local, intravesical, contralateral and lymph node recurrence).

4. Statistical analysis

The relationship between inflammatory ratios and indexes with clinically relevant prognostic parameters, as well as differences between categorical, was assessed using chi-square (χ^2) tests. AUC values (area under the ROC curve) were applied to appraise the prognostic accuracy of the candidate markers. OS, MFS, and RFS were estimated by the Kaplan–Meier method and the corresponding curves were compared using log-rank test. Univariate and multivariate analysis were performed using general linear models to identify risk factors for prognosis. For multivariate analysis, potential confounders were incorporated as covariates in order to estimate their total causal effect on UTUC prognosis.

IBM SPSS Statistics software (ver. 23.0; IBM Corp.) and XLSTAT were adopted for all statistical analyses. $p<0.05$ was considered statistically significant.

RESULTS

1. Patients' characteristics

Overall, 107 patients were included in the study. Baseline characteristics of the training cohort are detailed in Table 1. The mean age of the patients at diagnosis was 66.6 years ranging from 29 to 87 years. Among them, 90 (84.1%) were males and 17 (15.9%) were females.

In the training cohort, 83 (77.6%) were active smokers, 26 (24.3%) had hypertension, 15 (14.0%) had diabetes and 15 (14.0%) had BMI ≥25 kg/m^2. Preoperative imaging revealed hydronephrosis in 69 patients (64.5%), multifocal tumors in 21 patients (19.6%), tumor size greater than 2 cm in 76 patients (71.0%), and tumor localization in the renal pelvic/calyx in 53 patients (49.5%). Additionally, preoperative urine cultures was positive in 13 patients (12.1%).

Regarding pathology staging on specimen report, 49 (45.8%) were pTa/pT1, 20 (18.7%) were pT2, and 37 (34.6) were

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Table 1. Demographic and clinical characteristics of the study cohort (n=107)

Characteristic		NLR			MLR			PLR			SII			SIRI		
		Group 1 <1.5 (n=15)	Group 2 ≥1.5 (n=92)	p-value	Group 1 <0.358 (n=61)	Group 2 ≥0.358 (n=46)	p-value	Group 1 <175 (n=70)	Group 2 ≥175 (n=37)	p-value	Group 1 <668 (n=49)	Group 2 ≥668 (n=58)	p-value	Group 1 <1,904 (n=65)	Group 2 ≥1,904 (n=42)	p-value
Median age (y)		68.1	66.3	0.54	66.2	67.1	0.63	66.7	66.4	0.91	67.2	66.12	0.58	67	65	0.49
Sex	Male	11 (73.3)	79 (85.9)	0.22	50 (82.0)	40 (87.0)	0.49	59 (84.3)	31 (83.8)	0.95	40 (81.6)	50 (86.2)	0.52	54 (83.1)	36 (85.7)	0.76
	Female	4 (26.7)	13 (14.1)		11 (18.0)	6 (13.0)		11 (15.7)	6 (16.2)		9 (18.4)	8 (13.8)		11 (16.9)	6 (14.3)	
Tobacco use	Smokers	10 (66.7)	73 (79.3)	0.27	45 (73.8)	38 (82.6)	0.28	53 (75.7)	30 (81.1)	0.53	37 (75.5)	46 (79.3)	0.64	49 (75.4)	34 (81.0)	0.50
	Non smokers	5 (33.3)	19 (20.7)		16 (26.2)	8 (17.4)		17 (24.3)	7 (18.9)		12 (24.5)	12 (20.7)		16 (24.6)	8 (19.0)	
Hypertension	Yes	7 (46.7)	19 (20.7)	0.03*	17 (27.9)	9 (19.6)	0.32	18 (25.7)	8 (21.6)	0.64	14 (28.6)	12 (20.7)	0.34	15 (23.1)	11 (26.2)	0.43
	No	8 (53.3)	73 (79.3)		44 (72.1)	37 (80.4)		52 (74.3)	29 (78.4)		35 (71.4)	46 (79.3)		50 (76.9)	31 (73.8)	
Hydronephrosis	Yes	10 (66.7)	59 (64.1)	0.51	36 (59.0)	33 (71.7)	0.15	40 (57.1)	25 (67.6)	0.03*	31 (63.3)	38 (65.5)	0.54	40 (61.5)	29 (69.0)	0.54
	No	3 (20.0)	28 (30.4)		21 (34.4)	10 (21.7)		25 (35.7)	6 (16.2)		16 (32.7)	15 (25.9)		20 (30.8)	11 (26.2)	
Diabetes	Yes	2 (13.3)	13 (14.1)	0.57	13 (21.3)	7 (15.2)	0.42	13 (18.6)	7 (18.9)	0.97	7 (14.3)	13 (22.4)	0.28	11 (16.9)	9 (21.4)	0.56
	No	13 (86.7)	74 (80.4)		48 (78.7)	39 (84.8)		57 (81.4)	30 (81.1)		42 (85.7)	45 (77.6)		54 (83.1)	33 (78.6)	
BMI	<25 kg/m^2	2 (13.3)	14 (15.2)	0.58	10 (16.4)	6 (13.0)	0.81	11 (15.7)	5 (13.5)	0.61	8 (16.3)	8 (13.8)	0.35	11 (16.9)	5 (11.9)	0.61
	≥25 kg/m^2	1 (6.7)	14 (15.2)		10 (16.4)	5 (10.9)		9 (12.9)	6 (16.2)		5 (10.2)	10 (17.2)		9 (13.8)	6 (14.3)	
Tumor location	Ureteral	8 (53.3)	34 (37.0)	0.49	24 (39.3)	18 (39.1)	0.89	24 (34.3)	18 (48.6)	0.09	20 (40.8)	22 (37.9)	0.61	25 (38.5)	17 (40.5)	0.30
	Renal	7 (46.7)	46 (50.0)		31 (50.8)	22 (47.8)		39 (55.7)	14 (37.8)		28 (57.1)	25 (43.1)		37 (56.9)	16 (38.1)	
Tumor multifocality	1	12 (80.0)	71 (77.2)	0.90	50 (82.0)	33 (71.7)	0.41	55 (78.6)	28 (75.7)	0.50	36 (73.5)	47 (81.0)	0.32	50 (76.9)	33 (78.6)	0.89
	>1	3 (20.0)	18 (19.6)		9 (14.8)	12 (26.1)		13 (18.6)	8 (21.6)		11 (22.4)	10 (17.2)		13 (20.0)	8 (19.0)	
Tumor size	≤2 cm	3 (20.0)	14 (15.2)	0.74	11 (18.0)	6 (13.0)	0.61	12 (17.1)	5 (13.5)	0.78	11 (22.4)	6 (10.3)	0.14	12 (18.5)	5 (11.9)	0.28
	>2 cm	11 (73.3)	65 (70.7)		44 (72.1)	32 (69.6)		51 (72.9)	25 (67.6)		34 (69.4)	42 (72.4)		47 (72.3)	29 (69.0)	
CIS	Yes	1 (6.7)	10 (10.9)	0.69	5 (8.2)	6 (13.0)	0.69	6 (8.6)	5 (13.5)	0.51	4 (8.2)	7 (12.1)	0.69	6 (9.2)	5 (11.9)	0.86
	No	11 (73.3)	71 (77.2)		47 (77.0)	35 (76.1)		53 (75.7)	29 (78.4)		35 (71.4)	47 (81.0)		47 (72.3)	35 (83.3)	
TNM stage	pTa	7 (46.7)	23 (25.0)	0.14	21 (34.4)	9 (19.6)	0.02*	23 (32.9)	7 (18.9)	0.11	19 (38.8)	11 (19.0)	<0.001*	21 (32.3)	9 (21.4)	0.01*
	pT1	4 (26.7)	15 (16.3)		14 (23.0)	5 (10.9)		15 (21.4)	4 (10.8)		14 (28.6)	5 (8.6)		16 (24.6)	3 (7.1)	
	pT2	3 (20.0)	17 (18.5)		11 (18.0)	9 (19.6)		12 (17.1)	8 (21.6)		7 (14.3)	13 (22.4)		14 (21.5)	6 (14.3)	
	pT3	1 (6.7)	26 (28.3)		12 (19.7)	15 (32.6)		15 (21.4)	12 (32.4)		8 (16.3)	19 (32.8)		10 (15.4)	17 (40.5)	
	pT4	0 (0.0)	10 (10.9)		2 (3.3)	8 (17.4)		4 (5.7)	6 (16.2)		0 (0.0)	10 (17.2)		3 (4.6)	7 (16.7)	
Pathological grade	LG	11 (73.3)	42 (45.7)	0.048*	38 (62.3)	15 (32.6)	0.002*	41 (58.6)	12 (32.4)	0.01*	31 (63.3)	22 (37.9)	0.01*	38 (58.5)	15 (35.7)	0.01*
	HG	4 (26.7)	50 (54.3)		23 (37.7)	31 (67.4)		29 (41.4)	25 (67.6)		18 (36.7)	36 (62.1)		27 (41.5)	27 (64.3)	
Vascular emboli	Yes	1 (6.7)	24 (26.1)	0.09	12 (19.7)	13 (28.3)	0.30	14 (20.0)	11 (29.7)	0.26	6 (12.2)	19 (32.8)	0.01*	12 (18.5)	13 (31.0)	0.10
	No	14 (93.3)	68 (73.9)		49 (80.3)	33 (71.7)		56 (80.0)	26 (70.3)		43 (87.8)	39 (67.2)		53 (81.5)	29 (69.0)	
Positive surgical margins	Yes	0 (0.0)	10 (10.9)	0.18	4 (6.6)	6 (13.0)	0.25	1 (1.4)	9 (24.3)	<0.001*	0 (0.0)	10 (17.2)	0.002*	3 (4.6)	7 (16.7)	0.036*
	No	15 (100.0)	82 (89.1)		57 (93.4)	40 (87.0)		69 (98.6)	28 (75.7)		49 (100.0)	48 (82.8)		62 (95.4)	35 (83.3)	

Values are presented as median or number (%).

NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic immune-inflammation response index; BMI, body mass index; CIS, carcinoma *in situ*; LG, low grade; HG, high grade.

*p<0.05; p-values for Student test or χ^2 test.

pT3/pT4. Fifty-four patients (50.5%) had high grade tumor, 25 (23.4%) had vascular emboli, 10 (9.3%) had positive margins and 11 (10.3%) synchronous carcinoma *in situ* (CIS).

Mean follow-up was 27 months during which 23 (21.5%) of the cases had distant metastasis, 8 (7.5%) local recurrence, 19 (17.8%) lymph node recurrence, 25 (23.4%) intravesical recurrence, and 3 (2.8%) contralateral recurrence.

2. Association of hematological ratios and indexes related to inflammation to clinicopathological features

Patients were stratified according to the optimal threshold values of all ratios and indexes of interest (NLR, 1.5; MLR, 0.358; PLR, 175; SII, 668; and SIRI, 1,904).

The association to clinical prognostic parameters revealed no significant correlation between NLR, MLR, and PLR groups to age, sex, tobacco use, diabetes state, BMI, tumor localization, multifocality, size, concomitant CIS, and the presence of vascular emboli (p>0.05) (Table 1).

However, a significant association was highlighted between these ratios and pathological grade (p=0.048 for NLR, p=0.002 for MLR, and p=0.01 for PLR) (Table 1). In addition, MLR was associated to TNM stage (p=0.02) and PLR was significantly correlated to hydronephrosis status and positive surgical margins (p=0.03 and p<0.001, respectively) (Table 1).

On the other side, SII and SIRI were associated to pathological grade (p=0.01 and p=0.01, respectively), TNM stage (p<0.001 and p=0.01, respectively) and the presence of positive surgical margins (p=0.002 and p=0.036, respectively) (Table 1). SII was also correlated to the presence of vascular emboli (p=0.01). Nevertheless, there was no significant difference between SII and SIRI groups (according to the cut-off value) toward other clinical or pathological features (Table 1).

3. Survival prediction's efficiency of preoperative NLR, MLR, PLR, SII, and SIRI following RNU

NLR, MLR, PLR, SII, and SIRI were predictive risk markers associated to OS (p=0.024, p=0.025, p=0.004, p=0.006, and p=0.03, respectively) (Fig. 2). Correspondingly, UTUC patients having NLR or MLR or NLR or SII or SIRI counts below the threshold level have better survival outcome than those with elevated levels (Fig. 2). Even so, none of the above cited candidate markers was associated to MFS prediction (p>0.05) (Tables 2, 3).

Univariate analysis showed that multifocality, TNM stage, histopathological grade, presence of vascular emboli, and surgical margins were significant risk factors of OS in UTUC patients (p=0.04, HR 1.225, 95% CI 1.141-1.309; p<0.001, HR 1.437, 95% CI 1.357-1.517; p<0.001, HR 1.590, 95% CI 1.499-1.681; p=0.002, HR 1.758, 95% CI 1.676-1.839; and p=0.045, HR 1.890, 95% CI 1.732-2.024, respectively) (Table 2). Additionally, TNM stage, pathological grade, and the presence of vascular emboli were highlighted as potential risk factors for MFS in UTUC (p<0.001, HR 1.461, 95% CI 1.372-1.549; p<0.001, HR 1.264, 95% CI 1.183-1.345; and p=0.02, HR 1.354, 95% CI 1.231-1.477, respectively) (Table 2).

Notably, the univariate test confirmed the prognostic significance of NLR, MLR, PLR, SII, and SIRI in predicting OS in UTUC patients following RNU (p=0.01, HR 1.881, 95% CI 1.809-1.953; p=0.008, HR 1.461, 95% CI 1.360-1.562; p=0.006, HR 1.378, 95% CI 1.282-1.475; p=0.007, HR 1.544, 95% CI 1.442-1.647; and p=0.01, HR 1.417, 95% CI 1.170-1.410, respectively) (Table 2). Moreover, TNM stage, pathological grade and vascular emboli status were significantly correlated to MFS prediction (p<0.001, HR 1.461, 95% CI 1.372-1.549; p<0.001, HR 1.264, 95% CI 1.183-1.345; and p=0.02, HR 1.354, 95% CI 1.231-1.477, respectively).

The multivariate analysis underlined that preoperative NLR, MLR, PLR, SII, but not SIRI, were significant independent prognostic OS risk markers (p<0.05) (Table 3). As well, the combinations high SII+high SIRI and high NLR+high MLR+high PLR were significantly associated to OS prediction (p=0.01, HR 1.543, 95% CI 1.383-1.702 and p=0.006, HR 1.429, 95% CI 1.285-1.572, respectively) (Table 3). In fact, patients having high preoperative SII+high SIRI or high NLR+high MLR+high PLR have poorer OS after RNU (p=0.006 and p=0.002, respectively) (Fig. 3).

4. Prognostic value of preoperative NLR, MLR, PLR, SII, SIRI, and clinical risk factors in terms of recurrence prediction

PLR was underlined as being associated with local and lymph node RFS (p<0.001 and p=0.014, respectively) (Fig. 4A, B). Indeed, patients with PLR counts below 175 showed better local and lymph node RFS than those with PLR counts of 175 or higher (Fig. 4A, B).

Moreover, SII was demonstrated to be a potential risk factor for lymph node and contralateral RFS (p=0.034 and p=0.023) (Fig. 4C, D). Accordingly, patients with SII ≥668 experienced worse lymph node and contralateral RFS (Fig. 4C, D).

Besides, the univariate analysis emphasized that patient age (<66 years vs. ≥66 years) was a significant local RFS prognostic marker (p=0.02) (Table 2). Additionally, tumor multifocality and NLR were significantly associated with contralateral RFS' prediction (p=0.04, p=0.01) (Table 2). Furthermore, TNM stage (<pT3 vs. ≥pT3), pathological grade (LG

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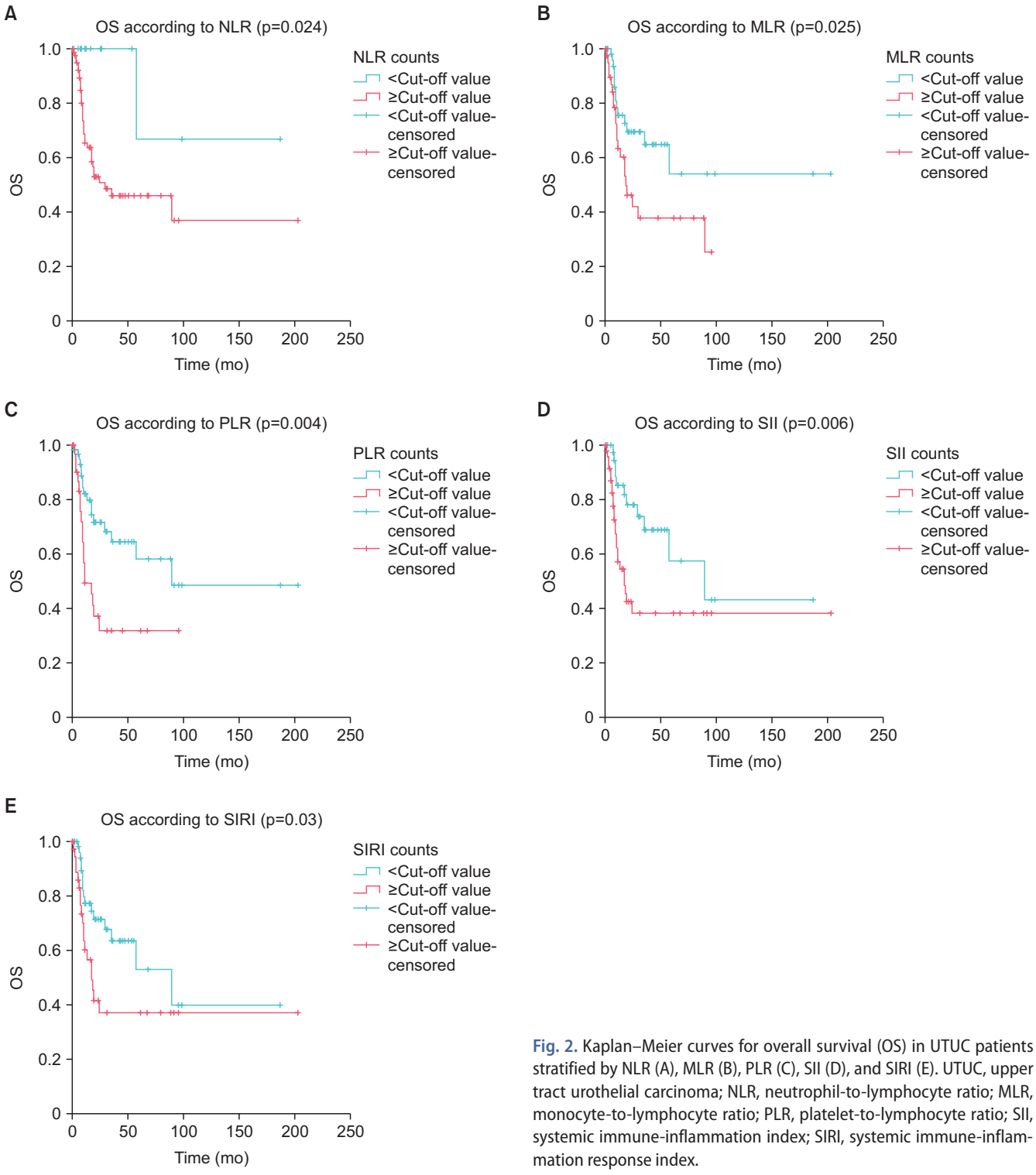

Fig. 2. Kaplan–Meier curves for overall survival (OS) in UTUC patients stratified by NLR (A), MLR (B), PLR (C), SII (D), and SIRI (E). UTUC, upper tract urothelial carcinoma; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic immune-inflammation response index.

vs. HG), the presence of vascular emboli and positive surgical margins, PLR and SII were revealed as significant predictive markers of lymph node RFS (p<0.001, p<0.001, p<0.001, p=0.004, p=0.04, and p=0.008, respectively) (Table 2).

As well, TNM stage (<pT3 vs. ≥pT3), pathological grade, the presence of positive surgical margins, and PLR were significantly correlated to local RFS prediction (p<0.001, p=0.001, p=0.03, and p=0.001, respectively) (Table 2). Though, tumor size, BMI, diabetes state, tobacco consumption, preoperative urine culture, hydronephrosis status, hypertension, and concomitant CIS were not associated with recurrence prediction of UTUC patients after RNU (p>0.05) (Table 2).

Ultimately, multivariate analysis confirmed that TNM stage (<pT3 vs. ≥pT3), pathological grade, and the presence

Table 2. Univariate analysis of variables for the prediction of survival outcomes in UTUC patients undergoing radical nephroureterectomy

Variable	Univariate analysis														
	Overall survival			Metastasis-free survival			Local recurrence			Lymph node recurrence			Contralateral recurrence		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (<66 y vs. ≥66 y)	1.539	1.434–1.645	0.64	0.259	0.167–0.350	0.21	1.667	1.523–1.810	0.02*	1.792	1.699–1.886	0.73	1.896	1.660–2.131	0.38
Sex (M vs. F)	1.165	1.088–1.241	0.36	0.244	0.113–0.374	0.86	1.128	1.003–1.253	0.96	1.184	1.100–1.268	0.38	1.071	0.869–1.274	0.49
Tobacco use (yes vs. no)	1.318	1.217–1.419	0.52	0.235	0.133–0.337	0.09	1.283	1.111–1.456	0.70	1.278	1.171–1.385	0.26	1.163	0.891–1.435	0.24
Hypertension (yes vs. no)	1.744	1.653–1.836	0.52	0.241	0.106–0.356	0.74	1.830	1.680–1.980	0.56	1.722	1.624–1.819	0.14	1.729	1.488–1.970	0.61
Diabetes (yes vs. no)	1.789	1.703–1.875	0.69	0.223	0.106–0.340	0.43	1.786	1.642–1.930	0.62	1.827	1.737–1.917	0.85	1.907	1.681–2.132	0.41
BMI (<25 kg/m^2 vs. ≥25 kg/m^2)	1.471	1.211–1.731	0.58	0.207	0.047–0.367	0.93	1.074	0.807–1.341	0.57	1.063	0.905–1.222	0.36	1.069	0.703–1.435	0.70
Hydronephrosis (yes vs. no)	1.710	1.609–1.810	0.13	0.240	0.140–0.340	0.51	1.749	1.562–1.936	0.25	1.746	1.639–1.853	0.13	1.661	1.380–1.942	0.97
Tumor location (ureteral vs. renal)	1.547	1.431–1.663	0.62	0.195	0.104–0.285	0.69	1.616	1.405–1.827	0.64	1.496	1.368–1.624	0.25	1.671	1.325–1.910	0.74
Tumor multifocality (1 vs. >1)	1.225	1.141–1.309	0.04*	0.351	0.125–0.578	0.67	1.274	1.129–1.419	0.17	1.219	1.126–1.311	0.39	1.424	1.195–1.654	0.04*
Tumor size (≤2 cm vs. >2 cm)	1.813	1.724–1.902	0.65	0.235	0.109–0.361	0.58	1.831	1.675–1.988	0.74	1.835	1.740–1.930	0.76	1.897	1.662–2.132	0.39
Preoperative urine culture (positive vs. negative)	1.880	1.814–1.946	0.13	0.295	0.139–0.451	0.63	1.819	1.696–1.941	0.27	1.849	1.771–1.926	0.07	1.931	1.731–2.131	0.45
TNM stage (<pT3 vs. ≥pT3)	1.437	1.357–1.517	<0.001*	1.461	1.372–1.549	<0.001*	1.564	1.405–1.723	<0.001*	1.523	1.432–1.613	<0.001*	1.322	1.049–1.595	0.93
Pathological grade (LG vs. HG)	1.590	1.499–1.681	<0.001*	1.264	1.183–1.345	<0.001*	1.702	1.528–1.877	0.001*	1.630	1.523–1.736	<0.001*	1.564	1.271–1.857	0.49
CIS (yes vs. no)	1.879	1.806–1.953	0.90	0.318	1.151–1.485	0.50	1.880	1.760–2.001	0.93	1.873	1.795–1.951	0.83	1.699	1.475–1.922	0.08
Vascular emboli (yes vs. no)	1.758	1.676–1.839	0.002*	1.354	1.231–1.477	0.02*	1.741	1.606–1.876	0.09	1.663	1.574–1.752	<0.001*	1.907	1.681–2.132	0.41
Positive surgical margins (yes vs. no)	1.890	1.732–2.024	0.045*	0.290	0.106–0.474	0.64	1.851	1.762–1.940	0.03*	1.850	1.786–1.914	0.004*	1.967	1.823–2.111	0.65
NLR (<1.5 vs. ≥1.5)	1.881	1.809–1.953	0.01*	0.179	0.054–0.303	0.09	1.923	1.794–2.051	0.23	1.902	1.823–1.981	0.16	1.601	1.398–1.803	0.01*
MLR (<0.358 vs. ≥0.358)	1.461	1.360–1.562	0.008*	0.264	0.172–0.356	0.20	1.515	1.333–1.697	0.23	1.464	1.350–1.578	0.53	1.542	1.252–1.832	0.40
PLR (<175 vs. ≥175)	1.378	1.282–1.475	0.006*	0.277	0.180–0.374	0.17	1.580	1.416–1.745	0.001*	1.420	1.313–1.527	0.04*	1.170	0.896–1.440	0.22
SII (<668 vs. ≥668)	1.544	1.442–1.647	0.007*	0.256	0.166–0.345	0.06	1.607	1.424–1.790	0.12	1.636	1.526–1.747	0.008*	1.258	0.969–1.548	0.08
SIRI (<1,904 vs. ≥1,904)	1.417	1.170–1.410	0.01*	0.277	0.183–0.370	0.70	1.429	1.250–1.607	0.43	1.444	1.333–1.556	0.23	1.192	0.910–1.474	0.18

UTUC, upper tract urothelial carcinoma; HR, hazard ratio; CI, confidence interval; M, male; F, female; BMI, body mass index; LG, low grade; HG, high grade; CIS, carcinoma *in situ*; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic immune-inflammation response index.
*p<0.05; p-values for univariate general linear model.

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Table 3. Multivariate analysis of variables for the prediction of survival outcomes in UTUC patients undergoing radical nephroureterectomy

Variable	Multivariate analysis														
	Overall survival			Metastasis-free survival			Local recurrence			Lymph node recurrence			Contralateral recurrence		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (<66 y vs. ≥66 y)	1.829	1.698–1.959	0.86	1.739	1.574–1.929	0.34	1.670	1.492–1.848	0.02*	1.842	1.662–2.022	0.71	1.898	1.625–2.170	0.39
Tumor multifocality (1 vs. >1)	1.314	1.181–1.447	0.03*	1.214	1.060–1.375	0.49	1.375	1.099–1.651	0.17	1.170	1.344–1.617	0.81	1.425	1.158–1.692	0.03*
TNM stage (≥pT3 vs. <pT3)	1.743	1.614–1.872	<0.001*	1.439	1.343–1.534	<0.001*	1.567	1.367–1.768	<0.001*	1.471	1.340–1.602	<0.001*	1.326	1.006–1.646	0.96
Pathological grade (LG vs. HG)	1.857	1.712–2.002	<0.001*	1.632	1.516–1.748	<0.001*	1.704	1.485–1.923	0.001*	1.603	1.441–1.765	<0.001*	1.567	1.224–1.909	0.50
Vascular emboli (yes vs. no)	1.629	1.500–1.757	0.001*	1.696	1.552–1.839	0.013*	1.745	1.578–1.912	0.08	1.789	1.665–1.913	0.02*	1.909	1.649–2.170	0.42
Positive surgical margins (yes vs. no)	1.829	1.731–1.926	0.06	1.913	1.807–2.019	0.68	1.851	1.737–1.964	0.03*	1.906	1.825–1.987	0.03*	1.966	1.796–2.137	0.64
SII+SIRI															
Low SII+low SIRI	0.314	1.150–1.478	0.09	0.348	0.142–0.553	0.07	0.391	0.160–0.621	0.13	0.439	0.265–0.612	0.06	0.739	0.401–1.076	0.07
High SII+high SIRI	1.543	1.383–1.702	0.01*	0.522	0.324–0.720	0.07	0.500	0.158–0.842	0.43	0.404	0.234–0.573	0.27	0.386	0.284–0.489	0.18
NLR+MLR+PLR															
Low NLR+low MLR+low PLR	0.112	0.034–0.189	0.05	0.957	0.815–1.099	0.13	1.000	0.768–1.232	0.27	0.890	0.768–1.013	0.21	0.771	0.540–1.002	0.33
High NLR+high MLR+high PLR	1.429	1.285–1.572	0.006*	1.206	1.100–1.313	0.35	1.217	1.042–1.339	0.001*	1.229	1.121–1.336	0.67	1.000	0.249–0.504	0.32
NLR (<1.5 vs. ≥1.5)	1.971	1.855–12.088	0.01*	1.957	1.710–2.107	0.08	2.000	1.751–2.249	0.22	1.875	1.745–2.005	0.14	1.599	1.359–1.838	0.01*
MLR (<0.358 vs. ≥0.358)	1.600	1.439–1.761	0.008*	1.522	1.318–1.726	0.21	1.625	1.276–1.974	0.24	1.434	1.260–1.608	0.54	1.544	1.205–1.882	0.40
PLR (<175 vs. ≥175)	1.514	1.360–1.669	0.006*	1.450	1.242–1.628	0.17	1.580	1.373–1.786	0.001*	1.392	1.232–1.553	0.03	1.171	0.850–1.491	0.22
SII (<668 vs. ≥668)	1.686	1.522–1.849	0.009*	1.652	1.447–1.858	0.07	1.750	1.399–2.101	0.13	1.562	1.388–1.736	0.06	1.262	0.924–1.599	0.08
SIRI (<1,904 vs. ≥1,904)	1.543	1.383–1.702	0.01*	1.522	1.324–1.720	0.07	1.500	1.158–1.842	0.43	1.404	1.234–1.573	0.27	1.193	0.864–1.522	0.18

UTUC, upper tract urothelial carcinoma; HR, hazard ratio; CI, confidence interval; LG, low grade; HG, high grade; SII, systemic immune-inflammation index; SIRI, systemic immune-inflammation response index; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
*p<0.05; p-values for multivariate general linear model.

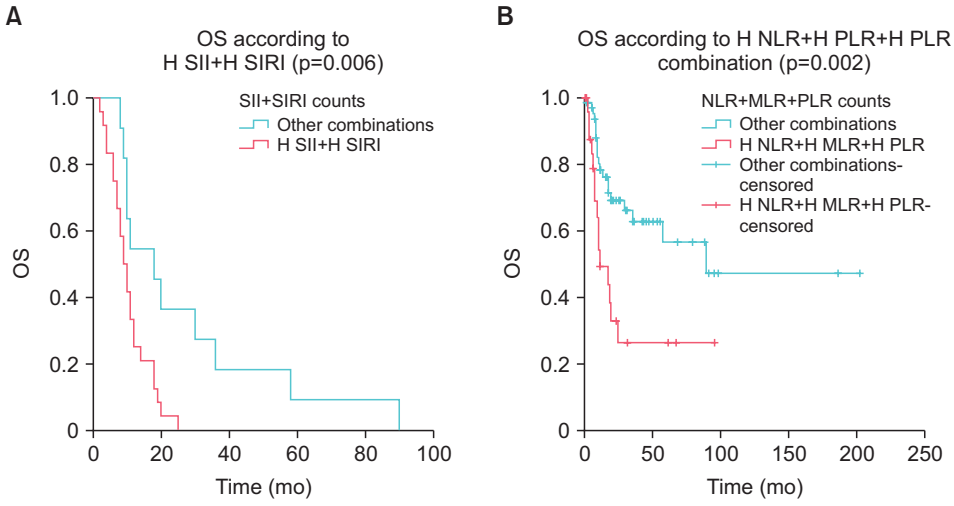

Fig. 3. Kaplan–Meier curves showing the correlation between H SII+H SIRI combination (A) and H NLR+H MLR+H PLR combination (B) to overall survival (OS) of UTUC patients following RNU. H, high; SII, systemic immune-inflammation index; SIRI, systemic immune-inflammation response index; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; UTUC, upper tract urothelial carcinoma.

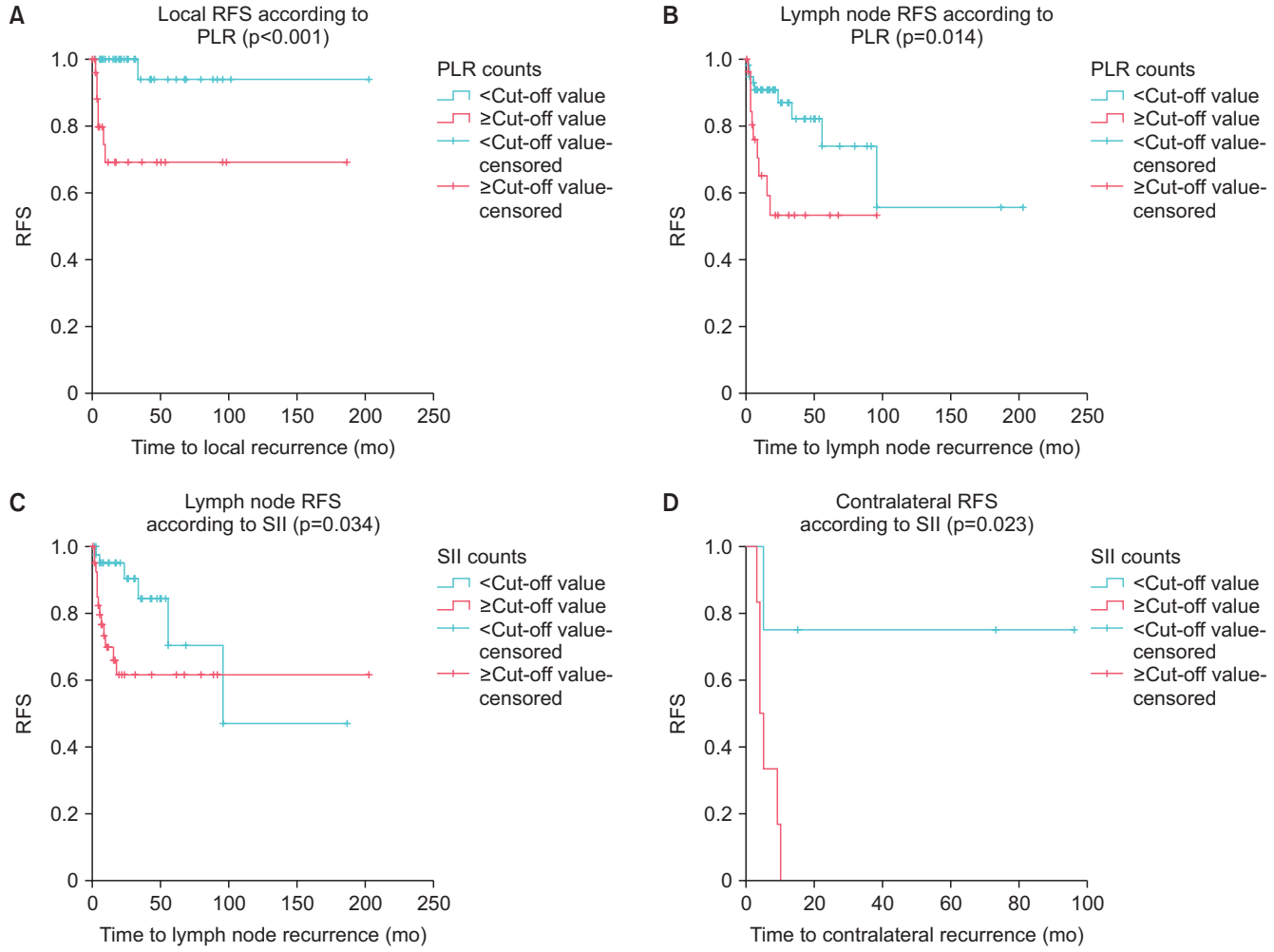

Fig. 4. Kaplan–Meier curves of local RFS, lymph node RFS and contralateral RFS of UTUC patients following RNU according to preoperative PLR and SII. RFS, recurrence-free survival; UTUC, upper tract urothelial carcinoma; RNU, radical nephroureterectomy; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

of positive surgical margins were significant independent predictors of local and lymph node recurrence (p<0.05) (Table 3). Patient's age was also predictive of local RFS and multi-focality was disclosed as an independent prognostic marker only associated to contralateral recurrence risk (p=0.02, HR 1.670, 95% CI 1.492-1.848 and p=0.03, HR 1.425, 95% CI 1.158-

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1.692, respectively) (Table 3).

When questioning the prognostic value of the systemic inflammation related markers through the multivariate model, we found that PLR was an effective independent predictor of local and lymph node RFS of UTUC patients following surgical treatment (p=0.001, HR 1.580, 95% CI 1.373-0.786 and p=0.03, HR 1.392, 95% CI 1.232-1.553, respectively) (Table 3). Furthermore, the independent prognostic efficiency of NLR in predicting contralateral RFS was emphasized (p=0.01, HR 1.599, 95% CI 1.359-1.838) (Table 3). Notably, the combination of high NLR+high MLR+high PLR was significantly predictive of local RFS (p=0.001, HR 1.217, 95% CI 1.042-1.339) (Table 3).

DISCUSSION

Numerous studies endeavor to set up potential biomarkers useful for oncological outcome prediction to help urologists choosing optimal personalized treatments for patients with UTUC after surgery. It has been lately proved that systemic inflammation, as one of the cardinal characteristics of cancer, may affect tumorigenesis and progression by remodeling the immune landscape thereby influencing oncological outcomes of cancer patients [10,21]. Accordingly, we interrogated in the present study the clinical and prognostic utility of preoperative hematological systemic inflammatory markers namely NLR, MLR, PLR, SII, and SIRI in UTUC patients following RNU. They are emerging preoperative prognostic markers recently described in urothelial carcinomas [8,9,14,15]. Even though, very few reports, so far, described their prognostic utility, specifically SIRI, in UTUC [14]. To our knowledge, our study ranks among the first line surveys [9,11,14] and is the first one in the region to investigate the prognostic value of the aforementioned markers in UTUC.

Correspondingly, preoperative NLR, MLR, PLR, SII, and SIRI were significantly associated to OS's prediction along with previous reports [7-9,15,22]. More importantly, preoperatory NLR, MLR, PLR or SII or SIRI and the combination high NLR+high MLR+high PLR were revealed in our study as powerful independent risk factors for OS pending toward a valuable efficiency in anticipating survival risk of UTUC patients after surgical treatment (Fig. 5A-G).

Besides survival prediction, the candidate markers demonstrated a potential effectiveness in predicting disease recurrence. In fact, NLR was significantly associated to contralateral RFS' prediction. Furthermore, PLR was demonstrated to be a valuable predictor of local RFS, SII of contralateral RFS and both were significantly associated to lymph node recurrence prediction. Moreover, we demonstrated that the combination high NLR+high MLR+high PLR was significantly predictive of local RFS. Taken together, PLR, NLR and the combination composed by high levels of all ratios were the most relevant for clinical practice since they were shown to be efficient independent prognosticators in terms of local, lymph node and contralateral recurrence (p<0.05) (Table 3, Fig. 5). By referring to literature, recent prognostic investigations evolve rather bladder recurrence and questioned NLR, MLR, PLR, and SII, but not SIRI's efficiency in recurrence prediction [7,11]. In addition, other studies communicated the predictive value of NLR, PLR, and SII in predicting general RFS risk, but not specific type of relapse [8,9,13]. Yet, no data regarding SIRI's role in predicting post-RNU recurrence in UTUC patients has been reported so far. In the light of the scarcity of data with this regard, we consider that it was worthy investigating the potential involvement of all the candidate markers in predicting the risk of local, lymph node and contralateral recurrence. Thus, their potential relevance in the clinical practice seems promising as they may potentially point out patients at higher risk of poor outcome and identify those who are illegible for aggressive therapy.

From the biological point of view, neutrophils, platelets, monocytes and lymphocytes levels were described to mirror certain systemic inflammatory responses to tumor aggressiveness [23]. Indeed, tumor linked inflammation generates hematologic changes, such as lymphocytes, monocytes, and hemoglobin secretion adding the recruitment of immune mediators mainly small inflammatory proteins, and immune cells [21]. Indeed, neutrophils, monocytes and platelets play a pro-tumoral role within the systemic inflammatory microenvironment growth through boosting the secretion of pro-inflammatory mediators mainly cytokines and chemokines [24]. Whereas platelets may also adopt a direct stimulation of tumor cells, thereby promoting tumor growth, invasion, and angiogenesis [9,25]. Besides, monocytes contribute to early tumor onset and progression and their level may reflect tumoral burden [26]. On the contrary, lymphocytes trigger specific anti-cancer immune microenvironment (mainly by the secretion of interferon-γ and tumor necrosis factor-α) and consequently enhance tumor surveillance, proliferation control and apoptosis induction clinically reflected by better patients' survival outcome [10,27]. Consequently, the ability of cancer to escape immune surveillance requires that pro-tumoral signals overweigh host immune system's anti-tumoral attempts to restrain tumor growth [28]. In view of these mechanisms, we can partially hypothesize that preoperatory high NLR, high MLR, high PLR, high SII or high

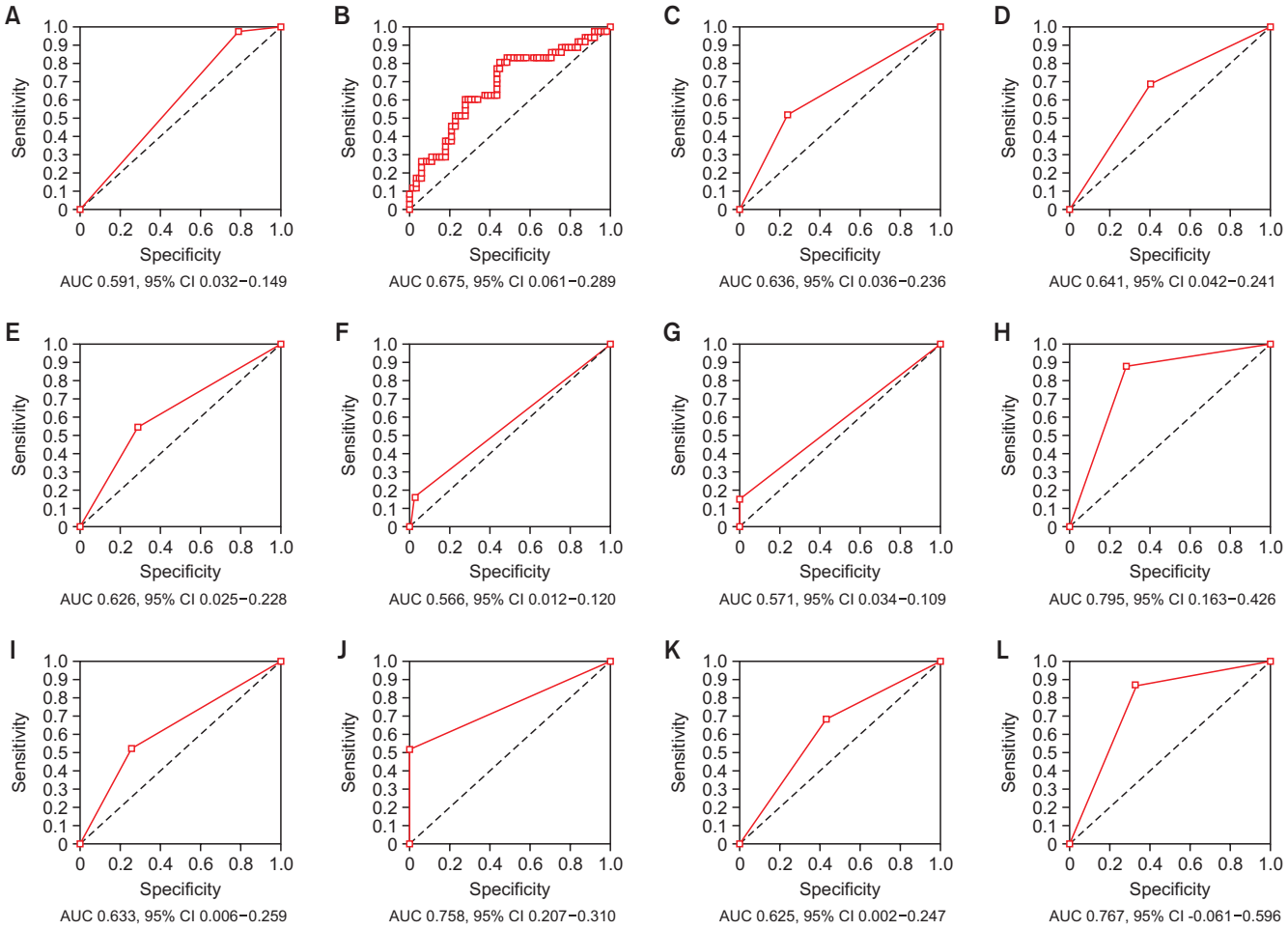

Fig. 5. ROC analysis of the prognostic accuracy of NLR, MLR, PLR, SII, SIRI (A-E), H NLR+H MLR+H PLR for OS and local RFS (F, G), PLR for local RFS and lymph node RFS (H, I), SII for contralateral RFS and lymph node RFS (J, K), NLR for contralateral RFS (L) in UTUC patients following RNU. ROC, receiver operating characteristic; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic immune-inflammation response index; H, high; OS, overall survival; RFS, recurrence-free survival; UTUC, upper tract urothelial carcinoma; RNU, radical nephroureterectomy; AUC, area under the ROC curve; CI, confidence interval.

SIRI with low lymphocytes counts may probably reflect protumoral inflammatory microenvironment, poor anti-tumor immune status clinically reflected by adverse poor outcomes [28].

Finally, we demonstrated that the candidate markers are not only useful for survival and recurrence prediction but were also correlated to pathologic and surgical outcomes namely T-stage, pathological grade, the presence of positive surgical margins, hydronephrosis and vascular emboli which could be also relevant to clinical practice (Table 3). Controversial data was reported within this regard [7,11,14].

Overall, integrating NLR, MLR, PLR, SII, and SIRI within the same report was an attempt to reveal as much prognostic data as possible from a simple preoperative routine blood test, as they are non-invasive for patients and easy obtainable in the clinical practice.

Yet, we are as well aware of the limitations of our study. Its retrospective nature may cause a selection bias during patient enrollment and data collection. Moreover, the clinical applicability of our candidate markers is restricted to patients unscathed from acute hematological or autoimmune disorders, active infection or chronic inflammation which could partially limit their applicability. Also, the predictive applicability of these markers in patients treated with neoadjuvant and adjuvant chemotherapy couldn't be assessed in our study. In fact, neoadjuvant chemotherapy was not routinely recommended by international guidelines when our patients underwent RNU for UTUC [29,30] and the number of patients who were treated with adjuvant chemotherapy in our cohort was very small and thus couldn't allow for a conclusion to be drawn. Accordingly, prospective studies are mandatory to evaluate and conclude to the predictive value of the systemic immune related markers in patients undergoing adjuvant and neoadjuvant chemotherapy for UTUC.

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Additionally, the absence of a control cohort and the uncertainty of the underlying biological mechanisms elucidating the significantly associated findings may reduce the robustness of our conclusions. On-going efforts are being made to set-up prospective cohorts to validate our results and to explore preoperative molecular markers such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed death 1 (PD1), and programmed death-ligand 1 (PD-L1) as well within the same tumor microenvironment like evaluating circulating tumor cells. These future prospects may strengthen and add more insights to our findings and prompt clinical decision-making in high-risk UTUCs.

CONCLUSIONS

Herein, we demonstrated the prognostic value of pretreatment NLR, MLR, PLR, SII, and SIRI in patients who underwent RNU for UTUC. As emerging non-invasive, easily assessed, and repeatable prognostic indicators, they may be potentially useful in guiding urologists setting up more accurate clinical decisions and rational individualized treatment regimens.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Bilel Saidani, Ahmed Saadi, and Nouha Setti Boubaker. Data acquisition: Bilel Saidani, Ahmed Saadi, Seif Mokadem, Marouen Chakroun, Haroun Ayed, Zeineb Naimi, Lotfi Kochbati, and Mohamed Riadh Ben Slama. Statistical analysis: Nouha Setti Boubaker. Data analysis and interpretation: Nouha Setti Boubaker, Bilel Saidani, and Ahmed Saadi. Drafting of the manuscript: Nouha Setti Boubaker. Critical revision of the manuscript: Bilel Saidani and Ahmed Saadi. Administrative, technical, or material support: Bilel Saidani and Ahmed Saadi. Supervision: Ahmed Saadi, Haroun Ayed, and Mohamed Riadh ben Slama. Approval of the final manuscript: all authors.

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