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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

Combination of the Preoperative Systemic Immune-Inflammation Index and Monocyte-Lymphocyte Ratio as a Novel Prognostic Factor in Patients with Upper-Tract Urothelial Carcinoma

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ABSTRACT

Background. This study aimed to evaluate the clinical significance of the preoperative systemic immune-inflammation index (SII) combined with the monocyte-lymphocyte ratio (MLR) for patients with upper-tract urothelial carcinoma (UTUC).

Methods. The clinical data of 424 patients who underwent radical nephroureterectomy from January 2007 to June 2017 were analyzed. Kaplan–Meier analyses and Cox proportional hazards models were used to evaluate associations of preoperative systemic immune-inflammatory biomarkers with overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS). Moreover, logistic regression preoperative models were applied to predict advanced disease.

Results. Multivariate analyses showed that SII significantly influenced both OS and CSS (both $P < 0.05$), whereas MLR exhibited the most significant association with OS ($P = 0.008$). In particular, simultaneously high SII and MLR values correlated significantly with OS, CSS, and PFS (all $P < 0.05$). Logistic regression preoperative models showed that the combination of high SII and high MLR was a significant predictor of non-organ-confined UTUC ($P = 0.001$). Furthermore, Kaplan–Meier analysis showed that the combination of high SII and high MLR was significantly linked with poor OS, CSS, and PFS in non-organ-confined UTUC (all $P < 0.05$).

Conclusion. The study reviewed serum inflammation biomarkers in a subset of patients with UTUC and demonstrated the ability of combined SII and MLR to predict disease progression and survival. Patients with both high SII and high MLR were significantly more likely to have non-organ-confined disease and poor survival outcomes.

Although upper-tract urothelial carcinoma (UTUC) is a rare malignancy of the urinary system,[1] a significantly higher prevalence of this malignancy has been noted in Taiwan.[2,3] Given the high recurrence and progression rates of UTUC,[4] radical nephroureterectomy (RNU) is considered the gold standard treatment.[5] However, prognostic factors must be identified to improve preoperative treatment choices and postoperative surveillance.

To date, many studies have shown that pathologic staging and lymphovascular invasion (LVI) are the most important independent predictors of survival for patients with UTUC.[6,7] However, postoperative information cannot determine preoperative treatment strategies. Therefore, identification of preoperatively available prognostic factors may enable physicians to make accurate pretreatment assessments regarding clinically valuable options in UTUC, such as the need for neoadjuvant chemotherapy.

The literature demonstrates a strong relationship between cancer and systemic inflammation. Preoperative serum inflammation biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the monocyte-to-lymphocyte ratio (MLR), and the systemic immune-inflammation index (SII: neutrophils × platelets/lymphocytes), have been shown to correlate with the outcomes for patients with several types

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of cancer.[8–11] Studies of UTUC have reported that the preoperatively assessed blood-based parameters NLR,[12–16] PLR,[17] and MLR[18] exhibit the potential to predict the prognosis of patients after RNU. However, the prognostic value of NLR in UTUC remains controversial, and the feasibility of the SII for UTUC has not been evaluated to date. Several studies have shown that SII is an integrative indicator with a significant prognostic value in other solid malignancies such as esophageal squamous cell carcinoma,[19,20] small cell lung cancer,[21,22] gastric cancer,[23,24] colorectal cancer,[25] pancreatic cancer,[26] and hepatocellular carcinoma.[8] This study aimed to explore associations of the preoperative NLR, PLR, MLR, and SII with clinicopathologic parameters and to identify the prognostic values of individual or combined inflammatory biomarkers using multivariate models.

PATIENTS AND METHODS

Study Populations and Data Collection

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital, Tainan, Taiwan (IRB No. NCKUH-10001008/ER-99-237). From January 2007 to June 2017, 424 patients with UTUC undergoing RNU were retrospectively analyzed. The RNU technique was performed according to standard procedures, and regional lymph nodes (LNs) were generally dissected if the preoperative imaging studies indicated that enlargement or palpable nodes were identified intraoperatively.

The following exclusion criteria were applied to potential subjects: active infection status, lack of differential count information from preoperative complete blood counts (CBCs) 30 days before surgery, bone or distant metastasis at the time of diagnosis, other malignancy, current use of immunosuppressive drugs, and a follow-up period shorter than 30 days. None of the patients received preoperative neoadjuvant chemotherapy, radiotherapy, or any other anti-tumor therapy.

The following clinicopathologic variables were recorded for analysis: sex, age, blood type, smoking status, comorbidities, symptoms, preoperative estimated glomerular filtration rate (eGFR), history of prior or concomitant bladder urothelial carcinoma, tumor location (renal pelvis, ureter, or synchronous), multifocality, tumor size, tumor necrosis, tumor architecture (papillary, sessile, or mixed), pT stage, tumor grade, LVI, LN metastasis, and CBC parameters (NLR, PLR, MLR, and SII).

Multifocality was defined as the presence of tumors in both the pelvis and ureter or two or more tumors. Overall survival (OS) was defined as the interval from RNU until death, whereas cancer-specific survival (CSS) was defined as the interval from RNU until death due to UTUC, and progression-free survival (PFS) was defined as the interval from RNU until disease progression (including local recurrence or distant metastasis) or death.

Tumor staging was determined according to the American Joint Committee on Cancer TNM Classification, 7th edition, and pathologic grades were determined according to the 2004 World Health Organization (WHO) classification. The preoperative eGFR was calculated using the following Modification of Diet in Renal Disease study equation:

$186 \times (\text{serum creatinine}) - 1.154 \times (\text{age}) - 0.203 \times (0.742 \text{ if female})$.[27] Patients were considered to have chronic kidney disease if they had an eGFR lower than 60 ml/min/1.73 m^2 or received regular dialysis. Follow-up evaluations included interval history-taking, physical examination, urinalysis, urine cytology, abdominal ultrasonography, and abdominal computed tomography. Cystoscopy was performed every 3 months for the first 2 years, every 6 months for the next 2 years, and annually thereafter.

Statistical Analysis

Data were analyzed using SPSS (version 17.0; SPSS Inc., Chicago, IL, USA). The predictive values of NLR, PLR, MLR, and SII were determined using receiver operating characteristic (ROC) curve analysis based on cancer-specific death as the end point. The cutoff values were determined with Youden's index and used to categorize the clinicopathologic variables into two groups (above and below the cutoff). Subsequently, the Chi square test was used to compare differences between the two groups. Kaplan–Meier analyses were performed to evaluate the associations of OS, CSS, and PFS with NLR, PLR, MLR, and SII. Significant differences were determined using the log-rank test. Uni- and multivariate Cox regression analyses were conducted to evaluate the significance of each parameter with respect to OS, CSS, and PFS. A P value lower than 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics of Patients with UTUC

The clinical and pathologic characteristics of the 424 patients in this study are shown in Table 1. Their ages ranged from 29 to 96 years (median, 70 years; interquartile range [IQR], 62–77 years) and a mean age of 68.5 ± 10.9 years. The patients were followed for a median of 35 months (IQR, 14–60 months; mean, 36.1 ± 28.6 months).

TABLE 1 Relationships between clinicopathologc parameters and NLR, PLR, MLR, and SII

	All *n* (%)	NLR			PLR			MLR			SII		
		>4 *n* (%)	≤4 *n* (%)	*P* value	>150 *n* (%)	≤150 *n* (%)	*P* value	>0.4 *n* (%)	≤0.4 *n* (%)	*P* value	>580 *n* (%)	≤580 *n* (%)	*P* value
No. of patients	424	108 (25)	316 (75)		187 (44)	237 (56)		136 (32)	288 (68)		215 (51)	209 (49)	
Gender				0.631			0.211			0.773			0.673
Male	189 (45)	46 (43)	143 (45)		77 (41)	112 (47)		62 (46)	127 (44)		98 (46)	91 (44)	
Female	235 (55)	62 (57)	173 (55)		110 (59)	125 (53)		74 (54)	161 (56)		117 (54)	118 (26)	
Blood type				0.064			0.228			0.177			0.474
O	182 (43)	58 (54)	124 (39)		89 (47)	93 (39)		68 (50)	114 (39)		97 (45)	85 (41)	
A	113 (27)	25 (23)	88 (28)		50 (27)	63 (27)		35 (26)	78 (27)		58 (27)	55 (26)	
B	107 (25)	20 (18)	87 (28)		39 (21)	68 (29)		27 (20)	80 (28)		52 (24)	55 (26)	
AB	22 (5)	5 (5)	17 (5)		9 (5)	13 (6)		6 (4)	16 (6)		8 (4)	14 (7)	
Age at RNU (years)				0.653			0.959			0.234			0.493
≤ 69	208 (49)	55 (51)	153 (48)		92 (49)	116 (49)		61 (45)	147 (51)		109 (51)	99 (47)	
> 69	216 (51)	53 (49)	163 (52)		95 (51)	121 (51)		75 (55)	141 (49)		106 (49)	110 (53)	
Smoking				0.606			0.622			0.377			0.513
No	375 (88)	96 (90)	279 (88)		167 (89)	208 (88)		123 (90)	252 (88)		188 (87)	187 (89)	
Yes	49 (12)	12 (10)	37 (12)		20 (11)	29 (12)		13 (10)	36 (12)		27 (13)	22 (11)	
Pre-eGFR (ml/min/1.73 m^2)				0.275			0.087			0.001			0.522
> 60	176 (42)	40 (37)	136 (43)		69 (37)	107 (45)		40 (29)	136 (47)		86 (40)	90 (43)	
≤ 60	248 (58)	68 (63)	180 (57)		118 (63)	130 (55)		96 (71)	152 (53)		129 (60)	119 (57)	
Hemodialysis				0.016			0.016			< 0.001			0.575
No	356 (84)	82 (77)	274 (87)		148 (79)	208 (88)		98 (72)	258 (90)		178 (83)	178 (85)	
Yes	68 (16)	26 (23)	42 (13)		39 (21)	29 (12)		38 (28)	30 (10)		37 (17)	31 (15)	
DM or HTN				0.270			0.530			0.683			0.663
Absent	181 (43)	51 (47)	130 (41)		83 (44)	98 (41)		60 (44)	121 (42)		94 (44)	87 (42)	
Present	243 (57)	57 (53)	186 (59)		104 (56)	139 (59)		76 (56)	167 (58)		121 (56)	122 (58)	
Previous or concomitant BC				0.258			0.523			0.003			0.329
Absent	289 (68)	71 (66)	226 (72)		128 (68)	169 (71)		82 (60)	215 (75)		146 (68)	151 (72)	
Present	127 (32)	37 (34)	90 (28)		59 (32)	68 (29)		54 (40)	73 (25)		69 (32)	58 (28)	
Hydronephrosis				0.644			0.116			0.722			0.376
Absent	80 (19)	22 (20)	58 (18)		29 (15)	51 (22)		27 (20)	53 (18)		37 (17)	43 (21)	
Present	344 (81)	86 (80)	258 (82)		158 (85)	186 (78)		109 (80)	235 (82)		178 (83)	166 (79)	

TABLE 1 continued

	All *n* (%)	NLR			PLR			MLR			SII		
		>4 *n* (%)	≤4 *n* (%)	*P* value	>150 *n* (%)	≤150 *n* (%)	*P* value	>0.4 *n* (%)	≤0.4 *n* (%)	*P* value	>580 *n* (%)	≤580 *n* (%)	*P* value
Hematuria				0.521			0.953			0.518			0.268
Absent	63 (15)	14 (13)	49 (15)		28 (15)	35 (15)		18 (13)	45 (16)		36 (17)	27 (13)	
Present	361 (85)	94 (87)	267 (85)		159 (85)	202 (85)		118 (87)	243 (84)		179 (83)	182 (87)	
Pathologic T stage				0.113			0.191			0.017			0.313
Ta/1	161 (38)	36 (33)	125 (40)		62 (33)	99 (42)		41 (30)	120 (41)		77 (36)	84 (40)	
T2	83 (20)	17 (16)	66 (20)		39 (21)	44 (19)		24 (18)	59 (21)		39 (18)	44 (21)	
T3 or T4	180 (42)	55 (51)	125 (40)		86 (46)	94 (39)		71 (52)	109 (38)		99 (46)	81 (39)	
Tumor grade				0.483			0.757			0.362			0.419
Low	22 (5)	7 (6)	15 (5)		9 (5)	13 (5)		9 (7)	13 (5)		13 (6)	9 (4)	
High	402 (95)	101 (94)	301 (95)		178 (95)	224 (95)		127 (93)	275 (95)		202 (94)	200 (96)	
Lympho-vascular invasion				0.152			0.346			0.096			0.003
Absent	299 (71)	73 (68)	236 (75)		132 (71)	177 (75)		92 (68)	217 (75)		143 (67)	166 (79)	
Present	115 (39)	35 (32)	80 (25)		55 (29)	60 (25)		44 (32)	71 (25)		72 (33)	43 (21)	
Tumor location				0.104			0.254			0.096			0.036
Renal pelvis	191 (45)	49 (45)	142 (45)		77 (41)	114 (48)		58 (42)	133 (46)		93 (43)	98 (47)	
Ureter	138 (33)	28 (26)	110 (35)		62 (33)	76 (32)		39 (29)	99 (34)		63 (30)	75 (36)	
Both	95 (22)	31 (29)	64 (20)		48 (26)	47 (20)		39 (29)	56 (20)		59 (27)	36 (17)	
Multifocality				0.266			0.400			0.176			0.178
No	308 (73)	74 (68)	234 (74)		132 (71)	176 (74)		93 (68)	215 (75)		150 (70)	158 (76)	
Yes	116 (27)	34 (32)	82 (26)		55 (29)	61 (26)		43 (32)	73 (25)		65 (30)	51 (24)	
Tumor size (cm)				0.039			0.014			0.002			0.004
≤ 3	203 (48)	43 (40)	160 (51)		77 (41)	126 (53)		50 (37)	153 (53)		88 (41)	115 (55)	
> 3	221 (52)	65 (60)	156 (49)		110 (59)	111 (47)		86 (63)	135 (47)		127 (59)	94 (45)	
Tumor architecture				0.913			0.141			0.198			0.030
Papillary	97 (23)	26 (24)	71 (23)		51 (27)	46 (20)		36 (26)	61 (21)		60 (28)	37 (18)	
Sessile	278 (66)	69 (64)	209 (66)		114 (61)	164 (69)		81 (60)	197 (69)		129 (60)	149 (71)	
Mixed	49 (11)	13 (12)	36 (11)		22 (12)	27 (11)		19 (14)	30 (10)		26 (12)	23 (11)	
Tumor necrosis				0.762			0.614			0.377			0.289
Absent	338 (80)	85 (79)	253 (80)		147 (79)	191 (81)		105 (77)	233 (81)		167 (78)	171 (82)	
Present	86 (20)	23 (21)	63 (20)		40 (21)	46 (19)		31 (23)	55 (19)		48 (22)	38 (18)	

TABLE 1 continued

	All *n* (%)	NLR			PLR			MLR			SII		
		>4 *n* (%)	≤4 *n* (%)	*P* value	>150 *n* (%)	≤150 *n* (%)	*P* value	>0.4 *n* (%)	≤0.4 *n* (%)	*P* value	>580 *n* (%)	≤580 *n* (%)	*P* value
Lymph node stage				0.213			0.148			0.188			0.028
$pN_0/_X$	399 (94)	99 (92)	300 (95)		173 (93)	226 (96)		125 (92)	274 (95)		197 (92)	202 (97)	
pN+	25 (6)	9 (8)	16 (5)		14 (7)	15 (4)		11 (8)	14 (5)		18 (8)	7 (3)	
Adjuvant chemotherapy				0.404			0.905			0.768			0.367
No	384 (91)	100 (93)	284 (90)		169 (90)	215 (91)		124 (91)	260 (90)		192 (89)	192 (92)	
Yes	40 (9)	8 (7)	32 (10)		18 (10)	22 (9)		12 (9)	28 (10)		23 (11)	17 (8)	
NLR				–			<0.001			< 0.001			< 0.001 0.001
≤ 4	316 (75)	–	–		96 (51)	220 (93)		58 (43)	258 (90)		114 (53)	202 (97)	
> 4	108 (25)	–	–		91 (49)	17 (7)		78 (57)	30 (10)		101 (47)	7 (3)	
PLR				<0.001 0.001			–			< 0.001			< 0.001
≤ 150	237 (56)	17 (16)	220 (70)		–	–		36 (26)	201 (70)		61 (28)	176 (84)	
> 150	187 (44)	91 (84)	96 (30)		–	–		100 (74)	87 (30)		154 (72)	33 (16)	
MLR				<0.001			<0.001 0.001			–			< 0.001
≤ 0.4	288 (68)	30 (28)	258 (82)		87 (47)	202 (85)		–	–		109 (51)	179 (86)	
> 0.4	136 (32)	78 (72)	58 (18)		100 (53)	35 (15)		–	–		106 (49)	30 (14)	
SII				<0.001			<0.001			< 0.001 0.001			–
≤ 580	209 (49)	7 (6)	202 (64)		33 (18)	177 (75)		30 (22)	179 (62)		–	–	
> 580	215 (51)	101 (94)	114 (36)		154 (82)	60 (25)		106 (78)	109 (38)		–	–	

NLR neutrophil-to-lymphocyte ratio; *PLR* platelet-to-lymphocyte ratio; *MLR* monocyte-to-lymphocyte ratio; *SII* systemic immune-inflammation index; *RNU* radical nephroureterectomy; *Pre-eGFR* preoperative estimated glomerular filtration rate; *DM* diabetes mellitus; *HTN* hypertension; *BC* bladder urothelial carcinoma

Of the 424 patients, 344 (81%) presented with hydronephrosis, and 361 (85%) had microscopic or gross hematuria. Preoperatively, 248 patients (58%) had chronic kidney disease (eGFR, $\leq$ 60 ml/min/1.73 m^2) and 68 (16%) required regular hemodialysis. The findings showed 243 patients (57%) with underlying hypertension or diabetes mellitus and 49 patients (12%) with a prior or current smoking history.

Tumors were located in the renal pelvis in 191 (45%) patients, the ureter in 138 patients (33%), and both locations in 95 patients (22%). Multifocal tumors were found in 116 patients (27%). Prior or concomitant bladder tumors were noted in 127 patients (32%).

Regarding pathologic staging, 161 patients (38%) had pTa/1, 83 patients (20%) had pT2, and 180 patients (72%) had pT3/4 disease. Furthermore, 25 patients (6%) had positive LN metastases, 402 patients (95%) had a high tumor grade, 221 patients (52%) had a tumor larger than 3 cm, 86 patients (20%) had tumor necrosis, and 115 patients (39%) had LVI. Regarding tumor architecture, the study identified papillary tumor in 97 patients (23%), sessile tumor in 278 patients (66%), and mixed type tumor in 49 patients (11%).

Associations of NLR, PLR, MLR, and SII with Clinicopathologic Parameters

Using cancer-specific death as the end point, ROC analysis was performed to identify the optimal cutoff values with the highest sensitivity and specificity as follows: NLR (4), PLR (150), MLR (0.4), and SII (580) (Fig. S1). The highest AUC was 0.71 for SII, indicating the superiority of this factor relative to NLR, PLR, or MLR as a predictive factor for survival for UTUC patients.

Next, the patients were subdivided into two groups based on the cutoff value of each of the four immune-inflammation biomarkers. As shown in Table 1, the patients receiving hemodialysis had significantly higher NLR ($P = 0.016$), PLR ($P = 0.016$), and MLR ($P < 0.001$) values. The patients with a large tumor volume had significantly higher NLR ($P = 0.039$), PLR ($P = 0.014$), MLR ($P = 0.002$), and SII ($P = 0.004$) values. In addition, the patients with impaired renal function, prior or concurrent bladder cancer, or advanced T stage disease (T3 or T4) had significantly higher MLR values, with P values of 0.001, 0.003, and 0.017, respectively. The patients with significantly higher SII levels were more likely to have a large tumor volume ($P = 0.004$), LVI ($P = 0.003$), and LN involvement ($P = 0.028$), as well as tumor located in the renal pelvis and ureter ($P = 0.036$). No significant differences in sex, age, blood type, smoking, preoperative clinical symptoms, multifocal tumors, tumor grade, tumor configuration, or tumor necrosis were observed between the high and low groups stratified by each immune-inflammation biomarker.

Survival Analysis for NLR, PLR, MLR, and SII

A Kaplan–Meier analysis was used to study the associations of the four inflammatory markers with OS and CSS. We found that higher NLR, PLR, MLR, and SII were significantly related to lower OS, with respective P values of 0.002, 0.001, < 0.001, and < 0.001 (Fig. S2). Similarly, a lower CSS was observed in patients with a higher NLR, PLR, MLR, and SII (all P values < 0.001; Fig. S3). The patients with a higher PLR, MLR, or SII had a significantly worse PFS, with respective P values of 0.003, 0.007, and 0.001 (Fig. S4).

Uni- and multivariate Cox regression analyses were performed to determine the factors affecting survival for our patients. The univariate analysis identified pT stage, LN status, LVI, tumor location, multifocality, tumor size, tumor architecture, NLR, PLR, MLR, and SII as significant risk factors (Table 2). In a multivariate analysis, pT stage and LN metastasis were identified as risk factors associated with OS, CSS, and PFS. The MLR was identified as a risk factor for OS ($P = 0.008$), and SII was shown to have a significant influence on both OS ($P = 0.019$) and CSS ($P = 0.004$) (Table 2).

Association of Survival with the Combination of SII and MLR

The SII is derived from the neutrophil, platelet, and lymphocyte counts but does not include the monocyte count. Because several previous studies have shown the prognostic importance of monocytes,[28,29] we further evaluated whether the combination of SII and MLR would have a better predictive value.

In this study, a significant positive correlation (Spearman's correlation coefficient, $\gamma_s = 0.374$; $P < 0.001$) was observed between the SII and MLR. The patients then were subdivided into four groups as follows: high SII and high MLR, high SII and low MLR, low SII and high MLR, and low SII and low MLR. As shown in Fig. 1, the patients with high SII and high MLR had not only the worst OS and CSS, but also the poorest PFS (all P values < 0.001).

A multivariate Cox regression analysis was performed to determine the effects of different SII and MLR combinations on OS, CSS, and PFS. The results showed that patients with high SII and high MLR had significantly worse OS, CSS, and PFS than those with low SII and low MLR (hazard ratios [HRs] of 4.030 [$P < 0.001$], 5.962 [$P < 0.001$], and 2.032 [$P = 0.004$], respectively; Table 3). Therefore, simultaneously high SII and MLR values can be

TABLE 2 Uni- and multivariate analyses for overall survival, cancer-specific survival, and progression-free survival

	Overall survival				Cancer-specific survival				Progression-free survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	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	HR (95% CI)	*P* value
Gender												
Female vs male	0.711 (0.460-1.100)	0.126	0.715 (0.428–1.193)	0.199	0.635 (0.385–1.048)	0.075	0.624 (0.343–1.133)	0.121	0.853 (0.595–1.225)	0.390	0.709 (0.468–1.073)	0.104
Blood type				0.637				0.658				0.571
A vs O	0.749 (0.422–1.330)	0.324	0.684 (0.372–1.257)	0.221	0.874 (0.457–1.675)	0.686	0.918 (0.446–1.887)	0.816	0.826 (0.520–1.311)	0.417	0.841 (0.517–1.369)	0.487
B vs O	1.026 (0.605–1.740)	0.923	0.899 (0.490–1.648)	0.731	1.249 (0.691–2.258)	0.461	1.265 (0.617–2.594)	0.522	0.862 (0.543–1.368)	0.527	0.975 (0.585–1.625)	0.923
AB vs O	1.004 (0.395–2.556)	0.993	0.711 (0.260–1.943)	0.506	0.844 (0.255–2.790)	0.781	0.583 (0.157–2.163)	0.420	1.595 (0.812–3.134)	0175	1.466 (0.705–3.048)	0.306
Age at RNU (years)												
> 69 vs ≤ 69	1.115 (0.721–1.724)	0.625	1.206 (0.710–2.048)	0.488	1.232 (0.748–2.030)	0.412	1.479 (0.784–2.788)	0.227	1.023 (0.713–1.468)	0.903	1.038 (0.685–1.573)	0.860
Smoking												
Yes vs no	1.136 (0.601–2.147)	0.696	1.234 (0.581–2.622)	0.585	1.091 (0.519–2.294)	0.819	0.913 (0.362–2.299)	0.846	0.797 (0.438–1.449)	0.457	0.756 (0.385–1.482)	0.415
Pre-eGFR (ml/min/ 1.73 m^2)												
≤ 60 vs > 60	1.106 (0.708–1.727)	0.658	0.751 (0.410–1.374)	0.353	0.821 (0.498–1.352)	0.438	0.657 (0.340–1.270)	0.211	0.881 (0.612–1.267)	0.493	0.882 (0.560–1.390)	0.588
Hemodialysis												
Yes vs no	0.915 (0.495–1.691)	0.778	0.851 (0.401–1.803)	0.673	0.566 (0.244–1.314)	0.186	0.576 (0.208–1.596)	0.289	0.614 (0.345–1.093)	0.097	0.734 (0.379–1.421)	0.359
DM or HTN												
Present vs absent	1.309 (0.831–2.062)	0.246	1.336 (0.806–2.214)	0.261	1.076 (0.648–1.787)	0.778	1.169 (0.658–2.079)	0.594	1.151 (0.795–1.666)	0.457	1.253 (0.842–1.865)	0.266
Previous or concomitant BC												
Yes vs no	1.359 (0.866–2.134)	0.182	1.045 (0.620–1.762)	0.868	1.271 (0.755–2.138)	0.367	0.984 (0.523–1.850)	0.960	1.143 (0.779–1.678)	0.494	1.086 (0.705–1.673)	0.707
Hydronephrosis												
Present vs absent	1.549 (0.799–3.004)	0.195	1.170 (0.562–2.438)	0.674	1.730 (0.788–3.800)	0.172	1.349 (0.550–3.308)	0.513	1.067 (0.660–1.726)	0.792	0.918 (0.538–1.569)	0.756
Hematuria												
Present vs absent	0.832 (0.467–1.481)	0.531	1.087 (0.577–2.049)	0.796	0.714 (0.380–1.340)	0.294	1.013 (0.493–2.082)	0.971	0.937 (0.567–1.548)	0.799	1.137 (0.660–1.957)	0.644
Pathologic T stage				0.001				<0.001				<0.001
T2 vs Ta/1	1.866 (0.823–4.231)	0.135	1.377 (0.563–3.367)	0.483	2.958 (0.866–10.106)	0.084	2.101 (0.564–7.832)	0.269	2.495 (1.251–4.977)	0.009	2.071 (0.985–4.353)	0.055

TABLE 2 continued

	Overall survival				Cancer-specific survival				Progression-free survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	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	HR (95% CI)	*P* value
T3/4 vs Ta/1	5.779 (3.030–11.020)	<0.001	3.440 (1.628–7.270)	0.001	13.785 (4.979–38.162)	<0.001	7.683 (2.502–23.592)	<0.001	7.447 (4.226–13.122)	<0.001	4.684 (2.444–8.978)	<0.001
Tumor grade												
High vs low	2.183 (0.536–8.888)	0.276	1.594 (0.312–8.133)	0.575	3.377 (0.468–24.375)	0.227	3.829 (0.341–43.021)	0.277	3.354 (0.829–13.576)	0.090	1.002 (0.229–4.386)	0.998
Lympho-vascular invasion												
Present vs absent	2.619 (1.687-4.065)	<0.001	1.235 (0.720–2.118)	0.443	3.328 (1.966–5.344)	<0.001	1.081 (0.579–2.017)	0.807	3.075 (2.139–4.421)	<0.001	1.538 (1.005–2.355)	0.048
Tumor location				0.119				0.093				0.327
Ureter vs renal pelvis	1.550 (0.851-2.823)	0.152	1.768 (0.875–3.574)	0.112	1.445 (0.715–2.924)	0.305	2.033 (0.886–4.667)	0.094	1.154 (0.730–1.822)	0.540	1.352 (0.790–2.315)	0.271
Both vs renal pelvis	4.312 (2.508–7.413)	<0.001	2.964 (0.930–9.446)	0.072	4.660 (2.515–8.635)	<0.001	3.723 (0.973–14.245	0.055	2.593 (1.689–3.982)	<0.001	1.753 (0.785–3.911)	0.171
Multifocality												
Yes vs no	2.862 (1.851–4.425)	<0.001	1.211 (0.425–3.454)	0.720	3.124 (1.898–5.142)	<0.001	1.140 (0.334–3.892)	0.834	2.116 (1.467–3.053)	<0.001	1.407 (0.686–2.888)	0.352
Tumor size												
> 3 vs ≤ 3	1.707 (1.087–2.682)	0.020	1.178 (0.678–2.044)	0.561	2.245 (1.308–3.855)	0.003	1.690 (0.864–3.306)	0.125	1.575 (1.088–2.281)	0.016	1.112 (0.720–1.719)	0.632
Tumor architecture				0.394				0.322				0.487
Sessile vs papillary	0.363 (0.227–0.580)	<0.001	0.685 (0.384–1.223)	0.201	0.301 (0.173–0.522)	<0.001	0.666 (0.326–1.358)	0.263	0.371 (0.250–0.552)	<0.001	0.831 (0.516–1.341)	0.449
Mixed vs papillary	0.695 (0.353–1.370)	0.294	0.687 (0.316–1.495)	0.344	0.856 (0.426–1.721)	0.653	1.009 (0.432–2.357)	0.984	0.889 (0.521–1.518)	0.667	1.161 (0.642–2.100)	0.622
Tumor necrosis												
Present vs absent	1.528 (0.928–2.515)	0.096	1.196 (0.656–2.181)	0.560	1.409 (0.787–2.523)	0.249	0.914 (0.446–1.875)	0.807	1.797 (1.205–2.679)	0.004	0.955 (0.595–1.535)	0.851
Lymph node stage												
pN + vs $pN_0/_X$	5.039 (2.872–8.841)	<0.001	2.738 (1.224–6.126)	0.014	6.490 (3.572–11.791)	<0.001	3.186 (1.312–7.737)	0.010	4.960 (3029–8.121)	<0.001	1.848 (1.042–3.275)	0.036
Adjuvant chemotherapy												
Yes vs no	2.218 (1.245–3.950)	0.007	0.673 (0.280–1.617)	0.375	2.817 (1.526–5.200)	0.001	0.657 (0.249–1.730)	0.395	3.477 (2.233–5.414)	<0.001	1.161 (0.611–2.206)	0.648
NLR												
> 4 vs ≤ 4	2.018 (1.280–3.183)	0.003	0.751 (0.390–1.447)	0.392	2.576 (1.554–4.269)	<0.001	1.080 (0.498–2.342)	0.846	1.413 (0.984–2.106)	0.090	0.738 (0.412–1.322)	0.307

TABLE 2 continued

	Overall survival				Cancer-specific survival				Progression-free survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	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	HR (95% CI)	*P* value
PLR												
> 150 vs ≤ 150	2.170 (1.385–3.400)	0.001	1.008 (0.548–1.854)	0.980	2.594 (1.532–4.391)	<0.001	0.887 (0.428–1.839)	0.747	1.724 (1.199–2.480)	0.003	1.229 (0.740–2.040)	0.425
MLR												
> 0.4 vs ≤ 0.4	2.761 (1.784–4.274)	<0.001	2.192 (1.227–3.917)	0.008	2.941 (1.783–4.852)	<0.001	1.847 (0.913–3.735)	0.088	1.655 (1.146–2.390)	0.007	1.392 (0.847–2.287)	0.192
SII												
> 580 vs ≤ 580	2.919 (1.788–4.765)	<0.001	2.194 (1.140–4.221)	0.019	4.049 (2.196–7.465)	<0.001	3.428 (1.486–7.908)	0.004	1.842 (1.268–2.676)	0.001	1.555 (0.937–2.583)	0.088

HR hazard ratio; *CI* confidence interval; *RNU* radical nephroureterectomy; *Pre-eGFR* preoperative estimated glomerular filtration rate; *DM* diabetes mellitus; *HTN* hypertension; *BC* bladder urothelial carcinoma; *NLR* neutrophil-to-lymphocyte ratio; *PLR* platelet-to-lymphocyte ratio; *MLR* monocyte-to-lymphocyte ratio; *SII* systemic immune-inflammation index

considered an independent predictor of a poorer OS, CSS, and PFS.

Association of Organ-Confined and Non-Organ-Confined Disease with the Combination of SII and MLR

To further compare the abilities of different SII and MLR combinations to predict OS, CSS, and PFS at different pathologic tumor stages, the patients were divided into two groups as follows: organ-confined and non-organ-confined UTUC. Among the patients with non-organ-confined UTUC, those with high SII and high MLR had significantly shorter OS ($P < 0.001$), CSS ($P < 0.001$), and PFS ($P = 0.024$) than those with other combinations. However, the patients with organ-confined UTUC exhibited no significant differences among the groups (Fig. 2).

We further tested the feasibility of the SII and MLR combination for predicting non-organ-confined disease (≥ pT3 and/or positive LNs). As shown in Table 4, the combination of high SII and high MLR acted as a significant predictive factor for advanced UTUC ($P = 0.001$).

DISCUSSION

In this study, a high SII (> 580) correlated with LVI, LN involvement, a larger tumor size, and a more aggressive phenotype in patients with UTUC. Findings have shown that SII is superior to NLR, PLR, or MLR as a predictor of survival, and a high SII is an independent predictor of a decreased OS and CSS. In addition, the combination of SII and MLR comprises a good independent predictor of the extent and prognosis of UTUC. To the best of our knowledge, this is the first report to describe an association of combined high SII and high MLR with poor oncologic outcomes, suggesting that this factor may contribute to pre- or postoperative decision-making for patients with UTUC.

Previous studies have demonstrated the prognostic value of the preoperative NLR, PLR, or MLR for patients with UTUC. Specifically, an elevated NLR, PLR, or MLR was found to be associated with disease recurrence and decreases in OS, CSS, or both.[13–15,17,18] Conversely, the relationships of the SII with clinical variables in patients with UTUC has not been reported to date. The literature suggests that SII represents the host inflammatory status for patients with hepatocellular carcinoma, and that a higher SII level is associated with a higher level of circulating tumor cells (CTCs).[8] A handful of studies have demonstrated that the SII could independently predict survival and recurrence for patients with several types of solid malignancies.[19–26] In our study, the findings were

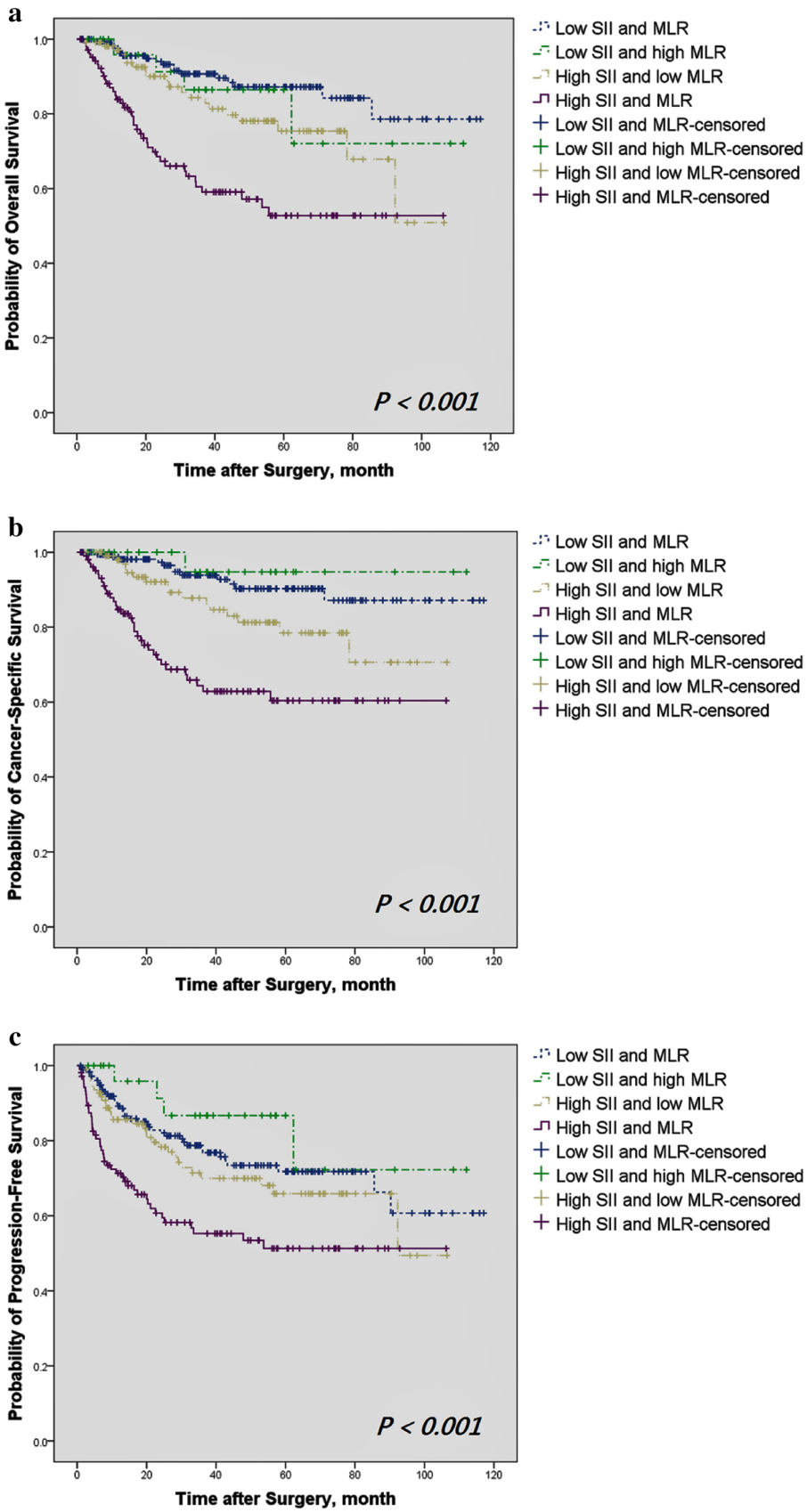

FIG. 1 Kaplan-Meier analysis for overall survival (**a**), cancer-specific survival (**b**), and progression-free survival (**c**) in patients with UTUC who divided into 4 groups based on combination of SII with MLR

TABLE 3 Multivariate analysis for overall survival, cancer-specific survival, and progression-free survival when interrelated SII and MLR are combined

	Overall survival HR (95% CI)	*P* value	Cancer-specific survival HR (95% CI)	*P* value	Progression-free survival HR (95% CI)	*P* value
Gender						
Female vs male	0.725 (0.437–1.203)	0.213	0.620 (0.343–1.121)	0.114	0.732 (0.486–1.102)	0.135
Blood type		0.639		0.721		0.690
A vs O	0.698 (0.380–1.282)	0.246	0.943 (0.456–1.950)	0.875	0.903 (0.555–1.466)	0.679
B vs O	0.968 (0.539–1.741)	0.914	1.248 (0.632–2.466)	0.523	1.011 (0.612–1.671)	0.965
AB vs O	0.709 (0.259–1.938)	0.503	0.594 (0.160–2.200)	0.436	1.506 (0.725–3.127)	0.272
Age at RNU (years)						
> 69 vs ≤ 69	1.216 (0.722–2.047)	0.462	1.462 (0.780–2.739)	0.236	1.070 (0.708–1.615)	0.749
Smoking						
Yes vs no	1.190 (0.555–2.550)	0.654	0.940 (0.381–2.319)	0.892	0735 (0.375–1.440)	0.370
Pre-eGFR (ml/min/1.73 m^2)						
< 60 vs ≥ 60	0.780 (0.429–1.419)	0.417	0.574 (0.283–1.163)	0.124	0891 (0.564–1.405)	0.619
Hemodialysis						
Yes vs no	0.832 (0.394–1.757)	0.629	0.580 (0.208–1.615)	0.297	0722 (0.374–1.395)	0.332
DM or HTN						
Present vs absent	1.370 (0.829–2.263)	0.219	1.185 (0.665–2.111)	0.564	1.310 (0.880–1.950)	0.183
Previous or concomitant BC						
Yes vs no	1.060 (0.629–1.786)	0.828	0.985 (0.526–1.845)	0.963	1.087 (0.711–1.662)	0.700
Hydronephrosis						
Present vs absent	1.234 (0.593–2.568)	0.575	1.309 (0.538–3.183)	0.552	0.928 (0.545–1.582)	0.785
Hematuria						
Present vs absent	1.083 (0.574–2.044)	0.804	1.020 (0.494–2.106)	0.958	1.125 (0.653–1.939)	0.672
Pathologic T stage		0.001		< 0.001		< 0.001
T2 vs Ta/1	1.302 (0.540–3.139)	0.557	2.059 (0.563–7.530)	0.275	2.024 (0.967–4.239)	0.061
T3/4 vs Ta/1	3.285 (1.572–6.866)	0.002	7.499 (2.487–22.613)	< 0.001	4.512 (2.365–8.608)	< 0.001
Tumor grade						
High vs low	1.721 (0.338–8.758)	0.513	3.863 (0.357–41.765)	0.266	1.002 (0.231–4.356)	0.998
Lympho-vascular invasion						
Present vs absent	1.202 (0.706–2.048)	0.499	1.101 (0.595–2.036)	0.759	1.480 (0.973–2.252)	0.067
Tumor location		0.120		0.106		0.267
Ureter vs renal pelvis	1.774 (0.885–3.557)	0.106	2.036 (0.891–4.650)	0.092	1.438 (0.846–2.444)	0.180
Both vs renal pelvis	2.963 (0.902–9.733)	0.073	3.433 (0.880–13.388)	0.076	1.665 (0.738–3.755)	0.219
Multifocality						
Yes vs no	1.190 (0.406–3.482)	0.751	1.217 (0.347–4.276)	0.759	1.508 (0.723–3.144)	0.273

TABLE 3 continued

	Overall survival HR (95% CI)	*P* value	Cancer-specific survival HR (95% CI)	*P* value	Progression-free survival HR (95% CI)	*P* value
Tumor size						
> 3 vs ≤ 3	1.193 (0.688–2.069)	0.530	1.675 (0.858–3.271)	0.131	1.124 (0.730–1.731)	0.595
Tumor architecture		0.392		0.490		0.459
Sessile vs papillary	0.680 (0.381–1.213)	0.191	0.681 (0.335–1.386)	0.289	0.802 (0.500–1.287)	0.361
Mixed vs papillary	0.700 (0.322–1.523)	0.369	1.008 (0.437–2.325)	0.984	1.121 (0.622–2.02)	0.704
Tumor necrosis						
Present vs absent	1.229 (0.678–2.229)	0.497	0.973 (0.473–2.002)	0.942	0.970 (0.606–1.552)	0.898
Lymph node stage						
pN + vs $pN_0/_X$	2.637 (1.192–5.836)	0.017	3.268 (1.366–7.818)	0.008	1.817 (1.027–3.215)	0.040
Adjuvant chemotherapy						
Yes vs no	0.724 (0.310–1.689)	0.455	0.634 (0.248–1.625	0.343	1.240 (0.663–2.319)	0.500
Combined SII + MLR		< 0.001		< 0.001		0.022
Low SII and high MLR vs low SII and MLR	2.313 (0.723–7.399)	0.158	1.118 (0.127–9.864)	0.920	0.796 (0.274–2.314)	0.675
High SII and low MLR vs low SII and MLR	2.120 (1.072–4.195)	0.031	2.980 (1.302–6.821)	0.010	1.404 (0.852–2.313)	0.183
High SII and MLR vs low SII and MLR	4.030 (2.140–7.592)	< 0.001	5.962 (2.737–12.988)	< 0.001	2.032 (1.262–3.270)	0.004

HR hazard ratio; *CI* confidence interval; *RNU* radical nephroureterectomy; *Pre-eGFR* preoperative estimated glomerular filtration rate; *DM* diabetes mellitus; *HTN* hypertension; *BC* bladder urothelial carcinoma; *MLR* monocyte-to-lymphocyte ratio; *SII* systemic immune-inflammation index

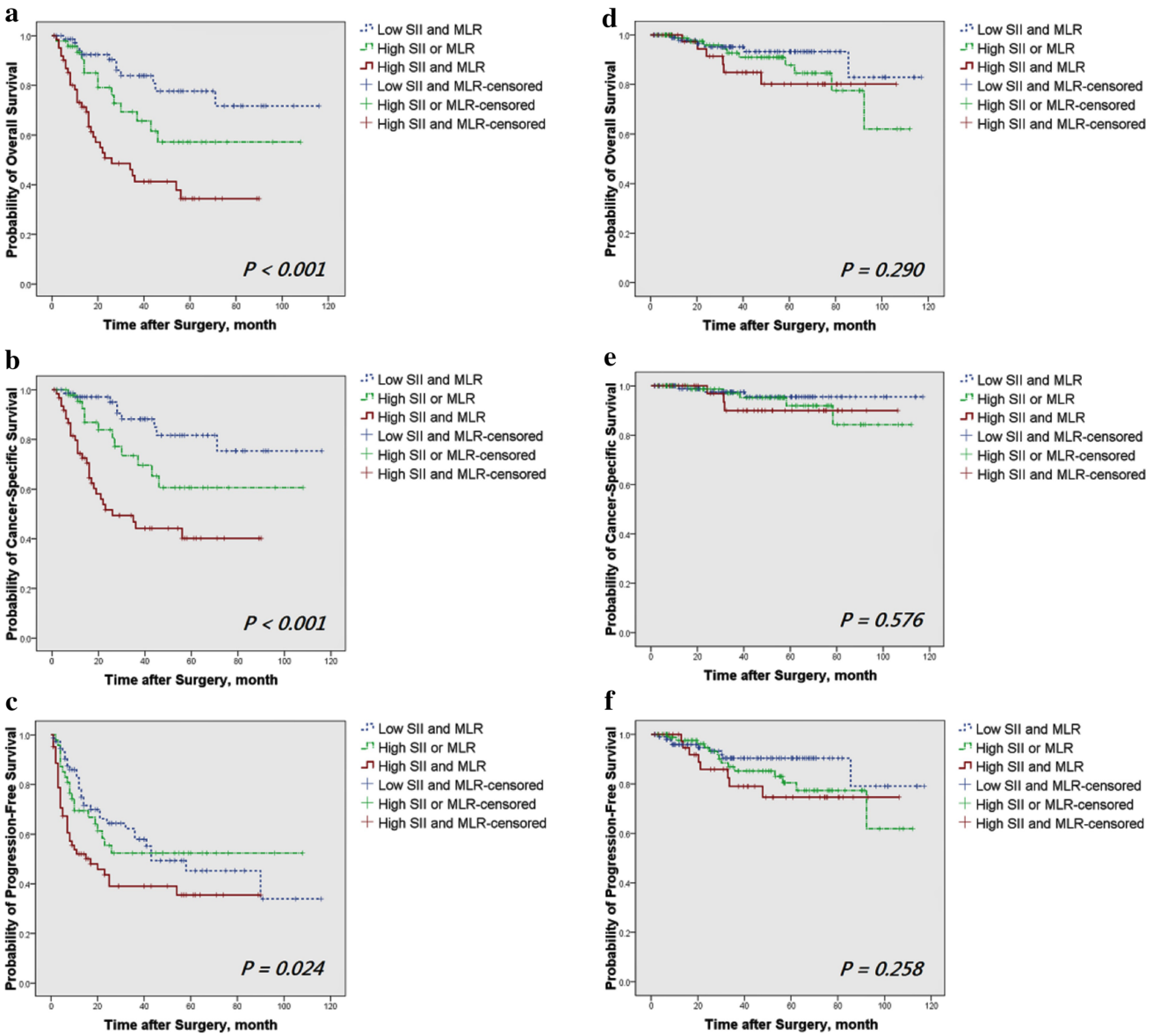

FIG. 2 Kaplan-Meier analysis for overall survival (**a** and **d**), cancer-specific survival (**b** and **e**), and progression-free survival (**c** and **f**) in patients with non-organ-confined (**a**, **b** and **c**) and organ-confined (**d**, **e** and **f**) UTUC stratified based on combination of SII with MLR

consistent with those of the previous reports, but only SII and MLR were found to correlate with OS, CSS, and PFS in a multivariate analysis.

Our study showed that the combination of a high SII and high MLR correlated significantly with advanced UTUC and a poor prognosis. The mechanisms responsible for the clinical significance of this combination with respect to survival might be explained by the functions of neutrophils, platelets, lymphocytes, and monocytes. Neutrophils not only facilitate cancer cell invasion, proliferation, and metastasis, but also protect cancer cells from immune surveillance.[30,31] Platelets shield cancer cells from immune cells cytotoxicity and facilitate the extravasation of cancer cells, leading to the formation of a metastatic niche and contributing to the survival and metastasis of cancer cells.[32–34] In contrast, lymphocytes block the proliferation and migration of cancer cells by promoting cytotoxic cell death and secreting cytokines.[31]

Furthermore, some studies have shown that macrophages derived from monocytes interact with CTCs to release cytokines and growth factors that promote the aggressive invasion behaviors of CTCs in a tumor-associated microenvironment.[35,36] Accordingly, these cell types might enable cancer cells to disseminate into circulation, evade immune destruction, and increase the peripheral CTC level. Thus, we can assume that the combination of

TABLE 4 Uni- and multivariate logistic regression preoperative model analyses for prediction of non-organ-confined disease (≥ pT3 and/or positive lymph nodes) when interrelated SII and MLR are combined

	Non-organ-confined disease			
	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at RNU (years)				
> 69 vs ≤ 69	1.156 (0.787–1.699)	0.459	1.085 (0.709–1.661)	0.706
Gender				
Female vs male	0.910 (0.618–1.339)	0.632	0.847 (0.546–1.314)	0.459
Smoking				
Yes vs no	0.897 (0.490–1.643)	0.725	0.830 (0.421–1.635)	0.590
Preoperative eGFR (ml/min/1.73 m^2)				
< 60 vs ≥ 60	0.819 (0.55–1.210)	0.316	0.871 (0.555–1.369)	0.551
Hemodialysis				
Yes vs no	0.640 (0.371–1.105)	0.109	0.597 (0.312–1.141)	0.118
DM or HTN				
Present vs absent	0.893 (0.606–1.317)	0.568	0.917 (0.607–1.386)	0.682
Previous or concomitant BC				
Yes vs no	0.879 (0.576–1.339)	0.547	0.596 (0.561–1.430)	0.645
Hydronephrosis				
Present vs absent	1.101 (0.672–1.804)	0.702	1.016 (0.603–1.710)	0.953
Hematuria				
Present vs absent	0.751 (0.439–1.284)	0.295	0.794 (0.454–1.387)	0.418
Mutifocality				
Yes vs no	1.209 (0.787–1.857)	0.387	1.187(0.753–1.869)	0.461
Combined SII + MLR		0.001		0.001
Low SII and high MLR vs. low SII and MLR	0.645 (0.278–1.494)	0.306	0.737 (0.311–1.746)	0.488
High SII and low MLR vs low SII and MLR	0.756 (0.462–1.237)	0.266	0.739 (0.447–1.220)	0.236
High SII and MLR vs low SII and MLR	2.065 (1.266–3.369)	0.004	2.292 (1.377–3.816)	0.001

HR hazard ratio; *CI* confidence interval; *RNU* radical nephroureterectomy; *Pre-eGFR* preoperative estimated glomerular filtration rate; *DM* diabetes mellitus; *HTN* hypertension; *BC* bladder urothelial carcinoma; *SII* systemic immune-inflammation index; *MLR* monocyte-to-lymphocyte ratio

high SII and high MLR in a patient with advanced UTUC indicates a lower anti-cancer immune response, a higher level of CTCs in circulation, increased participation of monocytes, and accumulation of cytokines and growth factors. The details of these mechanisms will be further studied in the future.

Nonetheless, our study had some limitations, such as data collected at a single institution, the retrospective nature of data assessment, and participation of multiple surgeons. Moreover, the study lacked ideal and generalizable thresholds regarding blood-based parameters in UTUC because the respective cutoffs were mathematically derived. Therefore, our results should be validated in different populations and/or ethnic groups. Additional studies and meta-analyses will advance our understanding concerning the use of inflammatory biomarkers in UTUC.

CONCLUSIONS

We reviewed serum inflammation biomarkers in a subset of patients with UTUC and demonstrated the feasibility of SII and MLR combined as a predictor of disease extent and survival. Patients with both high SII and high MLR were significantly more likely to have non-organ-confined disease and poor survival outcomes. We believe that the use of both the SII and MLR could facilitate the risk stratification of patients with UTUC and identify those at high risk for disease progression.

DISCLOSURE There are no conflicts of interest.

ETHICAL APPROVAL The article does not contain any studies involving human participants or animals performed by any of the authors. Formal consent is not required for this retrospective type of study.

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