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Immune-imaging biomarkers: Prognostic value of splenic volume and circulating lymphocytes in upper tract urothelial carcinoma

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Abstract. Splenomegaly has been linked to a poor prognosis in certain cancer types, possibly due to a weakened immune system. The present study evaluated the association between splenic volume (SV) and oncological outcomes in patients with upper tract urothelial carcinoma (UTUC) after radical nephroureterectomy (RNU). A total of 465 patients with non-metastatic UTUC who underwent RNU between 2009 and 2020, with available preoperative abdominal computed tomography scans and hemogram data collected within 1 month before the operation, were retrospectively analyzed. SV (cm^3) was calculated using the cross-sectional area summation method and standardized by body surface area (m^2). A receiver operating characteristic curve identified 79 cm^3/m^2 as the optimal SV cut-off. Patients were stratified by SV and lymphocyte percentage (lym%) values. Survival outcomes were evaluated using Kaplan-Meier analysis and multivariate Cox regression analysis. Among the 465 patients, those with high SV (n=206; 44.3%) demonstrated significantly shorter overall survival (OS) and cancer-specific survival (CSS) times. Stratified analysis showed that patients with both elevated SV and low lym% had the poorest outcomes, including significantly shorter metastasis-free survival (MFS) time. Multivariate analysis confirmed that the combined high SV/low lym% phenotype was an independent predictor of OS, CSS and MFS. In conclusion, the combination of high standardized SV and low lym% was independently associated with an unfavorable prognosis following RNU in UTUC. This dual biomarker approach may enhance risk stratification and inform tailored postoperative management.

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Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon malignancy, accounting for 5-10% of all UCs worldwide (1). Notably, its incidence is disproportionately higher in certain geographic regions, such as Southwestern Taiwan, possibly due to environmental exposures or underlying genetic susceptibility (2). Radical nephroureterectomy (RNU) with excision of the bladder cuff remains the gold-standard treatment for high-risk localized UTUC, especially in cases presenting with multifocality, large tumor burden (>2 cm), high-grade histology or advanced clinical stage at diagnosis (3-5). Postoperative management following RNU is guided by established prognostic indicators, including pathological stage, tumor grade, lymphovascular invasion and margin status, with adjuvant chemotherapy or salvage radiotherapy considered for patients at increased risk of recurrence or progression (6).

More recently, neoadjuvant chemotherapy has emerged as a potential strategy for selected patients with high-risk UTUC, aiming to optimize cisplatin eligibility prior to nephrectomy-induced renal function decline, while immune checkpoint inhibitors have shown promise in advanced and metastatic UC and are being explored in perioperative settings (7,8). However, despite these systemic treatment advances, their precise role in localized UTUC is still evolving, and robust preoperative biomarkers to guide patient selection are still lacking. As for adjuvant chemotherapy, platinum-based treatment was demonstrated to improve outcomes for patients with high-risk UTUC following RNU in the POUT trial (9). Hence, an increasing number of studies have been dedicated to discovering more reliable and feasible prognosticators for selecting high-risk patients who may truly benefit from adjuvant therapy.

Despite adherence to surgical guidelines, clinical outcomes in UTUC remain heterogeneous. Risk stratification after RNU typically incorporates established pathological factors such as tumor stage, grade, lymphovascular invasion (LVI) and surgical margin status (6). However, these parameters alone often fail to capture the broader immunological and systemic context influencing tumor progression. Consequently, recent efforts have turned toward identifying systemic biomarkers, particularly those linked to host immunity and inflammation, to improve prognostication (10-12).

Studies have highlighted the prognostic relevance of various systemic inflammatory markers in UTUC, including the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio and the systemic immune-inflammation index (10-13). Yet, their predictive precision remains limited. Given the immune-mediated nature of cancer progression, a more integrated approach involving immune organ metrics may enhance clinical risk models.

The spleen, as the largest secondary lymphoid organ and a key component of the reticuloendothelial system, plays a central role in both innate and adaptive immunity (14). Emerging evidence suggests that immune dysregulation, manifesting as splenic enlargement due to the accumulation of immune cells, may influence oncological outcomes in various malignancies, including hepatocellular carcinoma (HCC), colorectal cancer and lung cancer (15-18). In particular, the spleen has been implicated in the production and mobilization of tumor-associated macrophages, tumor-associated neutrophils and myeloid-derived suppressor cells (MDSCs), all of which contribute to tumor immune evasion and progression (19). Clinical studies in diverse cancer types, including HCC, colorectal cancer and lung cancer, have suggested that increased splenic volume (SV) may correlate with immune suppression and a poor prognosis, possibly mediated through depletion of cytotoxic lymphocyte subsets such as $CD4^+$ T cells and natural killer cells (16-18,20,21).

To date, no study has systematically examined the prognostic relevance of SV or its interplay with circulating lymphocyte parameters in UTUC. Therefore, the current study aimed to explore the independent and synergistic prognostic value of baseline standardized SV and lymphocyte percentage (lym%) in patients with non-metastatic UTUC undergoing RNU.

Materials and methods

Study design and patient selection. The present retrospective cohort study included patients with non-metastatic UTUC who underwent RNU at National Cheng Kung University (Tainan, Taiwan) between November 2008 and December 2020. The inclusion criteria were as follows: i) Histologically confirmed UTUC; ii) no evidence of distant metastasis at diagnosis; and iii) availability of preoperative abdominal computed tomography (CT) imaging. Patients were excluded due to any of the following criteria: i) Prior splenectomy; ii) known splenic pathology (e.g., thrombosed splenic aneurysm); iii) no accessible preoperative CT scan; or iv) a postoperative follow-up duration of <24 months. Clinical and pathological variables were reviewed from electronic medical records, including age, sex, renal function, tumor characteristics and concomitant bladder cancer. Peripheral lym% was extracted from preoperative complete blood count results, collected within 1 month prior to RNU. A diagram of the study design is shown in Fig. 1A.

Imaging analysis and SV measurement. For each patient, the most recent abdominal CT scan prior to surgery was retrieved from the Picture Archiving and Communication System. Two experienced readers independently delineated the spleen on axial slices from upper to lower poles using a manual contouring method. The SV was calculated by summing the area of each outlined slice multiplied by the corresponding slice thickness. To account for individual body size differences, SV was standardized to body surface area (m^2), resulting in a unit of cm^3/m^2. Details of the segmentation procedure are shown in Fig. S1. Intra- and inter-observer reliabilities of the SV measurement were assessed by intraclass correlation coefficient (ICC). An ICC value >0.75 was considered indicative of excellent agreement (22). The SV measurements demonstrated excellent reliability, with an intra-observer ICC of 0.943 (95% CI, 0.791-0.984) and an inter-observer ICC of 0.951 (95% CI, 0.821-0.989).

Statistical analysis. All analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp.). Receiver operating characteristic (ROC) curve analysis was applied to determine optimal cut-off values for standardized SV and lym%, using all-cause mortality as the endpoint. Continuous variables were compared using independent t-tests or the Mann-Whitney U test, as appropriate, and categorical variables were compared using χ^2 tests. Correlations between SV and hematological parameters were evaluated using Pearson's correlation coefficient.

Survival outcomes, including overall survival (OS), cancer-specific survival (CSS) and metastasis-free survival (MFS), were defined as the interval from RNU to death or last follow-up. Patients lost to follow-up or alive at the final follow-up were censored. Survival curves were generated using Kaplan-Meier analysis, and differences were assessed by the log-rank test. Prognostic factors were analyzed using univariate and multivariate Cox proportional hazards models. Two-tailed P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics of patients with UTUC. Between November 2008 and December 2020, a total of 542 patients who underwent RNU for UTUC at National Cheng Kung University were identified. After excluding 1 patient with a history of a splenic calcified aneurysm with thrombosis, 3 patients who had undergone a splenectomy and 73 patients lacking preoperative abdominal CT imaging, 465 patients were included in the final analysis (Fig. 1A).

The mean age of the cohort was 69.5±10.4 years (range, 29-95 years). Based on ROC analysis using all-cause mortality as the endpoint, the optimal threshold for standardized SV was determined to be 79 cm^3/m^2 [sensitivity, 52%; specificity, 58%;

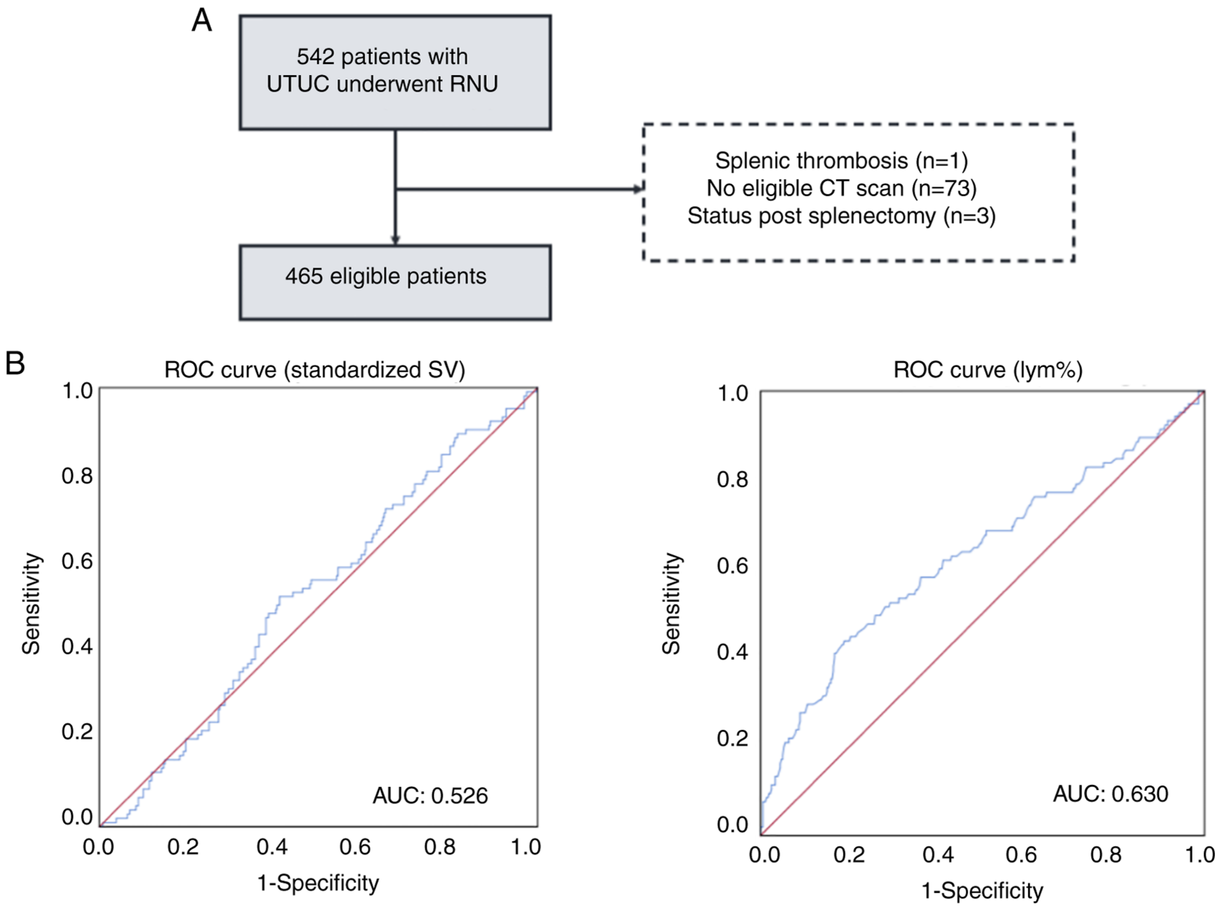

Figure 1. (A) Study flowchart. (B) ROC curve of baseline standardized SV and lym%, showing the cut-off value of 79 cm^3/m^2 for SV and 21% for lym%. Lym%, lymphocyte percentage; SV, splenic volume; ROC, receiver operator characteristic; UTUC, upper tract urothelial carcinoma; CT, computed tomography; RNU, radical nephroureterectomy; AUC, area under the curve.

area under the curve (AUC), 0.526; 95% confidence interval (CI), 0.466-0.587], while the optimal cut-off for lym% was 21% (sensitivity, 58%; specificity, 64%; AUC, 0.630; 95% CI, 0.565-0.696) (Fig. 1B). Of the 465 patients, 206 (44.3%) were categorized into the high SV (SV >79 cm^3/m^2) group. These patients had a significantly higher proportion of males (P=0.015) and worse baseline renal function (P=0.017) than those in the low SV group (n=259). Detailed clinicopathological features are presented in Table I.

Association between SV and peripheral blood parameters. Given that SV is associated with systemic immune status (17,23), the differences in peripheral immune cell counts and percentages between high and low SV were evaluated. Results from a comparative analysis (Table II) showed significantly lower lymphocyte count (P=0.001), lym% (P<0.001) and neutrophil percentage (P=0.001) in patients with high SV compared to those with low SV. No significant difference in platelet count (P=0.167), monocyte count (P=0.959), monocyte percentage (P=0.795), white blood cell count (0.079) or neutrophil count (0.251) was noted. Furthermore, Pearson's correlation showed that the standardized SV was negatively associated with lym% (r=-0.175, P<0.001) (Fig. 2). Additionally, when patients were stratified based on SV and lym%, higher neutrophil percentage showed a trend toward lower lym%, independent of SV (Fig. S2).

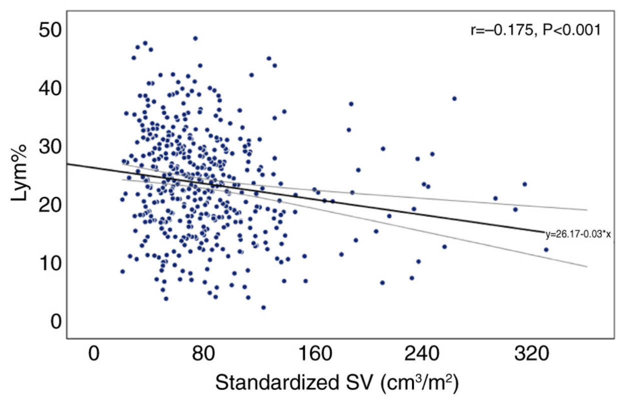

Figure 2. Correlation of standardized baselined SV and peripheral lym%. SV, splenic volume; lym%, lymphocyte percentage.

Impact of SV and lym% on oncological outcomes. Kaplan-Meier analysis revealed that patients with high SV had significantly shorter OS (P=0.027) and CSS (P=0.020) times, and also showed a non-significant trend toward poorer MFS time (P=0.189) (Fig. 3). Given the observed negative correlation between SV and peripheral lym%, both parameters were further integrated to assess their combined impact on patient outcomes. Patients with high SV and low lym% exhibited significantly worse OS (P<0.001), CSS (P<0.001) and MFS

Table I. Baseline characteristics of the cohort (n=465) according to low (n=259) or high (n=206) SV.

		Standardized SV		
Characteristics	All patients	Low SV	High SV	P-value
Mean age at diagnosis of UTUC, years	69.5±10.4	70.8±9.6	68.4±11.5	0.015
Median follow-up duration after RNU, months	45.8±25.1	50.0±25.0	38.2±24.9	0.011
Age, n (%)				0.112
≤69 years	219 (47)	113 (44)	106 (51)	
>69 years	246 (53)	146 (56)	100 (49)	
Sex, n (%)				0.015
Male	203 (44)	100 (39)	103 (50)	
Female	262 (56)	159 (61)	103 (50)	
Renal function, n (%)				0.017
eGFR ≤60 ml/min/1.73 m^2	274 (59)	141 (54)	133 (65)	
eGFR >60 ml/min/1.73 m^2	191 (41)	118 (46)	73 (35)	
HTN or DM, n (%)				0.511
No	204 (44)	110 (42)	94 (46)	
Yes	261 (56)	149 (58)	112 (54)	
Previous BC, n (%)				0.195
No	395 (85)	225 (87)	170 (83)	
Yes	70 (15)	34 (13)	36 (17)	
Concomitant BC, n (%)				0.480
No	375 (81)	212 (82)	163 (79)	
Yes	90 (19)	47 (18)	43 (21)	
Tumor location, n (%)				0.683
Pelvis	213 (46)	119 (46)	94 (46)	
Ureter	156 (34)	90 (35)	66 (32)	
Both	96 (21)	50 (19)	46 (22)	
Pathological T stage, n (%)				0.309
Tis/a/1	158 (34)	86 (33)	72 (35)	
T2	89 (19)	56 (22)	33 (16)	
T3/4	218 (47)	117 (45)	101 (49)	
Lymph node status, n (%)				>0.999
N0/x	435 (94)	242 (93)	193 (94)	
N+	30 (6)	17 (7)	13 (6)	
Tumor grade, n (%)				0.291
Low	15 (3)	6 (2)	9 (4)	
High	450 (97)	253 (98)	197 (96)	
Lymphovascular invasion, n (%)				>0.999
Absent	324 (70)	180 (69)	144 (70)	
Present	141 (30)	79 (31)	62 (30)	
Adjuvant chemotherapy, n (%)				0.467
No	411 (88)	226 (87)	185 (90)	
Yes	54 (12)	33 (13)	21 (10)	
Tumor necrosis, n (%)				0.185
No	380 (82)	206 (80)	174 (84)	
Yes	85 (18)	53 (20)	32 (16)	

RNU, radical nephroureterectomy; eGFR, preoperative estimated glomerular filtration rate; HTN, hypertension; DM, diabetes mellitus; BC, bladder cancer; SV, splenic volume.

(P=0.008) times compared with those with high SV and high lym%, or low SV regardless of lym% status (Fig. 4).

To assess the prognostic significance of the combined SV and lym%, univariate Cox regression analyses were

Table II. Comparison of peripheral blood parameters in patients with low and high SV.

Serum immune cells	Low SV	High SV	P-value
White blood cell counts (x10^9/l)	6,600 (2,600)	6,300 (2,900)	0.079
Lymphocyte count (x10^9/l)	1,602 (801)	1,389 (727)	0.001
Lymphocyte percentage	24.8 (13.0)	21.7 (12.2)	<0.001
Neutrophil count (x10^9/l)	4,320 (2,406)	4,163 (2,156)	0.241
Neutrophil percentage	64.9 (15.2)	67.6 (11.5)	0.001
Monocyte count (x10^9/l)	507 (234)	504 (297)	0.959
Monocyte percentage	7.9 (3.2)	7.7 (3.5)	0.795
Platelet (x10^9/l)	225 (88)	212 (100)	0.167

Data are presented as median (IQR). SV, splenic volume.

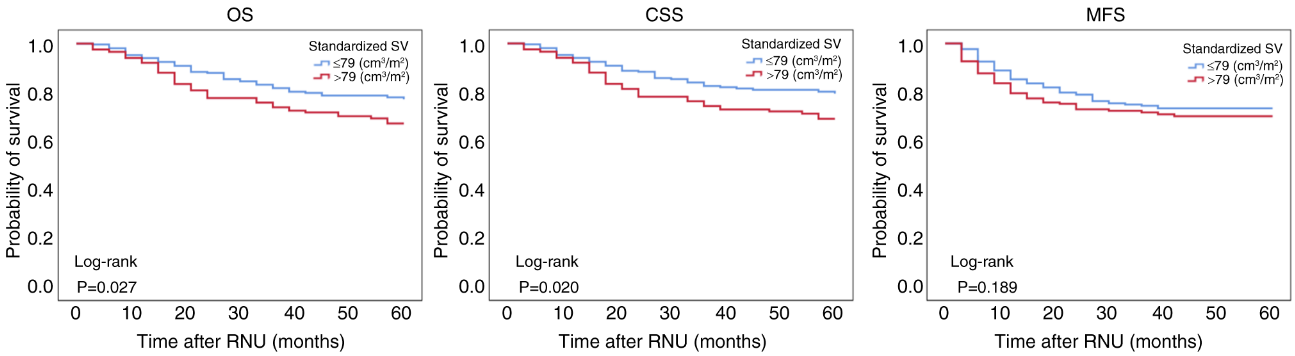

Figure 3. Kaplan-Meier analyses for OS, CSS and MFS based on standardized baseline SV (cm^3/m^2). OS, overall survival; CSS, cancer-specific survival; MFS, metastasis-free survival; SV, splenic volume; RNU, radical nephroureterectomy.

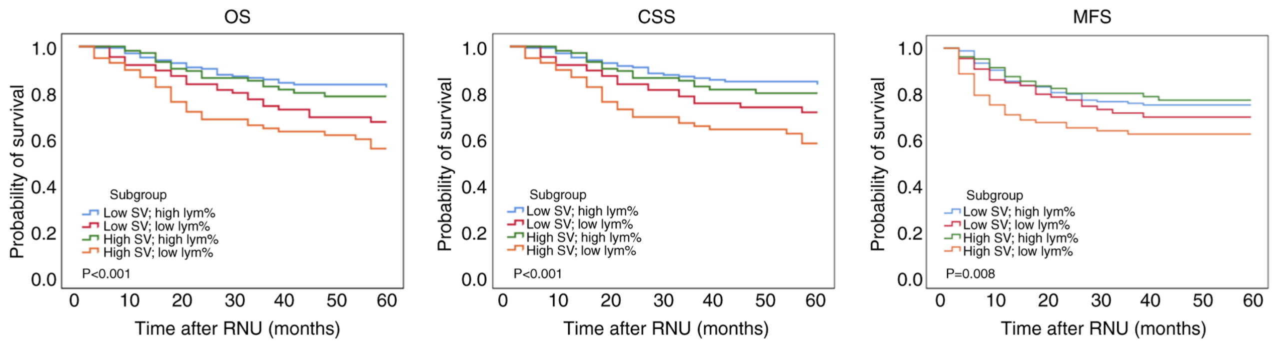

Figure 4. Kaplan-Meier analyses for OS, CSS and MFS based on baseline standardized SV (cm^3/m^2) and lym%. OS, overall survival; CSS, cancer-specific survival; MFS, metastasis-free survival; SV, splenic volume; RNU, radical nephroureterectomy; lym%, lymphocyte percentage.

performed for OS, CSS and MFS (Tables III-V). In the univariate analysis, factors significantly associated with poorer outcomes across all three survival endpoints included the combination of high SV with low lym%, LVI, lymph node involvement, multifocal tumor location (involving both renal pelvis and ureter), advanced pathological T stage (pT stage), male sex and concomitant bladder cancer. Notably, concomitant bladder cancer and the low SV with low lym% subgroup were associated with worse OS and CSS, but not MFS. Multivariate analyses identified LVI, lymph node involvement, advanced pT stage, multifocal tumor location (involving both renal pelvis and ureter), male sex, and high SV with low lym% as consistent independent predictors of inferior OS, CSS and MFS.

Discussion

In the present retrospective cohort study of 465 patients with non-metastatic UTUC who underwent RNU, a higher preoperative SV and lower peripheral lym% were found to be independently associated with inferior OS, CSS and MFS. Notably, the combined presence of high SV and low lym% was the strongest prognostic indicator across all endpoints. These findings suggest that baseline immune and hematological

Table III. Univariate and multivariate Cox regression analyses for predicting cancer-specific survival in patients with upper tract urothelial carcinoma after RNU.

	Univariate		Multivariate	
Characteristic	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at RNU				
>69 vs. ≤69 years	1.472 (0.997-2.172)	0.052	1.722 (1.154-2.568)	0.008
Sex				
Female vs. male	0.475 (0.321-0.702)	<0.001	0.561 (0.373-0.845)	0.006
Renal function status				
eGFR <60 vs. ≥60 ml/min/1.73 m^2	1.317 (0.882-1.965)	0.178		
Hematuria				
Yes vs. no	0.890 (0.523-1.516)	0.668		
Hydronephrosis				
Yes vs. no	1.187 (0.7361.915)	0.483		
Previous BC				
Yes vs. no	1.120 (0.666-1.882)	0.670		
Concomitant BC				
Yes vs. no	1.614 (1.052-2.476)	0.028	0.937 (0.583-1.505)	0.788
Tumor location				
Ureter vs. renal pelvis	0.870 (0.539-1.404)	0.569	1.241 (0.751-2.050)	0.400
Both vs. renal pelvis	1.979 (1.263-3.100)	0.003	1.739 (1.078-2.805)	0.023
Pathological T stage				
pT2 vs. pTa/1	4.230 (1.641-10.906)	0.003	3.468 (1.320-9.110)	0.012
pT3/4 vs. pTa/1	12.886 (5.627-29.511)	<0.001	9.216 (3.887-21.852)	<0.001
Lymph node involvement				
N+ vs. Nx/0	6.097 (3.728-9.969)	<0.001	3.862 (2.187-6.819)	<0.001
Tumor grade				
High vs. low	3.236 (0.451-23.190)	0.243		
Lymphovascular invasion				
Presence vs. absence	3.854 (2.613-5.686)	<0.001	1.857 (1.197-2.883)	0.006
Adjuvant chemotherapy				
Yes vs. no	1.321 (0.764-2.283)	0.319	0.382 (0.203-0.717)	0.003
Standardized SV and lym% subgroup				
Low SV with high lym%	Reference		Reference	
Low SV with low lym%	1.795 (1.029-3.131)	0.039	1.611 (0.911-2.850)	0.101
High SV with high lym%	1.176 (0.654-2.116)	0.588	1.140 (0.626-2.077)	0.668
High SV with low lym%	2.847 (1.727-4.692)	<0.001	2.142 (1.253-3.662)	0.005

RNU, radical nephroureterectomy; eGFR, estimated glomerular filtration rate; BC, bladder cancer; SV, splenic volume; lym%, serum lymphocyte percentage; HR, hazard ratio; CI, confidence interval.

parameters, quantified through imaging and routine blood tests, may offer valuable insights into host-tumor dynamics and support individualized risk stratification.

The present analysis expands on existing literature linking splenomegaly to adverse outcomes in solid malignancies. Prior studies have demonstrated that elevated SV is associated with a poor prognosis in hepatocellular carcinoma, pancreatic cancer, gastric cancer, metastatic colorectal cancer and non-small cell lung cancer (17,20,21,24). Consistent with these observations, the present study found that larger baseline SV predicted worse oncological outcomes in UTUC. Importantly, to the best of our knowledge, the present study is the first to evaluate SV in the context of urothelial carcinoma of the upper tract and to integrate peripheral immune status (lym%) as a complementary biomarker.

While the mechanistic link between splenic remodeling and cancer outcomes remains under investigation, accumulating evidence from preclinical models supports the role of the spleen in tumor-induced immune suppression (23,25). Han *et al* (26) found that tumor-bearing mice produced

Table IV. Univariate and multivariate Cox regression analyses for predicting overall survival in patients with upper tract urothelial carcinoma after RNU.

Characteristic	Univariate HR (95% CI)	Univariate P-value	Multivariate HR (95% CI)	Multivariate P-value
Age at RNU				
>69 vs. ≤69 years	1.493 (1.025-2.173)	0.037	1.729 (1.176-2.542)	0.005
Sex				
Female vs. male	0.525 (0.362-0.763)	0.001	0.603 (0.408-0.892)	0.011
Renal function status				
eGFR <60 vs. ≥60 ml/min/1.73 m^2	1.474 (0.995-2.184)	0.053		
Hematuria				
Yes vs. no	0.907 (0.541-1.519)	0.710		
Hydronephrosis				
Yes vs. no	1.161 (0.734-1.836)	0.523		
Previous BC				
Yes vs. no	1.254 (0.773-20.32)	0.359		
Concomitant BC				
Yes vs. no	1.670 (1.109-2.515)	0.014	1.013 (0.645-1.592)	0.954
Tumor location				
Ureter vs. renal pelvis	0.948 (0.601-1.495)	0.818	1.333 (0.827-2.150)	0.238
Both vs. renal pelvis	2.003 (1.293-3.102)	0.002	1.759 (1.106-2.799)	0.017
Pathological T stage				
pT2 vs. pTa/1	2.391 (1.142-5.008)	0.021	1.932 (0.903-4.137)	0.090
pT3/4 vs. pTa/1	6.489 (3.543-11.887)	<0.001	4.601 (2.397-8.831)	<0.001
Lymph node involvement				
N+ vs. Nx/0	5.749 (3.529-9.365)	<0.001	3.968 (2.253-6.990)	<0.001
Tumor grade				
High vs. low	1.738 (0.429-7.036)	0.439		
Lymphovascular invasion				
Presence vs. absence	3.534 (2.436-5.129)	<0.001	1.898 (1.237-2.912)	0.003
Adjuvant chemotherapy				
Yes vs. no	1.227 (0.712-2.114)	0.461	0.385 (0.206-0.723)	0.003
Standardized SV and lym% subgroup				
Low SV with high lym%				
Low SV with low lym%	1.902 (1.120-3.231)	0.017	1.743 (1.014-2.996)	0.044
High SV with high lym%	1.160 (0.656-2.051)	0.609	1.158 (0.647-2.073)	0.621
High SV with low lym%	2.821 (1.738-4.577)	<0.001	2.201 (1.314-3.688)	0.003

RNU, radical nephroureterectomy; eGFR, estimated glomerular filtration rate; BC, bladder cancer; SV, splenic volume; lym%, serum lymphocyte percentage.

erythroblast-like Ter cells in the spleen that promoted hepatocellular carcinoma progression. Additional studies by Zhao *et al* (27) and Sano *et al* (28) identified $CD71^+TER119^+$ erythroid progenitor cells in the spleen that exert immunosuppressive effects on effector T cells. Moreover, the spleen has been shown to facilitate the generation and expansion of MDSCs in the tumor-bearing state, further contributing to an immunosuppressive milieu and enhanced tumor aggressiveness (23,29,30). Jiang *et al* (31) demonstrated a positive correlation between splenic weight and serum mMDSC levels in a mouse model of hepatocellular carcinoma. The clinical relevance of these findings is underscored by the study by Levy *et al* (32), which demonstrated that splenectomy inhibited tumor growth and metastasis in non-small cell lung cancer by depleting MDSCs and enhancing cytotoxic T-cell activation. The present findings may therefore reflect a broader impairment of systemic immunity in UTUC. An enlarged spleen may indicate an activated yet functionally exhausted immune state, accompanied by peripheral lymphocyte depletion, diminished antitumor immune surveillance and a pro-inflammatory

Table V. Univariate and multivariate Cox regression analyses for predicting metastasis-free survival in patients with upper tract urothelial carcinoma after radical nephroureterectomy.

	Univariate		Multivariate	
Characteristic	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at RNU, years				
>69 vs. ≤69	1.005 (0.704-1.435)	0.978	1.203 (0.833-1.737)	0.325
Sex				
Female vs. male	0.572 (0.399-0.817)	0.002	0.658 (0.453-0.954)	0.037
Renal function status, ml/min/1.73 m^2				
eGFR <60 vs. ≥60	0.942 (0.657-1.350)	0.942		
Hematuria				
Yes vs. no	0.832 (0.505-1.373)	0.473		
Hydronephrosis				
Yes vs. no	0.991 (0.646-1.521)	0.969		
Previous BC				
Yes vs. no	1.239 (0.774-1.983)	0.372		
Concomitant BC				
Yes vs. no	1.461 (0.971-2.197)	0.069		
Tumor location				
Ureter vs. renal pelvis	1.048 (0.680-1.616)	0.832	1.674 (1.063-2.637)	0.026
Both vs. renal pelvis	2.057 (1.339-3.162)	0.001	2.212 (1.428-3.425)	<0.001
Pathological T stage				
pT2 vs. pTa/1	2.952 (1.224-7.122)	0.016	2.320 (0.949-5.672)	0.065
pT3/4 vs. pTa/1	12.885 (6.266-26.495)	<0.001	8.707 (4.100-18.490)	<0.001
Lymph node involvement				
N+ vs. Nx/0	5.842 (3.506-9.733)	<0.001	3.292 (1.843-5.880)	<0.001
Tumor grade				
High vs. low	4.029 (0.563-28.838)	0.165		
Lymphovascular invasion				
Presence vs. absence	4.305 (2.996-6.186)	<0.001	2.060 (1.388-3.057)	<0.001
Adjuvant chemotherapy				
Yes vs. no	2.584 (1.673-3.993)	<0.001	0.786 (0.475-1.302)	0.350
Standardized SV and lym% subgroup				
Low SV with high lym%				
Low SV with low lym%	1.234 (0.744-2.046)	0.416	1.076 (0.641-1.807)	0.782
High SV with high lym%	0.889 (0.528-1.495)	0.656	0.857 (0.502-1.463)	0.571
High SV with low lym%	1.834 (1.165-2.888)	0.009	1.649 (1.031-2.636)	0.037

RNU, radical nephroureterectomy; eGFR, estimated glomerular filtration rate; BC, bladder cancer; SV, splenic volume; lym%, serum lymphocyte percentage; HR, hazard ratio; CI, confidence interval.

milieu. Additionally, tumor-stroma interactions likely amplify this process by promoting cytokine-driven immune evasion, neutrophil recruitment and microenvironmental immunosuppression (17,19,29). Together, these mechanisms offer a biological explanation for why patients with high standardized SV and low circulating lym% are prone to early metastasis and inferior oncological outcomes.

The combination of imaging-derived SV and routine lym% may serve as a non-invasive, cost-effective method for identifying high-risk patients with UTUC who might benefit from intensified surveillance or consideration of adjuvant systemic therapies. Given the lack of robust predictive biomarkers in this population, the present results provide a potentially actionable stratification tool that complements established clinicopathological factors such as stage, LVI and nodal status.

Nevertheless, several limitations warrant consideration. First, the retrospective nature and single-center design of the present study may introduce selection bias and limit generalizability. Second, the study was lacking post-operative immune profiling or longitudinal SV measurements, which restricts the ability to evaluate dynamic immunological changes over time. Finally, although ROC-based cutoffs were used to dichotomize SV and lym%, external validation of these thresholds is necessary before clinical application.

In conclusion, higher standardized SV combined with lower circulating lym% was identified as a novel, independent predictor of worse survival outcomes in patients with UTUC following RNU. These findings suggest that incorporating baseline standardized SV and lym%, alongside established clinicopathological risk factors, can enhance risk stratification and support more individualized postoperative management strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CHL and HCJ were responsible for the study concept and design. Data acquisition was performed by CHL, CYH, CHO and HCJ. Quality control of data and algorithms was performed by KCL, CYH and CHO. Data analysis and interpretation was performed by CHL, KCL and CAW. The statistical analysis was performed by CHL and KCL. CHL and KCL prepared the manuscript. The manuscript was edited by CHO and HCJ, and reviewed by CAW, CYH, CHO and HCJ. CHL and HCJ confirm the authenticity of all the raw data. All authors have read and agreed to the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of National Cheng Kung University Hospital (Tainan, Taiwan; approval no. B-ER-112-214). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study, and access to follow-up clinical records was granted. All procedures were conducted in accordance with the ethical standards outlined in the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Raman JD, Messer J, Sielatycki JA and Hollenbeak CS: Incidence and survival of patients with carcinoma of the ureter and renal pelvis in the USA, 1973-2005. BJU Int 107: 1059-1064, 2011.
2. Colin P, Koenig P, Ouzzane A, Berthon N, Villers A, Biserte J and Rouprêt M: Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. BJU Int 104: 1436-1440, 2009.
3. Rouprêt M, Babjuk M, Burger M, Capoun O, Cohen D, Comperat EM, Cowan NC, Dominguez-Escrig JL, Gontero P, Hugh Mostafid A, *et al*: European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. Eur Urol 79: 62-79, 2021.
4. Clark PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, Herr HW, Inman BA, Kuban DA, Kuzel TM, Lele SM, *et al*: Bladder cancer. J Natl Compr Canc Netw 11: 446-475, 2013.
5. Rouprêt M, Zigeuner R, Palou J, Boehle A, Kaasinen E, Sylvester R, Babjuk M and Oosterlinck W: European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. Eur Urol 59: 584-594, 2011.
6. Rouprêt M, Seisen T, Birtle AJ, Capoun O, Compérat EM, Dominguez-Escrig JL, Gürses Andersson I, Liedberg F, Mariappan P, Hugh Mostafid A, *et al*: European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2023 update. Eur Urol 84: 49-64, 2023.
7. Oswald D, Pallauf M, Deininger S, Törzsök P, Sieberer M and Eiben C: Neoadjuvant chemotherapy before nephroureterectomy in high-risk upper tract urothelial cancer: A systematic review and meta-analysis. Cancers (Basel) 14: 4841, 2022.
8. Piombino C, Tonni E, Oltrecolli M, Pirola M, Pipitone S, Baldessari C, Dominici M, Sabbatini R and Vitale MG: Immunotherapy in urothelial cancer: Current status and future directions. Expert Rev Anticancer Ther 23: 1141-1155, 2023.
9. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, Harris C, Winterbottom A, Blacker A, Catto JWF, *et al*: Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): A phase 3, open-label, randomised controlled trial. Lancet 395: 1268-1277, 2020.
10. Jan HC, Hu CY, Yang WH and Ou CH: Combination of Platelet-lymphocyte ratio and Monocyte-lymphocyte ratio as a new promising prognostic factor in upper tract urothelial carcinoma with large Tumor Sizes >3 cm. Clin Genitourin Cancer 18: e484-e500, 2020.
11. Li T, Xu H, Yang L, Tan P and Wei Q: Predictive value of preoperative lymphocyte-to-monocyte ratio for patients with upper tract urothelial carcinoma. Clin Chim Acta 492: 50-56, 2019.
12. Vartolomei MD, Kimura S, Ferro M, Vartolomei L, Foerster B, Abufaraj M and Shariat SF: Is neutrophil-to-lymphocytes ratio a clinical relevant preoperative biomarker in upper tract urothelial carcinoma? A meta-analysis of 4385 patients. World J Urol 36: 1019-1029, 2018.
13. Jan HC, Yang WH and Ou CH: Combination of the preoperative systemic Immune-inflammation index and Monocyte-lymphocyte ratio as a novel prognostic factor in patients with Upper-tract urothelial carcinoma. Ann Surg Oncol 26: 669-684, 2019.
14. Steenbrugge J, De Jaeghere EA, Meyer E, Denys H and De Wever O: Splenic hematopoietic and stromal cells in cancer progressionthe spleen in cancer progression. Cancer Res 81: 27-34, 2021.
15. Mebius RE and Kraal G: Structure and function of the spleen. Nat Rev Immunol 5: 606-616, 2005.
16. Bae JS, Lee DH, Yoo J, Yi NJ, Lee KW, Suh KS, Kim H and Lee KB: Association between spleen volume and the post-hepatectomy liver failure and overall survival of patients with hepatocellular carcinoma after resection. Eur Radiol 31: 2461-2471, 2021.

17. Zeng Z, Liu Z, Li J, Sun J, Ma M, Ye X, Yu J and Kang W: Baseline splenic volume as a biomarker for clinical outcome and circulating lymphocyte count in gastric cancer. Front Oncol 12: 1065716, 2023.
18. Galland L, Lecuelle J, Favier L, Fraisse C, Lagrange A, Kaderbhai C, Truntzer C and Ghiringhelli F: Splenic volume as a surrogate marker of immune checkpoint inhibitor efficacy in metastatic non small cell lung cancer. Cancers 13: 3020, 2021.
19. Cortez-Retamozo V, Etzrodt M, Newton A, Rauch PJ, Chudnovskiy A, Berger C, Ryan RJ, Iwamoto Y, Marinelli B, Gorbatov R, *et al*: Origins of tumor-associated macrophages and neutrophils. Proc Natl Acad Sci USA 109: 2491-2496, 2012.
20. Niogret J, Limagne E, Thibaudin M, Blanc J, Bertaut A, Le Malicot K, Rinaldi Y, Caroli-Bosc FX, Audemar F, Nguyen S, *et al*: Baseline splenic volume as a prognostic biomarker of FOLFIRI efficacy and a surrogate marker of MDSC accumulation in metastatic colorectal carcinoma. Cancers (Basel) 12: 1429, 2020.
21. Müller L, Gairing SJ, Kloeckner R, Foerster F, Weinmann A, Mittler J, Stoehr F, Emrich T, Düber C, Galle PR and Hahn F: Baseline splenic volume outweighs Immuno-modulated size changes with regard to survival outcome in patients with hepatocellular carcinoma under immunotherapy. Cancers (Basel) 14: 3574, 2022.
22. Koo TK and Li MY: A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 15: 155-163, 2016.
23. Jordan KR, Kapoor P, Spongberg E, Tobin RP, Gao D, Borges VF and McCarter MD: Immunosuppressive myeloid-derived suppressor cells are increased in splenocytes from cancer patients. Cancer Immunol Immunother 66: 503-513, 2017.
24. Aarnink A, Richard C, Truntzer C, Vincent J, Bengrine L, Vienot A, Borg C and Ghiringhelli F: Baseline splenic volume as a surrogate marker of FOLFIRINOX efficacy in advanced pancreatic carcinoma. Oncotarget 9: 25617, 2018.
25. Ugel S, Peranzoni E, Desantis G, Chioda M, Walter S, Weinschenk T, Ochando JC, Cabrelle A, Mandruzzato S and Bronte V: Immune tolerance to tumor antigens occurs in a specialized environment of the spleen. Cell Rep 2: 628-639, 2012.
26. Han Y, Liu Q, Hou J, Gu Y, Zhang Y, Chen Z, Fan J, Zhou W, Qiu S, Zhang Y, *et al*: Tumor-induced generation of splenic Erythroblast-like Ter-cells promotes tumor progression. Cell 184: 1392, 2021.
27. Zhao L, He R, Long H, Guo B, Jia Q, Qin D, Liu SQ, Wang Z, Xiang T, Zhang J, *et al*: Late-stage tumors induce anemia and immunosuppressive extramedullary erythroid progenitor cells. Nat Med 24: 1536-1544, 2018.
28. Sano Y, Yoshida T, Choo MK, Jiménez-Andrade Y, Hill KR, Georgopoulos K and Park JM: Multiorgan signaling mobilizes Tumor-associated erythroid cells expressing immune checkpoint molecules. Mol Cancer Res 19: 507-515, 2021.
29. Wu C, Ning H, Liu M, Lin J, Luo S, Zhu W, Xu J, Wu WC, Liang J, Shao CK, *et al*: Spleen mediates a distinct hematopoietic progenitor response supporting tumor-promoting myelopoiesis. J Clin Invest 128: 3425-3438, 2018.
30. Tavukcuoglu E, Horzum U, Yanik H, Uner A, Yoyen-Ermis D, Nural SK, Aydin B, Sokmensuer C, Karakoc D, Yilmaz KB, *et al*: Human splenic polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC) are strategically located immune regulatory cells in cancer. Eur J Immunol 50: 2067-2074, 2020.
31. Jiang W, Li Y, Zhang S, Kong G and Li Z: Association between cellular immune response and spleen weight in mice with hepatocellular carcinoma. Oncol Lett 22: 625, 2021.
32. Levy L, Mishalian I, Bayuch R, Zolotarov L, Michaeli J and Fridlender ZG: Splenectomy inhibits non-small cell lung cancer growth by modulating anti-tumor adaptive and innate immune response. Oncoimmunology 4: e998469, 2015.