# Preoperative systemic inflammation response index enhances the prognostic value of tumor multifocalityin upper tract urothelial carcinoma

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**Abstract.** In cancer, tumor-related inflammation affects disease progression and survival outcomes. However, the role of systemic inflammation in tumor multifocality in upper tract urothelial carcinoma (UTUC) is not well understood. The aim of the present study was to evaluate the impact of the systemic inflammation response index (SIRI) on tumor multifocality for predicting oncological outcomes in patients with UTUC after radical nephroureterectomy (RNU). For this purpose, data from 645 patients with non-metastatic UTUC who underwent RNU between 2008 and 2020 were retrospectively analyzed. Survival outcomes such as overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS) RATES were assessed using the Kaplan-Meier method, and independent prognostic factors were identified through a multivariable Cox proportional hazards regression model. Of the 645 patients with UTUC included in the present study, 163 (25%) had multifocal UTUC. Kaplan-Meier analysis indicated that multifocal UTUC synchronous with a high-level SIRI was significantly associated with poorer outcomes after RNU. Furthermore, the results of the multivariate Cox proportional hazards model analysis demonstrated that multifocal tumor coupled with a high-level SIRI was an independent factor for predicting a shorter survival and disease progression. In conclusion, the results of the present study indicated that an elevated SIRI significantly influenced the survival rate of patients with multifocal UTUC. Specifically, integrating multifocal UTUC with a high-level SIRI emerged as an independent risk factor for poorer OS, CSS and RFS. These findings highlighted the potential role of SIRI in the risk stratification and management of patients with multifocal UTUC.

## Introduction

Upper tract urothelial carcinoma (UTUC) represents only 5% of all urothelial carcinoma cases globally (1); however, UTUC is more prevalent in Taiwan, specifically in the Southwest region (2,3). As UTUC has a high risk of recurrence and progression, radical nephroureterectomy (RNU) with bladder cuff excision has served as the standard treatment for localized disease (4,5). In high-risk patients with UTUC, including those with an advanced tumor stage, regional lymph node (LN) metastasis and lymphovascular invasion (LVI) positivity, neoadjuvant or adjuvant systemic therapy has shown promising results (6-9). Hence, identification of pre-and postoperative prognostic factors for high-risk disease progression is a major focus of numerous studies, which will aid in conducting accurate pretreatment assessments of UTUC.

Tumor multifocality, defined as the simultaneous occurrence of multiple (>1) tumors, in the renal pelvis and/or ureter has been considered a potential risk biomarker for UTUC (10-12). Some studies have suggested that multifocal UTUC is associated with a more aggressive biological behavior and poorer clinical outcome (10,13,14). Some evidence showed that multifocal tumors, regardless of the tumor location, are only significantly associated with bladder tumor recurrence and not cancer-specific survival (CSS) (15-17). In addition, emerging research has highlighted the role of inflammatory markers in tumor development and progression (18-23). Previous studies have shown that the systemic inflammation response index (SIRI) is a useful inflammation biomarker associated with poorer urologic outcomes (24-26). However, whether the systemic inflammation state influences the prognostic

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significance of tumor multifocality remains unclear. Therefore, the aim of the present study was to investigate the effect of tumor multifocality with different inflammation states (high vs. low-level SIRI) on clinical outcomes in patients with UTUC after RNU.

## Materials and methods

*Patient population and selection*. The present single-center retrospective study included 645 patients with UTUC who received RNU at National Chen-Kung University Hospital (Tainan, Taiwan) from January-2008 to December-2020. The exclusion criteria included: i) Patients who did not undergo RNU; ii) patients with an active infection status; iii) lack of differential count information from preoperative complete blood counts (CBCs) 30 days before surgery; iv) visceral or bone metastasis at the time of diagnosis; v) other concurrent cancer; vi) the use of immunosuppressive drugs; vii) a follow-up duration of <30 days; and viii) treatment with neo-adjuvant systemic therapy or radiotherapy. Multifocal UTUC was defined as the synchronous presence of pathologically confirmed >1 tumor in the upper urinary tract. All enrolled patients were divided into the multifocal and non-multifocal groups, and clinicopathological parameters collected from medical records were compared, including age, sex, renal function, hemodialysis, comorbidities (hypertension or diabetes mellitus), associated symptoms (gross hematuria and hydronephrosis), prior or concomitant bladder cancer, pathological tumor (pT) stage, LN status, tumor grade, tumor size, tumor necrosis, LVI, adjuvant chemotherapy, white blood cell count (WBC), absolute neutrophil count (ANC) and SIRI. SIRI was calculated as follows: Neutrophil count x monocyte count/lymphocyte count. The present study was approved by The Cheng Kung University Hospital Institutional Review Board (IRB no. B-ER-112-216).

*Collection of tumor pathological characteristics*. All tumor characteristics were collected from the medical records. All slides from surgical specimens were reviewed by genitourinary pathologists based on the same criteria. Tumors were staged according to the American Joint Committee on Cancer TNM Classification (7th edition) (27) and graded according to the 2004 World Health Organization/International Society of Urological Pathology consensus classification (28).

*Follow-up schedule*. Generally, patients were scheduled for postoperative follow-up every 3-6 months in the first year following RNU, every 6 months in the second to fifth year and annually thereafter. During each visit, clinical evaluations included updating the medical history, physical examination, blood tests, urinary cytology and imaging studies. Disease recurrence was defined as distant metastasis or local recurrence in the tumor bed or regional LNs. The cause of death was determined by the death certificate, medical notes or the attending doctor. The primary endpoints were overall survival (OS), CSS and recurrence-free survival (RFS). OS was defined as the interval from RNU until death; CSS was defined as the interval from RNU until UTUC-related death; RFS was defined as the duration from RNU until local recurrence or distant metastases (did not include intravesical or contralateral upper tract recurrence).

*Statistical analysis*. Descriptive statistics were performed for all variables. Categorical variables were compared using the $\chi^2$ test. Continuous variables were evaluated using the unpaired Student's t-test or the Mann-Whitney U test, depending on the data distribution. The optimal SIRI cut-off value was determined as 1.95 using receiver operating characteristic (ROC) curve analysis with Youden's index based on CSS (Fig. S1). Specifically, a SIRI of ≥1.95 or <1.95 were defined as high or low level in the setting. The cut-off values for WBC and ANC were set based on the median counts. Survival curves were plotted using the Kaplan-Meier method, and the differences were assessed using the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify significant prognostic factors for OS, CSS and RFS. All statistical analyses were performed using SPSS version 26.0 (IBM Corp.), and $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Demographic and clinicopathological features of the study population*. In the population of 645 patients, tumor multifocality was absent in 482 and present in 163 patients. The mean age was 69.2±11.0 years and the median follow-up time was 66.0±45.0 months. No significant differences were noted in age, sex, hemodialysis, DM or HTN, gross hematuria, pT stage, LN status, LVI, tumor grade and adjuvant chemotherapy between the two multifocality groups. Conversely, the presence of tumor multifocality was significantly associated with higher rates of renal function impairment, hydronephrosis, prior or concomitant BC, larger tumor size, tumor necrosis, WBC, ANC and SIRI (Table I).

*Prognostic impact of tumor multifocality and SIRI*. Kaplan-Meier analysis revealed that multifocal UTUC was significantly associated with a poorer OS, CSS and RFS compared with non-multifocal UTUC (all $P<0.05$; Fig. S2). ROC analysis showed SIRI was preferred over WBC or ANC for predictive ability on oncological outcomes (Fig. S3). Also in the multivariate analysis, SIRI, pT stage, LN stage, LVI, and tumor multifocality were independent factors for OS, CSS and RFS (Table SI). SIRI was used as systemic inflammation state as appropriate. To further investigate the effect of the systemic inflammation state on tumor multifocality, patients were categorized into four groups based on tumor multifocality and SIRI, including multifocal with a high-level SIRI, non-multifocal with a high-level SIRI, multifocal with a low-level SIRI and non-multifocal with a low-level SIRI. Kaplan-Meier analysis revealed that multifocal UTUC coupled with a high-level SIRI was significantly associated with a worse OS, CSS and RFS compared with the other groups (Fig. 1).

Additionally, as non-organ-confined (NOC) and OC) diseases have different pathophysiological characteristics, all patients were stratified into the NOC and OC groups, before evaluating the combinatorial impact of tumor multifocality and SIRI on OS, CSS and RFS. Kaplan-Meier analyses showed that multifocal UTUC with a high-level SIRI was significantly associated with a poorer OS, CSS and RFS in both OC and NOC UTUC compared with the other three groups (Fig. 2).

Table I. Association between clinicopathological characteristics and multifocal tumors in 645 patients with upper tract urothelial carcinoma.

| | | Multifocality | | |
|---|---|---|---|---|
| Clinicopathological characteristics | All patients, n=645 | Absence, n=482 | Presence, n=163 | P-value |
| Mean age ± SD, years | 69.2±11.0 | 69.2±10.8 | 69.2±11.5 | |
| Mean follow-up after surgery ± SD, months | 66.0±45.0 | 68.1±44.6 | 60.2±45.9 | |
| Age, n (%) | | | | 0.867 |
| ≤69 years | 305 (47) | 227 (47) | 78 (48) | |
| >69 years | 340 (53) | 255 (53) | 85 (52) | |
| Sex, n (%) | | | | 0.926 |
| Male | 279 (43) | 209 (43) | 70 (43) | |
| Female | 366 (57) | 273 (57) | 93 (57) | |
| Hemodialysis, n (%) | | | | 0.180 |
| No | 529 (82) | 401 (83) | 128 (79) | |
| Yes | 116 (18) | 81 (17) | 35 (21) | |
| eGFR[a], n (%) | | | | 0.019 |
| ≥60 ml/min/1.73 $m^2$ | 256 (40) | 204 (42) | 52 (32) | |
| <60 ml/min/1.73 $m^2$ | 389 (60) | 278 (58) | 111 (68) | |
| DM or HTN, n (%) | | | | 0.715 |
| Absent | 273 (42) | 206 (43) | 67 (41) | |
| Present | 372 (58) | 276 (57) | 96 (59) | |
| Hematuria (%) | | | | 0.373 |
| No | 82 (13) | 58 (12) | 24 (15) | |
| Yes | 563 (87) | 424 (88) | 139 (85) | |
| Hydronephrosis, n (%) | | | | 0.005 |
| No | 137 (21) | 115 (24) | 22 (13) | |
| Yes | 508 (79) | 367 (76) | 141 (87) | |
| Prior BC, n (%) | | | | <0.001 |
| No | 540 (84) | 422 (88) | 118 (72) | |
| Yes | 105 (16) | 60 (12) | 45 (28) | |
| Concomitant BC (%) | | | | <0.001 |
| No | 515 (80) | 402 (83) | 113 (69) | |
| Yes | 130 (20) | 80 (17) | 50 (31) | |
| Pathological T stage, n (%) | | | | 0.057 |
| Tis/a/1 | 238 (37) | 189 (39) | 49 (30) | |
| T2 | 126 (20) | 86 (18) | 40 (25) | |
| T3/T4 | 281 (43) | 207 (43) | 74 (45) | |
| LN status, n (%) | | | | 0.091 |
| N0/x | 607 (94) | 458 (95) | 149 (91) | |
| N+ | 38 (6) | 24 (5) | 14 (9) | |
| Tumor grade, n (%) | | | | 0.058 |
| Low | 29 (5) | 26 (5) | 3 (2) | |
| High | 616 (95) | 456 (95) | 160 (98) | |
| Tumor size, n (%) | | | | 0.014 |
| ≤2 cm | 183 (28) | 149 (31) | 34 (21) | |
| >2 cm | 462 (72) | 333 (69) | 129 (79) | |
| Tumor necrosis, n (%) | | | | 0.046 |
| No | 521 (81) | 398 (83) | 123 (75) | |
| Yes | 124 (19) | 84 (17) | 40 (25) | |
| LVI, n (%) | | | | 0.104 |
| No | 452 (70) | 346 (72) | 106 (65) | |
| Yes | 193 (30) | 136 (28) | 57 (35) | |

Table I. Continued.

| Clinicopathological characteristics | All patients, n=645 | Multifocality | | P-value |
|---|---|---|---|---|
| | | Absence, n=482 | Presence, n=163 | |
| Adjuvant chemotherapy, n (%) | | | | 0.526 |
| No | 582 (90) | 437 (91) | 145 (89) | |
| Yes | 63 (10) | 45 (9) | 18 (11) | |
| WBC, n (%) | | | | 0.001 |
| ≤6.610$^9$/l | 317 (49) | 255 (53) | 62 (38) | |
| >6.610$^9$/l | 328 (51) | 227 (47) | 101 (62) | |
| ANC, n (%) | | | | 0.044 |
| ≤4,235/mm$^3$ | 321 (50) | 251 (52) | 70 (43) | |
| >4,235/mm$^3$ | 324 (50) | 231 (48) | 93 (57) | |
| SIRI, n (%) | | | | <0.001 |
| ≤1.95 | 428 (66) | 338 (70) | 90 (55) | |
| >1.95 | 217 (34) | 144 (30) | 73 (45) | |

[a]Determinant of renal function. eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; HTN, hypertension; BC, bladder cancer; WBC, white blood cell count; ANC, absolute neutrophil count; SIRI, systemic inflammation response index; LN, lymph node; LVI, lympho-vascular invasion; T, tumor.

Thus, multifocal UTUC with a high-level SIRI was considered a reliable and feasible risk factor for discriminating survival outcomes.

*Multifocal UTUC with a high-level SIRI as an independent factor.* In the univariate analyses for OS and CSS, variables including sex, age, pT stage, LN stage, LVI, tumor size, tumor necrosis, adjuvant chemotherapy and multifocal tumor with a high-level SIRI, were potential prognostic factors. After controlling for confounding variables, the multivariate analysis confirmed that sex, age, pT stage, LN stage, LVI, adjuvant chemotherapy, non-multifocal tumor with a high SIRI, and multifocal tumor with a high-level SIRI were indicated as independent factors for predicting OS and CSS (Table II). Regarding RFS, the univariate analysis showed significant variables, including sex, hemodialysis, pT stage, LN stage, tumor grade, LVI, tumor size, tumor necrosis, adjuvant chemotherapy and multifocal tumor with a high-level SIRI. The multivariate analysis revealed that advanced pT stage, LN stage, LVI and multifocal tumor with a high-level SIRI were independent prognostic factors for RFS (Table II).

Overall, the findings indicated a strong association between prognoses and the integration of tumor multifocality. In particular, multifocal tumors coupled with a high-level SIRI were significantly associated with poorer OS, CSS and RFS.

*Combining multifocal UTUC and SIRI increased the prediction ability of survival outcomes.* Further ROC analyses were conducted to evaluate predictive ability of a combination of tumor multifocality and SIRI including the basal model (consisting of the relevant prognostic factors pT stage, LN status and tumor grade) for OS, CSS and RFS in UTUC, compared with the basal model. The predictive model combining tumor multifocality and SIRI showed AUCs of 0.803, 0.825 and 0.800 for OS, CSS and RFS, respectively (all P<0.001) (Fig. 3), which was further demonstrated to have an improved predictive accuracy of survival than the basal model (all P<0.05; Fig. 3).

## Discussion

Multifocal UTUC tends to correlate with a poorer survival, possibly indicating a more extensive disease burden (14). Moreover, profound systemic inflammation has been reported to be closely associated with a higher tumor burden (29). Accordingly, the present study assessed the influence of the preoperative SIRI on the prognostic relevance of tumor multifocality among patients with UTUC following RNU. The results demonstrated that patients with multifocal UTUC and a high preoperative SIRI exhibited shorter survival rates and a more unfavorable disease progression compared with those with multifocal UTUC and a low-level SIRI or non-multifocal UTUC. More notably, SIRI was found to increase the clinical value of tumor multifocality in predicting OS, CSS and RFS. Furthermore, incorporating SIRI into tumor multifocality assessment proved to be an independent prognostic indicator of OS, CSS and RFS, potentially aiding adjuvant systemic treatment planning after RNU.

Although most studies demonstrate that multifocal tumors are linked to a poorer outcome in UTUC, there remains room for discussion. Previous studies observed a trend towards decreased survival rates and worse disease extension in patients with multifocal UTUC after surgery, compared with their non-multifocal counterparts (10,13,14). However, the association between tumor multifocality with oncological outcomes has been controversial in UTUC. Milojevic *et al* (16) highlighted a significant association between multifocal UTUC and disease recurrence but not CSS. Moreover, Sheu *et al* (17) found that multifocal tumors in

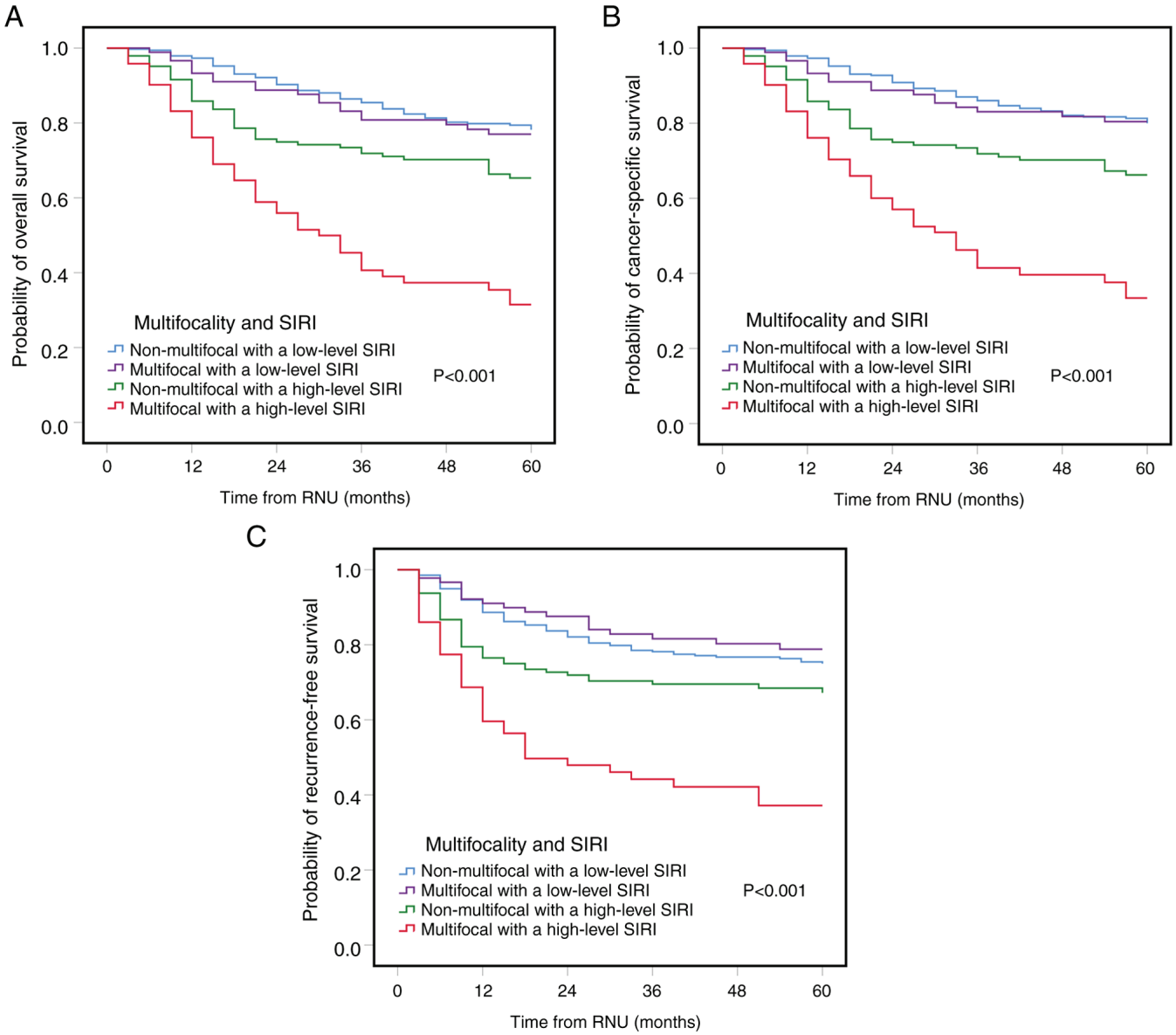


Figure 1. Kaplan-Meier survival curve analysis based on tumor multifocality and SIRI. (A) Overall, (B) cancer-specific survival and (C) recurrence-free survival. RNU, radical nephroureterectomy; SIRI, systemic inflammation response index.

different locations of the upper urinary tract did not influence survival or disease progression, but synchronous involvement of the ureter and pelvis resulted in a significantly higher rate of subsequent bladder cancer recurrence compared with multiple renal pelvic/ureter tumors. These findings indicated that tumor number had a significant impact on survival outcomes independent of tumor distribution. Consistent with previous studies, the present study demonstrated that multifocal UTUC predicted poorer outcomes following RNU.

Previous studies suggest that inflammation is widely recognized for promoting cancer development/growth, progression and metastasis (30,31). Inflammatory responses triggered by tumor-stimulated immune cells and mediators can foster an inflammatory microenvironment inside/around tumors that benefits tumor growth, angiogenesis and metastasis (32,33). Recently, an increasing number of studies have indicated that various blood-based immune cell parameters may be indicators of the tumor-related inflammation state for predicting oncological outcomes in a number of solid malignancies (34-36). Furthermore, in the multivariate analyses for OS, CSS and RFS, only SIRI retained prognostic significance, whereas WBC and ANC did not. Accordingly, SIRI was adopted as an optimal systemic inflammation marker to predict the prognosis of patients after surgery. The results indicated that a higher SIRI led to a lower survival rate. An elevated SIRI represented an increase in serum neutrophils and/or monocytes and a decrease in serum lymphocytes. Neutrophils have been identified as key contributors to this process by enhancing tumor angiogenesis and metastasis (32,31). Tumor-activated macrophages, differentiated from circulating monocytes, may also advance tumor growth, invasion and migration (37,38). By contrast, lymphocytes serve as protective prognostic factors for patients with cancer as they inhibit tumor cell proliferation and metastasis (33). Therefore, a higher SIRI indicated a systemic inflammation state and implied a weak antitumor potential or a build-up of immunosuppression.

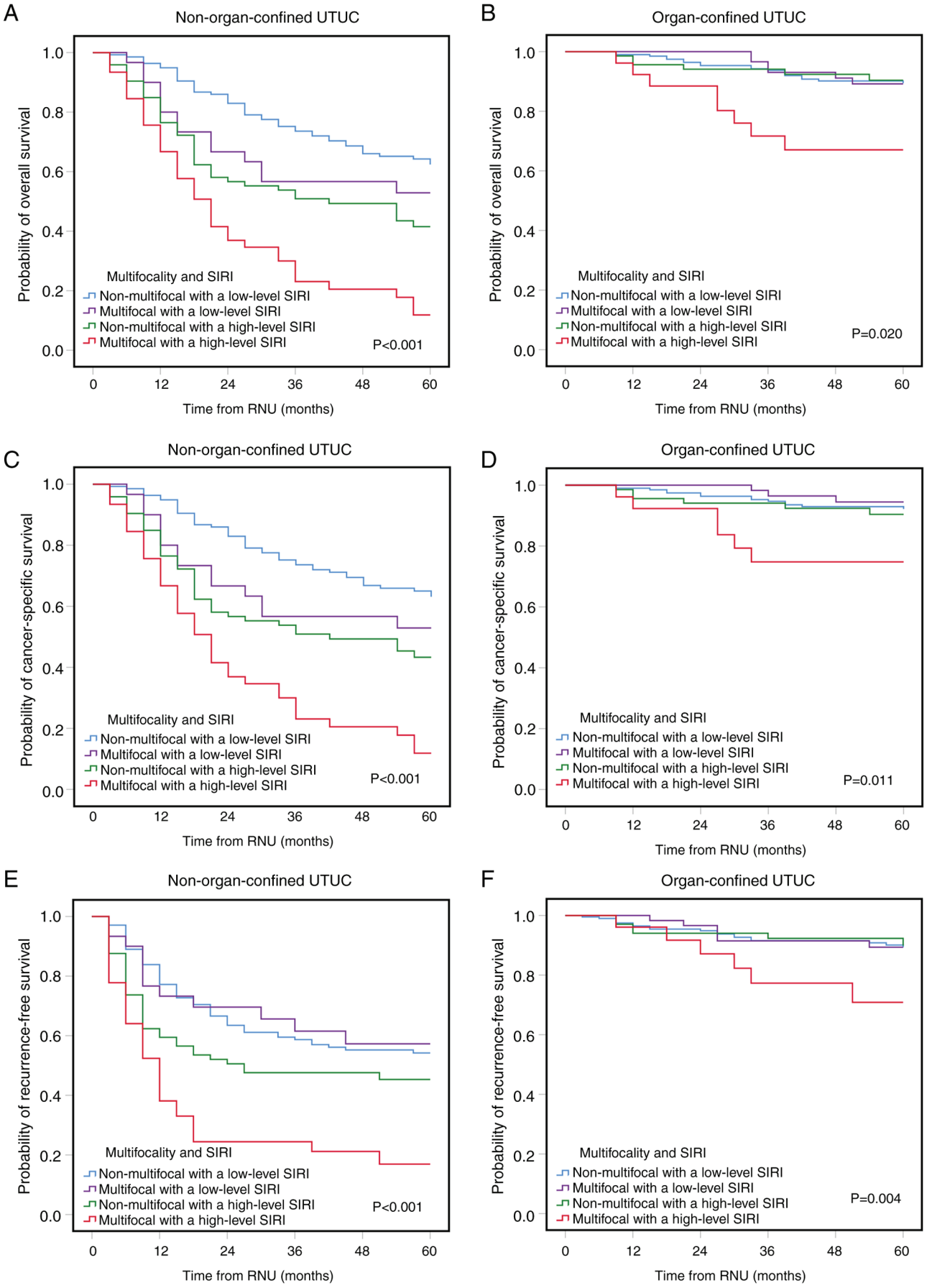


Figure 2. Kaplan-Meier survival curve analysis for non-organ-confined and organ-confined UTUC based on tumor multifocality and SIRI. Overall survival in (A) non-organ-confined UTUC and (B) organ-confined UTUC, cancer-specific survival in (C) non-organ-confined UTUC and (D) organ-confined UTUC, and recurrence-free survival in (E) non-organ-confined UTUC and (F) organ-confined UTUC. SIRI, systemic inflammation response index; UTUC, upper tract urothelial carcinoma.

Table II. Multivariate cox regression analyses for predicting overall survival, cancer-specific survival, and recurrence-free survival in patients with UTUC who underwent radical nephroureterectomy.

| | Overall survival | | Cancer-specific survival | | Recurrence-free survival | |
|---|---|---|---|---|---|---|
| Characteristic | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Sex, female vs. male | 0.793 (0.598-1.053) | 0.109 | 0.780 (0.586-1.039) | 0.089 | 0.782 (0.584-1.047) | 0.098 |
| Age at RNU | | | | | | |
| >69 vs. ≤69 year | 1.773 (1.320-2.238) | 0.001 | 1.713 (1.265-2.320) | 0.001 | 1.209 (0.895-1.634 | 0.216 |
| Pre-eGFR (ml/min/1.73 $m^2$) | | | | | | |
| ≥60 vs. <60 | - | | - | | - | |
| Hemodialysis | | | | | | |
| Yes vs. no | - | | - | | 0.672 (0.422-1.071) | 0.094 |
| DM or HTN | | | | | | |
| Present vs. absent | - | | - | | - | |
| Prior BC | | | | | | |
| Yes vs. no | - | | - | | - | |
| Concomitant BC | | | | | | |
| Yes vs. no | - | | - | | - | |
| Hydronephrosis | | | | | | |
| Present vs. absent | - | | - | | - | |
| Hematuria | | | | | | |
| Present vs. absent | - | | - | | - | |
| Pathological T stage | | | | | | |
| T2 vs. Tis/a/1 | 1.871 (1.049-3.339) | 0.034 | 3.031 (1.537-7.860) | 0.001 | 1.780 (0.956-3.312) | 0.069 |
| T3/4 vs. Tis/a/1 | 5.481 (3.393-8.853) | 0.001 | 9.253 (5.124-16.709) | <0.001 | 5.695 (3.461-9.371) | <0.001 |
| Lymph node stage | | | | | | |
| N+ vs. Nx/0 | 2.106 (1.336-3.321) | 0.001 | 2.170 (1.370-3.436) | 0.001 | 2.073 (1.301-3.305) | 0.002 |
| Tumor grade | | | | | | |
| High vs. low | 0.992 (0.304-3.237) | 0.989 | 0.687 (0.208-2.271) | 0.538 | 0.873 (0.398-1.913) | 0.734 |
| LVI, yes vs. no | 1.814 (1.305-2.522) | 0.001 | 1.729 (1.232-2.427) | 0.002 | 1.920 (1.363-2.706) | <0.001 |
| Tumor size | | | | | | |
| >2 cm vs. ≤2 cm | 1.117 (0.755-1.652) | 0.579 | 1.113 (0.741-1.673) | 0.606 | 1.316 (0.866-2.001) | 0.199 |
| Tumor necrosis | | | | | | |
| Yes vs. no | 1.027 (0.742-1.423) | 0.872 | 1.015 (0.727-1.417) | 0.932 | 1.035 (0.738-1.451) | 0.842 |
| Adjuvant chemotherapy | | | | | | |
| Yes vs. no | 0.532 (0.337-0.838) | 0.007 | 0.533 (0.337-843) | 0.007 | 0.838 (0.549-1.277) | 0.410 |
| Non-multifocal with high SIRI | 1.611 (1.124-2.307) | 0.009 | 1.680 (1.163-2.426) | 0.006 | 1.296 (0.894-1.879) | 0.171 |
| Multifocal with low SIRI | 1.253 (0.789-1.992) | 0.339 | 1.199 (0.734-1.958) | 0.468 | 0.960 (0.584-1.578) | 0.873 |
| Multifocal with high SIRI | 3.364 (2.432-6.822) | <0.001 | 3.581 (2.411-5.318) | <0.001 | 2.634 (1.753-3.957) | <0.001 |

Previously, Zheng *et al* (26) attempted to incorporate SIRI with platelet-to-lymphocyte ratio (PLR) and demonstrated that the combination of these two preoperative inflammation markers had an improved prognostic significance in UTUC after surgery than SIRI or PLR alone. The present study emphasized that preoperative SIRI can be employed to improve the prognostic value of postoperative pathological character such as tumor multifocality. Next, tumor multifocality was defined as a tumor number of >1 regardless of tumor location. The results of the present study demonstrated that high-level SIRI (>1.95) significantly influenced survival and disease progression in multifocal cases, particularly in locally advanced UTUC. Conversely, without significant immune inflammation, indicated by low-level SIRI (<1.95), tumor multifocality lost its prognostic value. Notably, integrating SIRI and multifocality improved the predictive accuracy for OS, CSS and RFS with corresponding AUC values of 0.803, 0.827 and 0.800 (all P<0.001). These findings underscored the compelling utility of combining SIRI and multifocality as a new prognostic tool, indicative of heightened predictive accuracy for OS, CSS and RFS. This strategic combination of SIRI and tumor multifocality holds promise in identifying high-risk patients, thereby

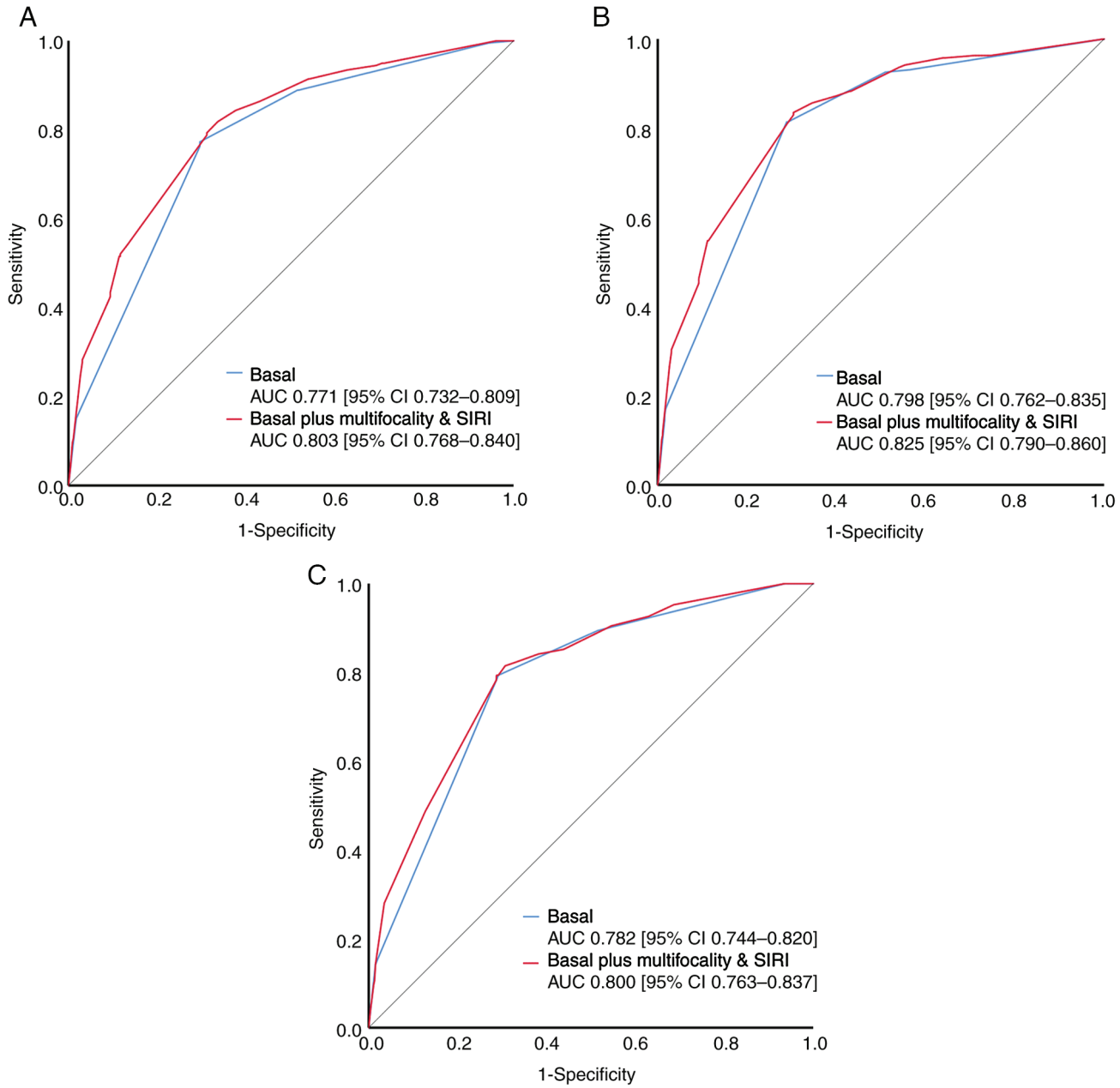


Figure 3. Receiver operating characteristic curve analyses. Predictive accuracy of (A) overall survival, (B) cancer-specific survival and (C) recurrence-free survival in patients with UTUC according to the basal model (blue solid line) and the basal model plus tumor multifocality and SIRI (red dot line). SIRI, systemic inflammation response index; UTUC, upper tract urothelial carcinoma.

necessitating close surveillance and potential consideration for adjunctive therapeutic interventions. We suggest that a higher SIRI could represent the active immune-inflammation state, which may positively affect the aggressiveness of UTUC tumors. When multifocal tumors are under relatively energetic immune-inflammatory circumstances, more inflammatory immune cells participate in the tumor microenvironment and facilitate the invasiveness/dissemination and viability of tumor cells (39,40). Increase in SIRI signifies a diminished anticancer immune response, possibly due to the increased involvement of neutrophils and macrophages, decreased cytotoxic effect of lymphocytes and an accumulation of cytokines and growth factors. However, further studies are needed to elucidate the underlying mechanisms involved. Therefore, in multifocal UTUC, SIRI may be considered for identifying high-risk patients with unfavorable outcomes. Chemotherapy and immunotherapy as optimal systemic treatments for high risk UTUC. Immunotherapy response is warranted based on PD-L1 expression of tumor now, but this method is still not sufficient. Thereafter, except for PD-L1 expression, this combination marker may be employed to assess response to immunotherapy. To the best of our knowledge, the present study is the first to demonstrate that incorporating SIRI with tumor multifocality could be a useful prognostic indicator of worse clinical outcomes in UTUC. The SIRI is a cost-effective and easily obtainable method for assessing inflammation derived from a CBC with differential count. However, there were several limitations in the present study. First, this retrospective study of reviewing medical records was from a single-center institution and all enrolled patients were Taiwanese. The

incidence of UTUC in Taiwan is relatively higher than U.S. and European. Second, the optimal SIRI cut-off value that adequately corresponds to systemic inflammation has yet to be determined in UTUC. Therefore, further studies with external validation are required to establish the optimal SIRI cut-off value. Third, relevant inflammation markers as a reference, such as C-reactive protein andIL-6, were also missing from the present study. Lastly, the present study could not evaluate the effects of dynamic changes of SIRI on survival due to incomplete data. Therefore, future studies are warranted to explore this issue. In addition, combining multifocality and SIRI may be applied as a complementary tool to evaluate immunotherapy responses when integrating programmed cell death protein 1/programmed death ligand 1 expression in tumor specimens.

In conclusion, the present study provided an insight into the significant impact of tumor multifocality and SIRI on the prognosis of patients with UTUC after RNU. Specifically, multifocal tumors with a high-level SIRI independently predicted worse oncological outcomes. Combining tumor multifocality and SIRI maybe a potentially useful marker and assist with planning therapeutic strategies, such as in adjuvant systemic treatment, for improving outcomes.

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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**

LCY and HCJ conceived the study and analyzed data. CYH, KCL, CHO and HCJ collected data. CAW, CYH, KCL and CHO interpreted data. LCY and CAW wrote the manuscript. CHO and HCJ supervised the study and reviewed and edited the manuscript. LCY, CAW, CHO and HCJ confirm the authenticity of all the raw data. All authors read and approved 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-112-216), who waived the requirement for informed consent from participants and allowed access to the follow-up clinical records. The present study was conducted based on the guidelines of the Declaration of Helsinki.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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