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Prognostic value of the endothelial activation and stress index in patients with upper tract urothelial cancer undergoing radical nephroureterectomy

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Purpose: The relationship with endothelial activation and stress index (EASIX), which represents the degree of endothelial dysfunction, is unwell known in upper tract urothelial carcinoma (UTUC). The present study aims to assess the prognostic value of the EASIX for recurrence-free survival (RFS) and overall survival (OS) in patients with UTUC who underwent radical nephroureterectomy (RNU).

Materials and Methods: We retrospectively reviewed the clinical data of 627 patients with UTUC who underwent RNU without neoadjuvant chemotherapy at three hospitals between 2002 and 2019. EASIX scores were calculated using the formula "serum lactate dehydrogenase (U/L)×creatinine (mg/dL) /platelet count (10^9/L)" and evaluated based on $\log_2$-transformed values. We divided the patients according to the EASIX score (>1.27 vs. ≤1.27).

Results: Among 627 patients, 380 were finally analyzed. Using maximally selected log-rank statistics, the optimal EASIX cutoff value was 1.27 on the $\log_2$ scale. The baseline characteristics were similar between the two groups except for age. The high EASIX score group had worse RFS and OS than the low EASIX score group (log-rank p=0.001 and p=0.006, respectively). At 5 years, the mean RFS and OS difference between the low and high EASIX score groups was 11.1 and 7.35 months, respectively. High EASIX score remained a key prognosticator of RFS and OS after RNU in multivariable analysis.

Conclusions: EASIX score may represent endothelial dysfunction in patients with UTUC and may serve as a readily available prognostic factor for oncologic outcomes.

Keywords: Blood platelets; Carcinoma, transitional cell; Creatinine; Lactate dehydrogenase; Prognosis

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a relatively rare disease that accounts for approximately 5% to 10% of all urothelial carcinomas (UCs) [1]. Although the cause of UTUC remains unknown, many environmental factors have been linked to its development, such as cigarette smoking, use of medications (e.g., Chinese herbs and aristolochic acid),

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chronic infection, exposure to carcinogenic chemicals, and occupational carcinogenesis [2]. Additionally, gene mutations and hereditary nonpolyposis colorectal carcinoma, a genetic condition also known as Lynch syndrome, have been linked to the development of UTUC [3].

Currently, the gold standard treatment method for UTUC is radical nephroureterectomy (RNU) with bladder cuff excision. The patients' survival after RNU mainly depends on the pathologic stage; however, Eastern Cooperative Oncology Group performance status (ECOG-PS), age, diabetes mellitus, and preoperative hydronephrosis are also prognostic factors in UTUC [4].

Recently, the endothelial activation and stress index (EASIX) score, which represents the degree of endothelial dysfunction, was reported to be a reliable prognostic factor in hematologic diseases [5,6]. This score is calculated using the following formula: serum lactate dehydrogenase (LDH) level (U/L)×creatinine level (mg/dL)/platelet count (10^9/L). UC is also associated with angiogenesis and endothelial dysfunction [7]. In addition, platelet count, serum creatinine level, and LDH level, which comprise the EASIX score, have been suggested as prognostic factors in UC [8-10]. Therefore, we aimed to investigate the prognostic role of EASIX in predicting recurrence-free survival (RFS) and overall survival (OS) in patients with UTUC undergoing RNU.

MATERIALS AND METHODS

1. Study population and design

This study was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (IRB no. CNUH-2020-277) and was conducted in accordance with the Declaration of Helsinki. Patient consent was waived. Three tertiary academic hospitals in Korea participated in this retrospective study. Patients who underwent RNU for UTUC without neoadjuvant chemotherapy between 2002 and 2019 were eligible for the study (n=627). We excluded patients with a previous history of bladder cancer, contralateral UTUC, distant metastasis, positive surgical margin status, variant histology, and missing essential data (n=247). A total of 380 patients were finally included in the analysis. Fig. 1 shows the patient flow diagram. Owing to the retrospective study design, postoperative follow-up was not standardized. However, at our institution, patients are generally followed up every 3 to 4 months in the first year after RNU, every 6 months in the second to fifth years, and annually thereafter. The follow-up evaluation generally includes history taking, physical examination, performance status assessment, serum laboratory tests, chest radiography, urinary cytology, cystoscopic bladder evaluation, and abdominopelvic computed tomography.

2. Data collection

The clinical and pathologic data included the following parameters: age, sex, body mass index (BMI), ECOG-PS, underlying disease, operation method, tumor location, tumor stage and grade, tumor size, lymphovascular invasion, concomitant carcinoma *in situ* (CIS), adjuvant chemotherapy, synchronous bladder tumor, LDH level, serum creatinine level, and platelet count.

3. EASIX score estimation

EASIX was assessed at the time of diagnosis. The EASIX score was calculated as "LDH level (U/L)×creatinine level (mg/dL)/platelet count (10^9/L)" and evaluated based on $\log_2$-transformed values [5]. Thereafter, the patients were categorized into two groups according to the EASIX score: high EASIX score ($\log_2$ EASIX >1.27) and low EASIX score ($\log_2$ EASIX ≤1.27) groups.

4. Study outcomes

The outcome measures in both groups were RFS and OS, measured in months from the date of RNU. RFS was defined as the time from RNU to any recurrence or death or the last follow-up. Bladder recurrence was not included in

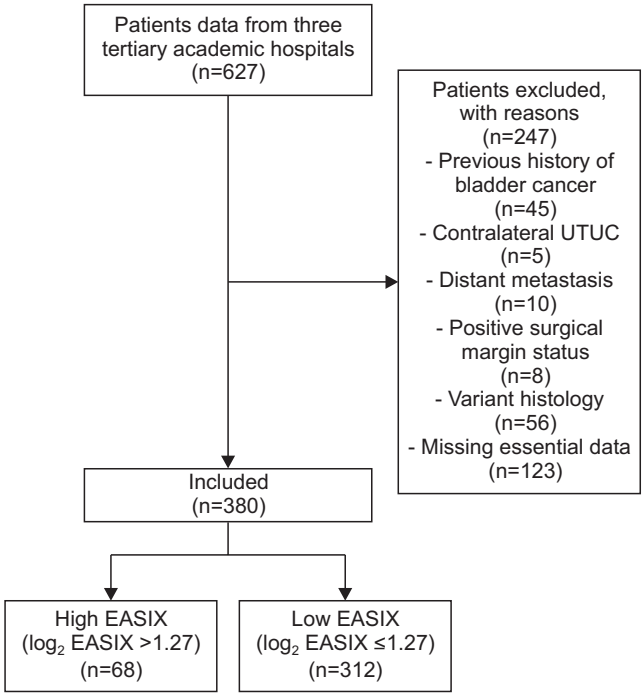

Fig. 1. Flowchart diagram for the patient selection process. UTUC, upper tract urothelial carcinoma; EASIX, endothelial activation and stress index.

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the calculation of RFS or OS because it did not affect survival in the current patient population. OS was defined as the time from RNU to any cause of death or the last follow-up. The cutoff date of the last follow-up was December 31, 2019.

5. Statistical analysis

Maximally selected log-rank statistics using an exact Gauss method were applied to calculate an optimal cutoff in survival distributions according to EASIX [6,11]. Maximally selected log-rank statistics evaluate cutoff, classifying observations into two groups by a continuous or ordinal prognostic variable [11]. The clinicopathologic variables were compared between groups using the chi-squared and independent t-tests. Kaplan–Meier survival curves with log-rank tests were used to compare RFS and OS between the two groups. We calculated life months gained using differences in restricted mean survival time [12]. Variables associated with RFS and OS were determined by univariable and multivariable Cox proportional hazard regression models. Among the variables, those with p<0.25 were selected (on univariable analysis for RFS and OS) and included in the multivariable analysis (stepwise forward procedure) using Cox proportional hazards regression model, which was performed to achieve adjusted hazard ratio (HR) to determine independent prognostic factors for RFS and OS. All data were analyzed using MedCalc for Windows (ver. 19.6, MedCalc Software, Ostend, Belgium) and R (version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at 0.05.

RESULTS

1. Study population

The clinicopathologic data of the 380 patients are summarized in Table 1. The median follow-up period was 32.1 months (interquartile range, 15.2–61.5 months). We compared patient factors (age, sex, BMI, diabetes mellitus, hypertension, ECOG-PS, operation method, and adjuvant chemotherapy) and tumor factors (tumor location, stage, grade, and size; lymphovascular invasion; synchronous bladder tumor; concomitant CIS) between the high and low EASIX score groups. The baseline characteristics of patients in the two groups were similar except for age. Patients in the high EASIX score group were older than those in the low EASIX score group (71.1±7.8 vs. 68±9.6 years, p=0.011).

In both group, male patients were dominant (75.0%, 69.2%, p=0.346). BMI was not different between two groups (23.8%±3.7%, 23.7%±3.0%, p=0.716). The prevalence of hyper-

Table 1. Comparison of baseline clinicopathologic characteristics

Characteristic	High EASIX (log_2 EASIX >1.27) (n=68)	Low EASIX (log_2 EASIX ≤1.27) (n=312)	p-value
Patient factor			
Age (y)	71.1±7.8	68±9.6	0.011[a]*
Sex			
Male	51 (75.0)	216 (69.2)	0.346[b]
Female	17 (25.0)	96 (30.8)	
Body mass index (kg/m^2)	23.8±3.7	23.7±3.0	0.716[a]
Diabetes mellitus			
Yes	23 (33.8)	73 (23.4)	0.073[b]
No	45 (66.2)	239 (76.6)	
Hypertension			
Yes	28 (41.2)	122 (39.1)	0.751[b]
No	40 (58.8)	190 (60.9)	
ECOG-PS			
0–1	64 (94.1)	293 (93.9)	0.948[b]
>2	4 (5.9)	19 (6.1)	
Operation method			
Open	21 (30.9)	71 (22.8)	0.156[b]
Laparoscopic	47 (69.1)	241 (77.2)	
Adjuvant chemotherapy			
Yes	27 (39.7)	101 (32.4)	0.246[b]
No	41 (60.3)	211 (67.6)	
Tumor factor			
Tumor location			
Renal pelvis	26 (38.2)	155 (49.7)	0.087[b]
Ureter	42 (61.8)	157 (50.3)	
Stage			
Tis–T2	42 (61.8)	198 (63.5)	0.792[b]
T3–T4	26 (38.2)	114 (36.5)	
Grade			
High	54 (79.4)	232 (74.4)	0.382[b]
Low	14 (20.6)	80 (25.6)	
Size (cm)	3.6±2.2	3.4±2.3	0.626[a]
Lymphovascular invasion			
Yes	18 (26.5)	52 (16.7)	0.059[b]
No	50 (73.5)	260 (83.3)	
Synchronous bladder tumor			
Yes	18 (26.5)	57 (18.3)	0.124[b]
No	50 (73.5)	255 (81.7)	
Concomitant carcinoma *in situ*			
Yes	7 (10.3)	38 (12.2)	0.663[b]
No	61 (89.7)	274 (87.8)	

Values are presented as mean±standard deviation or number (%).
EASIX, endothelial activation and stress index; ECOG-PS, European Cooperative Oncology Group performance status.
[a]:Student t-test; [b]:chi-squared test.
*Statistically significant p<0.05.

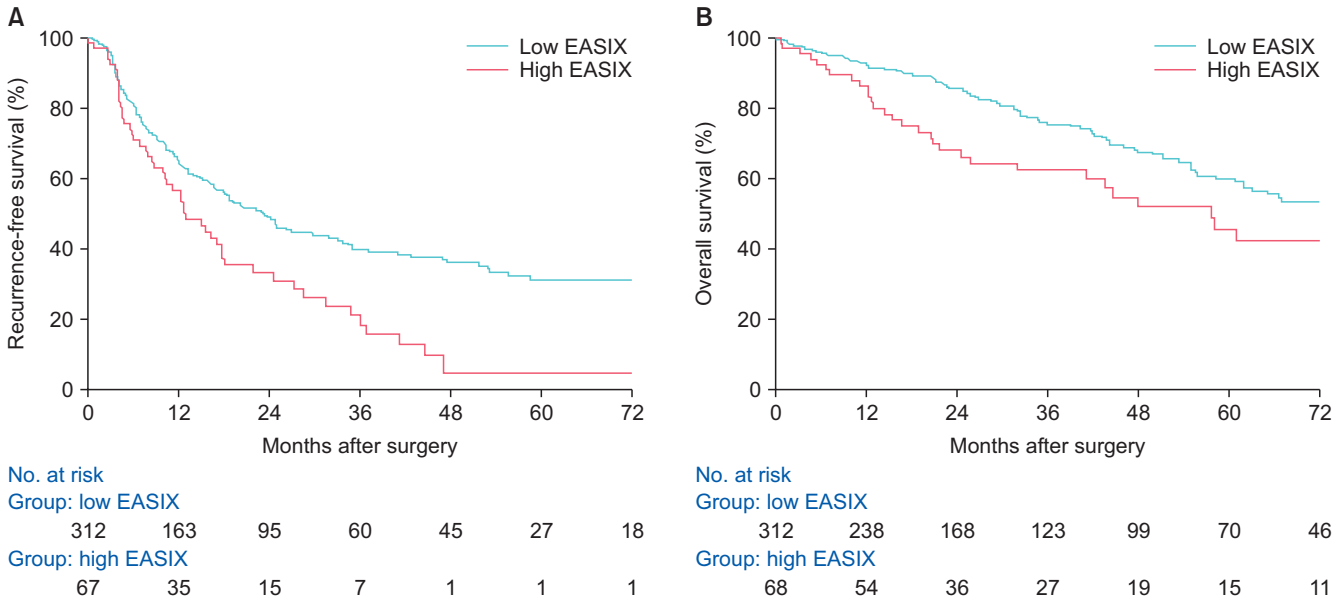

Fig. 2. Kaplan–Meier survival curves for recurrence-free survival (A) and overall survival (B) according to the endothelial activation and stress index (EASIX) score.

tension and diabetes mellitus were higher in high EASIX group (41.2% vs. 39.1%, 33.8% vs. 23.4%) but not statistically significant. Operation was more performed by laparoscopic method than open method in both group (69.1%, 77.2%, p=0.156). In tumor factors, patients with ureter tumor outnumbered patients with renal pelvis tumor (61.8%, 50.3%, p=0.087). By biopsy results from operation, patients with Tis-T2 cancer stage were more than patients with T3-T4 cancer stage (61.8%, 63.5%, p=0.792), and high-grade carcinoma were more observed (79.4%, 74.4%, p=0.382) in both groups. Lymphovascular invasion (26.5%, 16.7%, p=0.059), synchronous bladder tumor (26.5%, 18.3%, p=0.124) and concomitant CIS (10.3%, 12.2%, p=0.663) were not different in both groups.

2. Survival analysis

1) RFS

Patients with a high EASIX score had worse median RFS than those with a low EASIX score (13.0 months, 95% confidence interval [CI]: 9.9–17.8 months vs. 23.4 months, 95% CI 18.1–119.3 months; log-rank p=0.001; Fig. 2A). At 5 years, the mean RFS difference between patients with low EASIX scores and those with high EASIX scores was 11.1 months (95% CI: 5.84–16.3 months). Along with previously reported prognostic factors [13], such as age (HR 1.02, 95% CI: 1.00–1.03, p=0.045; Table 2), pathologic T stage (≥T3) (HR: 1.40, CI: 1.07–1.84, p=0.014), diabetes mellitus (HR: 1.67, CI: 1.25–2.24, p=0.005), lymphovascular invasion (HR: 1.92, CI: 1.36–2.72, p=0.002), synchronous bladder tumor (HR: 1.90, CI: 1.39–2.60, p=0.001), a high EASIX score was independently associated with worse RFS (HR: 1.68, CI: 1.22–2.30, p=0.001) compared with a low EASIX score in the multivariable Cox regression model.

2) OS

Patients with high EASIX scores had worse median OS than those with low EASIX scores (57.7 months, 95% CI: 31.8–198.4 months vs. 88.0 months, 95% CI: 62.0–101.4 months; log-rank p=0.006; Fig. 2B). At 5 years, the mean OS difference between patients with low EASIX scores and those with high EASIX scores was 7.35 months (95% CI: 1.34–13.4 months). Along with previously reported prognostic factors [13], like age (HR: 1.06, 95% CI: 1.03–1.08, p=0.001; Table 2), pathologic T stage (≥T3) (HR: 1.78, CI: 1.11–2.85, p=0.016), lymphovascular invasion (HR: 2.97, CI: 1.96–4.49, p=0.001), concomitant CIS (HR: 1.74, CI: 1.06–2.84, p=0.026), a high EASIX score was associated with worse OS (HR: 1.71, CI: 1.16–2.54, p=0.006) compared with a low EASIX score in the multivariable Cox regression model.

DISCUSSION

To our best knowledge, this study is the first to evaluate the prognostic value of EASIX in patients with UTUC who underwent RNU. Our results suggested that a high EASIX score was associated with poor RFS and OS. EASIX comprises serum LDH level, creatinine level, and platelet count. These three factors have been suggested as prognostic factors in UTUC and to be related to endothelial dysfunction

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Table 2. Univariable and multivariable Cox proportional hazard regression analysis for recurrence-free and overall survival (n=380)

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Recurrence-free survival				
Age	1.01 (1.00–1.05)	0.021*	1.02 (1.00–1.03)	0.045*
BMI >25 kg/m^2	1.09 (0.82–1.45)	0.551		
Diabetes mellitus	1.57 (1.17–2.09)	0.002*	1.67 (1.25–2.24)	0.005*
ECOG-PS ≥2	1.43 (0.81–2.51)	0.207		
Laparoscopic surgery	0.93 (0.69–1.26)	0.675		
Adjuvant chemotherapy	1.23 (0.93–1.61)	0.139		
Ureter tumor	1.38 (1.05–1.82)	0.019*		
T stage (≥pT3)	1.67 (1.02–2.05)	0.002*	1.40 (1.07–1.84)	0.014*
High grade	1.39 (1.01–1.92)	0.042*		
Size ≥3 cm	1.27 (0.97–1.67)	0.079		
Lymphovascular invasion	2.10 (1.51–2.92)	0.001*	1.92 (1.36–2.72)	0.002*
Synchronous bladder tumor	1.75 (1.29–2.37)	0.003*	1.90 (1.39–2.60)	0.001*
Concomitant CIS	1.46 (0.98–2.18)	0.059		
LDH ≥472	0.91 (0.54–1.51)	0.717		
Serum creatinine	1.13 (0.97–1.31)	0.111		
Thrombocytopenia	0.86 (0.41–1.84)	0.714		
High EASIX (>1.27)	1.98 (1.35–2.71)	0.001*	1.68 (1.22–2.30)	0.001*
Overall survival				
Age	1.05 (1.03–1.07)	0.001*	1.06 (1.03–1.08)	0.001*
BMI >25 kg/m^2	0.86 (0.59–1.25)	0.438		
Diabetes mellitus	1.03 (0.71–1.51)	0.841		
ECOG-PS ≥2	0.84 (0.34–2.06)	0.711		
Laparoscopic surgery	1.03 (0.70–1.51)	0.862		
Adjuvant chemotherapy	2.43 (1.71–3.46)	0.001*	1.52 (0.97–2.40)	0.067
Ureter tumor	1.23 (0.86–1.75)	0.247		
T stage (≥pT3)	3.16 (2.21–4.51)	0.001*	1.78 (1.11–2.85)	0.016*
High grade	2.35 (1.46–3.77)	0.004*		
Size ≥3 cm	1.27 (0.89–1.81)	0.182		
Lymphovascular invasion	3.81 (2.59–5.59)	0.001*	2.97 (1.96–4.49)	0.001*
Synchronous bladder tumor	0.98 (0.64–1.49)	0.927		
Concomitant CIS	2.28 (1.41–3.72)	0.009*	1.74 (1.06–2.84)	0.026*
LDH ≥472	1.61 (0.93–2.76)	0.083		
Serum creatinine	1.12 (0.86–1.43)	0.389		
Thrombocytopenia	2.01 (0.93–4.31)	0.074		
High EASIX (>1.27)	2.13 (1.32–3.12)	0.001*	1.71 (1.16–2.54)	0.006*

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ECOG-PS, European Cooperative Oncology Group performance status; pT3, pathologic T stage; CIS, carcinoma *in situ*; LDH, lactate dehydrogenase; Thrombocytopenia, platelet <150,000/μL; EASIX, endothelial activation and stress index.
*Statistically significant p<0.05.

[8-10,14-16]. Elevated levels of preoperative serum LDH were reported to be related to poor survival in UTUC after RNU [10,16]. A study from China that evaluated 100 UTUC patients who underwent RNU showed that high preoperative serum LDH was associated with shorter disease-free survival and OS [10]. A similar finding was reported in another study that analyzed 668 UTUC patients who received RNU [16]. In this cohort, elevated preoperative LDH was associated with poor RFS and OS in univariable analysis but lost significance in multivariable analysis [16]. Patients with preexisting renal insufficiency had a significantly lower survival probability and a high disease recurrence after RNU for UTUC than those without preexisting renal insufficiency [9,15]. A multicenter study from Korea revealed that preop-

erative chronic kidney disease was independently related to worse RFS and OS [9]. A study from Japan showed that preoperative severe renal insufficiency (estimated glomerular filtration rate<45 mL/min/1.73 m^2) had a higher risk for relapse and lower survival probability [15]. In addition, preoperative or postoperative thrombocytosis is also associated with aggressive tumor characteristics and worse survival outcomes [8,14]. Foerster et al. [8] reported that preoperative thrombocytosis was associated with advanced tumor stage and grade, lymph node metastasis, lymphovascular invasion, tumor architecture, necrosis, and concomitant CIS and predicted shorter RFS. In another study, which studied for 269 patients undergoing RNU in three tertiary care centers and revealed that postoperative thrombocytosis was associated with shorter RFS after RNU for UTUC [14]. However, we did not find any studies investigating the relationship between preoperative thrombocytopenia and oncologic outcomes in UTUC. We investigated the prognostic value of each variable (serum LDH, creatinine, and platelet count) for RFS and OS, but univariable analysis showed no meaningful results (Table 2). This result may suggest that the EASIX score rather than one single factor is more associated with oncological outcomes in UTUC.

Endothelial dysfunction and tumor angiogenesis are known to play key roles in tumorigenesis, growth, and metastasis [17-19]. Angiogenesis is directly associated with the development of metastasis and is closely related to the expression of vascular endothelial growth factor (VEGF) in cancer. For example, high VEGF expression is a prognostic factor for unfavorable prognosis, and the VEGF level is proportional to both malignant tumor potential and tumor progression, indicating that VEGF has a role as a prognostic marker in kidney cancer [20]. Furthermore, proliferation of tumor-associated endothelial cells guides angiogenesis, which has a role in the carcinogenesis of colorectal cancer [17]. In UC, the most commonly investigated in bladder cancer, angiogenesis is associated with endothelial dysfunction, which causes the overexpression of several growth factors (e.g., VEGF, basic fibroblast growth factor, hypoxia-inducible factor 1α, platelet-derived endothelial growth factor, and epidermal growth factor receptor) that are positively correlated with a poor prognosis [7,18,20]. Recently, microvessel density has been shown to be an independent prognostic factor for survival and used to quantify tumoral angiogenesis in UC [18,20]. However, the evaluation of these factors requires immunohistochemical staining of tumor tissue, which means that the patients' prognosis can only be predicted after surgery. Predicting the prognosis of cancer patients before treatment irrespective of surgery or chemotherapy may be useful in counseling the patients and their families. Therefore, if endothelial dysfunction can be measured before treatment, it would be helpful in predicting the prognosis of the disease. However, the measurement of endothelial dysfunction is limited by the lack of specific routine tests.

The EASIX score, which has been proposed to represent endothelial dysfunction, has been reported to predict OS after allogeneic stem cell transplantation and lower-risk myelodysplastic syndrome [5,21]. The prognostic value of the EASIX score has been externally validated in other cohorts of patients with hematologic disorders [22]. Moreover, in patients with newly diagnosed multiple myeloma, a high EASIX score at diagnosis was associated with unfavorable disease characteristics, advanced disease stage, and poor survival outcomes [6]. In line with these studies, our study showed similar results. Therefore, the EASIX score is a simple and readily available tool for measuring endothelial dysfunction in hematologic or solid malignancies. However, these results should be interpreted with caution. There is currently no direct evidence of an EASIX score and angiogenesis, but the EASIX score is suggested as a surrogate for endothelial dysfunction. Therefore, we inferred that the EASIX score might be associated with angiogenesis since angiogenesis is related to endothelial dysfunction. As this study is the first report to investigate the prognostic role of EASIX in UTUC or solid tumors, the exact mechanism of EASIX and angiogenesis should be elucidated in future studies.

Several recent studies have shown that biochemical markers in the blood can predict the prognosis of patients with UTUC [23-28]. These factors have also been evaluated by other studies that showed similar results. From one meta-analysis article, the low preoperative serum albumin level is positively associated with a worse prognosis of UC based on ethnicity, cut-off value, tumor type, analyses type, and sample size. The patients with decreased preoperative serum albumin had more unfavorable long-term survival and short-term outcomes [23]. Also, Mori et al. [24,25] reviewed 54 studies with 22,513 patients and uncovered that several preoperative blood-based biomarkers were significantly associated with cancer-specific survival (CSS). These were neutrophil-lymphocyte ratio, c-reactive protein, platelet-lymphocyte ratio, white blood cell, De Ritis ratio, fibrinogen, albumin-globulin ratio, hemoglobin and estimate glomerular filtration rate. Modified Glasgow prognostic score mirrors of systematic inflammation response of the body, is associated with poor oncological outcomes in UTUC patients treated with RNU [26]. In another cohort study, increased derived neutrophil-lymphocyte ratio was statistically significantly

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associated with shorter CSS, as well as with shorter OS in European patients with UTUC [27]. Before the publication of recent studies [23-27], these blood-based prognostic markers were not included in the European Association of Urology guidelines [28]; however, they are now reflected in the guidelines [4]. Therefore, preoperative blood-based prognostic factors are not negligible in patients with UTUC undergoing RNU. Moreover, recently preoperative sterile pyuria was independently associated with intravesical recurrence but was not associated with OS after RNU in patients with UTUC [29]. Therefore, patient-derived laboratory biomarkers should be more investigated in future studies.

Our study had some limitations inherent to its multicenter nature, including possible variations in laboratory, pathologic, and surgical assessments. First, we did not collect data on pathologic lymph node status because most surgeries were performed without routine lymph node dissection at each institution. As the current evidence on the benefit of lymph node dissection in UTUC is limited [30], further studies are warranted to investigate the association between pathologic nodal involvement and EASIX score. Second, the formula for calculating the EASIX score includes hematologic factors (serum LDH level, creatinine level, and platelet count), which can be affected by underlying diseases other than malignancy. Moreover, based on the formula, thrombocytopenia rather than thrombocytosis is probably more highly associated with poor oncologic outcomes in patients with UTUC; however, we could not find any evidence of an association between thrombocytopenia and UTUC prognosis. Third, we only assessed preoperative laboratory values. However, after nephroureterectomy, the serum creatinine level of patients may be elevated. Thereby, some patients in the low EASIX score group can be reclassified into the high EASIX score group. Finally, similar to other blood-based prognostic factors, the definite cutoff value of the EASIX score needs to be established. Despite these limitations, given the rarity of UTUC, we believe that our study cohort may be representative of the UTUC population and that the EASIX score may have a prognostic value in patients with UTUC.

CONCLUSIONS

The EASIX score may represent endothelial dysfunction in patients with UTUC and may serve as a readily available prognostic factor for oncologic outcomes. The findings of this study may help urologists in providing advice to patients with a high EASIX score before surgical management and may offer a rationale for the stratification of patients according to the EASIX status (high vs. low) in future biomarker studies.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Eu Chang Hwang. Data acquisition: Jin Seok Gu, Ji Won Ryu, Seong Hyeon Yu, Ho Seok Chung, Ja Yoon Ku, Chan Ho Lee, and Hong Koo Ha. Statistical analysis: Jun Eul Hwang. Data analysis and interpretation: Jun Eul Hwang and Eu Chang Hwang. Drafting of the manuscript: Jin Seok Gu. Critical revision of the manuscript: Eu Chang Hwang. Obtaining funding: Eu Chang Hwang. Administrative, technical, or material support: Woo Kyun Bae, Seung Il Jung. Supervision: Dong Deuk Kwon. Approval of the final manuscript: all authors.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29. Erratum in: CA Cancer J Clin 2014;64:364.
2. Colin P, Koenig P, Ouzzane A, Berthon N, Villers A, Biserte J, et al. Environmental factors involved in carcinogenesis of urothelial cell carcinomas of the upper urinary tract. BJU Int 2009;104:1436-40.
3. Lim A, Rao P, Matin SF. Lynch syndrome and urologic malignancies: a contemporary review. Curr Opin Urol 2019;29:357-63.
4. Rouprêt M, Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2020 update. Eur Urol 2021;79:62-79.
5. Luft T, Benner A, Jodele S, Dandoy CE, Storb R, Gooley T, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. Lancet Haematol 2017;4:e414-23.
6. Song GY, Jung SH, Kim K, Kim SJ, Yoon SE, Lee HS, et al. Endothelial activation and stress index (EASIX) is a reliable predictor for overall survival in patients with multiple myeloma. BMC Cancer 2020;20:803.
7. John A, Robador JR, Vidal-Y-Sy S, Houdek P, Wladykowski E,

Günes C, et al. Urothelial carcinoma of the bladder induces endothelial cell activation and hypercoagulation. Mol Cancer Res 2020;18:1099-109.
8. Foerster B, Moschini M, Abufaraj M, Soria F, Gust KM, Rouprêt M, et al. Predictive and prognostic value of preoperative thrombocytosis in upper tract urothelial carcinoma. Clin Genitourin Cancer 2017;15:e1039-45.
9. Yu HS, Hwang JE, Chung HS, Cho YH, Kim MS, Hwang EC, et al. Is preoperative chronic kidney disease status associated with oncologic outcomes in upper urinary tract urothelial carcinoma? A multicenter propensity score-matched analysis. Oncotarget 2017;8:66540-9.
10. Zhang XK, Zhang ZL, Lu X, Yang P, Cai MY, Hu WM, et al. Prognostic significance of preoperative serum lactate dehydrogenase in upper urinary tract urothelial carcinoma. Clin Genitourin Cancer 2016;14:341-5.e3.
11. Hothorn T, Lausen B. On the exact distribution of maximally selected rank statistics. Comput Stat Data Anal 2003;43:121-37.
12. Zhao L, Claggett B, Tian L, Uno H, Pfeffer MA, Solomon SD, et al. On the restricted mean survival time curve in survival analysis. Biometrics 2016;72:215-21.
13. Mbeutcha A, Rouprêt M, Kamat AM, Karakiewicz PI, Lawrentschuk N, Novara G, et al. Prognostic factors and predictive tools for upper tract urothelial carcinoma: a systematic review. World J Urol 2017;35:337-53.
14. Gakis G, Fritsche HM, Hassan F, Kluth L, Miller F, Soave A, et al. Prognostic relevance of postoperative platelet count in upper tract urothelial carcinoma after radical nephroureterectomy. Eur J Cancer 2014;50:2583-91.
15. Momota M, Hatakeyama S, Tokui N, Sato T, Yamamoto H, Tobisawa Y, et al. The impact of preoperative severe renal insufficiency on poor postsurgical oncological prognosis in patients with urothelial carcinoma. Eur Urol Focus 2019;5:1066-73.
16. Tan P, Chen J, Xie N, Xu H, Ai J, Xu H, et al. Is preoperative serum lactate dehydrogenase useful in predicting the outcomes of patients with upper tract urothelial carcinoma? Cancer Med 2018;7:5096-106.
17. Chen WZ, Jiang JX, Yu XY, Xia WJ, Yu PX, Wang K, et al. Endothelial cells in colorectal cancer. World J Gastrointest Oncol 2019;11:946-56.
18. Pinto A, Redondo A, Zamora P, Castelo B, Espinosa E. Angiogenesis as a therapeutic target in urothelial carcinoma. Anticancer Drugs 2010;21:890-6.
19. Sawhney R, Kabbinavar F. Angiogenesis and angiogenic inhibitors in renal cell carcinoma. Curr Urol Rep 2008;9:26-33.
20. Charlesworth PJ, Harris AL. Mechanisms of disease: angiogenesis in urologic malignancies. Nat Clin Pract Urol 2006;3:157-69.
21. Merz A, Germing U, Kobbe G, Kaivers J, Jauch A, Radujkovic A, et al. EASIX for prediction of survival in lower-risk myelodysplastic syndromes. Blood Cancer J 2019;9:85.
22. Shouval R, Fein JA, Shouval A, Danylesko I, Shem-Tov N, Zlotnik M, et al. External validation and comparison of multiple prognostic scores in allogeneic hematopoietic stem cell transplantation. Blood Adv 2019;3:1881-90.
23. Liu J, Wang F, Li S, Huang W, Jia Y, Wei C. The prognostic significance of preoperative serum albumin in urothelial carcinoma: a systematic review and meta-analysis. Biosci Rep 2018;38:BSR20180214.
24. Mori K, Janisch F, Mostafaei H, Kimura S, Lysenko I, Karakiewicz PI, et al. Prognostic role of preoperative De Ritis ratio in upper tract urothelial carcinoma treated with nephroureterectomy. Urol Oncol 2020;38:601.e17-24.
25. Mori K, Janisch F, Mostafaei H, Lysenko I, Kimura S, Egawa S, et al. Prognostic value of preoperative blood-based biomarkers in upper tract urothelial carcinoma treated with nephroureterectomy: a systematic review and meta-analysis. Urol Oncol 2020;38:315-33.
26. Soria F, Giordano A, D'Andrea D, Moschini M, Rouprêt M, Margulis V, et al. Prognostic value of the systemic inflammation modified Glasgow prognostic score in patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy: results from a large multicenter international collaboration. Urol Oncol 2020;38:602.e11-9.
27. Dalpiaz O, Pichler M, Mannweiler S, Martín Hernández JM, Stojakovic T, Pummer K, et al. Validation of the pretreatment derived neutrophil-lymphocyte ratio as a prognostic factor in a European cohort of patients with upper tract urothelial carcinoma. Br J Cancer 2014;110:2531-6.
28. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on upper urinary tract urothelial cell carcinoma: 2015 update. Eur Urol 2015;68:868-79.
29. Jeon BJ, Tae BS, Choi H, Bae JH, Kim JW, Park HS, et al. Preoperative sterile pyuria as a prognostic biomarker for intravesical recurrence in upper urinary tract urothelial carcinoma. Investig Clin Urol 2020;61:51-8.
30. Inokuchi J, Kuroiwa K, Kakehi Y, Sugimoto M, Tanigawa T, Fujimoto H, et al. Role of lymph node dissection during radical nephroureterectomy for upper urinary tract urothelial cancer: multi-institutional large retrospective study JCOG1110A. World J Urol 2017;35:1737-44.

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