ORIGINAL ARTICLE

De Ritis Ratio (Aspartate Transaminase/Alanine Transaminase) as a Significant Prognostic Factor With Upper Urinary Tract Carcinoma Who Underwent Radical Nephroureterectomy and Adjuvant Chemotherapy

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Purpose: To investigate the correlation between preoperative De Ritis ratio (aspartate transaminase [AST]/alanine transaminase [ALT]) and postoperative clinical outcome in patients with upper urinary tract carcinoma (UTUC) who underwent radical nephroureterectomy (RNU) and adjuvant chemotherapy (ACH).

Materials and Methods: We respectively analyzed the clinical and pathological data of 102 patients who underwent RNU and ACH for UTUC. Patients were divided into 2 groups, according to the optimal value of AST/ALT ratio. The effect of the AST/ALT ratio was analyzed by the Kaplan-Meier method and Cox regression hazard models for patients' cancer-specific survival (CSS) and overall survival (OS).

Results: Mean survival time was 50.5±41.2 months. Mean age was 61.4±9.7 years. Forty-one of the patients (46.5%) were in the high AST/ALT group. According to receiver operating characteristic analysis, the optimal AST/ALT ratio was 1.2. In Kaplan-Meier analyses, the high AST/ALT group showed worse outcomes in OS ($p=0.007$) and CSS ($p=0.011$). Using Cox regression models of clinical and pathological parameters to predict OS, high AST/ALT ratio (hazard ratio [HR], 5.428; 95% confidence interval [CI]; 1.803–16.334; $p=0.002$), pathological T3 (pT3) or higher (HR, 1.464; 95% CI; 1.156–1.857; $p=0.002$), and to predict CSS, high AST/ALT ratio (HR, 4.417; 95% CI; 1.545–12.632; $p=0.005$), and pT3 or higher (HR, 1.475; 95% CI; 1.172–1.904; $p=0.002$) were determined as independent prognostic factors.

Conclusions: Pretreatment AST/ALT ratio is a significant independent predictor of CSS and OS in advanced UTUC patients receiving systemic ACH after RNU.

Key Words: Alanine transaminase, Aspartate transaminase, Chemotherapy, Upper urinary tract carcinoma, Urothelial cell carcinoma

Received October 11, 2021

Revised October 28, 2021

Accepted November 9, 2021

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INTRODUCTION

Upper urinary tract carcinoma (UTUC) is a malignant tumor of the urothelium of the urinary tract from calyx to distal ureter.¹ UTUC is relatively uncommon, and represents only 5%–7% of the

tumors that develop in the kidneys.¹ UTUC accounts for approximately 5%–10% of all genitourinary malignancies.¹ The disease has a multifocal nature and is diagnosed twice as often in the renal pelvis, as in the ureters.² The standard treatment for localized UTUC is a radical nephroureterectomy

(RNU), with bladder cuff excision.³ RNU series studies performed in the last years have shown that the proportion of locally advanced UTUC is about 60%, the proportion of high-grade tumors is about 70%, and that the proportion of aggressive disease is increasing.⁴ The 5-year survival rate of UTUC is 20%, and the prognosis is relatively poor.⁵ For these advanced UTUCs, adjuvant chemotherapy (ACH) is recommended to improve long-term prognosis.⁶ However, some advanced UTUC patients progress or the disease recurs to a distant metastasis site.⁷ About 7% of patients experience metastatic disease.⁸ It is important to accurately predict oncologic outcomes and to properly classify patients at risk for progression or recurrence, to perform additional salvage treatments. For this reason, prognostic factors of survival before treatment are clinically important. We have focused on alanine aminotransferase (ALT) and aspartate aminotransferase (AST), among the many pretreatment predictive factors. ALT and AST are liver enzymes commonly used in different clinical fields, and have been reported in several studies as important biomarkers in various malignant tumors, such as kidney cancer, lung cancer, pancreatic cancer, and colorectal cancer, as well in as chronic liver disease.⁹⁻¹² Recent studies have also shown that UTUC was useful as a preoperative predictor.¹³⁻¹⁵ However, no studies have been reported on the role of AST and ALT as prognostic factors in patients with end-stage UTUC, who received ACH. Therefore, we aimed to identify the prognostic significance of AST and ALT before ACH, in patients with UTUC who underwent RNU and ACH.

MATERIALS AND METHODS

1. Ethics Statement

The study was approved by the Institutional Review

Board of Seoul National University Hospital (IRB No. 2018-11-018). We conducted a retrospective case study and were exempted from obtaining prior consent of the patients. The research protocol was in accordance with the Declaration of Helsinki guidelines.

2. Study Sample

We retrospectively analyzed the medical records of 204 patients with advanced UTUC. (pathologic T3 or T4 or pathologic T1- T2N1-N3 without distant metastasis) who were treated in 2 institutions from January 2000 to December 2017. These patients underwent RNU after being diagnosed with UTUC, followed by first line ACH after diagnosis with advanced-stage disease. Of 204 patients, 16 patients suspected of fatty liver and chronic liver disease, and 8 patients suspected of systemic infection and inflammation, were excluded, and 4 patients with incomplete data were also excluded. A total of 176 patients were included in the analyses.

3. Study Design

We divided the patients into 2 groups, according to the optimal value of the AST/ALT ratio. The optimal AST/ALT ratio was determined to have the highest sensitivity and specificity in the receiver operating characteristic curve. Patients were divided into 2 groups based on an optimal AST/ALT of 1.2.

ACH usually started within 3 months after surgery, depending on the general condition and renal function of the patients. Laboratory tests including AST and ALT were routinely performed the day before the first cycle of ACH.

The clinical and pathological data collected on patients for this study were: patient age, body mass index (BMI), sex; underlying diseases, such as hypertension and diabetes; RNU surgery methods; pathologic T stage and N stage; tumor grade,

presence of lymphovascular invasion, presence of concurrent carcinoma *in situ*, presence of ipsilateral hydronephrosis, presence of multifocality, presence of positive surgical margin, regimen and cycle of ACH, American Society of Anesthesiologists (ASA) physical status classification before ACH, and AST and ALT before ACH. Oncologic outcomes data were also collected for mortality, and mortality due to cancer.

Histopathological evaluation of surgical specimens was examined by pathologists skilled in the genital area. The TNM stage and tumor grade were assessed using the 2010 American Joint Committee on Cancer Tumor, Node, Metastases classification, and the World Health Organization/International Society of Urological Pathology consensus classification.

Follow-up was performed every 3 months for the first 2 years, then every 6 months for 2 to 5 years, and every 1 year thereafter. Physical examination, routine laboratory tests, urine analysis, urine cytology, and cystoscopy were performed at every follow-up. Chest computed tomography (CT), abdominal pelvic CT were performed routinely every year.

4. Statistical Analysis

Clinical and pathological characteristics were analyzed by independent t-tests between groups. The continuous variables were expressed as mean, standard deviation, median and interquartile range, and the nominal variables were expressed as probability through crossover analysis. The oncologic outcome was analyzed by Kaplan-Meier survival analysis and log-rank test. Several pretreatment factors affecting the oncologic outcome were analyzed by multivariate Cox proportional hazard regression analysis. A total of 82 patients with high AST/ALT ratios were matched in a 1:1 ratio to 94 patients with low AST/ALT

ratios using the nearest neighbor method with 0.02 calibrated. Propensity matching was performed to compensate for the difference between age, sex, BMI, ASA, Tumor location, operative type. The propensity score matching was calibrated and differentiated in most items with a standardized mean difference of less than 0.05. All statistical tests were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA), and a p-value of <0.05 was considered to indicate statistical significance.

RESULTS

The clinicopathologic characteristics of all patients are shown in Table 1. Patients were divided into 2 groups based on an AST/ALT ratio of 1.2. Mean age was 61.4 years and mean AST/ALT ratio was 1.2. Overall mortality was 47.7%, cancer-specific mortality was 44.3%, and mean survival time was 50.5 months. Twenty-eight percent of patients experienced recurrence within the bladder during follow-up. In the high AST/ALT group, the mean age was 64.1 years ($p=0.015$), the mean mortality rate was 65.9% and the cancer-specific mortality rate was 61.0% ($p=0.003$ and $p=0.006$), higher than the low AST/ALT group. The mean survival time of the high AST/ALT group was 40.4 months ($p=0.020$), which was shorter than the low AST/ALT group. Overall survival (OS) was poor in the high AST/ALT group compared to the low AST/ALT group ($p=0.007$), and the cancer-specific survival was also poor in the high AST/ALT group, compared to the low AST/ALT group ($p=0.011$) (Fig. 1).

In multivariate analysis, age (hazard ratio [HR], 1.041; 95% confidence interval [CI], 1.003–1.074; $p=0.039$), pT3 or higher (HR, 1.464; 95% CI, 1.156–1.857; $p=0.002$), LVI (HR, 1.445; 95% CI, 1.153–1.854; $p=0.005$), pN1–N2 (HR, 1.342; 95% CI, 1.011–1.773), pN3 (HR, 3.893; 95% CI, 2.284–6.648; $p<0.001$), high AST/ALT ratio (HR, 5.428; 95% CI, 1.803–16.334; $p=0.002$), were significant pre-

Table 1. Clinicopathological characteristics of patients before and after propensity score matching

Variable	Before propensity score matching			After propensity score matching		
	Low AST/ALT (N=94)	High AST/ALT (N=82)	p-value	Low AST/ALT (N=82)	High AST/ALT (N=82)	p-value
Age (yr)	59.1±9.9	64.1±8.9	0.015	60.9±8.7	64.1±8.9	0.109
BMI (kg/m ²)	28.8±8.8	24.2±9.3	0.020	28.3±7.9	24.2±9.3	0.037
Male sex	78 (83.0)	54 (65.9)	0.109	68 (82.9)	54 (65.9)	0.129
AST	22.3±10.0	23.2±8.5	0.662	21.4±8.8	23.2±8.5	0.348
ALT	28.4±14.2	15.6±6.8	<0.001	27.2±13.3	15.6±6.8	<0.001
AST/ALT ratio	0.8±0.2	1.6±0.4	<0.001	0.8±0.2	1.6±0.4	<0.001
HTN	28 (29.8)	44 (53.7)	0.058	24 (29.3)	44 (53.7)	0.059
DM	16 (17.0)	16 (19.5)	0.623	16 (19.5)	16 (19.5)	0.602
Operation type			0.380			0.467
Open	72 (76.6)	54 (65.9)		62 (75.6)	54 (65.9)	
Laparoscopic	22 (23.4)	28 (34.1)		20 (24.4)	28 (34.1)	
ASA PS classification			0.104			0.061
I	52 (55.3)	26 (31.7)		46 (56.1)	26 (31.7)	
II	42 (44.7)	54 (65.9)		36 (43.9)	54 (65.9)	
≥III	0 (0)	2 (2.4)		0 (0)	2 (2.4)	
Pathologic T stage			0.490			0.648
pTa	0 (0)	2 (2.4)		0 (0)	2 (2.4)	
pT1	2 (2.1)	6 (7.3)		2 (2.4)	6 (7.3)	
pT2	10 (10.6)	4 (4.9)		6 (7.3)	4 (4.9)	
pT3	74 (78.7)	62 (75.6)		68 (82.9)	62 (75.6)	
pT4	8 (8.5)	8 (9.8)		6 (7.3)	8 (9.8)	
Tumor grade			0.802			0.672
Low	8 (8.5)	4 (4.9)		8 (9.8)	4 (4.9)	
High	86 (91.5)	78 (95.1)		74 (90.2)	78 (95.1)	
Lymphovascular invasion	36 (38.3)	32 (39.0)	0.956	32 (39.0)	32 (39.0)	1.000
Concurrent CIS	10 (10.6)	10 (12.2)	1.000	8 (9.8)	10 (12.2)	1.000
Ipsilateral hydronephrosis	56 (59.6)	50 (61.0)	0.985	50 (61.0)	50 (61.0)	1.000
Multifocality	16 (17.0)	20 (24.4)	0.555	16 (19.5)	20 (24.4)	0.790
Tumor location			0.664			0.714
Pelvis	38 (40.4)	28 (34.1)		30 (36.6)	28 (34.1)	
Ureter	40 (42.6)	34 (41.5)		38 (46.3)	34 (41.5)	
Both	16 (17.0)	20 (24.4)		14 (17.1)	20 (24.4)	
Pathologic N stage			0.674			0.609
pNx–N0	86 (91.4)	68 (82.9)		74 (90.2)	68 (82.9)	
pN1–N2	4 (4.3)	8 (9.8)		4 (4.9)	8 (9.8)	
pN3	4 (4.3)	6 (7.3)		4 (4.9)	6 (7.3)	
Positive surgical margin	8 (8.5)	12 (14.6)	0.571	8 (9.8)	12 (14.6)	0.736
Neoadjuvant chemotherapy	2 (2.1)	1 (1.2)	0.453	1 (1.0)	1 (1.2)	0.521
Adjuvant chemotherapy regimens			0.430			0.415
Gemcitabine - carboplatin	16 (17.0)	14 (17.1)		12 (14.6)	14 (17.1)	
Gemcitabine - cisplatin	70 (74.4)	62 (75.6)		62 (73.2)	62 (75.6)	
G - cisplatin & G - carboplatin	2 (2.1)	6 (7.3)		2 (2.4)	6 (7.3)	
MVAC	2 (2.1)	0 (0)		2 (2.4)	0 (0)	
Others	4 (4.3)	0 (0)		4 (4.9)	0 (0)	
Chemotherapy cycle	4.0±1.6	4.3±2.3	0.566	4.0±1.6	4.3±2.3	0.548
Survival duration (mo)	59.4±49.2	40.4±26.7	0.025	61.1±52.1	40.4±26.7	0.027
Overall mortality	30 (31.9)	54 (65.9)	0.003	28 (34.1)	54 (65.9)	0.008
Cancer-specific mortality	28 (29.8)	50 (61.0)	0.006	26 (31.7)	50 (61.0)	0.015

Values are presented as mean±standard deviation or number (%).

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, ASA PS: American Society of Anesthesiologists physical status, CIS: carcinoma *in situ*, MVAC: methotrexate, vinblastine, adriamycin and cisplatin.

Fig. 1. Overall and cancer-specific survival analyses. Kaplan-Meier survival curves comparing overall and cancer-specific survivals according to the aspartate aminotransferase/alanine aminotransferase (AST/ALT).

Table 2. Multivariate Cox proportional hazards analyses of the AST/ALT ratio on overall survival and cancer-specific survival

Parameter	Overall survival		Cancer-specific survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.041 (1.003–1.074)	0.039	1.033 (0.994–1.075)	0.083
BMI	0.994 (0.932–1.061)	0.842	1.011 (0.954–1.085)	0.738
Sex				
Men	Reference		Reference	
Women	0.423 (0.114–1.582)	0.198	0.482 (0.136–1.738)	0.262
ASA PS classification				
I	Reference		Reference	
≥II	1.038 (0.790–1.358)	0.207	1.048 (0.795–1.384)	0.185
Pathologic T stage				
<pT3	Reference		Reference	
≥pT3	1.464 (1.156–1.857)	0.002	1.497 (1.174–1.903)	0.001
Tumor grade				
Low	Reference		Reference	
High	2.665 (0.368–19.883)	0.340	2.437 (0.323–18.302)	0.386
Lymphovascular invasion	1.445 (1.153–1.854)	0.005	1.475 (1.172–1.904)	0.002
Concurrent CIS	0.709 (0.151–3.347)	0.658	0.877 (0.192–4.003)	0.856
Multifocality	0.662 (0.154–2.946)	0.590	0.759 (0.173–3.194)	0.692
Pathologic N stage		<0.001		<0.001
pNx–N0	Reference		Reference	
pN1–N2	1.342 (1.011–1.773)	0.038	1.304 (0.982–1.735)	0.066
pN3	3.893 (2.284–6.648)	<0.001	3.815 (2.235–6.493)	<0.001
Positive surgical margin	2.155 (0.927–5.026)	0.075	2.412 (1.028–5.674)	0.043
AST/ALT ratio				
Low	Reference		Reference	
High	5.428 (1.803–16.334)	0.002	4.417 (1.545–12.632)	0.005

AST: aspartate aminotransferase, ALT: alanine aminotransferase, HR: hazard ratio, CI: confidence interval, BMI: body mass index, ASA PS: American Society of Anesthesiologists physical status, CIS: carcinoma *in situ*.

dictors of poor OS. And pT3 or higher (HR, 1.475; 95% CI, 1.172–1.904; $p=0.002$), pN3 (HR, 3.815; 95% CI, 2.235–6.493; $p<0.001$), high AST/ALT ratio (HR, 4.417; 95% CI, 1.545–12.632; $p=0.005$) were

significant predictors of poor cancer-specific survival (CSS) (Table 2).

After propensity score matching, the overall mortality rate was significantly higher (65.9%

vs. 34.1%) in the high AST/ALT group ($p=0.008$) and the cancer-specific mortality rate were also significantly higher (61.0% vs. 31.7%) in the high AST/ALT group ($p=0.015$) than in the low AST/ALT group (Table 1). The multivariate Cox analysis showed that a high prechemotherapy AST/ALT ratio was a significant independent predictor of poor prognosis such as OS (HR, 2.095; 95% CI, 1.090–4.024; $p=0.026$), CSS (HR, 2.074; 95% CI, 1.053–4.086; $p=0.035$) (Table 3). In addition, pathologic T stage, N stage, positive surgical margin are also associated with poor prognosis (Table 3).

DISCUSSION

In this study, we evaluated patients with increased AST/ALT. We observed poor survival outcomes

after ACH for advanced UTUC. The AST/ALT ratio was a predictor of OS (HR, 5.428; 95% CI, 1.803–16.334; $p=0.002$) and CSS (HR, 4.417; 95% CI, 1.545–12.632; $p=0.005$). Previous studies on UTUC have also reported that the AST/ALT ratio is a predictor of oncological prognosis.^{13–15} Lee et al.¹⁴ reported that preoperative high AST/ALT ratio was significantly associated with a poor prognosis of progression-free survival (PFS), CSS, and OS (all $p<0.001$) in 263 UTUC patient who underwent RNU. They also reported that a high preoperative AST/ALT ratio greater than 1.5 was an independent predictor of PFS (HR, 2.335; 95% CI, 1.633–3.340; $p=0.001$), CSS (HR, 2.550; 1.689–3.851; $p=0.001$), and OS (HR, 2.069; 95% CI, 1.409–3.038; $p<0.001$) through Cox multivariate analysis.¹⁴ Cho et al.¹³ reported that a high preoperative AST/ALT ratio

Table 3. Multivariate Cox proportional hazards analyses of the AST/ALT ratio on overall survival and cancer-specific survival after propensity score matching

Parameter	Overall survival		Cancer-specific survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.046 (1.005–1.090)	0.029	1.031 (0.992–1.071)	0.119
BMI	0.994 (0.958–1.031)	0.748	1.001 (0.964–1.038)	0.983
Sex				
Men	Reference		Reference	
Women	0.631 (0.301–1.323)	0.228	0.603 (0.276–1.317)	0.205
ASA PS classification				
I	Reference		Reference	
≥II	1.080 (0.601–1.939)	0.797	1.158 (0.630–2.129)	0.636
Pathologic T stage				
<pT3	Reference		Reference	
≥pT3	1.358 (1.059–1.744)	0.018	1.600 (1.251–2.062)	0.002
Tumor grade				
Low	Reference		Reference	
High	3.321 (0.439–25.128)	0.245	2.500 (0.331–18.907)	0.374
Lymphovascular invasion	1.366 (0.737–2.532)	0.322	1.417 (0.747–2.687)	0.285
Concurrent CIS	0.809 (0.228–2.271)	0.687	0.883 (0.313–2.491)	0.814
Multifocality	0.422 (0.178–1.002)	0.051	0.628 (0.276–1.429)	0.267
Pathologic N stage		<0.001		<0.001
pNx–N0	Reference		Reference	
pN1–N2	1.362 (1.051–1.753)	0.018	1.702 (1.132–2.558)	0.010
pN3	3.301 (1.182–9.215)	<0.001	5.364 (2.125–13.512)	<0.001
Positive surgical margin	2.398 (1.018–5.651)	0.046	2.882 (1.256–6.612)	0.013
AST/ALT ratio				
Low	Reference		Reference	
High	2.095 (1.090–4.024)	0.026	2.074 (1.053–4.086)	0.035

AST: aspartate aminotransferase, ALT: alanine aminotransferase, HR: hazard ratio, CI: confidence interval, BMI: body mass index, ASA PS: American Society of Anesthesiologists physical status, CIS: carcinoma *in situ*.

was significantly associated with a poor prognosis of CSS and OS (all $p=0.001$), in a multicenter study of 1,049 patients who underwent RNU. They also reported that a preoperative AST/ALT ratio higher than 1.6 was an independent predictor of CSS (HR, 2.49; 95% CI, 1.70–3.64; $p=0.001$) and OS (HR, 1.84; 95% CI, 1.34–2.52; $p=0.001$) through Cox multivariate analysis.¹³ In Nishikawa's study of 109 patients with localized UTUC who underwent RNU, a high AST/ALT was significantly independent of extravesical recurrence-free survival (HR, 4.21; 95% CI, 1.95–9.08; $p<0.001$). In a study of 153 patients with urothelial bladder cancer who underwent radical cystectomy, Gorgel et al.¹⁶ reported that the preoperative AST/ALT ratio was significantly associated with a poor prognosis of disease-specific survival (DSS) and OS (all $p<0.001$). They also reported that preoperative AST/ALT ratios higher than 1.3 were independent predictors of DSS (HR, 5.79; 95% CI, 2.25–15.13; $p<0.001$) and OS (HR, 2.61; 95% CI, 1.49–4.56; $p<0.001$) through Cox multivariate analysis.¹⁶

The exact mechanism of the relationship between elevated AST/ALT and poor prognosis of cancer patients, including those with UTUC is not yet known. But there are several hypotheses that explain the relationship between AST/ALT ratio and cancer. The most prominent of them is the Warburg effect.¹⁷ In normal cells, energy is produced by mitochondrial oxidative phosphorylation. However, cancer cells produce energy through lactic acid fermentation glycolysis, rather than oxidative phosphorylation, even under oxygen-rich conditions. This aerobic glycolysis is a less efficient pathway than oxidative phosphorylation, and increases the production of metabolites that can contribute to cancer cell proliferation. These metabolites provides anabolic support essential for cancer cell proliferation and growth.¹⁷ Increased lactate has been suggested to play an important role in maintaining glycolysis, affecting

lactate dehydrogenase, the Nicotinamide adenine dinucleotide (NADH)/Nicotinamide adenine dinucleotide (NAD)+ratio, and affecting glucose transport materials. AST plays an important role in the process by relocating NADH to the mitochondria.^{18,19} In addition, increases in glucose metabolites due to increased lactate, affects the microenvironment of the tumor and promotes local invasion, progression, and metastasis of cancer cells.^{18,19}

This study has some limitations. First, since this was a retrospective study of a relatively small number of patients, there may be a recall bias. However, the study population was limited to UTUC patients who underwent RNU and ACH, and that limited the number of patients. Second, we didn't know whether the patient was taking unchecked drugs that would affect AST/ALT.

Despite the limitations, this is the first study to identify the AST/ALT ratio as an important prognostic biomarker of ACH in advanced UTUC. There are many cancer biomarkers, but the AST/ALT ratio has the merit of cost effectiveness, compared with other methods, and the advantage that it is a quick method that may predict prognosis before cancer treatment.

CONCLUSIONS

An increased AST/ALT ratio is a significant independent predictor of CSS and OS in advanced UTUC patients receiving systemic ACH after RNU. We suggest that the AST/ALT ratio is a useful and valuable biomarker for predicting oncological outcomes after systemic ACH, as well as RNU in UTUC. The results presented here provide an important insight into the clinical significance of aminotransferase-based markers in postoperative UTUC patients with progressive stage disease, receiving ACH.

NOTES

• Conflicts of interest: No potential conflict of interest relevant to this article was reported.

• Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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