Evaluation of Preoperative Aspartate Transaminase/Alanine Transaminase Ratio as an Independent Predictive Biomarker in Patients With Metastatic Renal Cell Carcinoma Undergoing Cytoreductive Nephrectomy: A Propensity Score Matching Study

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Evaluation of the preoperative aspartate transaminase/alanine transaminase (De Ritis) ratio as an independent predictive biomarker in patients with metastatic renal cell carcinoma undergoing cytoreductive nephrectomy: A propensity score matching study

[1]Hiroki Ishihara, *[1,] [2]Tsunenori Kondo, [1]Kazuhiko Yoshida, [1,3,4]Kenji Omae, [1]Toshio Takagi, [1]Junpei Iizuka, [1]Kazunari Tanabe

[1]Department of Urology, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan, 162-8666

[2] Department of Urology, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu, Arakawa-ku, Tokyo, Japan, 116-8567

[3]Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine/ School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto, Japan, 606-8501

[4]Center for Innovative Research for Communities and Clinical Excellence, Fukushima Medical University, 1 Hikarigaoka, Fukushima City, Fukushima, Japan, 960-1295

*Correspondence author:

Dr. Tsunenori Kondo

Tokyo Women's Medical University Medical Center East

Department of Urology, Tokyo Women's Medical University Medical Center East,

2-1-10 Nishiogu, Arakawa-ku, Tokyo, Japan, 116-8567

Tel: +81-3-3810-1111

FAX: +81-3-5855-6319

E-mail address: tkondo@twmu.ac.jp

Short title

De Ritis ratio on cytoreductive nephrectomy

Conflicts of interest statement

Tsunenori Kondo received honoraria from Pfizer, Bayer, and Novartis. All other authors declare no conflict of interest.

MicroAbstract

We evaluated the aspartate transaminase/alanine transaminase (De Ritis) ratio as a predictive biomarker for metastatic renal cell carcinoma patients undergoing cytoreductive nephrectomy, using propensity score matching. The ratio was an independent predictor for cancer-specific and overall survival after cytoreductive nephrectomy. This novel biomarker can be used to predict the prognosis of metastatic renal cell carcinoma patients before cytoreductive nephrectomy.

Abstract

Background: The effect of the aspartate transaminase (AST)/alanine transaminase (ALT) ratio (De Ritis ratio) as a predictive biomarker for patients with metastatic renal cell carcinoma (mRCC) undergoing cytoreductive nephrectomy (CN) remains unclear.

Patients and Methods: One hundred and eighteen patients were retrospectively evaluated. Endpoints were set as cancer-specific survival (CSS) and overall survival (OS) after CN, and compared according to the AST/ALT ratio before and after 1:1 propensity score matching. The independent predictors for CSS and OS were also analyzed.

Results: A result of the receiver operating characteristic curve showed that the area under the curve was 0.603. The maximum Youden index indicated that the cut-off value for the AST/ALT ratio was 1.24. Before matching, a high AST/ALT ratio was significantly associated with inferior CSS and OS (all $p < 0.05$). After matching, 34 patients each were allocated to the high and low AST/ALT ratio groups. In the matched cohort, CSS and OS tended to be lower in patients in the high AST/ALT ratio group, although the results were not significant (median CSS: 18.4 months vs. not reached, $p = 0.121$; OS: 18.4 months vs. not reached, $p =$

0.0957). Furthermore, multivariate analyses revealed that the AST/ALT ratio was an independent predictor for CSS and OS (CSS: hazard ratio [HR] 2.17, p = 0.0472; OS: HR 2.30, p = 0.0258).

Conclusion: The preoperative AST/ALT ratio can be an effective predictive biomarker for CSS and OS.

Keywords

metastatic renal cell carcinoma; AST; ALT; nephrectomy; De Ritis ratio

Introduction

Nearly one of five patients have a distinct metastasis at the time that renal cell carcinoma (RCC) is diagnosed [1]. The prognosis of patients with metastatic RCC (mRCC) was poorer than that of others with stage I to III RCC; the 5-year relative survival in patients with stage IV did not reach 10% in a prior targeted therapy era [1]. Therefore, numerous studies have been performed to seek a proper and effective treatment strategy for mRCC, and to categorize patients into several prognostic models such as the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification [2]. Cytoreductive nephrectomy (CN) has been identified as effective treatment for mRCC according to previous studies in the cytokine therapy era [3, 4] as well as those in the targeted therapy era [5, 6].

Aminotransaminase, including the aspartate transaminase (AST) and alanine transaminase ratio (ALT), are enzymes released from liver cells into the blood stream, causing hepatocellular damage; thus, these are recognized as a part of the commonly requested panel for assessing liver function [7]. The AST/ALT ratio (De Ritis ratio) has been identified as an independent predictor of patient survival from chronic hepatic disease [8] and solid organ malignancies [9-11]. Moreover, two recent studies have reported that the preoperative AST/ALT ratio was significantly

associated with postoperative survival with localized RCC [12, 13]. However, the effect of the AST/ALT ratio on survival after CN for mRCC remains unclear. Thus, we evaluated the effect of the preoperative AST/ALT ratio as a predictive biomarker of survival in patients with mRCC after CN. Moreover, to minimize selection bias, we adjusted patient variables using 1:1 propensity score matching.

Patients and Methods

This retrospective analysis included 140 consecutive patients with mRCC undergoing CN at our department between January 2003 and December 2015. Among them, patients who underwent hemodialysis (n = 16) and those whose clinicopathological data were missing (n = 6), were excluded from this analysis. The remaining 118 patients were enrolled. The endpoint was patient survival, including cancer-specific survival (CSS) and overall survival (OS) after CN. Predictors for CSS and OS were evaluated according to several perioperative clinicopathological parameters, including the preoperative AST/ALT ratio. A blood sample was obtained within 1 week preoperatively. All patients underwent imaging examinations, including computed tomography of the chest, abdomen and pelvis within 2 months preoperatively. The tumors were classified according

to the 2009 Union for International Cancer Control/American Joint Committee on Cancer consensus and the World Health Organization (2004) classification systems. Cellular grading was performed using the Fuhrman grading system [14]. The CSS and OS were determined at the last follow-up using the date of surgery to the date of cancer-specific mortality and any cause mortality, respectively. To minimize selection bias between patients with a high AST/ALT ratio and those with a low AST/ALT ratio, patients' variables were adjusted using 1:1 propensity score matching.

Clinicopathological and laboratory data were extracted from an electronic database and patients' medical records. The Internal Ethics Review Board of Tokyo Women's Medical University approved this retrospective study (ID: 4109), which was performed in accordance with the principles outlined in the Declaration of Helsinki.

Statistical analysis

All analyses were performed using JMP software (version 11; SAS Institute Inc., Cary, NC, USA). Propensity scores were calculated using multivariable logistic regression. Continuous variables were analyzed using the Mann-Whitney *U*-test,

and categorical variables were analyzed using the χ^2 test. The CSS and OS were calculated using the Kaplan-Meier method, and statistical significance was determined using the log-rank test. The efficacy of using the AST/ALT ratio to predict CSS was analyzed using the receiver operating characteristic (ROC) curve and the area under curve (AUC). The cut-off value for this marker was also defined using the maximum Youden index [15]. Univariate and multivariate analyses were used to identify factors associated with CSS and OS using Cox proportional hazards regression models. The risk of survival is expressed as hazard ratios (HRs) and 95% confidence intervals (CIs), and differences were considered statistically significant at *p*-values < 0.05.

Results

Patients' characteristics

According to the maximum Youden index value, the cut-off value for the AST/ALT ratio was set at 1.24; therefore, patients with an AST/ALT ratio ≥ 1.24 were classified into the high AST/ALT group, whereas the remaining patients (i.e., those with an AST/ALT ratio < 1.24) were classified into the low AST/ALT group.

Of the 118 patients, 52 (44.1%) had a high AST/ALT ratio. Patient characteristics

before and after propensity score matching are summarized in Table 1. We were able to match 68 patients (34 patients in each group) (Figure 1). Before matching, the high AST/ALT group contained significantly more women ($p < 0.001$), and tended to be associated with older age, higher grades of pT and pN factors, and higher MSKCC risk. After matching, these differences between the two groups were acceptable.

ROC curve of the AST/ALT ratio

ROC analysis was generated for CSS, and the AUC value was statistically evaluated the discrimination ability of the AST/ALT ratio. The AUC of the AST/ALT ratio was 0.602 (95%CI 0.492 – 0.700), as shown in Figure 2.

Survival according to AST/ALT ratio in cohorts before and after propensity score matching

Figures 3a and 3b show that CSS and OS were significantly lower in patients with a high AST/ALT ratio than in those with a low AST/ALT ratio before propensity score matching (median CSS: 18.4 months vs. not reached, $p = 0.0116$; OS: 17.5 months vs. 81.5 months, $p = 0.0040$). After matching, Figures 4a and 4b show

that CSS and OS tended to be lower in patients with a high AST/ALT ratio; however, results were not significant (median CSS: 18.4 months vs. not reached, $p = 0.121$; OS: 18.4 months vs. not reached, $p = 0.0957$).

Results of univariate and multivariate analyses for CSS and OS in cohorts before and after propensity score matching

Before matching, results of univariate analyses for CSS and OS showed that sex, the MSKCC risk classification, AST/ALT ratio, and CRP level were significant predictors (all, $p < 0.05$). Other parameters, including age, the number of metastatic lesions, presence of liver metastasis, surgical approach, pathology, nuclear grade, pT and pN factors, or presence of adjuvant systematic therapy were not statistically significant (all, $p > 0.05$). Results of multivariate analysis for CSS showed that the AST/ALT ratio was an independent predictor (HR 2.15 $p = 0.0119$), together with the CRP level (HR 2.48 $p = 0.0042$) and MSKCC risk classification (HR 2.05 $p = 0.0279$). Results of multivariate analysis for OS showed that the AST/ALT ratio was an independent predictor (HR 2.26 $p = 0.0047$), together with the MSKCC risk classification (HR 2.25 $p = 0.0096$) and CRP level (HR 2.05 $p = 0.0153$) (Table 2).

After matching, on univariate analyses for CSS and OS, there was no significant difference in AST/ALT ratio (both $p > 0.05$). However, multivariate analyses for CSS and OS revealed that the AST/ALT ratio was an independent predictive factor (CSS: HR 2.17, $p = 0.0472$; OS: HR 2.30, $p = 0.0258$), after adjustment for possible factors including MSKCC risk classification and CRP level (Table 3).

Discussion

The present study showed that the preoperative AST/ALT ratio (De Ritis ratio) was an independent predictive biomarker for CSS and OS in patients with mRCC after CN. In a matched cohort, the Kaplan-Meier survival curve showed that the AST/ALT ratios were not significant; this result may have been due to the small sample size after propensity score matching. Indeed, on final multivariate analyses, after adjusting for other well-established predictors, including the MSKCC risk classification and CRP level [2, 16-19], the AST/ALT ratio was significant; therefore, we believe that the AST/ALT ratio could possibly be used to predict patient outcomes after CN for mRCC.

The AST and ALT levels are effective predictive markers used to determine hepatic function, and to identify hepatic disease such as viral hepatitis and alcohol

abuse. AST is commonly produced in several organs such as the liver, heart, skeletal muscle, kidney, and brain, whereas ALT is specifically found in the liver [8]. Importantly, these aminotransaminases are also expressed in different cellular subcomponents by cancerous cells. The significant association between the AST/ALT ratio and various malignancies such as lung cancer [10], pancreatic cancer [11], and cholangiocarcinoma [9], has been indicated. In this context, Bezan et al. [12] first reported the AST/ALT ratio as an independent predictive biomarker for patients' survival, including metastasis-free survival and OS, after curative nephrectomy for non-metastatic RCC. They also stated that this effective predictor might improve the predictive accuracy of a well-established prognostic model, as demonstrated in a cohort of 698 patients with non-metastatic RCC. Thereafter, Lee et al. [13] indicated that an increased AST/ALT ratio was significantly associated with worse postoperative survival, including progression-free survival, CSS and OS, in patients surgically treated for localized clear-cell RCC in a cohort of 2965 patients in a propensity score-matched study. Although these two previous studies demonstrated the efficacy of the AST/ALT ratio as a useful biomarker for survival after curative nephrectomy for localized RCC, it remains unclear whether this novel marker can be effective in a population with

mRCC. To the best of our knowledge, this is the first study to indicate that the preoperative AST/ALT ratio has a potentially prognostic value for CSS and OS in patients with mRCC after CN.

Although the mechanism of how the AST/ALT ratio predicts survival in patients with RCC remains unclear, previous studies have referenced the Warburg's effect, which was the study of biochemical markers in neoplasms in regard to Warburg's theory that cancer tissue showed a greater rate of aerobic glycolysis than normal tissue [20]. For example, Lee et al. [13] hypothesized that von-Hippel-Lindau (VHL) loss, which was a key trigger of clear-cell RCC, induced hypoxia-induced factor expression, which had a relationship with extensively increased glycolysis [21]. Moreover, AST has a vital role in glycolysis through the malate-aspartate shuttle pathway [22]. Thus, they speculated that the AST and ALT levels may be involved in the glycolysis mechanism in clear-cell RCC with VHL loss. According to their hypothesis, as patients with mRCC are expected to have more cancer cells (i.e., they may have a much greater rate of aerobic glycolysis), there may be a stronger association with the AST/ALT ratio in the glycolysis mechanism, as shown in our results.

Interestingly and importantly, we confirmed that the significant effect of the

AST/ALT ratio together with the CRP level. The CRP level is an independent predictive biomarker in patients with RCC with or without metastasis [16-19, 23, 24]. The strong association between the CRP level and patient's prognosis has been explained by previous experimental studies; CRP is produced in the liver and is strongly induced by interleukin-6 (IL-6). RCC cells can produce IL-6, and IL-6 itself is recognized as a growth promoter in RCC cells [25, 26]. Indeed, the CRP level was an independent predictor for CSS and OS in the present study. This result may represent different aspects of the mechanism of mRCC with regard to the prediction of prognosis; the CRP level may represent a systematic inflammatory response, whereas the AST/ALT ratio may represent a metabolic response under RCC cell condition. Indeed, there was no significant association between the AST/ALT ratio and CRP level (Table 1).

There were several limitations to this study. This was a retrospective study, performed at a single center with a small cohort; these factors may have introduced inherent selection bias of patients or treatments. Thus, patient backgrounds were matched between the high and low AST/ALT groups using propensity scoring, resulting in groups that were as well adjusted for analyses as possible. However, our findings should be confirmed in a prospective, multi-

institution study with a large cohort. Moreover, because this was a retrospective study, we could not completely exclude the potential influence of undetected hepatic disorder (e.g., fatty liver or chronic liver disease) on AST and ALT levels.

Conclusion

The present study's findings indicated that the preoperative AST/ALT ratio was an independent predictive biomarker for CSS and OS in patients with mRCC who underwent CN. The AST and ALT levels can be easily evaluated and monitored in routine clinical practice without invasive procedures. This novel biomarker can help predict prognosis in patients with mRCC before CN.

Clinical practice points

- Recent studies have reported that the preoperative aspartate transaminase (AST)/alanine transaminase (ALT) ratio (De Ritis ratio) was significantly associated with postoperative survival with localized renal cell carcinoma.
- The effect of the AST/ALT ratio on survival after cytoreductive nephrectomy for metastatic renal cell carcinoma remains unclear.
- We demonstrated that preoperative AST/ALT ratio was an independent

predictive biomarker for cancer-specific and overall survival after cytoreductive nephrectomy in a propensity score-matched cohort.

- The AST/ALT ratio can help predict prognosis in patients with metastatic renal cell carcinoma before cytoreductive nephrectomy.

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Figure legends

Figure 1: Study design

AST, aspartate transaminase; ALT, alanine transaminase

Figure 2: Receiver operating characteristic analysis of AST/ALT ratio

Receiver operating characteristic analysis for cancer-specific survival included 118 patients. The AUC of the preoperative AST/ALT ratio was 0.602.

AUC, area under the curve; AST, aspartate transaminase; ALT, alanine transaminase

Figure 3: Cancer-specific and overall survivals after cytoreductive nephrectomy according to the preoperative AST/ALT ratio before propensity score matching

The survival rate was calculated using the Kaplan-Meier method and compared using the log-rank test.

AST, aspartate transaminase; ALT, alanine transaminase

Figure 4: Cancer-specific and overall survivals after cytoreductive nephrectomy according to the preoperative AST/ALT ratio after propensity score matching

The survival rate was calculated using the Kaplan-Meier method and compared using the log-rank test.

AST, aspartate transaminase; ALT, alanine transaminase

Table 1: Patients demographics and clinical characteristics before and after propensity score matching

	Before matching			**After matching**		
Parameters	**Low AST/ALT (n = 66)**	**High AST/ALT (n = 52)**	**p**	**Low AST/ALT (n = 34)**	**High AST/ALT (n = 34)**	**p**
Age, years ≥ 65 (vs. < 65)	28 (42.4%)	28 (53.9%)	0.217	16 (47.1%)	19 (55.9%)	0.466
Sex Female (vs. male)	9 (13.6%)	24 (46.2%)	<0.0001	7 (20.6%)	7 (20.6%)	1.000
Number of metastatic lesions Multiple (vs. solitary)	17 (25.8%)	13 (25.0%)	0.925	9 (26.5%)	8 (23.5%)	0.779
Liver metastasis With (vs. without)	5 (7.58%)	4 (7.69%)	0.981	3 (8.82%)	3 (8.82%)	1.000
Surgical approach Open (vs. laparoscopy)	57 (86.4%)	42 (80.8%)	0.412	28 (82.4%)	26 (76.5%)	0.549
Pathology CCC (vs. non-CCC)	59 (89.4%)	46 (88.5%)	0.872	27 (79.4%)	30 (88.2%)	0.323
Nuclear grade 3 (vs. 1 and 2)	39 (59.1%)	33 (63.5%)	0.629	20 (58.8%)	21 (61.8%)	0.804
pT factor ≥ 3 (vs. < 3)	47 (71.2%)	43 (82.7%)	0.146	28 (82.4%)	28 (82.4%)	1.000
pN factor ≥ 1 (vs. 0 and X)	14 (21.2%)	18 (34.6%)	0.104	23 (67.6%)	23 (67.6%)	1.000
MSKCC risk Poor (vs. intermediate)	10 (15.2%)	14 (26.9%)	0.115	26 (76.5%)	26 (76.5%)	1.000

Systematic therapy Without (vs. with)	11 (52.4%)	10 (47.6%)	0.718	9 (26.5%)	9 (26.5%)	1.000
CRP level, mg/ dl ≥ 1.0 (vs. < 1.0)	41 (57.8%)	30 (42.3%)	0.626	18 (52.9%)	20 (58.8%)	0.625
*Follow-up period, months	25.9 ± 26.8	20.5 ± 25.3	0.274	21.0 ± 24.3	23.0 ± 28.8	0.751

*Mean ± standard deviation

AST, aspartate transaminase; ALT, alanine transaminase; CCC, clear-cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; CRP, C-reactive protein; ref., reference

Table 2: Results of univariate and multivariate analyses for cancer-specific and overall survivals before propensity score matching

Parameters	**CSS Univariate HR (95% CI)**	***p***	**CSS Multivariate HR (95% CI)**	***p***	**OS Univariate HR (95% CI)**	***p***	**OS Multivariate HR (95% CI)**	***p***
Age, years ≥ 65 (vs. < 65)	0.94 (0.54 – 1.61)	0.815			1.09 (0.65 – 1.83)	0.742		
Sex Female (vs. male)	1.90 (1.05 – 3.33)	0.0339	1.18 (0.62 – 2.18)	0.611	1.79 (1.01 – 3.06)	0.0466	1.08 (0.58 – 1.95)	0.794
Number of metastatic lesions Multiple (vs. solitary)	1.74 (0.92 – 3.13)	0.0873			1.82 (1.00 – 3.18)	0.0514		
Liver metastasis With (vs. without)	1.88 (0.56 – 4.66)	0.268			2.14 (0.74 – 4.90)	0.145		
Surgical approach Open (vs. laparoscopy)	1.26 (0.61 – 3.06)	0.558			1.20 (0.60 – 2.74)	0.627		
Pathology CCC (vs. non-CCC)	0.55 (0.25 – 1.47)	0.216			0.62 (0.28 – 1.63)	0.302		
Nuclear grade 3 (vs. 1 and 2)	1.31 (0.76 – 2.31)	0.333			1.22 (0.72 – 2.08)	0.460		
pT factor ≥ 3 (vs. < 3)	1.06 (0.59 – 1.99)	0.850			1.25 (0.71 – 2.32)	0.459		
pN factor ≥ 1 (vs. 0 and X)	1.29 (0.66 – 2.36)	0.440			1.35 (0.72 – 2.38)	0.333		

MSKCC Poor (vs. intermediate)	2.85 (1.55 – 5.04)	0.0011	2.05 (1.08 – 3.76)	0.0279	2.94 (1.65 – 5.06)	0.0004	2.25 (1.23 – 4.01)	0.0096
Systematic therapy With (vs. without)	1.02 (0.49 – 2.48)	0.960			0.98 (0.49 – 2.23)	0.948		
AST/ALT ratio ≥ 1.24 (vs. < 1.24)	1.99 (1.16 – 3.46)	0.0128	2.15 (1.18 – 3.92)	0.0119	2.10 (1.26 – 3.57)	0.0046	2.26 (1.28 – 4.00)	0.0047
CRP, mg/dl ≥ 1.0 (vs. < 1.0)	2.54 (1.41 – 4.86)	0.0016	2.48 (1.32 – 4.88)	0.0042	2.12 (1.23 – 3.79)	0.0064	2.05 (1.15 – 3.80)	0.0153

CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; CCC, clear-cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein

Table 3: Results of univariate and multivariate analyses for cancer-specific and overall survivals after propensity score matching

Parameters	**CSS Univariate HR (95% CI)**	***p***	**CSS Multivariate HR (95% CI)**	***p***	**OS Univariate HR (95% CI)**	***p***	**OS Multivariate HR (95% CI)**	***p***
Age, years ≥ 65 (vs. < 65)	0.69 (0.33 – 1.43)	0.319			0.83 (0.41 – 1.66)	0.588		
Sex Female (vs. male)	1.55 (0.61 – 3.45)	0.331			1.38 (0.55 – 3.03)	0.462		
Number of metastatic lesions Multiple (vs. solitary)	1.83 (0.78 – 3.98)	0.155			1.92 (0.86 – 4.02)	0.109		
Liver metastasis With (vs. without)	1.60 (0.38 – 4.59)	0.471			1.44 (0.34 - 4.08)	0.572		
Surgical approach Open (vs. laparoscopy)	1.22 (0.53 – 3.31)	0.661			1.14 (0.52 – 2.85)	0.764		
Pathology CCC (vs. non-CCC)	0.84 (0.31 – 2.91)	0.755			0.89 (0.33 – 3.07)	0.830		
Nuclear grade 3 (vs. 1 and 2)	0.90 (0.44 – 1.88)	0.778			0.84 (0.42 – 1.70)	0.630		
pT factor ≥ 3 (vs. < 3)	1.20 (0.52 – 3.27)	0.682			1.32 (0.58 – 3.57)	0.527		
pN factor ≥ 1 (vs. 0 and X)	0.74 (0.27 – 1.70)	0.494			0.80 (0.32 – 1.77)	0.600		

MSKCC Poor (vs. intermediate)	1.99 (0.89 – 4.18)	0.0904	1.62 (0.68 – 3.66)	0.268	2.31 (1.10 – 4.65)	0.0283	1.95 (0.87 – 4.23)	0.104
Systematic therapy With (vs. without)	0.70 (0.31 – 1.92)	0.469			0.67 (0.31 – 1.69)	0.373		
AST/ALT ratio ≥ 1.24 (vs. < 1.24)	1.81 (0.86 – 4.03)	0.117	2.17 (1.01 – 4.98)	0.0472	1.83 (0.91 – 3.93)	0.0921	2.30 (1.10 – 5.08)	0.0258
CRP, mg/dl ≥ 1.0 (vs. < 1.0)	2.66 (1.27 – 5.98)	0.0095	2.46 (1.10 – 5.79)	0.0280	2.64 (1.30 – 5.70)	0.0070	2.31 (1.06 – 5.23)	0.0340

Figure 1

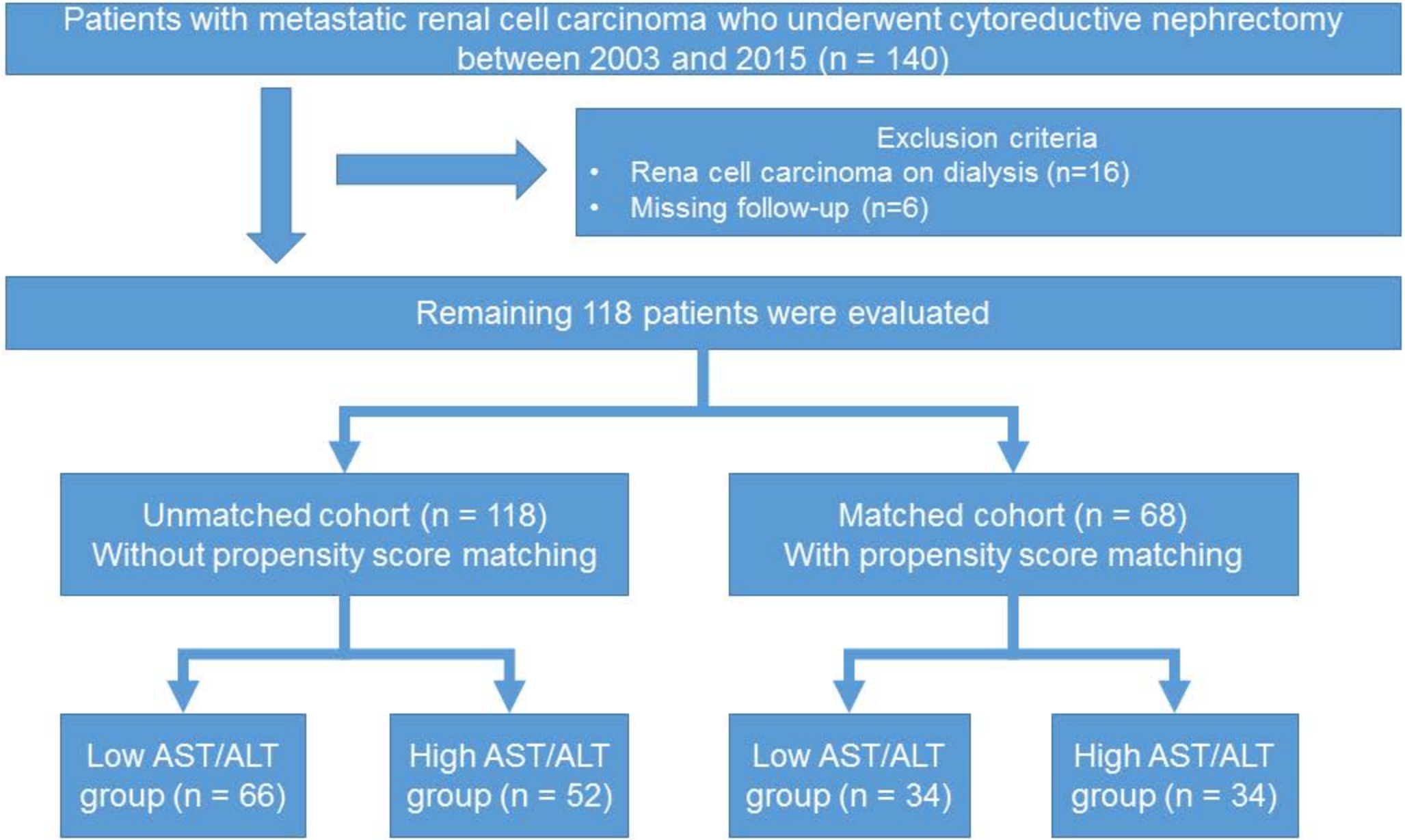

Patients with metastatic renal cell carcinoma who underwent cytoreductive nephrectomy between 2003 and 2015 (n = 140)
Exclusion criteria
• Rena cell carcinoma on dialysis (n=16)
• Missing follow-up (n=6)
Remaining 118 patients were evaluated
Unmatched cohort (n = 118) Without propensity score matching
Matched cohort (n = 68) With propensity score matching
Low AST/ALT group (n = 66)
High AST/ALT group (n = 52)
Low AST/ALT group (n = 34)
High AST/ALT group (n = 34)

Figure 2

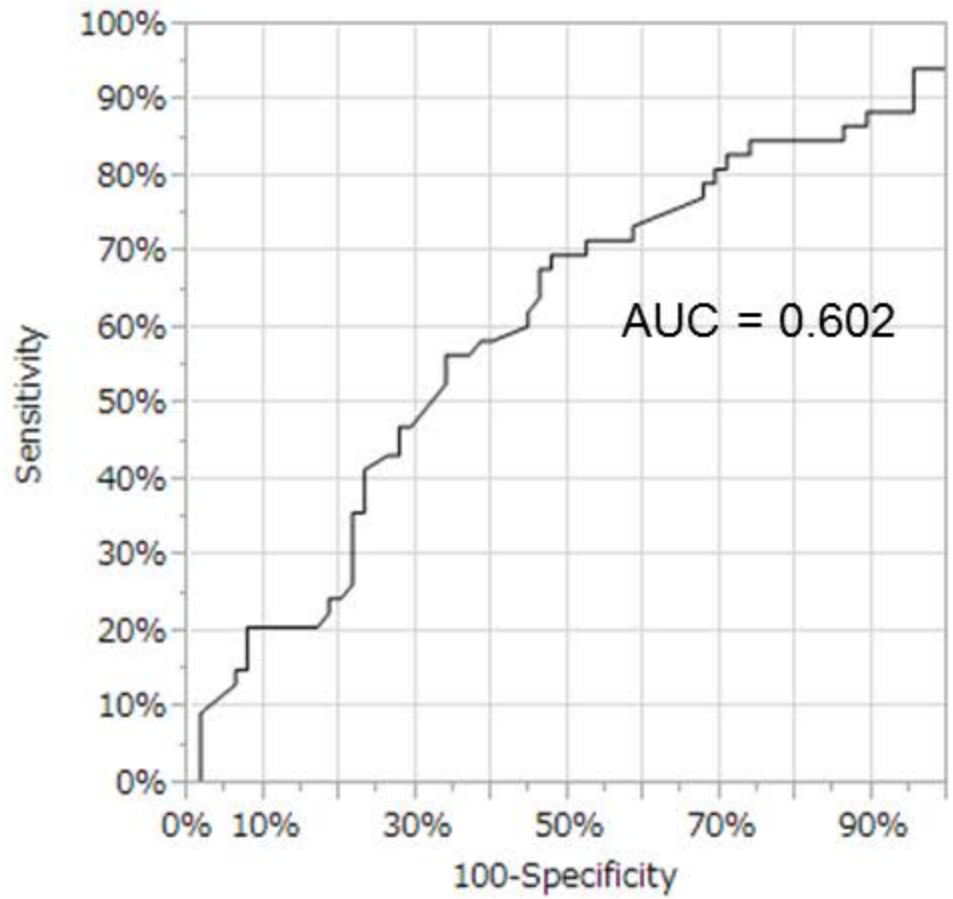

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Sensitivity
AUC = 0.602
0%
10%
30%
50%
70%
90%
100-Specificity

Figure 3

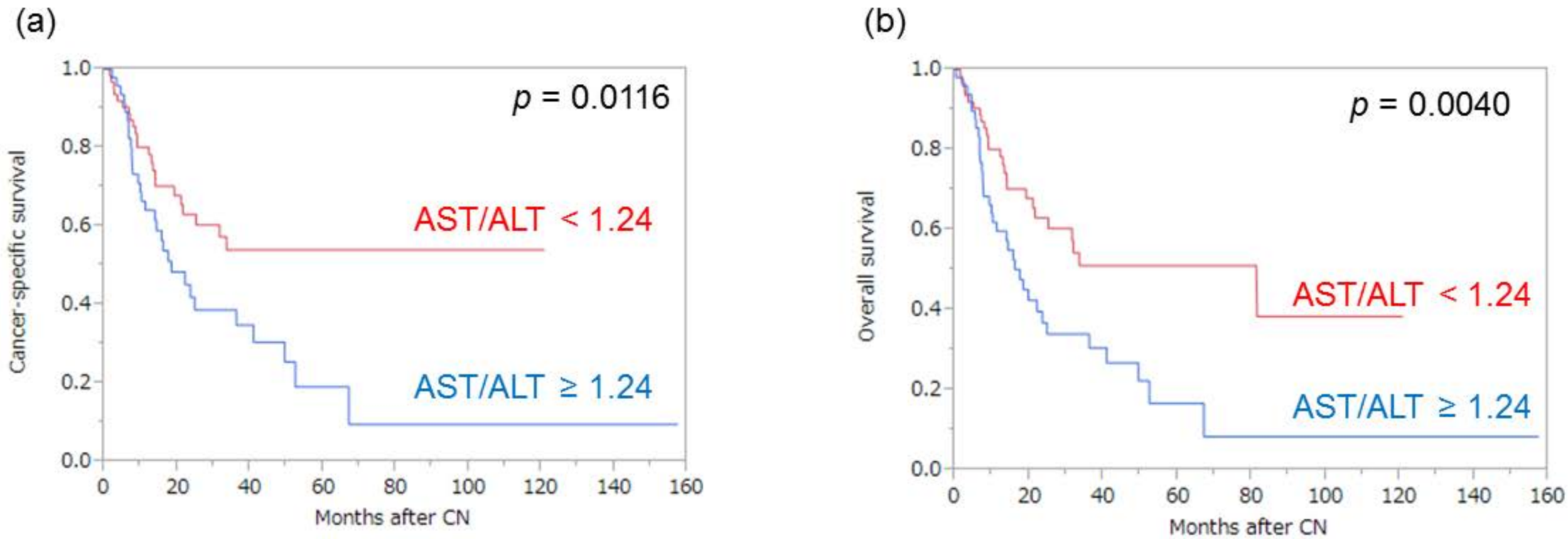
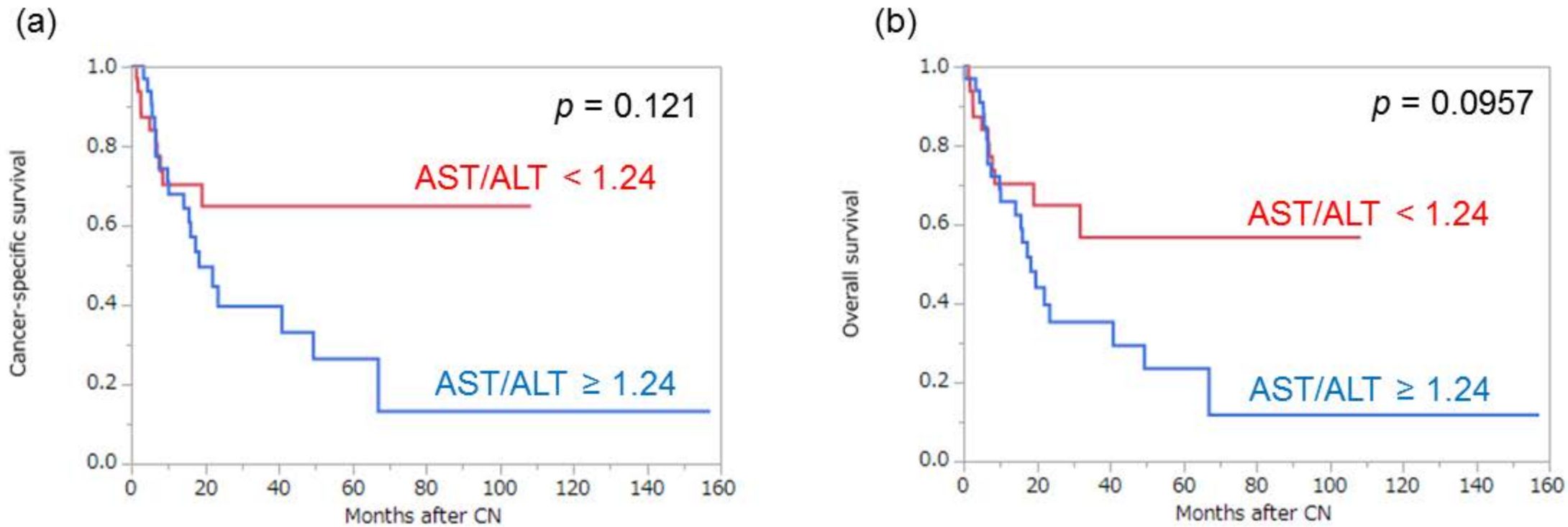

(a)
p = 0.0116
AST/ALT < 1.24
AST/ALT ≥ 1.24
Cancer-specific survival
Months after CN
(b)
p = 0.0040
AST/ALT < 1.24
AST/ALT ≥ 1.24
Overall survival
Months after CN

Figure 4


(a)
Cancer-specific survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
160
Months after CN
p = 0.121
AST/ALT < 1.24
AST/ALT ≥ 1.24
(b)
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
160
Months after CN
p = 0.0957
AST/ALT < 1.24
AST/ALT ≥ 1.24