

# The Association of Aspartate Aminotransferase/Alanine Aminotransferase Ratio with Diabetic Nephropathy in Patients with Type 2 Diabetes

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**Purpose:** To investigate the relationship between aspartate aminotransferase to alanine aminotransferase ratio (AST/ALT) and diabetic nephropathy (DN).

**Patients and Methods:** A total of 402 patients with type 2 diabetes mellitus were divided into three groups, such as normoalbuminuria ( $n = 196$ ), microalbuminuria ( $n = 131$ ) and macroalbuminuria ( $n = 75$ ) groups. Basic information and laboratory results were collected. Serum AST/ALT, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-2, IL-4, IL-6, IL-10 and interferon- $\gamma$  (INF- $\gamma$ ) were also measured. DN was defined as microalbuminuria or macroalbuminuria. The estimated glomerular filtration rate (eGFR) was calculated using the following formula:  $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$ .

**Results:** The AST/ALT in the macroalbuminuria group was higher than in the microalbuminuria and normoalbuminuria groups. The concentrations of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-2, IL-4, IL-10 and INF- $\gamma$  in the macroalbuminuria group were significantly higher than those in the two other groups. Multivariate logistical analysis showed that after adjusting confounding factors, TNF- $\alpha$  and high AST/ALT were independent risks for DN and macroalbuminuria. Furthermore, the AST/ALT had significantly positive correlation with TNF- $\alpha$  ( $r = 0.101$ ,  $P = 0.048$ ), IL-4 ( $r = 0.185$ ,  $P = 0.005$ ) and IL-6 ( $r = 0.274$ ,  $P < 0.001$ ) levels.

**Conclusion:** This study showed that high AST/ALT was an independent risk factor for the DN. Additionally, AST/ALT was positively correlated with inflammation cytokines, such as TNF- $\alpha$ , IL-4 and IL-6 levels.

**Keywords:** AST/ALT, diabetic nephropathy, inflammatory factors, tumor necrosis factor- $\alpha$

## Introduction

China has the highest incidence rate of diabetes mellitus in the world, and there is a growing trend. In China, the latest publications show that the prevalence of diabetes mellitus has risen to 12.8% nationwide.<sup>1</sup> By the year 2045, an estimated 693 million people had diabetes mellitus.<sup>2</sup> DN affects about 25% of patients with type 2 diabetes mellitus (T2DM), which is the main cause of end-stage renal disease (ESRD) in high income countries.<sup>3,4</sup> In addition, the cardiovascular risk of DN is very high, and the cardiovascular risk is similar to that of patients with coronary heart disease.<sup>5,6</sup> Therefore, it is very important to identify and manage the risk factors of DN and diagnose and treat the disease in time.

Serum transaminase, aspartate transaminase (AST) and alanine transaminase (ALT) are routine indexes of liver function. In 1957, the serum AST and ALT activity ratio of was first proposed as De Ritis ratio.<sup>7</sup> AST/ALT is correlated with

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oxidative stress and systemic inflammation.<sup>8</sup> Although it was originally proposed as a feature of viral hepatitis, such a ratio seems to serve as a practical biomarker for other diseases. It has been reported that AST/ALT is correlated with chronic kidney disease (CKD) and metabolic syndrome (MetS).<sup>9,10</sup> However, there are no studies about the relationship between AST/ALT and DN.

Inflammation plays a crucial role in the development and progression of DN, as many inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) contribute in the pathogenesis of DN.<sup>8</sup> This study aims to analyze the correlation between AST/ALT and inflammatory factors and DN.

## Materials and Methods

### Study Design and Participants

Patients with type 2 diabetes (T2DM) were recruited in Department of Endocrinology, the second affiliated hospital of Wenzhou Medical University from October 2019 to March 2021. There were 402 T2DM patients aged 40–83 years with complete data. According to the American Diabetes Association standard, the 75g oral glucose tolerance test was diagnosed as diabetes mellitus. The exclusion criteria included type 1 diabetes, alcohol consumption equal to or greater than 20g/day in the last 3 month, viral or autoimmune hepatitis, previous diagnosis of acute or chronic liver disease, intake of hepatotoxic drugs, inflammatory diseases, malignancy. All participants in our study were divided into three group, such as diabetes mellitus with normoalbuminuria (n=196), microalbuminuria (n=131) and macroalbuminuria (n=75) groups. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (No. LCKY2019-21, date: Jan 2019) and written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

### Data Collection

Detailed clinical history, included gender, age. The weight and height of each participant were measured to the nearest 0.1kg and 0.1cm, respectively. The formula of body mass index (BMI) is as follows: BMI = weight (kg)/height (m<sup>2</sup>). Their blood pressure was measured with automatic instruments while they were sitting (HEM-907, Omron, Kyoto, Japan). The use history of oral RAAS inhibitor drugs and statins were recorded.

Blood samples were collected from the anterior cubital vein during fasting at night. Renal function, liver function, blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum uric acid, serum creatinine, urea, glycated hemoglobin (HbA1c) and lipid profiles, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). Urinary albumin and creatinine excretion were measured by immunoturbidimetric assay and enzymatic method, and the clinical stage of proteinuria was evaluated by the urine albumin and creatinine ratio (UACR, mg/g) (macroalbuminuria, ACR $\geq$ 300; microalbuminuria, ACR 30–299; normoalbuminuria, ACR <30). eGFR was calculated using the following formula:  $186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$ . DN is defined as microalbuminuria or macroalbuminuria.

### Serum Cytokine Levels

Serum samples for cytokine detection were collected and stored at  $-70^{\circ}\text{C}$ . The serum levels of TNF- $\alpha$ , INF- $\gamma$ , IL-10, IL-6, IL-4, IL-2, were detected by Luminex xMAP (Ceger Biotechnology Co., Ltd., China) according to the manufacturer's instructions. Serum levels were measured in pg/mL.

### Statistical Analysis

SPSS 21.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis. Data were expressed as mean  $\pm$  (SD), percentage or median with quartile range. The differences between groups were analyzed by ANOVA. Count data were analyzed by  $\chi^2$  test. Spearman correlation was used to analyze the correlation between AST/ALT and clinical/biochemical parameters. The independent variables were analyzed by multivariate logistic analysis, and the odds ratio (OR) between the two groups was calculated by 95% confidence interval (CI). All tests were bilateral,  $P < 0.05$ , with statistical significance. Multicollinearity was tested using the variance inflation factor (VIF) and tolerance test. For this study multicollinearity was ruled-out with VIF <1.8/tolerance >0.54.

## Results

A total of 402 patients aged 40–83 years old were recruited. Table 1 shows the baseline characteristics. No significant difference in BMI, gender and waist/hip ratio was found among the normoalbuminuria, microalbuminuria and macroalbuminuria groups (all  $P > 0.05$ ). No

**Table 1** Characteristics of the Study Populations

Parameters	Total	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
N	402	196	131	75
Men, n (%)	244 (60%)	121 (61.1%)	78 (58.6)	45 (59.2%)
Age, years	59.19±9.28	57.52±9.49	60.37±9.17*	61.49±8.13*
BMI, Kg/m <sup>2</sup>	24.42±3.39	24.17±3.20	24.46 ±3.09	25.01±4.24
Waist/Hip ratio	0.93±0.10	0.92± 0.10	0.94±0.12	0.94 ±0.08
SBP, mmHg	143±26	138±23	144±25*	156±30*#
DBP, mmHg	83±8	83±8	83±8	85±8*#
HbA1c	9.12±1.99	9.11±1.95	9.21±2.19	8.99±1.76
TC, mmol/L	4.53±1.37	4.46±1.46	4.51±1.16	4.76±1.48
TG, mmol/L	1.91±1.43	1.82±1.40	1.78±0.99	2.37±1.97*#
HDL-C, mmol/L	1.05±0.29	1.05±0.29	1.07±0.30	1.03±0.25
LDL-C, mmol/L	2.75±1.06	2.76±1.08	2.80±1.02	2.66±1.09
Blood urea, mmol/L	6.44±2.16	5.94±1.68	6.38±1.79*	7.86±3.10*#
Serum creatinine, mmol/L	70.00±36.92	59.53±16.80	67.54±26.21*	101.67±64.16*#
eGFR, mL/min/1.73m <sup>2</sup>	100.97±26.40	113.70±20.77	99.90±22.93*	69.58±26.76*#
Serum uric, mmol/L	330.0±93.94	304.72±81.97	336.21±90.82*	386.21±103.73*#
UACR(mg/g)	32 (0–140)	3 (0–17)	80 (47–122)*	1281 (696–3115)*
24-hour urinary protein, g	0.38±1.00	0.06±0.04	0.12±0.11*	1.70±1.81*#
Medicine used, %				
RAAS inhibitor	27.6%	20.9%	26%*	48%*#
Statin	26.1%	19.4%	25.2%*	45.3%*#

**Notes:** Values are mean±SD or median with quartile range. \*Refers to patients with normoalbuminuria, P<0.05; #refers to patients with microalbuminuria, P<0.05.

**Abbreviations:** BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACR, urine albumin and creatinine ratio.

significant differences in the levels of HbA1c, HDL-c, TC and LDL-c was observed among the three groups (all P>0.05). The levels of 24-hour urinary protein, UACR, age, systolic blood pressure (SBP), blood urea, serum creatinine, the proportion of oral RAAS inhibitor and statin in the microalbuminuria and macroalbuminuria groups were significantly higher than those in the normoalbuminuria group (all P<0.05). The level of eGFR in the microalbuminuria and macroalbuminuria groups were significantly lower than that in the normoalbuminuria group

(P<0.05). The levels of TG and diastolic blood pressure (DBP) in the macroalbuminuria group were significantly higher than those in the normoalbuminuria and the microalbuminuria groups (all P<0.05).

There was significant difference in the AST/ALT level was found among the three groups (Table 2). The levels of AST/ALT in normoalbuminuria, microalbuminuria and macroalbuminuria groups were 0.95±0.34, 1.01±0.44, 1.25±0.71, respectively (P<0.05). No significant difference was observed in IL-6, INF-γ levels among the three groups. The

**Table 2** AST/ALT Level and Serum Cytokine in Study Subjects

	Total	Normoalbuminuria	Microalbuminuria	macroalbuminuria
ALT, U/L	24.77±19.29	25.47±22.20	25.06±13.51	22.40±19.76
AST, U/L	22.19±14.35	21.25±16.09	23.09±11.64	23.07±13.85
AST/ALT	1.03±0.48	0.95±0.34	1.01±0.44*	1.25±0.71*#
IL-2, pg/mL	3.19± 0.97	3.11±0.91	3.23±1.05	3.29±0.99*
IL-4, pg/mL	2.81±1.17	2.71±1.12	2.88±1.27	2.91±1.19*
IL-6, pg/mL	5.65±3.75	5.54±3.82	5.51±2.02	6.21±2.57
IL-10, pg/mL	4.33±1.05	4.23±0.99	4.40±1.09*	4.43±1.1*
TNF-α, pg/mL	2.93±0.70	2.86±0.70	2.99±0.61*	3.05±0.84*
INF-γ, pg/mL	2.84±1.82	2.82±1.87	2.85±1.37	2.88±1.87

**Notes:** Values are mean±SD or median with quartile range. \*Refers to patients with normoalbuminuria, P<0.05; #refers to patients with microalbuminuria, P<0.05.

**Abbreviations:** IL, interleukin; TNF-α, tumor necrosis factor-α; INF- γ, interferon- γ.

macroalbuminuria group had significantly higher AST/ALT levels compared with the normoalbuminuria and the microalbuminuria groups (all  $P<0.01$ ). The microalbuminuria and the macroalbuminuria groups had significantly higher serum IL-10, TNF- $\alpha$  levels compared with the normoalbuminuria group (all  $P<0.05$ ). The macroalbuminuria group had significantly higher serum IL-2, IL-4 levels compared with the normoalbuminuria group.

The Spearman correlations between the AST/ALT and biochemical and clinical parameters are shown in Table 3. The age ( $r=0.208$ ,  $P<0.001$ ), TG ( $r=0.208$ ,  $P<0.001$ ), UACR ( $r=0.188$ ,  $P<0.001$ ), 24-hour urinary protein ( $r=0.154$ ,  $P<0.001$ ), IL4 ( $r=0.185$ ,  $P=0.005$ ), IL-6 ( $r=0.274$ ,  $P<0.001$ ) and TNF- $\alpha$  ( $r=0.101$ ,  $P=0.048$ ) showed significantly correlations with AST/ALT. The Spearman correlations analyses showed that the AST/ALT level was negatively associated with HDL-c ( $r=-0.170$ ,  $P=0.001$ ) and BMI ( $r=-0.144$ ,  $P=0.004$ ).

Multivariate logistic model was constructed to detect the risk factors of DN and macroalbuminuria. As shown in Table 4, the multivariate analysis after adjusting age, gender, waist/hip ratio and using RAAS inhibitor, statin, SBP, DBP, TG, serum creatinine, serum uric and urea nitrogen,

AST/ALT was still strongly associated with DN (OR=1.770, 95% CI, 1.002–3.127,  $P=0.044$ ), macroalbuminuria (OR=2.471, 95% CI=1.113–5.487,  $P=0.026$ ) and TNF- $\alpha$  levels were also significantly associated with the DN (OR=1.590, 95% CI=1.081–2.374,  $P=0.047$ ), macroalbuminuria (OR=2.347, 95% CI, 1.185–4.651,  $P=0.014$ ).

## Discussion

In 1957, Italian pathologist Fernando De Ritis first described it as an enzyme for viral hepatitis.<sup>7</sup> As a potential predictor of many diseases, the ratio of AST to ALT has attracted much attention in recent years. To our knowledge, it is the first study to detect the correlation between AST/ALT and DN. According to our results, AST/ALT showed an independent correlation with DN, which was still obvious after adjustment for AST/ALT associated factors related to DN. Therefore, AST/ALT could serve as a strong predictor for DN.

More and more evidences emphasize the key role of inflammation in the development of DN.<sup>11</sup> Macrophages are the main mediators.<sup>12</sup> Macrophages are the main inflammatory cells involved in kidney damage, and their accumulation is related to the severity of DN.<sup>13–15</sup> The aggregation of renal macrophages in patients with DN is associated with decreased renal function.<sup>16</sup> Our findings are consistent with previous studies. It is found that the levels of IL-10, IL-4, IL-2, and TNF- $\alpha$  in patients in the macroalbuminuria group are significantly higher than those in the microalbuminuria and normoalbuminuria group ( $P<0.01$ ). In addition, after adjusting age, gender, waist/hip ratio and using RAAS inhibitor, statin, SBP, DBP, TG, serum creatinine, serum uric and urea nitrogen, TNF- $\alpha$  is independent risk factor for DN. Tumor necrosis factor receptors (TNFRs) are regulated by TNF- $\alpha$ , which plays an important role in the process of inflammation.<sup>17</sup> TNFRs mainly exist in glomeruli and peritubular capillary endothelial cells.<sup>18</sup> In T2DM patients, high levels of serum TNFRs are associated with global sclerosis, decreased glomerular filtration, and foot process regression.<sup>19</sup>

This study confirmed that AST/ALT was associated with IL-4 ( $r = 0.185$ ,  $P = 0.005$ ), IL-6 ( $r = 0.274$ ,  $P<0.001$ ) and TNF- $\alpha$  ( $r=0.101$ ,  $P=0.048$ ). AST/ALT was positively correlated with inflammatory cytokines, which was consistent with previous studies. Wang et al have confirmed the significant effect of the AST/ALT, as well as the CRP level.<sup>8</sup> Therefore, it is reasonable to guess that the increase of AST/ALT increased DN through inflammation cytokines.

**Table 3** Spearman Correlation of AST/ALT Levels with Clinical and Biochemical Parameters

Variable	AST/ALT	
	r	P
Age	0.208	<0.001
BMI	−0.144	0.004
HbA1c	−0.015	0.782
TC	0.094	0.106
TG	0.208	<0.001
HDL-C	−0.170	0.001
LDL-C	0.097	0.059
SBP	0.060	0.229
DBP	−0.075	0.136
UACR	0.188	<0.001
24-hour urinary protein	0.154	0.001
IL-2	0.027	0.596
IL-4	0.185	0.005
IL-6	0.274	<0.001
IL-10	0.041	0.425
TNF- $\alpha$	0.101	0.048
INF- $\gamma$	0.057	0.263

**Abbreviations:** BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; UACR, urine albumin and creatinine ratio; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; INF- $\gamma$ , interferon- $\gamma$ .

**Table 4** AST/ALT Associated with the Presence of Diabetic Nephropathy and Macroalbuminuria in Logistic Regression

	Diabetic Nephropathy		Macroalbuminuria	
	OR (95% CI)	P	OR	P
Age	1.016 (0.986, 1.046)	0.199	0.988 (0.944, 1.034)	0.604
Gender	0.519 (0.297, 0.904)	0.021	0.440 (0.203, 0.953)	0.037
Use RAAS inhibitor	1.107 (0.634, 1.933)	0.720	1.743 (0.840, 3.617)	0.136
Use statin	1.172 (0.664, 2.068)	0.583	2.089 (0.984, 4.433)	0.055
Waist/Hip ratio	5.600 (0.449, 11.769)	0.139	4.935 (0.275, 10.080)	0.392
SBP	1.012 (1.001, 1.023)	0.036	1.016 (0.999, 1.034)	0.062
DBP	0.994 (0.959, 1.030)	0.723	1.010 (0.958, 1.065)	0.714
TG	1.024 (0.851, 1.232)	0.801	1.162 (0.933, 1.447)	0.180
Serum creatinine	1.027 (1.012, 1.042)	0.001	1.040 (1.023, 1.058)	<0.001
Urea nitrogen	1.004 (0.879, 1.194)	0.762	1.055 (0.865, 1.293)	0.542
Serum uric	1.004 (1.001, 1.007)	0.021	1.003 (0.999, 1.007)	0.116
IL-2	1.170 (0.861, 1.590)	0.293	0.964 (0.603, 1.541)	0.878
IL-4	1.056 (0.812, 1.374)	0.498	1.141 (0.975, 1.630)	0.390
IL-10	0.996 (0.761, 1.303)	0.974	1.071 (0.790, 1.524)	0.894
TNF- $\alpha$	1.590 (1.081, 2.374)	0.047	2.347 (1.185, 4.651)	0.014
AST/ALT	1.770 (1.002, 3.127)	0.044	2.471 (1.113, 5.487)	0.026

**Abbreviations:** TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

AST/ALT is often used to evaluate liver function and reflect the severity of liver disease. The first report on AST/ALT appeared in 1957.<sup>20</sup> AST/ALT can be used to detect extrahepatic diseases and evaluate the prognosis of patients with renal function. Feng et al found that ALT level decreased with the progression of renal dysfunction, resulting in a higher prevalence of AST/ALT in peritoneal dialysis patients.<sup>21</sup> Miyuki et al found that subjects with high AST/ALT had lower BMI and eGFR levels.<sup>22</sup> Zhao et al reported that high AST/ALT is a risk factor for insulin resistance.<sup>23</sup> Weng et al reported that high AST/ALT was a risk factor for cardiovascular disease in males during a 10-year long-term follow-up.<sup>24</sup> In addition, Canat et al reported that high AST/ALT value is a risk factor for poor prognosis of non-metastatic renal cell carcinoma.<sup>25</sup> In the present study, our results also revealed that high AST/ALT values were as risk factor for DN.

From the perspective of elevated AST/ALT, it is speculated that the change of this ratio reflects the inconsistency between AST and ALT. ALT is mainly distributed in the cytoplasm of hepatocytes, and AST is widely distributed in muscle, kidney, lung, brain and liver mitochondria.<sup>26</sup> The higher the value of AST/ALT is the more significant the release of AST. High AST/ALT can aggravate insulin resistance, and result in the release of a variety of proinflammatory, prooxidant and pro fibrinogen mediators, which are important in the pathogenesis of CKD and

CVD.<sup>27,28</sup> Insulin resistance can lead to the activation of renin-angiotensin system and atherosclerotic dyslipidemia, which is the key driving factor of renal and vascular injury.

There are several limitations in this study. Firstly, this study is a single center cross-sectional study with few cases. Secondly, due to other complications, T2DM usually needs to take multiple drugs at the same time. Therefore, it is difficult to determine which drugs may affect liver transaminase due to drug interactions. Further long-term prospective cohort studies or intervention studies are needed to confirm the causal relationship of DN.

## Conclusion

In summary, the findings of our study indicate that elevated AST/ALT was an independent factor for risk of DN. In addition, AST/ALT was positively correlated with inflammation cytokines, such as TNF- $\alpha$ , IL-4 and IL-6 levels.

## Abbreviations

AST/ALT, aspartate aminotransferase to alanine aminotransferase ratio; FBG, fasting blood glucose; BMI, body mass index; HbA1c, glycosylated hemoglobin; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.



## Data Sharing Statement

The data that support the findings of this study are available from Institutional Review Board of the second affiliated hospital and Yuying Children's Hospital of Wenzhou Medical University but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the Jing Xu and Youjin Pan upon reasonable request and with permission of Institutional Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University.

## Ethics Approval and Consent to Participate

This study has obtained the approval from the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (No. LCKY2019-21) and has obtained the written informed consent of all subjects following the Declaration of Helsinki.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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