

# Neutrophil-to-lymphocyte ratio is a predictor of renal dysfunction in diabetic patients

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## Research

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# Abstract

**Background:** Neutrophil-to-lymphocyte ratio (NLR) has been widely evaluated as a biomarker in various medical and surgical prognoses, but its usefulness in diabetic kidney disease is not yet known.

**Methods:** This prospective observational study included outpatients, comprised of 190 men aged  $73 \pm 11$  (mean  $\pm$  standard deviation) years and 175 women aged  $77 \pm 10$  years at baseline, from a rural hospital. We examined the relationship between baseline NLR calculated by analyzing the differential leukocyte counts in the complete blood count and the 1.5-year estimated glomerular filtration rate (eGFR) decline rate (i.e. 1.5-year eGFR - baseline eGFR)  $\times 100/\text{baseline eGFR}$ . Rapid eGFR decline rate was defined as a value  $< \geq 15\%$ .

**Results:** Multiple linear regression analysis using rapid eGFR decline rates as objective variables, adjusted for confounding factors as explanatory variables, showed that tertiles of NLR ( $\beta=0.120$ ,  $p=0.018$ ) as well as hemoglobinA1c, presence of antidiabetic medication, and urinary albumin excretion were significantly and independently associated with a rapid eGFR decline rate. The multivariate-adjusted odds ratios (95% confidence interval) of the 2<sup>nd</sup> and 3<sup>rd</sup> tertiles of baseline NLR for rapid eGFR decline rate were 3.94 (1.34-11.6) and 3.93 (1.26-12.3), respectively. Multivariate-adjusted mean eGFR (95% confidence interval) values after 1.5 years categorized by tertile of baseline NLR were: 1<sup>st</sup>, 64.2 (62.1-66.3); 2<sup>nd</sup>, 60.5 (58.5-62.6); and 3<sup>rd</sup>, 59.1 (57.0-61.2).

**Conclusions:** These results suggest that baseline NLR might be a useful biomarker for renal function decline in diabetic outpatients.

## Background

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) worldwide and one of the most serious complications of diabetes [1]. DKD still develops in approximately 30% of patients with type 1 diabetes and approximately 40% of patients with type 2 diabetes [2] [3] [4]. DKD is considered to begin from early glomerular hyperfiltration, followed by the development of microalbuminuria, macroalbuminuria, and then declined glomerular filtration rate (GFR), and ultimately, end stage renal disease (ESRD). Approximately 20 to 30% of the patients develop microalbuminuria after 15 years of having the disease and less than half develop renal nephropathy [5]. Several pathophysiologic pathways, including risk factors (e.g. age, male gender, race, and family history), initiating factors (e.g. hyperglycemia, which is the most important), and perpetuating factors (e.g. obesity, hypertension, dyslipidemia, inflammatory cytokines, oxidative stress), are involved in the development of DKD [6]. Management of the modifiable risk factors might help in reducing its incidence soon.

Recently, many studies have identified new pathways involved in the onset and progression of DKD and have shown an important role of inflammation in the pathogenesis of DKD [7] [8]. Proposed inflammatory indices, such as C-reactive protein (CRP) levels, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have been considered useful indicators and cost-effective tests that can be easily measured in the laboratory. Among these indices, NLR in total white blood cell (WBC) counts has been studied in cardiac diseases and non-cardiac diseases (e.g. malignancies) as an inflammatory marker and predictor of the prognosis of diseases such as recurrence and mortality of cardiovascular disease (CVD) [9] [10] [11] [12] [13] [14], and surgical conditions [15] [16] [17]. NLR has recently emerged from among inflammatory parameters as a significant independent predictor of CVD complications in diabetic patients during a 4-year follow-up study [18]. In a cross-sectional study, the data suggested that NLR might be important as a potential factor for evaluating patients with a higher degree of

albuminuria and decreased eGFR among diabetic outpatients [19]. However, the usefulness of NLR as a predictor of DKD has not been studied and its importance in nephrology has not yet been established.

Thus, the aim of this study was to examine the relationship between NLR, potential risk factors (such as age, gender, history of CVD, hypertension, hyperglycemia, lipids, serum uric acid [SUA]), and renal function by examining prospective data from diabetic outpatients.

## Methods

### Subjects

Participants were continuously recruited from diabetic outpatients that visited the medical department of Seiyō Municipal Nomura Hospital from April to June 2017 [19]. Those with an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m<sup>2</sup> were excluded. Patients who had severe tissue damage, acute massive hemorrhage, acute poisoning, cancer, acute coronary artery disease, heart failure, active infection, or blood diseases affecting neutrophils and lymphocytes were also excluded. Patients with medications that may affect neutrophils and lymphocytes were also excluded. The study complies with the Declaration of Helsinki and was approved by the Ehime University Ethics Committee (IRB Approval Number: 1709006). Written informed consent was obtained from each subject.

### Evaluation of confounding factors

All enrolled patients were interviewed and clinically examined at presentation. Their medical history, present conditions, smoking status, alcohol consumption, and medications (e.g. antihypertensives, antidiabetic drugs, and antilipidemics) were obtained by interview using a structured questionnaire. Body mass index (BMI) is calculated as a person's weight in kilograms divided by height in meters squared. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded using an automatic oscillometer at the right upper arm of patients while in a sedentary position. Smoking status was defined as the number of cigarette packs per day multiplied by the number of years smoked (pack-year), and the participants were classified as never smokers, past smokers, light smokers (<20 pack-year) or heavy smokers (≥ 20 pack-year). Alcohol consumption was measured using the Japanese liquor unit, in which a unit corresponds to 22.9 g of ethanol, and the participants were classified as never drinkers, occasional drinkers (<1 unit/day), daily light drinkers (< 2 units/day), or daily heavy drinkers (≥ 2 units/day). Total cholesterol (T-C), high-density lipoprotein cholesterol (HDL-C), hemoglobin A1c (HbA1c), creatinine (Cr), SUA, and WBC count were measured during fasting. NLR was the ratio of neutrophil to lymphocyte. Non-HDL cholesterol (Non-HDL-C) was calculated by subtracting HDL-C from T-C. Urinary spot samples were collected after rest in the morning for analysis of urinary albumin and creatinine. Urinary albumin excretion (UAE) was expressed by the albumin: creatinine ratio (mg/g), and the participants were classified into the A1 stage (<30 mg/g Cr), A2 stage (30 to 300 mg/g Cr), or A3 stage (≥ 300 mg/g Cr). The eGFR was calculated using the CKD Epidemiology Collection (CKD-EPI) equations modified with a Japanese coefficient: Male, Cr ≤ 0.9 mg/dl,  $141 \times (\text{Cr}/0.9)^{-0.411} \times 0.993^{\text{age}} \times 0.813$ ; Cr > 0.9 mg/dl,  $141 \times (\text{Cr}/0.9)^{-1.209} \times 0.993^{\text{age}} \times 0.813$ ; Female, Cr ≤ 0.7 mg/dl,  $144 \times (\text{Cr}/0.7)^{-0.329} \times 0.993^{\text{age}} \times 0.813$ ; Cr > 0.7 mg/dl,  $144 \times (\text{Cr}/0.7)^{-1.209} \times 0.993^{\text{age}} \times 0.813$  [20]. Moreover, past ischemic stroke, ischemic heart disease, and obstructive arteriosclerosis were defined as CVD.

### Outcomes

The eGFR decline rate was calculated from the difference between the eGFR value after 1.5 years and that of the baseline year, divided by baseline eGFR (i.e.  $[1.5 \text{ year eGFR} - \text{baseline eGFR}] * 100 / \text{baseline eGFR}$ ). A rapid eGFR decline rate was defined as a 1.5-year eGFR decline rate of  $< \geq 15\%$ .

## Statistical analysis

All continuous variables with normal distribution were presented as the mean  $\pm$  standard deviation (SD), and non-normal variables (e.g. TG, HbA1c, and NLR) were reported as the median (interquartile range). In all analyses, parameters with non-normal distributions were used after log-transformation. Subjects were divided into three groups based on tertile of baseline NLR (1<sup>st</sup>, 0.65-1.56; 2<sup>nd</sup>, 1.57-2.33; 3<sup>rd</sup>, 2.34-15.3). Differences in means and prevalence between the three groups were examined by analysis of variance (ANOVA) for continuous data and a  $\chi^2$  test for categorical data. Pearson's correlations were calculated in order to characterize the associations between baseline characteristics and rapid eGFR decline rate. Multiple logistic regression analysis was used to evaluate the contribution of each confounding factor, including NLR, to the rapid eGFR decline rate. Analysis of covariance (ANCOVA) was performed with the use of a general linear model approach to determine the association between baseline NLR and multivariate-adjusted eGFR after 1.5 years. In these analyses, eGFR values after 1.5 years were considered the dependent variables and the three ranges of NLR were considered the independent variables. Statistical analysis was performed using IBM SPSS Statistics software, version 21 (Statistical Package for Social Science Japan, Inc., Tokyo, Japan). A value of  $p < 0.05$  was considered significant.

## Results

### Baseline characteristics of subjects categorized by tertile of baseline NLR

Characteristics of the subjects categorized by tertile of baseline NLR are illustrated in Table 1. This prospective observational study included outpatients, comprised of 190 men aged  $73 \pm 11$  years and 175 women aged  $77 \pm 10$  years at baseline. Age was higher in correlation with increased tertile of NLR, but BMI, DBP, and eGFR were lower. There were no inter-group differences based on gender, period of diabetes, smoking status, daily alcohol consumption, CVD, SBP, presence of antihypertensive medication, HDL-C, Non-HDL-C, presence of antilipidemic medication, HbA1c, presence of antidiabetic medication, SUA, SUA-lowering medication, or UAE stage.

### 1.5-year eGFR decline rate of subjects categorized by tertile of baseline NLR

Fig. 1 shows the eGFR transition in subjects categorized by tertile of baseline NLR.

The change in mean eGFR during the 1.5 years of the 1<sup>st</sup> NLR tertile was more gradual compared with the 2<sup>nd</sup> and 3<sup>rd</sup> NLR tertiles. As shown in Table 2, the 1<sup>st</sup> NLR tertile had fewer patients (4.1%) with a primary outcome (i.e. 1.5-year eGFR decline rate  $< \geq 15\%$ ) compared with the 2<sup>nd</sup> and 3<sup>rd</sup> NLR tertiles, which had more patients with primary outcomes (19.5% and 17.4%, respectively) with a significant  $p$ -value of 0.006.

### Relationships between baseline confounding factors and early eGFR decline rate

Table 3 shows the simple relationship between baseline confounding factors and rapid eGFR decline rate. Pearson's correlation coefficient showed that tertile of NLR, age, SBP, presence of antihypertensive medication, HDL-C and UAE stage were significantly correlated with a rapid eGFR decline rate. Multiple linear regression

analysis using rapid eGFR decline rate as an objective variable, adjusted for baseline confounding factors as explanatory variables, showed that tertile of NLR, age, non-HDL-C, and UAE stage was significantly and independently associated with a rapid eGFR decline rate.

### **Non-adjusted and adjusted odds ratio (95% CI) of the tertiles of baseline NLR for the early 1.5-year eGFR decline rate**

As shown in Table 4, the non-adjusted and multivariate-adjusted odds ratios (ORs) (95% confidence interval [CI]) of the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> tertiles of baseline NLR for rapid eGFR decline rate were 1, 5.62 (2.07-15.3), and 4.87 (1.77-13.4) and 1, 3.94 (1.34-11.6), and 3.93 (1.26-12.3), respectively.

### **Non-adjusted and adjusted eGFR after 1.5 years of subjects categorized by tertile of baseline NLR**

The non-adjusted mean (95% CI) eGFR values after 1.5 years of the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> tertiles of baseline NLR were 65.5 (62.8-68.2) mL/min/1.73m<sup>2</sup>, 59.6 (56.9-62.4), and 58.7 (55.9-61.4), respectively; the multivariate-adjusted mean values were 64.2 (62.1-66.3), 60.5 (58.5-62.6), and 59.1 (57.0-61.2), respectively. Both eGFR values after 1.5 years of the 2<sup>nd</sup> and 3<sup>rd</sup> tertiles of baseline NLR were significantly lower compared with those of the 1<sup>st</sup> tertile (Table 5).

## **Discussion**

In this prospective study of 365 diabetic outpatients, we determined the rate of decline in renal function as assessed by eGFR. Baseline NLR was assessed for its significance in the development of DKD, independently of potential confounding factors. The important finding of this study was that baseline NLR levels were found to be significantly associated with 1.5-year eGFR decline rate and future eGFR after 1.5 years among diabetic outpatients, even after adjusting for possible confounders such as gender, age, BMI, lifestyle, history of CVD, medication, blood pressure, lipids, glucose control, SUA, and UAE stage. Since NLR values are used extensively in the medical field, NLR may be used as a cost-effective predictor of inflammation. Finally, we demonstrated that threshold values for NLR determine early eGFR decline rate.

NLR has been reported as an inflammatory-based marker that is widely available, easy to obtain, and inexpensive to measure, providing values that can aid in the risk stratification of patients with various diseases [14] [18] [21] [22] [23]. In addition, NLR is very stable compared with absolute counts (such as total leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts), which can be altered by various physical, physiological, and pathological factors [24]. Several recent studies have demonstrated possible associations between NLR and the development and acceleration of some diabetic complications such as diabetic retinopathy [25], nephropathy including UAE of 30–300 mg/g Cr or overt nephropathy [24] [26] [27] [28] [29] [30] [31], and neuropathy [32]. In a 3-year follow-up study of 338 diabetic patients, NLR predicted worsening of renal function as a continuous decrease in GFR > 12 mL/min with the final value being GFR < 60 mL/min [24]. In 253 patients with type 2 diabetes, the NLR values of the patients with early-stage diabetic nephropathy were higher than those of patients without diabetic nephropathy ( $p < 0.001$ ). NLR levels were positively correlated with diabetic nephropathy (OR, 2.09; 95% CI, 1.27–3.43) [29]. Furthermore, baseline NLR was significantly and independently associated with increased 1.5-year eGFR decline rate and decreased eGFR after 1.5 years as a primary outcome.

The mechanisms that lead to increased NLR in individuals with early stage DKD remain unknown. Diabetes is a chronic systemic disease. Many reports in the literature have suggested that various inflammatory responses play crucial roles in the pathogenesis and development of insulin resistance, which is one of the main causative factors for the etiology of type 2 diabetes [33]. Numerous studies have demonstrated that circulating biomarkers of these pathways such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, CRP, vascular cellular adhesion molecule-1, interstitial cellular adhesion molecule-1, E-selectin, von Willebrand factor (endothelial dysfunction), plasminogen activator inhibitor-1, fibrinogen, and P-selectin (procoagulant state) may be associated with the development of diabetes. Some studies, particularly those on type 2 diabetes, have demonstrated that certain biomarkers could contribute to increased diabetic vasculopathies [34]. Inflammation in particular plays an essential role in the progression of DKD. Therefore, the number and percentage of WBC fractions recognized as novel biomarkers for systemic inflammation were strongly correlated with the development of DKD. In addition, many studies have demonstrated that NLR is positively associated with metabolic syndrome [35] and the prognosis of diseases such as acute coronary atherosclerosis [21] [23] [36], stroke [37], and cancer [22] [38], in which inflammation is significantly involved in their onset and progression.

However, some limitations could not be avoided. First, estimation of GFR using CKD tends to be less accurate in subjects with normal kidney function and CKD compared to inulin clearance. It is, however, more accurate than Cr or eGFR when the Modification of Diet in Renal Disease (MDRD) formula is used [20]. Second, baseline confounders and eGFR are based on a single assessment of blood, which can cause misclassification bias. Third, the failure to perform a renal biopsy cannot eliminate the potential impact of underlying diseases and medications on hypertension, diabetes, and dyslipidemia on NLR and renal dysfunction. However, renal diseases other than DKD and diseases that may affect NLR were eliminated as much as possible. Nevertheless, the demographics and referral source may limit generalization.

## Conclusions

This study suggested that baseline NLR might be a surrogate marker of early eGFR decline rate in diabetic outpatients. The underlying mechanisms behind this relationship are completely unknown, and these factors seem to be independent of baseline confounding factors, such as age, gender, smoking status, alcohol consumption, history of CVD, hypertension, lipids, HbA1c, and SUA. Further studies are needed to evaluate whether baseline NLR is a useful marker to predict the incidence of early renal function decline.

## Declarations

### Authors' contributions

TA and RK participated in the design of the study, performed the statistical analysis and drafted the manuscript. TA, RK, DN, and AK contributed to the acquisition and interpretation of data. TA, RK, DN, and TK contributed to the conception and design of the statistical analysis. All authors read and approved the manuscript.

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### Competing interests

The authors declare that they have no competing interests.

### ***Availability of data and materials***

The data from this study can be acquired from the corresponding author upon reasonable request.

### ***Consent for publication***

Not applicable.

### ***Ethics approval and consent to participate***

This study conformed to the guidelines of the Declaration of Helsinki, and the study procedures were reviewed and approved by the medical research ethics committee of Ehime University Graduate School of Medicine. Each patient agreed to participate and signed the informed consent form.

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## Table

**Table 1. Baseline characteristics of subjects categorized by tertiles of baseline NLR.**

Baseline Characteristics N = 365	Tertiles of baseline NLR			P-value*
	1 <sup>st</sup> : 0.65-1.56 N = 121	2 <sup>nd</sup> : 1.57-2.33 N = 123	3 <sup>rd</sup> : 2.34-15.3 N = 121	
(Male, %)	53.7	49.6	52.9	0.792
(years)	73 ± 11	75 ± 10	77 ± 11	<b>0.042</b>
Body mass index (kg/m <sup>2</sup> )	25.2 ± 3.8	24.8 ± 3.3	23.3 ± 3.8	<b>&lt;0.001</b>
≥ 2 diabetes (%)	95.0	100	97.5	<b>0.044</b>
Onset of diabetes (years)	12.2 ± 10.0	11.2 ± 8.5	11.9 ± 8.3	0.647
Smoking status † (%)	62.0/28.1/2.5/7.4	69.1/26.0/3.3/1.6	62.0/30.6/1.7/5.8	0.404
Any alcohol consumption ‡ (%)	66.1/6.6/19.0/8.3	67.5/4.1/22.8/5.7	69.4/5.0/15.7/9.9	0.695
Cardiovascular disease (%)	31.4	33.3	33.1	0.942
Systolic blood pressure (mmHg)	144 ± 20	145 ± 20	140 ± 19	0.074
Diastolic blood pressure (mmHg)	74 ± 11	72 ± 14	70 ± 11	<b>0.030</b>
Hypertensive medication (%)	69.4	78.9	71.1	0.205
Total cholesterol (mg/dL)	61 ± 16	56 ± 15	60 ± 18	0.075
LDL cholesterol (mg/dL)	132 ± 31	137 ± 35	124 ± 32	<b>0.010</b>
Lipidemic medication (%)	36.4	32.5	30.6	0.623
Hemoglobin A1c (%)	6.5 (6.2-7.4)	6.6 (6.2-7.1)	6.7 (6.2-7.2)	0.787
Diabetic medication (%)	82.6	79.7	87.6	0.246
Uric acid (mg/dL)	5.5 ± 1.3	5.3 ± 1.2	5.1 ± 1.3	0.127
Uric acid lowering medication (%)	9.1	7.3	5.8	0.617
CKD stage # (%)	76.0/20.7/3.3	65.9/26.8/7.3	66.9/23.1/9.9	0.198

neutrophil to lymphocyte ratio; HDL, high-density lipoprotein; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate. †Smoking status was defined as the number of cigarette packs per day multiplied by the number of years smoked (pack-year), and the participants were classified into never-smokers, past smokers, light smokers (<20 pack-year) and heavy smokers (≥20 pack-year). ‡Drinking status was measured using a Japanese liquor unit which corresponds to 22.9g of ethanol (never-drinker, light-drinker (<1 unit/day), moderate-drinker (1 to 2 unit/day)/heavy-drinker (≥2 unit/day)). UAE was classified into A1 stage (<30 mg/g creatinine), A2 stage (30 to 300 mg/g creatinine), and A3 stage (≥300 mg/g creatinine). Data presented are mean ± standard deviation. Data for hemoglobin A1c were skewed, are presented as median (interquartile range) values, and were log-transformed for analysis using ANOVA for continuous variables or the  $\chi^2$ -test for categorical variables. The bold typeface indicates significance.

## 2. 1.5-year eGFR decline rate of subjects categorized by tertiles of baseline NLR.

Characteristics	N = 365	Tertiles of baseline NLR			P-value*
		1 <sup>st</sup> : 0.65-1.56 N = 121	2 <sup>nd</sup> : 1.57-2.33 N = 123	3 <sup>rd</sup> : 2.34-15.3 N = 121	
Baseline eGFR (mL/min/1.73 m <sup>2</sup> )		67.6 ± 12.9	63.3 ± 13.8	61.9 ± 15.3	<b>0.004</b>
eGFR after 1.5 years (mL/min/1.73 m <sup>2</sup> )		65.1 ± 12.3	58.8 ± 17.4	58.8 ± 19.0	<b>0.007</b>
Annual eGFR decline rate (mL/min/1.73 m <sup>2</sup> /year)		<0.001	<0.001	>0.001	
Percentage of patients with eGFR decline rate		37 (30.6%)	32 (26.0%)	33 (27.3%)	<b>0.006</b>
> 0%		79 (65.3%)	67 (54.5%)	67 (55.4%)	
> 5%		5 (4.1%)	24 (19.5%)	21 (17.4%)	

bold typeface indicates significance. \*P-value: ANOVA for continuous variables or the  $\chi^2$ -test for categorical variables. \*\* P-value: paired t- test.

### Table 3. Relationships between baseline confounding factors and early eGFR decline rate.

Baseline characteristics	N=365	Rate of 1.5-year GFR decline $\leq 15\%$		
		Simple correlation	Multiple correlation §	
		r (p-value)	Model 1 $\beta$ (p-value)	Model 2 $\beta$ (p-value)
Gender (Men = 0, Women = 1)		0.480 (0.358)	0.036 (0.601)	-----
Body mass index		<b>0.168 (0.001)</b>	0.124 (0.050)	<b>0.156 (0.002)</b>
Presence of diabetes (type 1 = 0, type 2 = 1)		0.016 (0.762)	0.059 (0.297)	-----
Duration of diabetes (years)		0.063 (0.227)	0.007 (0.897)	-----
Smoking status		0.013 (0.798)	0.014 (0.789)	-----
Smoking status		0.093 (0.077)	0.084 (0.165)	-----
Cardiovascular disease (N = 0, Yes = 1)		0.059 (0.261)	0.022 (0.723)	-----
Systolic blood pressure		0.046 (0.382)	0.047 (0.387)	-----
Systolic blood pressure		<b>0.122 (0.019)</b>	0.075 (0.214)	-----
Antihypertensive medication (N = 0, Yes = 1)		0.019 (0.723)	0.004 (0.952)	-----
Total cholesterol		<b>0.116 (0.027)</b>	0.038 (0.496)	-----
HDL cholesterol		0.112 (0.033)	0.095 (0.096)	-----
Diabetic medication (No = 0, Yes = 1)		0.089 (0.088)	0.109 (0.051)	<b>0.111 (0.026)</b>
Diabetic medication (No = 0, Yes = 1)		0.027 (0.612)	0.010 (0.851)	-----
Hemoglobin A1c		0.064 (0.224)	<b>0.141 (0.013)</b>	-----
Diabetic medication (No = 0, Yes = 1)		0.029 (0.581)	<b>0.112 (0.044)</b>	-----
Plasma uric acid		0.042 (0.429)	0.010 (0.847)	-----
Uric acid lowering medication (No = 0, Yes = 1)		0.009 (0.861)	0.034 (0.509)	-----
Baseline eGFR		<b>0.280 (&lt;0.001)</b>	<b>0.263 (&lt;0.001)</b>	<b>0.258 (&lt;0.001)</b>
Tertiles of NLR		<b>0.157 (0.003)</b>	<b>0.109 (0.040)</b>	<b>0.120 (0.018)</b>
		-----	<b>0.164 (&lt;0.001)</b>	<b>0.127 (&lt;0.001)</b>

neutrophil to lymphocyte ratio; HDL, high-density lipoprotein; UAE, urinary albumin excretion. r, Pearson's correlation coefficient.  $\beta$ , standard coefficient.  $R^2$ , multiple coefficient of determination. Data for hemoglobin A1c, NLR, and UAE were log and log-transformed for analysis. § Adjusted for all confounding factors in Table 1 by multiple linear regression models (Model 1: forced entry method; Model 2: stepwise method). The numbers in bold indicate significance.

**Table 4. Non-adjusted and adjusted odds ratio (95% CI) of tertiles of baseline NLR for 1.5-year early eGFR decline rate.**

1.5-year eGFR decline rate <math>\leq 15\%</math> N = 365	Tertiles of baseline NLR					
	1 <sup>st</sup> : 0.65-1.56 N = 121 OR (95% CI)	2 <sup>nd</sup> : 1.57-2.33 N = 123 OR (95% CI)	P-value	3 <sup>rd</sup> : 2.34-15.3 N = 121 OR (95%CI)	P-value	P-trend
Non-adjusted	Preference	5.62 (2.07-15.3)	0.001	4.87 (1.77-13.4)	0.002	<0.001
Age-adjusted	Preference	5.41 (1.98-14.8)	0.001	4.25 (1.53-11.8)	0.006	0.001
Multivariate-adjusted §	Preference	3.94 (1.34-11.6)	0.013	3.93 (1.26-12.3)	0.018	0.003

OR, odds ratio; CI, confidence interval. § Multivariate-adjusted for all confounding factors by multiple logistic regression analysis.

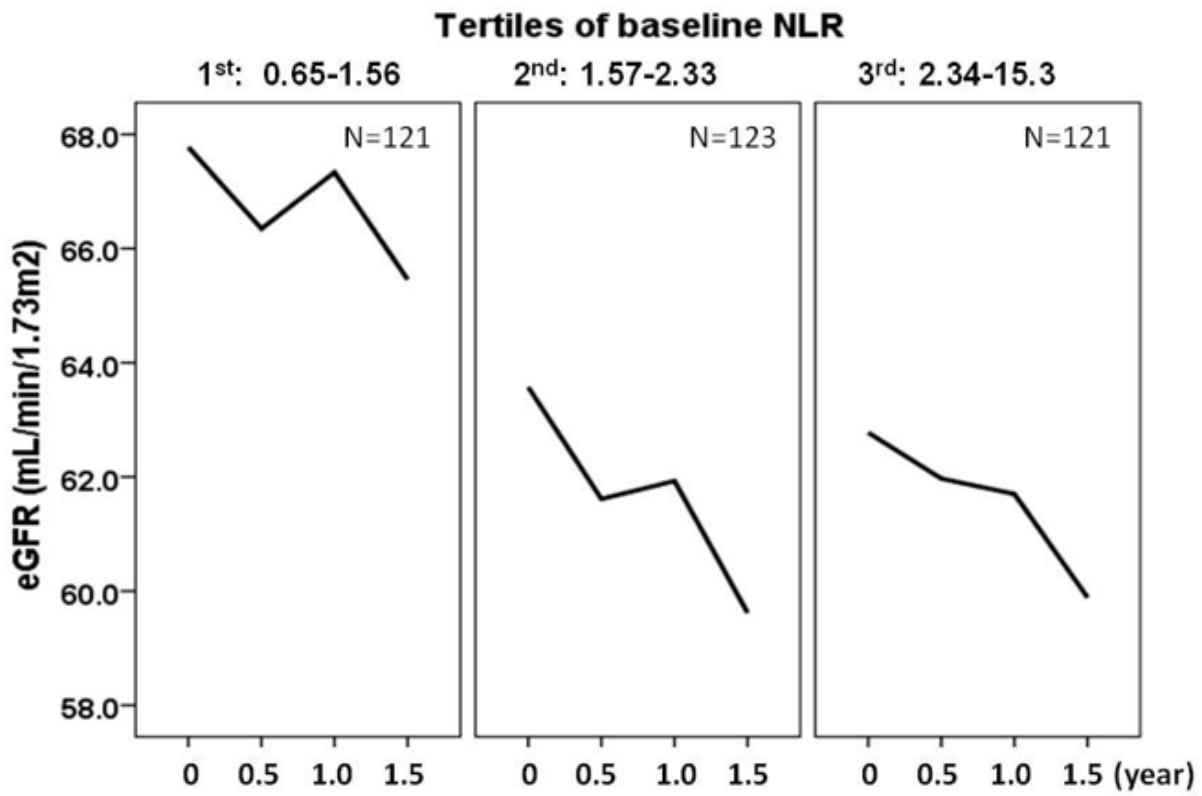
**Table 5. Non-adjusted and adjusted eGFR after 1.5-year of subjects categorized by tertiles of baseline NLR.**

eGFR after 1.5 years	N=365	Tertiles of baseline NLR			
		1 <sup>st</sup> : 0.65-1.56 N=121 Mean (95% CI)	2 <sup>nd</sup> : 1.57-2.33 N=123 Mean (95% CI)	3 <sup>rd</sup> : 2.34-15.3 N=121 Mean (95%CI)	P-value
Non adjusted		65.5 (62.8-68.2)	59.6 (56.9-62.4) <sup>b</sup>	58.7 (55.9-61.4) <sup>c</sup>	0.037
Age-adjusted		64.2 (61.8-66.6)	59.7 (57.3-62.0) <sup>a</sup>	60.0 (57.6-62.3) <sup>a</sup>	0.024
Multivariate-adjusted §		64.2 (62.1-66.3)	60.5 (58.5-62.6) <sup>a</sup>	59.1 (57.0-61.2) <sup>c</sup>	0.003

CI, confidence interval. § Multivariate-adjusted for all baseline confounding factors including eGFR.

<sup>a</sup>:  $p < 0.05$ , <sup>b</sup>:  $p < 0.01$ , <sup>c</sup>:  $p < 0.005$  versus 1<sup>st</sup> tertile of baseline NLR.

## Figures



**Figure 2**

Change in eGFR of subjects categorized by tertile of baseline NLR. The change in mean eGFR during 1.5 years of the 1st NLR tertile was more gradual compared with the 2nd and 3rd NLR tertiles.