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ORIGINAL ARTICLE

Neutrophil/lymphocyte ratio as a predictor of cardiovascular events in incident dialysis patients: a Japanese prospective cohort study

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Abstract
Background Previous studies have suggested that high neutrophil/lymphocyte ratios are related to worse outcome in patients with cardiovascular diseases. Patients with end-stage renal disease, especially those with inflammation, are at an increased risk of premature mortality, primarily because of cardiovascular disease. We aimed to clarify if high neutrophil/lymphocyte ratio is associated with increasing cardiovascular events in Japanese patients with end-stage renal disease.
Methods We enrolled 86 incident Japanese dialysis patients (58 men, age 58 ± 11 years) in a prospective cohort study. The median follow-up was for 38.7 months. The association between neutrophil/lymphocyte ratio at the start of dialysis therapy and clinical biomarkers was investigated. Relative risks and cumulative cardiovascular disease events were calculated.
Results The median neutrophil/lymphocyte ratio reported was 3.72. The duration from the start of the dialysis therapy to the first cardiovascular disease event was significantly shorter as a neutrophil/lymphocyte ratio increased (log-rank test, $P = 0.003$). The relative risk of cardiovascular disease events in patients with neutrophil/lymphocyte ratio > median to cardiovascular events in patients with the ratio < median as a reference was 3.02 (95 % CI 1.32–8.00) in a Cox proportional hazard model. The cumulative cardiovascular disease events during the observational period was higher in patients with neutrophil/lymphocyte ratio > median (23.0 events 100 person-years) than in patients with the ratio < median (6.8 events 100 person-years).
Conclusions A higher neutrophil/lymphocyte ratio is associated with increased risk of cardiovascular disease events and is a stronger predictor of future events.

Keywords Cardiovascular disease · Dialysis · Inflammation · Neutrophil/lymphocyte ratio

Introduction

Cardiovascular disease (CVD) is the leading cause of deaths in patients with chronic kidney disease (CKD); even young CKD patients have high mortality [1]. Identifying high-risk patients enables optimal therapy for prevention of CVD events, thus resulting in reduced premature mortality rates. Many risk factors and immune changes in the uremic milieu may contribute to the excessive risk of CVD in this population [2]. Whereas traditional risk factors, such as Framingham risk scores (age, lifestyle, left ventricular hypertrophy, dyslipidemia, hypertension, and diabetes mellitus), predict cardiovascular mortality in patients with mild CKD, not all risk factors are compatible in end-stage renal disease (ESRD) patients, which is so-called reverse epidemiology [3]. As novel risk factors for CVD, inflammation and protein-energy wasting (PEW) are highly prevalent in ESRD patients, and should play a far more important role in CVD in these patients than traditional risk

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factors [4]. The neutrophil/lymphocyte ratio (NLR) is easily calculated in peripheral blood. Since increasing neutrophil count reflects inflammation and lower lymphocyte counts may reflect general stress and malnutrition, NLR is hypothesized to be more sensitive at detecting patients at high risk for CVD. Indeed, NLR has been found to be a valuable index for predicting adverse clinical outcomes and estimates survival in various clinical settings in oncology [5] and cardiology practices [6–8]. Moreover, recently, NLR was associated with loss of renal function [9] and endothelial dysfunction [10] in CKD patients.

Therefore, in this study we evaluated the association between NLR and CVD events in Japanese ESRD patients who had just started renal replacement therapy (RRT).

Subjects and methods

Study design and patients

We enrolled 115 incident dialysis patients from June 2007 to February 2013 at Masuko Memorial Hospital and Meiyo Clinic in Aichi prefecture, Japan. This study was an analysis from an ongoing prospective cohort study approved by the Ethics Committee of Nagoya University Graduate School of Medicine (No 2012-0241); informed consent to participate in this study was obtained from all patients. We excluded patients older than 75 years of age, with acute infectious disease or severe liver dysfunction and those who were being administered steroids and/or immunosuppressants. The study therefore consisted of 86 patients (58 men and 28 women), with a mean age of 58 ± 11 years.

Baseline demographic and clinical data such as age, gender, primary cause of renal disease, and current medications were collected from the patients' records. Smoking habit and history of CVD, which was defined as cardiac, cerebrovascular, or peripheral vascular disease, were assessed during interviews. The primary causes of renal disease were glomerulonephritis ($n = 24$), nephrosclerosis ($n = 6$), diabetic nephropathy ($n = 42$) due to diabetes mellitus type 1 ($n = 4$) and type 2 ($n = 38$), polycystic kidney disease ($n = 4$), and other ($n = 2$) or unknown causes ($n = 8$). Among 79 patients who were started on HD, blood access in most cases was obtained by arteriovenous fistula ($n = 68$); five patients had received a graft, and seven had received a double lumen catheter into the jugular vein but showed no signs of infection. The remaining seven patients started on peritoneal dialysis (PD) and all received a peritoneal catheter in advance when PD was initiated. Subjective global nutritional assessment (SGA) was used to evaluate the patient's nutritional status [11]. In brief, each patient was given a score on the basis of their medical history, that is, weight loss, gastrointestinal symptoms, and functional capacity, and another score on the basis of a physical examination focused on the loss of subcutaneous fat and muscle, and the presence of edema. We classified the patients into three groups using the SGA score, A: well nourished, B: mild/moderately malnourished, and C: severely malnourished.

Blood sampling and laboratory analysis

Sample collection was performed at the beginning of a dialysis session in hemodialysis patients and at outpatient clinic in PD patients within 1 month of the dialysis initiation day, respectively. Complete blood cell count and differential leukocyte count were taken at the clinical laboratory in each facility using an automatic analyzer. Serum albumin, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, creatinine, intact parathyroid hormone (iPTH), ferritin, and C-reactive protein (CRP) concentrations were measured. Serum concentrations of interleukin (IL)-6, using samples kept frozen at −30 °C, were measured using a commercially available enzyme-linked immunosorbent assay kit (R & D systems, Inc., Minneapolis, MN).

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and/or median and interquartile range (25th to 75th percentiles). We divided the patients into four groups according to quartile value of NLR: quartile 1 with an NLR level of 1.19–2.78, (NLR lower), quartile 2 with an NLR level of 2.89–3.67, quartile 3 with an NLR level of 3.72–4.60, and quartile 4 with an NLR level of 4.66–10.75 (NLR higher). To evaluate baseline characteristics and laboratory biomarkers, comparisons of continual parameters between these four groups were performed with the analysis of variance (ANOVA). Nominal variables were tested using the χ^2 test. The duration from dialysis initiation to the first CVD event was analyzed with the Kaplan–Meier curve and differences were examined using the log-rank test. The Cox proportional hazard model was used to calculate relative risks (RR) of a CVD event after dialysis was initiated. The RRs with 95 % confidence intervals (CI) are shown, and analysis was adjusted by NLR, age, gender, and the presence of diabetes mellitus. The proportionality of hazards was examined graphically using log minus log survival curves. A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using statistical software JMP version 10.0.2 (SAS Campus Drive, Cary, NC, USA 27513).

Table 1 Baseline characteristics in this study

	Total	Quartile 1 NLR 1.19–2.78	Quartile 2 NLR 2.89–3.67	Quartile 3 NLR 3.72–4.60	Quartile 4 NLR 4.66–10.75	*P* value
Number	86	21	22	22	21	
Male (%)	58 (67.4)	14 (66.7)	11 (50.0)	18 (81.8)	15 (71.4)	0.15
Age (year)	57.6 ± 11.5	53.9 ± 13.6	59.6 ± 12.1	54.9 ± 11.4	62.0 ± 6.2	0.06
Body mass index (kg/m^2)	22.0 ± 4.0	21.3 ± 2.7	21.6 ± 2.9	22.5 ± 3.0	22.6 ± 6.4	0.66
Diabetes mellitus (%)	42 (48.8)	10 (47.6)	10 (45.5)	11 (50.0)	11 (52.4)	0.97
Systolic blood pressure (mmHg)	155.6 ± 23.4	158.4 ± 19.1	154.8 ± 27.0	160.3 ± 20.7	148.8 ± 25.6	0.39
Diastolic blood pressure (mmHg)	83.1 ± 12.6	85.9 ± 12.8	79.9 ± 13.5	87.3 ± 10.2	79.4 ± 12.6	0.08
Smoking (%)						0.02*
Current	16 (18.6)	7 (33.3)	0 (0.0)	5 (22.7)	4 (19.1)	
Ex-smokers	27 (31.4)	4 (19.1)	6 (27.3)	8 (36.4)	9 (42.9)	
Medication (%)						
ACE-i/ARBs	54 (62.8)	13 (61.9)	16 (72.7)	13 (59.1)	12 (57.1)	0.71
Statins	26 (30.2)	6 (28.6)	5 (25.0)	10 (45.4)	5 (23.8)	0.39
Vitamin D	49 (57.0)	6 (28.6)	13 (59.1)	16 (72.7)	14 (66.7)	0.02*
ESA	70 (81.4)	17 (81.0)	20 (90.9)	16 (76.2)	17 (81.0)	0.60
Malnutrition (%)						0.98
SGA category B (mild-moderate)	51 (60.0)	13 (61.9)	14 (63.6)	11 (52.4)	13 (61.9)	
SGA category C (severe)	11 (12.9)	3 (14.3)	2 (9.1)	3 (14.3)	3 (14.3)	
History of CVD	21 (24.4)	4 (19.1)	3 (13.6)	6 (27.3)	8 (38.1)	0.26
Hemoglobin (g/dl)	8.8 ± 1.3	8.7 ± 1.5	8.8 ± 1.1	8.7 ± 1.5	9.0 ± 1.2	0.83
White blood cell ($\times 10^3$/mm^3)	6.0 ± 2.0	5.0 ± 2.3	6.0 ± 2.3	5.9 ± 1.6	7.0 ± 2.3	0.01*
Neutrophils ($\times 10^3$/mm^3)	4.1 ± 1.7	3.0 ± 1.0	3.9 ± 1.4	4.1 ± 1.2	5.3 ± 2.1	0.0001*
Lymphocytes ($\times 10^3$/mm^3)	1.1 ± 0.4	1.4 ± 0.4	1.2 ± 0.5	1.0 ± 0.3	0.9 ± 0.2	<0.0001*
Neutrophils (% of WBC)	67.2 ± 7.8	59.3 ± 4.6	65.0 ± 5.5	69.0 ± 4.7	75.6 ± 5.6	<0.0001*
Lymphocytes (% of WBC)	19.7 ± 6.3	28.3 ± 4.5	20.5 ± 2.4	17.0 ± 1.6	13.0 ± 2.1	<0.0001*
Platelet ($\times 10^4$/mm^3)	20.6 ± 5.9	19.9 ± 5.6	22.0 ± 5.1	19.3 ± 6.2	21.2 ± 6.7	0.43
Albumin (g/dL)	3.5 ± 0.5	3.5 ± 0.6	3.5 ± 0.6	3.4 ± 0.6	3.5 ± 0.4	0.91
Total cholesterol (mg/dL)	161.7 ± 40.8	156.7 ± 41.5	173.7 ± 38.4	150.0 ± 38.8	168.3 ± 43.4	0.26
HDL cholesterol (mg/dL)	44.5 ± 14.2	43.0 ± 15.2	48.4 ± 16.6	42.1 ± 9.7	44.3 ± 14.3	0.50
LDL cholesterol (mg/dL)	93.0 ± 30.7	93.1 ± 27.8	100.8 ± 32.8	79.8 ± 33.8	96.7 ± 26.3	0.22
Triglycerides (mg/dL)	109.7 ± 55.5	101.7 ± 63.6	103.6 ± 42.8	112.8 ± 68.8	121.0 ± 64.4	0.66
Uric acid (mg/dL)	8.4 ± 2.1	8.1 ± 2.6	7.9 ± 1.7	8.3 ± 1.9	9.1 ± 1.9	0.29
Creatinine (mg/dL)	10.2 ± 3.4	10.6 ± 2.5	9.3 ± 3.3	10.1 ± 3.1	10.8 ± 4.5	0.47
Intact PTH (pg/mL)	344.4 ± 252.9	429.9 ± 255.7	323.5 ± 243.6	292.1 ± 144.1	333.2 ± 330.5	0.33
Ferritin (ng/mL)	148.9 ± 180.8	162.7 ± 190.1	130.6 ± 176.2	182.9 ± 230.3	118.9 ± 105.8	0.64
Log CRP	−2.16 (−6.91–1.89)	−2.86 (−3.87 to −1.60)	−2.93 (−3.70 to −1.62)	−2.31 (−2.85 to −1.02)	−1.47 (−2.87–0.05)	0.047*
Log IL-6	1.27 (−0.71–3.70)	1.02 (0.25–1.54)	1.17 (0.61–1.50)	1.05 (0.70–1.34)	1.82 (1.06–2.03)	0.177

NLR Neutrophil/lymphocyte ratio, *ACE-i/ARBs* angiotensin converting enzyme inhibitor/Angiotensin II Receptor Blockers, *ESA* erythropoiesis-stimulating agent, *SGA* Subjective global assessment, *CVD* cardiovascular disease, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *PTH* parathyroid hormone, *CRP* C-reactive protein, and *IL*-6 interleukin-6

*$P < 0.05$

Results

Characteristics and laboratory biomarkers

A total of 86 ESRD patients were enrolled this study. The clinical characteristics and laboratory biomarkers selected well-established risk factors for CVD at baseline and are reported in Table 1. They were divided according to the quartile value of NLR. The study consisted of 58 men (67.4 %), with an average age of 57.6 ± 11.5 years. White blood cell counts (WBC) ($P = 0.01$) and serum CRP levels ($P = 0.047$) were gradually higher in proportion to higher NLR. Other biomarkers did not differ between the groups.

Cardiovascular disease outcomes

We followed the patients until death, transfer to other clinic, renal transplantation, or until follow-up that ended in February 2013. The median follow-up was for 38.7 months (range, 1–68.9 months). During follow-up, nine patients died (infectious disease: $n = 2$, sudden death: $n = 4$, myocardial infarction: $n = 1$, cancer: $n = 1$, liver failure: $n = 1$), and eight patients were unable to take part in the follow-up survey because two patients had undergone a transplant and six were transferred to another clinic. In total, 39 CVD events were recorded, including four cases of myocardial infarction, 15 of angina, six of stroke, three transient ischemic attacks, eight of peripheral arterial disease, and three sudden deaths.

The free time of CVD event after the start of dialysis therapy

Kaplan–Meier curves of the period without CVD event showed (Fig. 1) that the period from the start of dialysis therapy to the first CVD event was significantly shorter as the NLR increased (log-rank test, 13.75, $P = 0.003$). Next, we calculated the RR of the first CVD event in Cox proportional hazard model (Table 2). Cox proportional hazard crude analysis showed that the patients with a high NLR had an increased CVD event risk [RR: 3.02 (95 % CI 1.34–7.43)]. Although the patients with high WBC and neutrophil counts also had increased risk, the RR of NLR was the highest among these. When adjusting for age, gender, and diabetes, NLR showed a persistent risk for CVD [RR: 2.54 (95 % CI 1.09–6.43)]. Moreover, we divided the patients into four groups according to quartile value of NLR: quartile 1 with an NLR level of 1.19–2.78, (NLR lower), quartile 2 with an NLR level of 2.89–3.67, quartile 3 with an NLR level of 3.72–4.60, and quartile 4 with an NLR level of 4.66–10.75 (NLR higher). When we calculated RR using quartile 1 as a reference, the patients with higher NLR had an increased CVD event risk, followed by quartile 2 [RR: 2.44 (95 % CI 0.92–7.12)], quartile 3 [RR: 2.90 (95 % CI 1.09–8.46)], and quartile 4 [RR: 9.61 (95 % CI 2.56–62.38)] (Table 3).

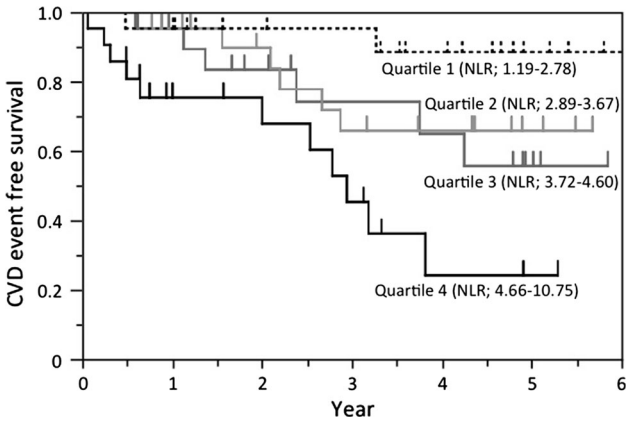

Fig. 1 Kaplan–Meier curves showing occurrence of the first CVD event from start of dialysis therapy in patients divided into four groups according to quartile. Log-rank test: 13.75, $P = 0.003$. *NLR* neutrophil/lymphocyte ratio

Table 2 Relative risks and 95 % CI for factors predicting the CVD events

Parameters	Relative risk (95 % CI)	*P* value
Unadjusted		
NLR > median	3.02 (1.34–7.43)	0.007*
White blood cell count > median	2.23 (1.01–5.15)	0.05*
Neutrophil count > median	2.64 (1.17–6.52)	0.02*
Lymphocyte count > median	0.92 (0.41–2.02)	0.83
Adjusted		
NLR > median	2.54 (1.09–6.43)	0.03*
Age > 60 years	2.18 (0.95–5.30)	0.06
Gender, man	3.88 (1.28–16.79)	0.01*
Diabetes mellitus, presence	6.07 (2.37–18.72)	<0.0001*

Crude relative risks and adjusted relative risks were calculated in a Cox proportional hazard model

CVD cardiovascular disease, *NLR* neutrophil/lymphocyte ratio, and *CI* confidence interval

*$P < 0.05$

Prediction of future CVD events using NLR

As stated previously, the adjusted RR in patients with NLR > median for developing CVD events in patients, with NLR < median as a reference, was 2.54. To evaluate the performance of NLR compared with other clinical biomarkers for inflammation and nutritional status, we also calculated the adjusted RR in patients with elevated levels of CRP, IL-6, and serum albumin and SGA category. In Cox proportional hazard

Table 3 Relative risks and 95 % CI for factors predicting CVD events in groups divided according to NLR quartiles

Parameters	Relative risk (95 % CI)	*P* value
Quartile 1 (1.19–2.78) (Reference)	1	
Quartile 2 (2.89–3.67)	2.44 (0.92–7.12)	0.07
Quartile 3 (3.72–4.60)	2.90 (1.09–8.46)	0.03*
Quartile 4 (4.66–10.75)	9.61 (2.56–62.38)	0.0004*

Relative risks and 95 % CI were calculated; the lowest quartile (Quartile 1) considered as a reference in a Cox proportional hazard model. Not adjusted

CVD cardiovascular disease, *CI* confidence interval

*$P < 0.05$

Table 4 Comparison of relative risks and 95 % CI for factors predicting the CVD events among representative laboratory markers for inflammation and nutritional status

Parameters	Relative risk (95 % CI)	*P* value
NLR > median	2.54 (1.09–6.43)	0.03*
CRP > median	1.39 (0.61–3.24)	0.43
Interleukin-6 > median	1.12 (0.51–2.59)	0.78
Serum albumin > median	0.87 (0.35–2.09)	0.76
SGA, category BC vs A	1.72 (0.58–7.33)	0.35

All Cox proportional hazard models were adjusted by age (>60 years), gender (man), and presence of diabetes mellitus

CVD cardiovascular disease, *NLR* neutrophil/lymphocyte ratio, *CI* confidence interval, *CRP* C-reactive protein, and *SGA* subjective global assessment

*$P < 0.05$

models adjusted by age, gender, and the presence of diabetes mellitus with CRP, IL-6, and serum albumin levels less than the median values as the reference and SGA category A as the reference, the RR in patients with CRP levels, IL-6, and serum albumin levels more than the median, and the SGA category BC were [RR: 1.39 (0.61–3.24)], [RR: 1.12 (0.51–2.59)], [RR: 0.87 (0.35–2.09)], and [RR: 1.72 (0.58–7.33)], respectively (Table 4).

Cumulative CVD events during the total observation period

Twenty-five patients experienced CVD events during the observational period: a single event occurred in 17 patients, four patients experienced two events, two patients had three events, and two patients had repeated CVD events four times. Therefore, a total of 39 CVD events were recorded with cumulative incidence of CVD events during the observation period. CVD events were more frequent in patients with NLR > median than that in patients with NLR < median (NLR > median: 23.0, NLR < median: 6.8, events per 100 person-years).

Discussion

In this study, we evaluated the prognostic value of NLR for CVD events in Japanese ESRD patients who had just started RRT. The main finding of this study was that higher NLR was associated with an increased risk for CVD events, both shortening free period and frequency during the follow-up time. Moreover, patients with higher NLR had an increased RR of CVD after adjusting for age, gender, and diabetes. When compared, prognostic power for CVD event among NLR, inflammatory markers, such as CRP and IL-6, and nutritional markers, such as serum albumin and SGA, NLR was the most superior marker for CVD.

NLR has been getting widely used to identify high-risk patients with various illnesses, including cancer and CVD [5–8]. It has been reported that a high NLR value is associated with the severity of coronary artery disease and 3-year survival in a large cohort of 3,005 patients undergoing coronary angiography [6]. Further, an increased NLR showed high risk for severe ischemic events in a retrospective study of peripheral arterial occlusive disease patients [8]. Recently, in an asymptomatic general population cohort of 7,363 subjects, NLR was reported to independently predict ischemic heart disease mortality [7]. In the oncology field, a systematic review of over 60 studies reported that NLR was elevated in patients with cancer of more advanced and aggressive stage, and that patients with high NLRs might present a particularly high-risk population [5]. Thus far, the association between NLR and CVD has been investigated less in CKD patients. In 2013, two cross-sectional studies showed the positive association between NLR and inflammatory markers including IL-6 and CRP and negative association between NLR and serum albumin in predialysis and dialysis patients [12], and elevated NLR in renal transplant patients compared with healthy subjects [13]. Kocyigit et al. demonstrated that patients with CKD stage 4 with a high NLR had worse prognosis and faster progression to RRT [9]. Solak et al. reported that a high NLR was related to endothelial dysfunction and increased CVD events in 225 Caucasian patients before dialysis [10]. We believe that the current study is the first report to demonstrate the prognostic ability of NLR for CVD events in ESRD patients just started on RRT.

In ESRD patients, the most widely studied marker associated with PEW and inflammation is CRP [14, 15]. In this study, a high CRP level as well as a high IL-6 level failed to predict worse CVD outcome. CRP levels may be not enough to detect low-grade inflammation, especially in Japanese CKD patients because their CRP levels seem to be much lower than those in Western CKD patients [16, 17]. Monitoring of CRP is still not a routine measurement in dialysis centers worldwide [14]. SGA is a reliable tool

for assessing PEW as per the guidelines released by the National Kidney Foundation Kidney Disease/Dialysis Outcomes and Quality Initiative in 2000 that recommended the use of SGA for assessing PEW of dialysis patients [18]. Mutsert et al. reported that PEW at 3 and 6 months after the start of dialysis therapy assessed with SGA can indicate increased mortality in Dutch incident dialysis patients [19]. We speculate that because we assessed SGA quite shortly after the start of the dialysis therapy (within 1 month) in our study, patients with subclinical PEW may have been missed, because of statistical significance between SGA and CVD events could not be reached. Moreover, serum albumin level also did not predict CVD events in our study. Similarly, serum albumin levels shortly after the start of the dialysis therapy may have been interfered by volume overload. Therefore, NLR should be suitable screening marker for patients at the start of dialysis therapy because it can be easily calculated, needs little or no added cost, and could enable the detection of high-risk patients who would require further examination.

Some limitations of this study should be acknowledged. First, although we excluded patients who were currently using steroid and immunosuppressive drugs, we enrolled patients who had suffered from diseases with alteration in NLR, such as asymptomatic infections, cancer, and collagen diseases. However, we believe the predictive power of NLR is meaningful in overall ESRD patients with various complications. Second, we checked NLR at only one time close to the start of dialysis, while serial measurements would have been more informative. Finally, this study included both hemodialysis patients and PD patients because we tried to verify NLR as the prognostic value in whole patients with end-stage renal disease. The difference in modality of dialysis might be influential in CVD events after initiation of dialysis.

In conclusion, this study demonstrated that a high NLR was associated with the increased risk of CVD in Japanese ESRD patients and that NLR was a stronger predictor than other common inflammatory markers. Although further study is needed, NLR may be useful and inexpensive marker for identifying high risk for CVD.

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Conflict of interest The authors have declared that no conflict of interest exists.

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