SPANDIDOS PUBLICATIONS

EXPERIMENTAL AND THERAPEUTIC MEDICINE 20: 1105-1114, 2020

Neutrophil-to-lymphocyte ratio and red blood cell distribution width-to-platelet ratio predict cardiovascular events in hemodialysis patients

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Received March 19, 2019; Accepted July 12, 2019

DOI: 10.3892/etm.2020.8756

Abstract. Cardiovascular diseases are among the primary causes of decreased quality of life as well as mortality of hemodialysis patients with end-stage renal disease. The aim of the present study was to evaluate the predictive value of the red blood cell distribution width (RDW)-to-platelet ratio (RPR) and neutrophil-to-lymphocyte ratio (NLR) regarding the occurrence or development of cardiovascular events in hemodialysis patients, as well as the prognostic value of this metric. A total of 219 hemodialysis patients with cardiovascular events (HCE group) and 276 hemodialysis patients with no cardiovascular events (HNCE group) were enrolled in the present study. The clinical characteristics and laboratory parameters on admission, including RDW, as well as neutrophil, lymphocyte and platelet counts, were recorded. The NLR and RPR were increased in the HCE group compared with those in the HNCE group and there was a positive association between the NLR or RPR and the incidence of cardiovascular events in hemodialysis patients. In the receiver operating characteristics curve analysis, the area under the curve of the RPR for predicting cardiovascular events in hemodialysis patients was 0.88, while that for the NLR was 0.84. The sensitivity and specificity of the RPR for predicting cardiovascular events in hemodialysis patients were 0.87 and 0.82 respectively, and for the NLR, they were 0.75 and 0.79, respectively. The RPR was an independent risk factor for the prognosis regarding cardiovascular events in hemodialysis patients. In addition, the NLR and RPR were correlated with brain natriuretic peptide (BNP), cardiac troponin I (cTnI), creatine kinase isoenzyme-MB (CK-MB), and associated with ST segment changes in HCE patients. In conclusion, it was possible to predict the incidence of cardiovascular events in hemodialysis patients using the NLR and RPR, while the RPR had a better sensitivity and specificity than the NLR. The RPR was an independent risk factor for the prognosis regarding cardiovascular events in hemodialysis patients. These routinely available parameters should be considered as novel diagnostic markers for the occurrence and development of cardiovascular events in hemodialysis patients and their prognosis.

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Key words: hemodialysis, cardiovascular events, red blood cell distribution width to platelet ratio, neutrophil to lymphocyte ratio, prognosis

Introduction

Chronic kidney disease has an incidence of ~10.8% and poses a threat to human health (1,2). Although chronic kidney disease may be effectively treated, a considerable number of patients with end-stage renal disease (ESRD) remain and hemodialysis is the primary alternative treatment option (3,4). However, hemodialysis is associated with numerous serious complications. Cardiovascular events are one of the primary causes of decreased quality of life and ultimately death in hemodialysis patients with ESRD (5,6). Numerous studies have demonstrated that the risk of death from cardiovascular events in patients with ESRD is >11 times greater compared with that in patients who did not receive any dialysis (7). After correction for risk factors, including hypertension, diabetes and hyperlipidemia, hemodialysis patients still have an elevated risk of cardiovascular events (8,9).

The neutrophil-to-lymphocyte ratio (NLR), defined as the ratio of the percentage of neutrophils to the percentage of lymphocytes, has been widely used to assess the prognosis

of patients with specific types of tumor, appendicitis and post-operative cardiovascular disease (10,11). Several studies have reported that the NLR may reflect the inflammatory state of hemodialysis patients, and may be associated with cardiovascular events in hemodialysis patients (12,13). The red blood cell distribution width (RDW)-to-platelet ratio (RPR) and NLR are routinely used biochemical parameters. Several studies have reported that increased RDW is an independent risk factor for cardiovascular death in hemodialysis patients (14,15). In addition, platelets serve an important role in the occurrence and development of cardiovascular events (16). The RPR, a combination of the two independent parameters, may be of high predictive value regarding cardiovascular events in hemodialysis patients.

The present study determined the predictive value of the NLR and RPR regarding the occurrence and development of cardiovascular events in hemodialysis patients, as well as their prognosis. The clinical data of 555 patients who were maintained on hemodialysis were retrospectively analyzed and the association between the NLR or RPR of dialysis patients and cardiovascular events, and the early diagnostic and prognostic value of these parameters was determined.

Materials and methods

Patients. In the present study, the clinical data of 555 hemodialysis patients who were undergoing dialysis at the First People's Hospital of Yancheng (Yancheng, China) and the Fifth People's Hospital of Wuxi (Wuxi, China) between May 2015 and March 2018 were analyzed. All patients had ESRD. The patients were divided into four groups: Patients on hemodialysis that experienced cardiovascular events (HCE) in the original cohort (n=219); those on hemodialysis that experienced cardiovascular events in the validation cohort (n=30); those with no cardiovascular events (HNCE) in the original cohort (n=276); and those on hemodialysis that experienced cardiovascular events in the validation cohort (n=30). The specific cardiovascular events included were angina pectoris, acute myocardial infarction, symptomatic heart failure and arrhythmia, and all patients were clinically diagnosed as presenting with one of these diseases.

The inclusion criteria were as follows: i) Patients received regular dialysis for >3 months; and ii) patients did not receive any other treatments during the same period. The following exclusion criteria were applied: i) Serious complications of any other organs; ii) patients who had previously undergone kidney transplantation and immunosuppressive therapy; iii) patients with an infection, blood transfusion or receiving immunosuppressive drugs, as this may have affected the inflammatory response within the 3 months; iv) patients who were pregnant; v) patients who had a mental illness; and vi) patients with diabetes, hypertension, or any other diseases; or smoking and other lifestyle choices that may have affected 'inflammation-malnutrition-atherosclerosis' and thus influenced the NRL and RDW.

The follow-up period was 24 months and all the patients were followed up using medical records and telephone interviews. The follow-up endpoints were all-cause death or new cardiovascular events (angina pectoris, acute myocardial infarction or acute cardiac insufficiency), stroke (hemorrhage or ischemia) and peripheral vascular events. If a patient had multiple cardiovascular events, the first cardiovascular event was considered the endpoint.

Hemodialysis treatment. The patients of the two groups were given dialysis for 12 h per week. The blood flow was maintained at 250-280 ml/min and the dialysate flow was maintained at 500-800 ml/min. Low molecular weight heparin was used to prevent coagulation. Dialysis management was performed according to the Guidelines for Clinical Practice of Chronic Kidney Disease and Dialysis (17).

Clinical information and laboratory examination. The clinical characteristics and laboratory test results on admission, including hemoglobin, neutrophil, lymphocyte and white blood cell (WBC) counts, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), total bilirubin (TBIL), albumin (ALB), creatinine (CR), blood urea nitrogen (UREA), uric acid (UA), parathyroid hormone (PTH), total cholesterol (TC), calcium (CA), platelet counts (PLT), hemoglobin (Hb), brain natriuretic peptide (BNP), creatine kinase isoenzyme-MB (CK-MB), cardiac troponin I (cTnI), glomerular filtration rate (GFR) and results of the electrocardiogram (ECG) examination in all patients were recorded. All patients were examined using a Philips iE33 real-time three-dimensional color doppler echocardiograph (Philips Medical Systems, Inc.) at one the day after dialysis. Systolic pulmonary pressure (SPAP), left ventricular diastolic diameter (LVDd), dialyzer clearance of urea (K), dialysis time (t), volume of distribution of urea (V), efficiency criteria for hemodialysis treatment (Kt/V), left ventricular systolic diameter (LVDs) and left atrial diameter were measured every 6 months and the average value was used.

Statistical analysis. Statistical analyses were performed using GraphPad Prism version 7 (GraphPad Software, Inc.). Values are expressed as the mean ± standard deviation when data were normally distributed or as the median and range if the distribution was skewed. Comparisons between groups were performed using analysis of variance. Correlation analyses between variables were performed using Pearson's rank correlation coefficient analysis. $P<0.05$ was considered to indicate a statistically significant difference. Receiver operating characteristic (ROC) curves were plotted and areas under the ROC curves (AUCs) were calculated to determine the discrimination threshold of each marker. The appropriate cut-off points for the optimal combination of sensitivity and specificity were determined using Youden's J statistics. Binary logistic regression analyses were used to determine factors associated with the incidence of cardiovascular events in hemodialysis patients. Binary logistic regression analyses were used to calculate the adjusted odds ratio and 95% confidence interval values based on maximum likelihood estimation of NLR and RPR.

Results

Patient characteristics. From a total of 715 hemodialysis patients, a cross-sectional group of 495 patients were enrolled

Table I. Characteristics of the patients enrolled.

Variable	HCE group (n=219)	HNCE group (n=276)	P-value
Age (years)	50.25 (29-79)	51.34 (28-81)	0.102
Gender (F/M)	124/95	166/110	0.117
Time of hemodialysis (months)	22 (9-43)	24 (10-47)	0.687
Hb (g/l)	75.24±13.11	94.53±20.11	0.036
Neutrophil ratio (%)	82.61±3.11	68.22.1±2.98	0.025
Lymphocyte count (10^9/l)	0.75±0.36	2.75±1.23	0.042
WBC (10^9/l)	13.22±3.65	7.11±2.17	0.032
PLT (10^9/l)	85.12±14.27	142.14±25.19	0.017
ALT (U/l)	30.12±8.72	29.92±7.22	0.513
AST (U/l)	67.02±4.75	16.06±4.09	0.029
GGT (U/l)	38.00 (27.00-44.00)	35.00 (23.00-41.00)	0.978
Kt/V	1.22±0.14	1.59±0.29	0.033
ALB (g/l)	34.02±3.21	45.56±4.29	0.021
TBIL (μmol/l)	8.98±3.87	9.04±4.12	0.679
Ca (mmol/l)	2.24±0.13	2.27±0.19	0.752
P (mmol/l)	2.12±0.64	1.79±0.52	0.035
PTH (pmol/l)	19.51 (7.12, 59.45)	12.44 (7.25, 29.45)	0.022
UREA (mmol/l)	29.61±5.94	19.61±4.11	0.029
CR (μmol/l)	882.21±113.21	712.61±103.61	0.039
UA (μmol/l)	412.01±97.45	389.01±87.11	0.895
TC (mmol/l)	3.98±0.36	3.83±0.32	0.357
GFR (ml/min x 1.73 m^2)	2.7 (0.72, 3.15)	2.6 (0.71, 3.2)	0.962
WBC (10^9/l)	13.22±3.65	7.11±2.17	0.032
BNP (pg/ml)	7565±873.12	4456±421.27	<0.001
CK-MB (U/l)	22.05±5.22	19.71±4.13	0.002
cTnI (ng/ml)	14.25±3.88	5.71±1.97	<0.001
LVDd (cm)	5.65±0.69	5.15±0.44	0.042
LVDs (cm)	3.89±0.43	3.14±0.35	0.007
SPAP (mmHg)	41.22±6.19	32.24±1.35	0.009
Left atrial diameter (cm)	4.29±0.47	3.80±0.39	0.005

Values are expressed as n (%) or the mean ± standard deviation. HCE group, hemodialysis patients with cardiovascular events; HNCE group, hemodialysis patients with no cardiovascular events. Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; WBC, white blood cells; UREA, urea nitrogen; CR, creatinine; UA, uric acid; TC, total cholesterol; PTH, parathyroid hormone; TBIL, total bilirubin; ALB, albumin; PLT, platelets; GFR, glomerular filtration rate; BNP, brain natriuretic peptide; CK-MB, creatine kinase isoenzyme-MB; cTnI, cardiac troponin I; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; SPAP, systolic pulmonary arterial pressure; Kt/V, urea clearance index; P, phosphorus.

in the original cohort. Fig. 1 presents a flow chart for the screening of hemodialysis patients from the two hospitals. The demographics, characteristics and biochemical parameters of HCE patients and HNCE patients are summarized in Table I. No significant differences between the two groups were identified regarding age, sex, time of hemodialysis, GGT, CA, UA, TC, ALT, TBIL and GFR. However, the average levels of serum AST, phosphorus, PTH, UREA, CR, neutrophil ratio, WBC, BNP, CK-MB, cTnI, LVDd, LVDs, SPAP and left atrial diameter in the HCE group were significantly higher compared with those in the HNCE group. The levels of ALB, Hb, Kt/V, lymphocyte count and PLT were significantly lower compared with those in the HNCE group.

NLR and RPR may be used to predict cardiovascular events in hemodialysis patients. The NLR and RPR of each group were determined and it was revealed that in the HCE group, these two ratios were significantly higher compared with those in the HNCE group (P<0.05; Fig. 2). ROC analysis was then performed for the NLR or RPR regarding the prediction of cardiovascular events in hemodialysis patients. The AUC of the RPR and NLR for predicting cardiovascular events in hemodialysis patients was 0.88 and 0.84, respectively. According to the cutoff values of RPR (0.075) and NLR (5.58), the sensitivity and specificity of the RPR for predicting cardiovascular events in hemodialysis patients were 0.87 and 0.82 respectively, and for NLR, they were 0.75 and 0.79, respectively (Fig. 3).

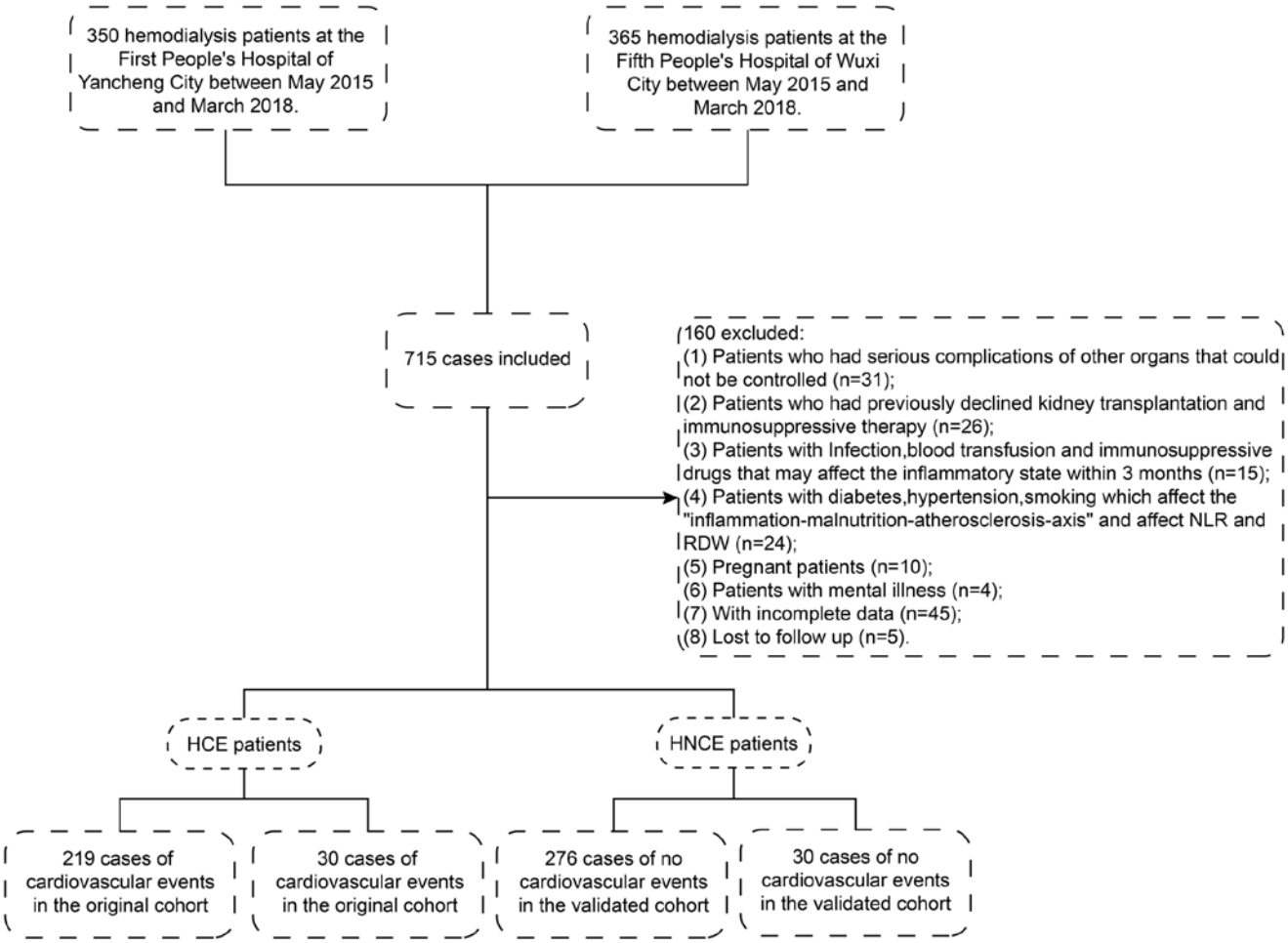

Figure 1. Screening flow chart for inclusion of hemodialysis patients. RDW, red blood cell distribution width; HCE group, hemodialysis patients with cardiovascular events; HNCE group, hemodialysis patients with no cardiovascular events; NLR, neutrophil-to-lymphocyte ratio.

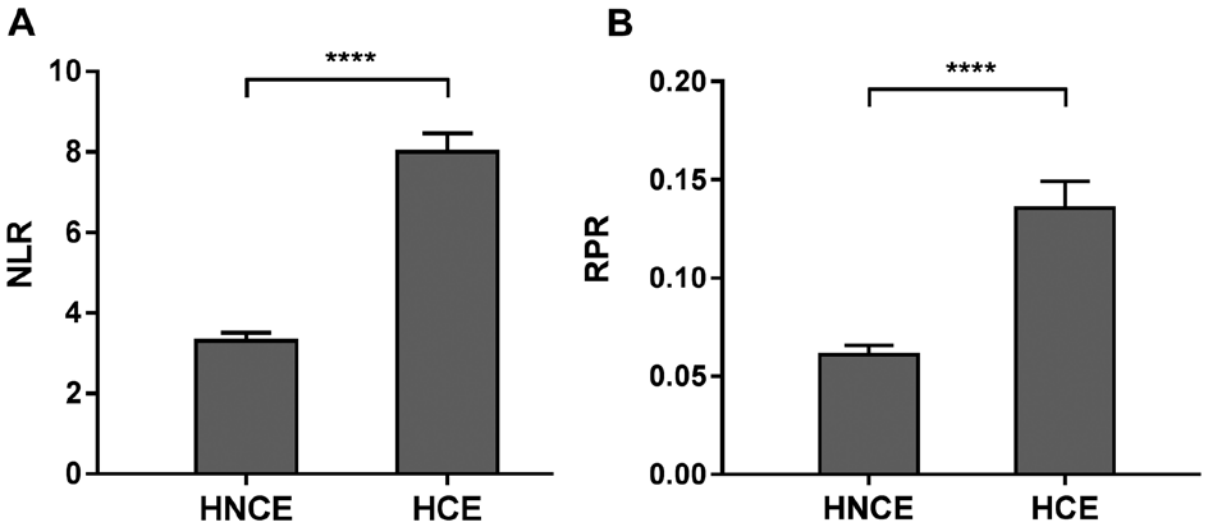

Figure 2. Levels of (A) NLR and (B) RPR in the HCE and HNCE groups. ****P<0.01. HCE group, hemodialysis patients with cardiovascular events; HNCE group, hemodialysis patients with no cardiovascular events; NLR, neutrophil-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio.

Logistic regression models adjusting for known risk factors (elevated BNP, elevated cTnI, increased LVD) were used to determine whether the NLR and RPR are significant predictors of cardiovascular events. The results of this analysis suggested that the RPR is an independent risk factor for cardiovascular events in hemodialysis patients (Table II).

Table II. Association of RDW or RPR with the risk of cardiovascular events in hemodialysis patients: OR (95%CI) using binary logistic regression.

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	P-value	OR (95% CI)	P-value
RPR	2.26 (1.23-4.16)	0.009	7.04 (3.44-14.44)	<0.0001
RDW	0.53 (0.28-0.99)	0.045	1.00 (0.84-1.19)	0.964

Adjustment was made for elevated brain natriuretic peptide, elevated cardiac troponin I and increased left ventricular diameter. RDW, red blood cell distribution width; RPR, RDW-to-platelet ratio; OR, odds ratio.

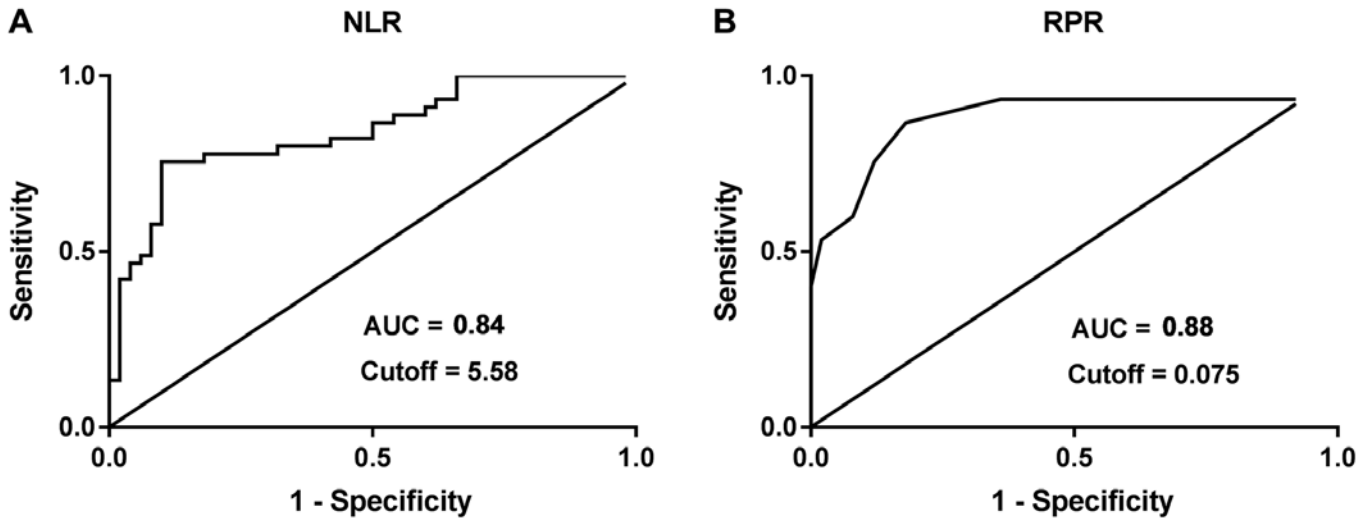

Figure 3. Ability of (A) NLR and (B) RPR to predict cardiovascular events in hemodialysis patients. NLR, neutrophil-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio; AUC, area under curve.

The diagnostic efficacy of the two parameters was validated with an additional 30 HCE patients and 30 HNCE patients. Using the cutoff values for the NLR (5.58) and the RPR (0.075) determined above, the predictive abilities of the NLR and RPR for cardiovascular events in hemodialysis patients were similar to the results obtained in the original cohort (Table III).

Correlations between NLR or RPR and parameters of cardiovascular function. To further confirm the roles of the NLR and RPR in predicating cardiovascular events, the correlation between the NLR or RPR and other cardiovascular function parameters in the HCE group were analyzed. In the HCE group, the NLR and RPR were positively correlated with serum BNP, cTnI and CK-MB (all P<0.05; Fig. 4). In order to investigate the correlations between the NLR or RPR and ST segment changes in the ECG, the HCE patients were divided into two groups based on whether ST segment changes were observed on the ECG (ST segment changes group and no ST segment changes group). The NLR and RPR in the ST segment changes group were significantly higher compared with those in the no ST segment changes group (P<0.0001 for each; Fig. 5A and B).

Predictive value of NLR and RPR regarding cardiovascular events and survival in hemodialysis patients. To determine the predictive value of the NLR and RPR regarding the prediction of cardiovascular events in hemodialysis patients and their survival, the HCE patients were divided into two groups based on treatment outcomes, namely the recovery/improvement group and the treatment failure/death group. AUC analysis was then performed for the NLR and RPR to predict cardiovascular events in hemodialysis patients. The AUC analysis revealed that the RPR was an independent risk factor for the prognosis of cardiovascular events in hemodialysis patients (Table IV). The correlations between the RPR and other prognostic parameters of cardiovascular events in hemodialysis patients of the HCE group were then analyzed by dividing them into two groups according to the cutoff value for RPR (0.08), namely the RPR ≤0.08 group and RPR >0.08 group. The levels of Hb and ALB in the RPR >0.08 group were significantly lower compared with those in the RPR ≤0.08 group (P<0.05 each), whereas the level of CREA in the RPR >0.08 group was significantly higher compared with that in the RPR ≤0.08 group (P<0.05). The survival time in the RPR >0.08 group was significantly shorter compared with that in the RPR ≤0.08 group (P<0.05 each; Fig. 5C-F).

Table III. Performances of NLR and RPR in the diagnosis of patients with hemodialysis in the validation cohort was performed using ROC analysis.

Parameter	HCE patients	HNCE patients	AUROC (95% CI)	Sensitivity	Specificity	+LR	-LR	PPV	NPV	Youden	P-value
NLR			0.83	0.73	0.80	3.27	0.23	43.18	94.87	0.59	<0.001
>5.58	22	6									
≤5.58	8	24									
RPR			0.87	0.87	0.83	4.32	0.07	63.46	97.14	0.73	<0.001
>0.075	26	5									
≤0.075	4	25									

HCE group, hemodialysis patients with cardiovascular events; HNCE group, hemodialysis patients with no cardiovascular events; NLR, neutrophil-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio; AUROC, area under receiver operating characteristic; CI, confidence interval; LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Discussion

In the present study, the role of the NLR and RPR in predicting the occurrence of cardiovascular events in hemodialysis patients and their prognosis was analyzed. Compared with those in patients from the HNCE group, the NLR and RPR were higher in patients from the HCE group. Positive associations between increased NLR and RPR and the incidence of cardiovascular events in hemodialysis patients were identified. The ROC analysis indicated a good sensitivity and specificity of the RPR for predicting cardiovascular events in hemodialysis patients. In addition, the RPR was an independent risk factor for the survival prognosis of cardiovascular events in hemodialysis patients. Encouragingly, the present study also showed that, RPR has a good relationship with other prognostic parameters of cardiovascular events in hemodialysis patients. The NLR and the RPR were correlated with BNP, cTnI and CK-MB, and associated with ST segment changes in HCE patients.

Microinflammation is the initial step in the development of 'inflammation-malnutrition-atherosclerosis' in hemodialysis patients with ESRD (18,19). The state of microinflammation is closely associated with cardiovascular events. The prevalence of microinflammation in hemodialysis patients results in an increased risk of cardiovascular events (20,21). The WBC count in the blood is closely associated with systemic inflammation, such as the involvement of neutrophils in vascular endothelial injury and atherosclerosis (22). Lymphocytes and neutrophils are subtypes of WBCs that participate in the pathogenesis of various diseases and serve important roles in the immune defense system of the body (23,24). Peripheral blood neutrophils are highly regulated and their count is significantly increased during infection (25). The neutrophil count reflects the inflammatory state in the course of disease progression, while the presence and abundance of lymphocytes represent the outcome of regulated immunity (26,27). Of note, blood viscosity plays a key role in the determination of atherosclerosis-related thrombosis (28). During the complex process, hematocrit is a key indicator. Lu *et al* (29), indicated that the low level of ALT prior to hemodialysis in patients with chronic renal failure may be due to hemodilution. In previous studies, the NLR was reported to be associated with cardiovascular events to reflect the inflammatory state in hemodialysis patients (30,31).

In the present study, the total WBC count and neutrophil count in the HCE group were significantly higher compared with those in the HNCE group, but the lymphocyte count in the serum was significantly lower compared with that in the HNCE group. Binary logistic regression analysis suggested that the NLR was an independent factor for predicting cardiovascular events in hemodialysis patients, but not for prognosis in the HCE group. However, the NLR was significantly different between the HCE and HNCE groups, with lower sensitivity and specificity compared with RPR. The NLR was positively correlated with the BNP, cTnI and CK-MB, and associated with ST segment changes in HCE patients.

The association between the RDW and cardiovascular events in hemodialysis patients has been investigated in several studies (32,33). It has been reported that an increased RDW is an independent risk factor for cardiovascular death

Table IV. Association of RPR with prognosis regarding cardiovascular events in hemodialysis patients: OR (95%CI) using binary logistic regression.

	Prognosis					
RPR	Treatment failure/death group	Recovery/improvement group	χ^2	P-value	OR	95% CI
>0.08	28	12	11.65	<0.01	4.42	1.88-10.38
≤0.08	19	36				

RPR, red blood cell distribution width-to-platelet ratio; OR, odds ratio; CI, confidence interval.

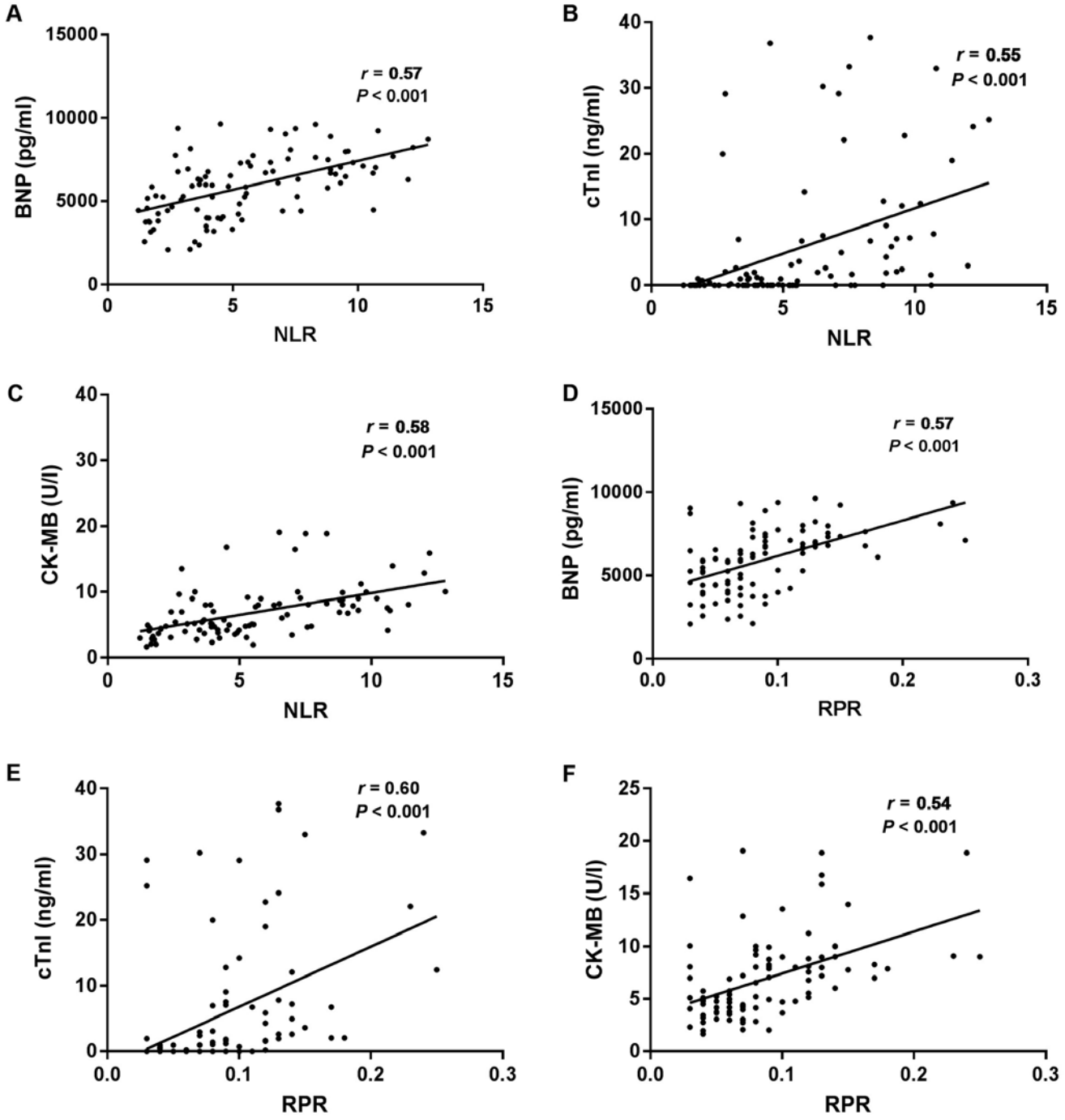

Figure 4. Correlation between NLR, RPR and BNP, cTnI and CK-MB in HCE patients. (A) BNP vs. NLR, (B) cTnI vs. NLR, (C) CK-MB vs. NLR, (D) BNP vs. RPR, (E) cTnI vs. RPR and (F) CK-MB vs. RPR. BNP, brain natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatine kinase isoenzyme MB; NLR, neutrophil-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio.

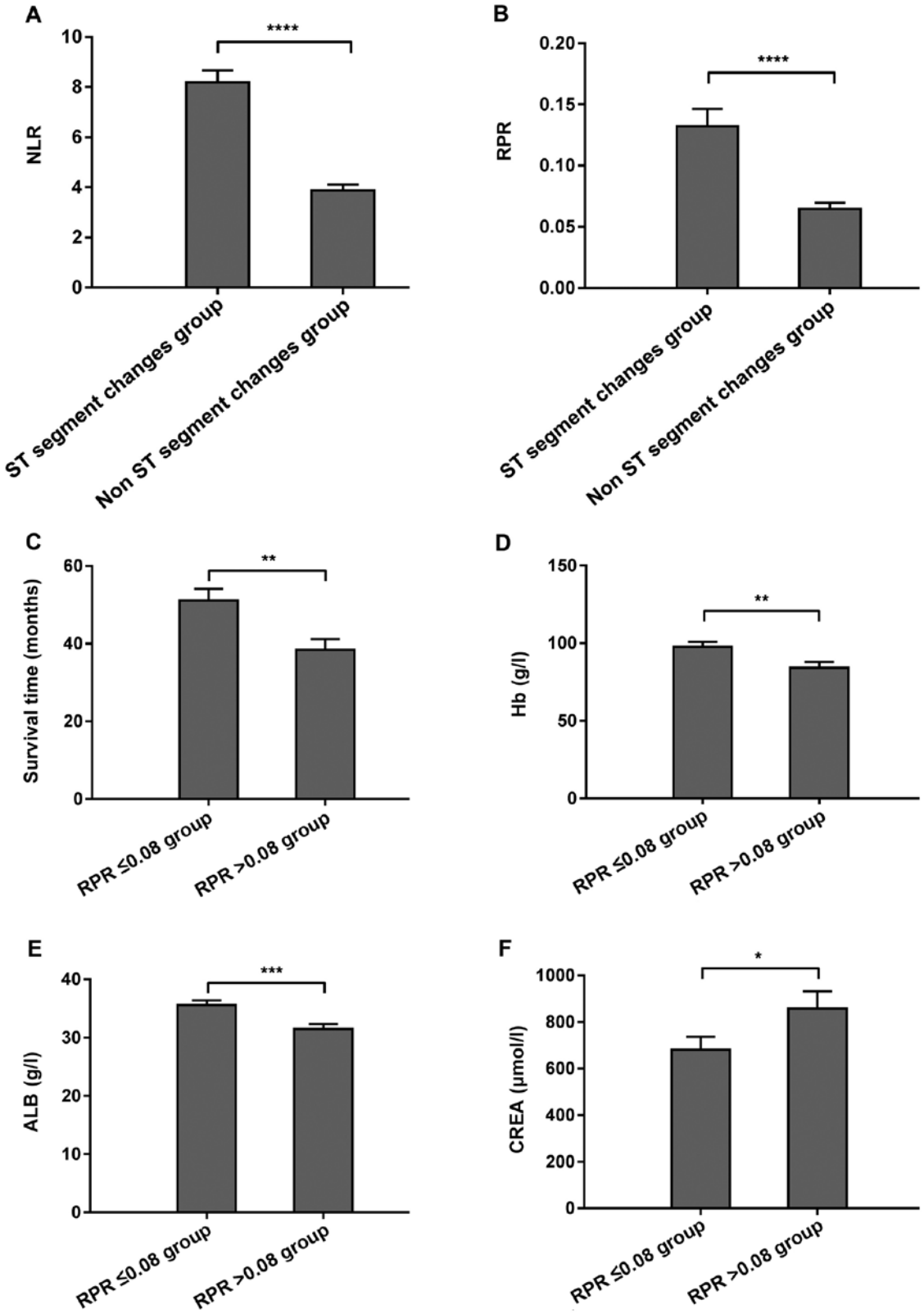

Figure 5. Associations between NLR or RPR and clinicopathological parameters of HCE patients. (A) NLR in HCE patients with and without ST segment changes; (B) RPR in HCE patients with and without ST segment changes. (C) Survival time, (D) Hb levels, (E) ALB and (F) CREA in HCE patients with RPR >0.08 and ≤0.08. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. ALB, serum albumin; Hb, hemoglobin; CREA, creatinine; NLR, neutrophil-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio; HCE patients, hemodialysis patients with cardiovascular events.

in hemodialysis patients (34). As platelets serve an important role in the occurrence and development of cardiovascular events, the ability of the RPR, the combination of the RDW and the platelet ratio, for predicting the occurrence and development of cardiovascular events in hemodialysis patients, as well as their prognosis, was assessed in the present study. It

was demonstrated that the RPR in patients from the HCE group was significantly increased compared with that in patients from the HNCE group. Furthermore, the RPR was correlated with the severity of cardiovascular events in HCE patients. The RPR was an independent predictive factor for the incidence of cardiovascular events in hemodialysis and HCE patients. In addition, the RPR had good sensitivity and specificity for predicting cardiovascular events in hemodialysis patients.

In conclusion, the present study demonstrated the value of the NLR and RPR in predicting the occurrence, development and prognosis of cardiovascular events in hemodialysis patients. The NLR and RPR were able to predict the occurrence and development of cardiovascular events in hemodialysis patients, among which RPR had a better efficacy. The RPR was also useful for predicting the prognosis of HCE patients. Taken together, the present results suggest that these routinely available parameters, which may be obtained non-invasively and economically, may be repurposed as novel diagnostic parameters for cardiovascular events in hemodialysis patients.

Acknowledgements

Not applicable.

Funding

This research was supported by the Youth Medical Talent of Jiangsu Province (grant no. QNRC2016163 to JL).

Availability of data and materials

All data generated or analyzed during this study are included in the published article.

Authors' contributions

XZ contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. GL and SL contributed to the statistical analysis. ZG contributed to the conception and supervision of the study, and the critical revision of the manuscript. JL and SS contributed to the study conception and design, study supervision and critical revision of the manuscript.

Ethics approval and consent to participate

The present study was approved by The Ethics Committees of the First People's Hospital of Yancheng (Yancheng, China) and the Fifth People's Hospital of Wuxi (Wuxi, China), and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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