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Original Article

Increased neutrophil/leukocyte ratio of the peripheral blood in chronic heart failure patients with renal dysfunction

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Abstract: Background: Chronic renal dysfunction (CRD) is highly prevalent in patients with chronic heart failure (CHF). Recently, the neutrophil/leukocyte ratio (NLR) has been recognized as an independent risk factor for both renal dysfunction and heart failure. However, the NLR in patients with both CHF and CRD remains largely unexplored. In the present study, we investigated whether NLR may be used as an indicator to reflect the effect of renal dysfunction on heart function in patients with CHF. Material and methods: Forty-five patients with CHF, 72 patients with both CHF and CRD, and 52 patients with CRD were randomly enrolled in our study and underwent laboratory analysis and echocardiography. The NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count. The patients were further divided into higher NLR (> 3.0) and lower NLR (≤ 3.0) groups. Results: The NLR in the CHF+CRD patients was higher than it was in the CHF patients. Between the higher and lower NLR groups of patients with CHF and/or CRD, there were no differences in terms of renal function, heart function or structure. In the lower NLR group, heart function and structure were not different between the CHF patients and those with both CHF and CRD. However, in the higher NLR group, the CHF+CRD patients exhibited a larger right ventricular internal diameter (RVID) as well as a higher BMI-normalized left ventricular internal diameter, a higher left atrial internal diameter, and a higher RVID and right atrial internal diameter compared with CHF patients. Conclusion: The NLR was significantly increased in CHF+CRD patients, and a higher NLR might indicate worsening renal function and heart function as well as cardiac remodeling.

Keywords: Chronic heart failure, chronic renal dysfunction, neutrophil/leukocyte ratio, echocardiography, cardiac remodeling

Introduction

Heart failure is very severe and usually occurs during the terminal stages of various cardiovascular diseases [1, 2]. Although treatments for heart failure have been greatly improved over the years, it is recognized as the leading cause of mortality worldwide [1-5]. Heart failure can either be acute or chronic. Chronic heart failure (CHF) is the main form and occurs due to the dysfunction of several organs [6-8]. Renal dysfunction (RD) is prevalent in CHF and the two have an interrelationship. Furthermore, 'cardiorenal syndrome' has been recently proposed to describe the combined failure of both organs [7]. Because myocardial remodeling is the pathophysiological basis of CHF, a number of studies have analyzed the effect of chronic renal dysfunction (CRD) on heart function in CHF patients [7, 9]. However, a consensus has not been attained from currently available results. In the present study, we aimed to compare the structural and functional changes of the heart among patients with CHF, CRD, or CHF+CRD.

The etiologies of both CHF and CRD are very complex [10]. Recent studies have confirmed that the immune system and inflammation play a pathophysiological role in both CHF and CRD [11, 12]. Numerous inflammatory biomarkers are well recognized as important prognostic risk factors in CHF and CRD, such as hs-CRP, IL-6, and TNF-α [13-15]. Peripheral blood leukocytes have received a lot of attention due to their substantial role in the inflammatory pro-

cess [10, 16, 17]. Even in healthy subjects, total and subgroup leukocyte counts are positively correlated with potential cardiovascular events [17]. The absolute leukocyte count and neutrophil/leukocyte ratio (NLR) have been reported as risk factors for atrial fibrillation in elderly patients with CHF [16]. They are associated with RD in CHF with reduced ejection fraction [16]. However, the relationship between NLR and cardiac function and structure in CHF+CRD patients remains largely unexplored. In the present study, we analyzed the effect of CRD on NLR in CHF patients and the effect of NLR on cardiac function and structure in CHF+CRD patients.

Materials and methods

Patients

From November 2017 to February 2018, 45 patients with CHF, 72 patients with CHF and CRD, and 52 patients with CRD were retrospectively recruited from the Department of Cardiovascular Disease and the Department of Nephrology, Qilu Hospital, Shandong University. CHF diagnosis was determined by a reduced left ventricular ejection fraction (LVEF) < 50% according to the ACCF/AHA guidelines and the Chinese guidelines for the management of heart failure [1, 18]. A diagnosis of CRD required a diagnosis of chronic kidney disease (CKD) with eGFR < 90 mL/min/1.73 m^2 [19].

Any patients who had acute coronary syndrome, cancer, rheumatic disease, systemic or localized infection, autoimmune diseases, or who were pregnant were excluded. Patients with end-stage renal or cardiovascular disease who required a kidney or heart transplant were also excluded. This study was approved by the Ethics Committee of Qilu Hospital, Shandong University, and was conducted in compliance with the Declaration of Helsinki.

Laboratory analysis

Serum was obtained from a fasting morning blood sample drawn from each patient and immediately stored at -80°C prior to further analyses. B-type natriuretic peptide (BNP) and other routine hematological measurements were determined by an enzyme-linked immunoassay and a clinical biochemical examination according to the manufacturer's instructions. The intra-assay coefficients of variation were 5% for both tests.

NLR

The white blood cell (WBC) count and its different subtypes were determined using automated differential leukocyte counter Sysmex KX-21N (TOA Medical Electronics, Kobe, Japan). The NLR was calculated from the ratio of the absolute neutrophil count to the absolute lymphocyte count (NLR = absolute neutrophil count/absolute lymphocyte count). The patients were divided into two subgroups based on their mean NLR values, with Group 1 having an NLR > 3.0 and Group 2 having an NLR ≤ 3.0, according to previous studies [20, 21].

Estimated glomerular filtration rate

The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation according to previous studies [16, 19]. Specifically, the eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation: men: 141 × (MIN[(creat/0.9, 1])-0.411 × (MAX[creat/0.9, 1])-1.209 × (0.993 age) (× 1.159 if black); women: 141 × (MIN[creat/0.7, 1])-0.329 × (MAX[(creat/0.7, 1])-1.209 × (0.993 age) × 1.018 (× 1.159 if black) [16, 19]. The serum creatinine concentration was determined using the Siemens Crea method (ref FD-33A) on a Dimension RxL Clinical Chemistry System (Siemens, Newark, New Jersey).

Echocardiography

Standard transthoracic echocardiography was carried out by two blinded operators using a Vivid 7 ultrasound system (General Electric, Milwaukee, WI) as previously described [22]. The left ventricular internal diameter (LVID), the interventricular septum (IVS), the left ventricular posterior wall (LVPW), and the left atrial internal diameter (LAID) were measured at end-diastole, and the average values were obtained from three consecutive cardiac cycles of M-mode recordings. The longitudinal right ventricular internal diameter (RVID) and the right atrial internal diameter (RAID) were measured at end-systole, and the average values were obtained from three consecutive cardiac cycles of an apical 4-chamber section. Early mitral inflow velocity (E) and late mitral inflow velocity (A) were measured using the pulsed wave Doppler

Table 1. Patient characteristics in three groups of subjects

	CHF (n = 45)	CRD (n = 52)	CHF+CRD (n = 72)
Age (year)	49.9 ± 14.4	52.3 ± 18.18	65.8 ± 13.07
Sex (F/M, n)	18/27	23/29	23/49
BMI	25.1 ± 5.77	25.2 ± 3.74	24.3 ± 3.92
SBP (mmHg)	118.2 ± 16.69	159.5 ± 25.33*,#	129.9 ± 23.65*
DBP (mmHg)	71.5 ± 12.78	89.17 ± 20.85*,#	77.4 ± 14.44*
HR (beats/min)	85.8 ± 22.57	79.53 ± 11.64	81.3 ± 23.24
Glucose (mmol/l)	5.94 ± 3.03	4.85 ± 0.95*,#	5.26 ± 1.73
TC (mmol/l)	4.40 ± 1.28	4.59 ± 1.38*,#	3.99 ± 1.05
LDL-C (mmol/l)	2.65 ± 0.74	2.55 ± 1.01	2.41 ± 0.79
HDL-C (mmol/l)	1.15 ± 0.35	1.27 ± 0.33*,#	1.06 ± 0.27
TG (mmol/l)	1.69 ± 2.21	1.71 ± 1.06	1.23 ± 0.51
BNP (pg/ml)	2691.1 ± 1843.49	3990.4 ± 6593.9*,#	7023.4 ± 5688.7*
CR (μmol/l)	63.3 ± 14.50	459.8 ± 293.33	115.7 ± 78.74*
BUN (mmol/l)	5.39 ± 2.01	22.09 ± 11.67*,#	8.47 ± 5.60*
CysC (mg/l)	0.99 ± 0.48	3.159 ± 1.40*,#	1.48 ± 0.71*
UA (μmol/l)	374.3 ± 135.30	483.8 ± 154.09*,#	453.4 ± 179.84*
eGFR (ml/min/1.73 m^2)	105.6 ± 105.62	19.5 ± 20.06*,#	62.8 ± 18.84*
LVEF (%)	29.6 ± 8.30	63.6 ± 6.79*,#	27.8 ± 8.70
NYHA			
I	1	22*,#	0
II	9	9	10
III	20	20	30
IV	15	1*,#	32
LAID (mm)	39.8 ± 6.36	39.8077 ± 6.36*,#	48.1 ± 7.70
LVID (mm)	60.8 ± 7.60	48.1 ± 4.96*,#	62.1 ± 9.41
RAID (mm)	51.5 ± 10.32	45.3 ± 5.48*,#	54.1 ± 9.47
RVID (mm)	24.9 ± 6.60	23.1 ± 2.87*,#	25.9 ± 4.59
E/A ratio	18.9 ± 6.21	15.5 ± 7.59	23.6 ± 8.55

CHF, chronic heart failure; CRD, chronic renal dysfunction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; LDL-C, high density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; BNP, B-type natriuretic peptide; CR, creatinine; BUN, blood urine nitrogen; CysC, cystatin C; UA, uric acid; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVID, left ventricular internal diameter; LAID, left atrial internal diameter; RVID, right ventricular internal diameter; RAID, right atrial internal diameter; E/A ratio, Early mitral inflow velocity (E)/late mitral inflow velocity (A); *$P < 0.05$ compared with CHF; #$P < 0.05$ compared with CHF+CRD.

method. The E/A ratio was then calculated accordingly. All measurements were taken according to the American Society of Echocardiography guidelines [23].

Statistics

Continuous variables were expressed as the mean ± SD and analyzed using one-way ANOVA tests with Scheffe posteriori comparisons (among three groups of CHF, CRD or CHF+CRD) and independent-samples *t*-tests (between subgroups with lower and higher NLR). The categorical variables were expressed as proportions and analyzed by χ^2 tests. $P < 0.05$ was considered statistically significant. The statistical analysis was performed with SPSS 15.0 for Windows.

Clinical data

Basic clinical characteristics of patients

Table 1 lists the basic clinical information of the patients with CHF, CRD or CHF+CRD. There were no differences among these groups in terms of sex, body mass index (BMI), and heart rate (HR). Renal function (CR and eGFR), heart function (LVEF, NYHA and E/A ratio), and structure (LVID, LAID, RVID, RAID), as well as serum levels of glucose, TC, HDL, BNP and UA were different between the patients with and without

Table 2. Blood cell counting, classification and NLR

	CHF (n = 45)	CRD (n = 52)	CHF+CRD (n = 72)
WBC (10^9/l)	6.11 ± 1.86	6.85 ± 2.45	6.49 ± 2.18
NEU (10^9/l)	3.78 ± 1.54	4.83 ± 2.04*	4.19 ± 1.58
LYM (10^9/l)	1.75 ± 0.47	1.38 ± 0.66	1.66 ± 1.12
MONO (10^9/l)	0.44 ± 0.18	0.39 ± 0.19	0.46 ± 0.17
EOS (10^9/l)	0.12 ± 0.11	0.20 ± 0.17	0.14 ± 0.13
NLR	2.24 ± 0.91	4.18 ± 2.45*,#	3.02 ± 1.56*
Percentage of NLR			
NLR > 3.0	13 (29%)	44 (85%)*,#	36 (50%)*
NLR ≤ 3.0	32 (71%)	8 (15%)	36 (50%)

WBC, white blood cell; NEU, neutrophils; LYM, lymphocytes; MONO, monocytes; EOS, eosinophil; NLR, neutrophil/lymphocyte ratio; *P < 0.05 compared with CHF; #P < 0.05 compared with CHF+CRD.

CHF, reflecting the different etiology of CRD and CRF. The levels of eGFR, BUN, CR, BNP and SBP were also different between patients with only CHF and patients with CHF+CRD.

Blood cell counting, classification and NLR

The number of WBCs, lymphocytes, monocytes and eosinophils were not different among the three groups. The number of neutrophils was significantly different between the CRD and CHF patients, but no difference was observed between the CHF patients and those with CHF+CRD. However, the NLR of patients with CHF+CRD (3.0235 ± 1.56101) was higher than the NLR of the CHF patients (2.2413 ± 0.90557) and lower than that of the CRD patients (4.1838 ± 2.44919). When the cut-off value of NLR was set at 3, the percentage of patients with a higher NLR was also significantly different among the three groups in the following order: CRD > CHF+CRD > CHF (**Table 2**).

Comparison of heart function and structure between the subgroups with lower and higher NLRs

Because CRD and CRF are different syndromes, we only evaluated heart function and structure between the patients with CHF and CHF+CRD. The patients were divided into subgroups of higher NLR (NLR > 3.0) and lower NLR (NLR ≤ 3.0) in order to assess the effect of CRD on heart remodeling in patients with CHF.

In CHF patients, those with higher NLR had a higher number of WBCs and neutrophils as well as greater levels of NLR and SBP. However, there were no differences in terms of age, sex, BNP, eGFR, LVEF, BMI, SBP, DBP, HR, LAID, LVID, RAID, RVID, E/A ratio and the number of lymphocytes. In patients with CHF+CRD, those with higher NLR exhibited higher counts of WBCs, neutrophils and lymphocytes as well as greater levels of NLR and SBP, while there were no differences in terms of age, gender, renal function, heart function and structure (**Table 3**).

In the lower NLR group, patients with CHF+CRD had higher levels of BNP, SBP and DBP, and lower eGFR compared with CHF patients. However, there were no differences in terms of age, gender, renal function, heart function and structure (**Table 3**).

In the higher NLR group, patients with CHF+CRD had higher levels of BNP, BUN, HDL and NLR but lower levels of BMI, LVEF and eGFR compared with CHF patients. Only the RVID of CHF+CRD patients was significantly increased compared with CHF patients. Because BMI is considered to have a great effect on heart structure, we normalized heart measurements by BMI. Although CHF+CRD patients had lower BMI, they showed higher BMI-normalized $LVID_n$, $LAID_n$, $RVID_n$ and $RAID_n$ compared with CHF patients (**Figure 1**).

Discussion

It has been recognized that CRD is common in CHF patients, and these two syndromes interact with each other [7-10]. In the present study, we used NLR to evaluate the effect of CRD on the structure and function of heart in CHF patients. Although the numbers of WBCs, lymphocytes and neutrophils were not different between CHF patients and those with CHF +CRD, the NLR of patients with CHF+CRD was higher than that of CHF patients but lower than that of CRD patients. Patients with CHF+CRD also had an increased NLR (NLR > 3.0). Several studies have reported similar results [16, 20, 21]. Argan determined that an NLR > 3 has a sensitivity of 68% and specificity of 75% to predict progression of kidney disease in CHF patients with reduced ejection fraction [16]. In elderly patients with CHF, NLR is identified as a risk factor for CKD, and the highest tertile of

Table 3. Comparison of heart function and structure between subgroups with lower and higher NLR

	CHF		CHF+CRD	
	NLR ≤ 3.0 (n = 32)	NLR > 3.0 (n = 13)	NLR ≤ 3.0 (n = 36)	NLR > 3.0 (n = 36)
Age (year)	49.2 ± 15.02	51.1 ± 13.40	63.4 ± 11.94	68.5 ± 14.63
Sex (F/M, n)	14/18	4/9	12/24	11/25
BMI	23.2 ± 5.78	28.7 ± 8.45	24.6 ± 3.90	24.16 ± 4.09$^{\&}$
SBP (mmHg)	114.6 ± 13.23	127.2 ± 22.41*	124.2 ± 21.79*	138.8 ± 25.67$^{\#}$
DBP (mmHg)	69.3 ± 9.71	80.4 ± 16.17	76.4 ± 14.34*	77.8 ± 15.89
HR (beats/min)	82.9 ± 24.10	94.5 ± 16.46	80.3 ± 25.52	81.5 ± 18.38
BNP (pg/ml)	2595.3 ± 1689.58	2570.6 ± 1938.32	5929.1 ± 4395.41*	6449.8 ± 4482.75$^{\&}$
eGFR (ml/min/1.73 m^2)	105.9 ± 13.74	105.1 ± 12.95	64.1 ± 18.05*	61.4 ± 21.06$^{\&}$
LVEF (%)	29.0 ± 8.67	31.2 ± 7.44	27.1 ± 8.22	28.3 ± 9.49$^{\&}$
LAID (mm)	45.0 ± 8.83	46.7 ± 5.96	49.0 ± 7.12	47.1 ± 8.63
LVID (mm)	60.9 ± 7.68	60.9 ± 7.94	63.2 ± 9.29	60.8 ± 9.31
RAID (mm)	51.2 ± 9.67	52.3 ± 12.57	54.6 ± 8.92	50.7 ± 14.41
RVID (mm)	24.6 ± 5.67	23.45 ± 11.81	26.1 ± 4.79	25.5 ± 4.44$^{\&}$
IVS (mm)	10.09 ± 2.38	10.09 ± 1.75	10.06 ± 2.35	10.30 ± 3.16
LVPW (mm)	9.34 ± 1.96	10.54 ± 1.50	9.58 ± 1.72	9.81 ± 2.93
E/A ratio	6.65 ± 10.20	5.83 ± 8.62	12.04 ± 13.83	12.40 ± 11.61
WBC (10^9/l)	5.11 ± 1.91	8.09 ± 1.57*	5.47 ± 3.22	6.77 ± 1.95$^{\#}$
NEU (10^9/l)	2.92 ± 1.21	5.72 ± 1.23*	3.11 ± 1.77	4.95 ± 1.71$^{\#}$
LYM (10^9/l)	1.69 ± 0.65	1.67 ± 0.39043	1.81 ± 1.51	1.17 ± 0.317$^{\#}$
NLR (10^9/l)	1.68 ± 0.68	3.46 ± 0.52*	1.65 ± 0.91	4.36 ± 1.49$^{\#,\&}$

CHF, chronic heart failure; CRD, chronic renal dysfunction; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVID, left ventricular internal diameter; LAID, left atrial internal diameter; RVID, right ventricular internal diameter; RAID, right atrial internal diameter; IVS, interventricular septum; LVPW, left ventricular posterior wall; E/A ratio, Early mitral inflow velocity (E)/late mitral inflow velocity (A); WBC, white blood cell; NEU, neutrophils; LYM, lymphocytes; NLR, neutrophil/lymphocyte ratio; $^{*}P < 0.05$ compared with CHF with NLR ≤ 3.0; $^{\#}P < 0.05$ compared with CHF+CRD with NLR ≤ 3.0; $^{\&}P < 0.05$ compared with CHF with NLR > 3.0.

NLR has been associated with an increased risk for major cardiovascular events. In addition, NLR has been shown to predict mortality in patients with cancer, ischemic heart disease, hemodialysis and stroke [24, 25]. These results suggested that NLR could be an important biomarker for RD in CHF patients.

Furthermore, we found that BUN and BNP were higher and eGFR was lower in patients with CHF+CRD compared with CHF patients. Since eGFR is a clear marker of renal injury [16, 19] and BNP is a clear marker of heart function [1, 13], RD should affect heart function and structure of CHF patients. Previous studies have demonstrated that kidney disease and/or RD are independently associated with poor prognosis both in acute heart failure (AHF) and CHF patients [11, 26]. Jain discovered that a worsening GFR is associated with a greater degree of left ventricular diastolic dysfunction (DD) and adverse clinical outcomes in a population with preserved systolic function; however, there is no interaction between GFR and DD [7]. In addition, Jenkins discovered that the prevalence of left ventricular systolic dysfunction is similar between HF patients with higher stages of CKD (stage 3a/b or stage 4/5) and lower stages (0-2) [27]. In the present study, measurements of heart function and structure were consistent between patients with CHF and CHF+CRD. These results suggest that the effect of CRD on heart function and structure in CHF patients is very complex, and might be related to the study subject, severity and evaluation criteria of renal and heart dysfunction.

An increasing amount of data has revealed that NLR is an independent risk factor for adverse cardiovascular outcomes in CHF patients [16, 17, 28]. However, the role of NLR remains largely unexplored in evaluating the effect of CRD on

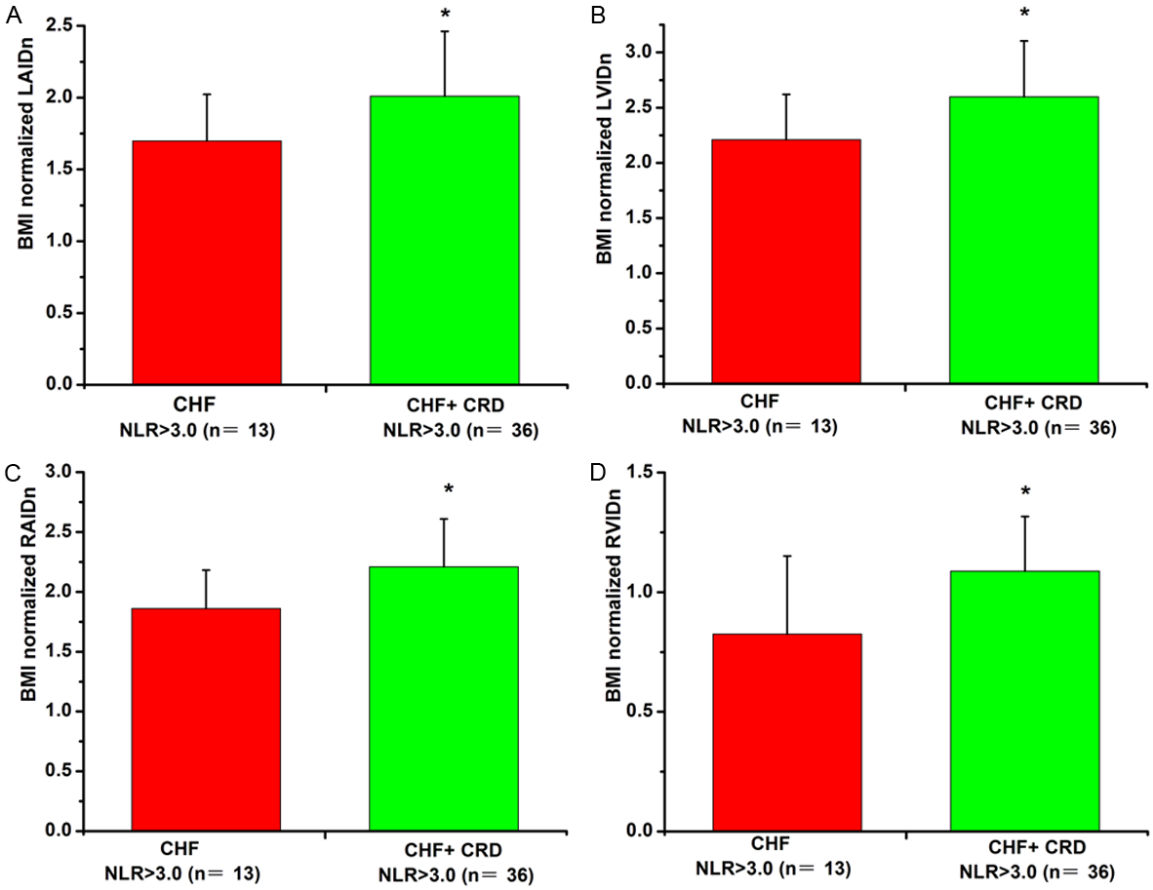

Figure 1. Comparison of heart structure between subgroups with higher NLRs. Although patients with CHF+CRD and NLR > 3.0 had lower BMI, they had higher BMI-normalized $LVID_n$ (A), $LAID_n$ (B), $RVID_n$ (C) and $RAID_n$ (D) compared with patients with CHF and NLR > 3.0 ($^*P < 0.05$). CHF, chronic heart failure; CRD, chronic renal dysfunction; BMI, body mass index; LVID, left ventricular internal diameter; LAID, left atrial internal diameter; RVID, right ventricular internal diameter; RAID, right atrial internal diameter.

heart function and structure in CHF. In the present study, patients were divided into subgroups with a cut-off value of the NLR > 3.0. This cutoff value has been used in numerous previous studies. In patients with CHF or CHF+CRD, the measurements of renal function, heart function and structure were consistent between patients with higher and lower NLRs. In the lower NLR group, patients with CHF+CRD had higher levels of BNP and BUN but lower eGFR compared with the CHF patients, and there were no differences in terms of heart function and structure. These results showed that a lower NLR could not be used to distinguish CHF+CRD from CHF. However, in the higher NLR group, patients with CHF+CRD had higher levels of BNP, BUN and NLR but lower levels of BMI, LVEF and eGFR compared with the CHF patients. Previous studies have also found an inverse correlation between the NLR and LVEF [28] or eGFR [29]. Therefore, a higher NLR is a potential risk factor for HD and RD in CHF patients.

More interestingly, CHF+CRD patients with higher NLRs had higher BMI-normalized LAID, LVID, RVID and RAID compared with the CHF patients, reflecting the aggravated heart remodeling induced by CRD in CHF patients. Previous studies have found that there is a higher incidence of left ventricular hypertrophy in CKD patients [30] and a greater left ventricular end-diastolic diameter and end-systolic diameter in patients with end-stage renal disease on maintenance hemodialysis [31]. Additionally, there are decreased high-flow arteriovenous fistulas in end-stage renal disease that can decrease left ventricular mass, left atrial diameter, right ventricular diameter, and pulmonary systolic pressure in the high cardiac index group [32]. In heart failure, CKD has been

recognized as an independent risk factor for ventricular dysfunction and dilation, and CRT improves the function and structure of the left ventricle to a lesser extent in CKD patients compared to those with normal kidney function [33]. Therefore, we concluded that CRD would worsen cardiac remodeling in CHF patients with a higher NLR. The underlying mechanism could be that higher NLR represents increased inflammation, which plays a very important role in both CRD and CHF [11-15]. In addition, RD may enhance overall inflammatory reactions due to the decreased renal clearance of inflammatory cytokines such as TNF-α, IL-6 and CRP, leading to injury of the myocardium and vascular endothelium [34].

Study limitations

A potential limitation is that this study was a single-institution study with a small population size, which did not predict the NLR for cardiac outcomes in patients with CHF+CRD. Moreover, we did not measure the levels of inflammatory markers such as TNF-α, IL-6 and CRP. Therefore, the direct relationship between NLR and systemic inflammation was not determined. Taken together, the role of NLR in patients with CHF+CRD should be further investigated in future prospective and randomized studies.

Conclusions

The NLR value, which reflects overall inflammation, was significantly increased in CHF patients with CRD. Therefore, a higher NLR could worsen renal function, heart function and cardiac remodeling in patients with CHF.

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Disclosure of conflict of interest

None.

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References

[1] Writing Committee Members, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation 2013; 128: e240-327.

[2] Dharmarajan K and Rich MW. Epidemiology, pathophysiology, and prognosis of heart failure in older adults. Heart Fail Clin 2017; 13: 417-426.

[3] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC). Developed with the special contribution of the heart failure association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891-975.

[4] Rajadurai J, Tse HF, Wang CH, Yang NI, Zhou J and Sim D. Understanding the epidemiology of heart failure to improve management practices: an asia-pacific perspective. J Card Fail 2017; 23: 327-339.

[5] Jiang H and Ge J. Epidemiology and clinical management of cardiomyopathies and heart failure in China. Heart 2009; 95: 1727-1731.

[6] Harjola VP, Mullens W, Banaszewski M, Bauersachs J, Brunner-La Rocca HP, Chioncel O, Collins SP, Doehner W, Filippatos GS, Flammer AJ, Fuhrmann V, Lainscak M, Lassus J, Legrand M, Masip J, Mueller C, Papp Z, Parissis J, Platz E, Rudiger A, Ruschitzka F, Schafer A, Seferovic PM, Skouri H, Yilmaz MB and Mebazaa A. Organ dysfunction, injury and failure in acute

heart failure: from pathophysiology to diagnosis and management. A review on behalf of the acute heart failure committee of the heart failure association (HFA) of the European society of cardiology (ESC). Eur J Heart Fail 2017; 19: 821-836.
[7] Jain A, Scott C and Chen HH. The renal-cardiac connection in subjects with preserved ejection fraction: a population based study. ESC Heart Fail 2017; 4: 266-273.
[8] Havakuk O, King KS, Grazette L, Yoon AJ, Fong M, Bregman N, Elkayam U and Kloner RA. Heart failure-induced brain injury. J Am Coll Cardiol 2017; 69: 1609-1616.
[9] Ross BA, Wald R, Goldstein MB, Yuen DA, Leipsic J, Kiaii M, Rathe A, Deva DP, Kirpalani A, Bello OO, Graham JJ, Leong-Poi H, Connelly KA and Yan AT. Relationships between left ventricular structure and function according to cardiac mri and cardiac biomarkers in end-stage renal disease. Can J Cardiol 2017; 33: 501-507.
[10] Vaduganathan M, Greene SJ, Butler J, Sabbah HN, Shantsila E, Lip GY and Gheorghiade M. The immunological axis in heart failure: importance of the leukocyte differential. Heart Fail Rev 2013; 18: 835-845.
[11] Schefold JC, Filippatos G, Hasenfuss G, Anker SD and von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. Nat Rev Nephrol 2016; 12: 610-623.
[12] Ter Maaten JM, Damman K, Verhaar MC, Paulus WJ, Duncker DJ, Cheng C, van Heerebeek L, Hillege HL, Lam CS, Navis G and Voors AA. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail 2016; 18: 588-598.
[13] Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM, Fonarow GC, Greenberg B, Januzzi JL Jr, Kiernan MS, Liu PP, Wang TJ, Yancy CW and Zile MR. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American heart association. Circulation 2017; 135: e1054-e1091.
[14] Udeanu M, Guizzardi G, Di Pasquale G, Marchetti A, Romani F, Dalmastri V, Capelli I, Stalteri L, Cianciolo G, Rucci P and La Manna G. Relationship between coronary artery disease and C-reactive protein levels in NSTEMI patients with renal dysfunction: a retrospective study. BMC Nephrol 2014; 15: 152.
[15] Siasos G, Tousoulis D, Michalea S, Oikonomou E, Vavuranakis M, Athanasiou D, Tourikis P, Gouliopoulos N, Miliou A, Mourouzis K, Limperi M, Mazaris S, Papavassiliou AG and Stefanadis C. Novel biomarkers assessing renal function in heart failure: relation to inflammatory status and cardiac remodelling. Curr Med Chem 2014; 21: 3976-3983.
[16] Argan O, Ural D, Kozdag G, Sahin T, Bozyel S, Aktas M, Karauzum K, Yilmaz I, Dervis E and Agir A. Associations between neutrophil gelatinase associated lipocalin, neutrophil-to-lymphocyte ratio, atrial fibrillation and renal dysfunction in chronic heart failure. Med Sci Monit 2016; 22: 4765-4772.
[17] Yan W, Liu C, Li R, Mu Y, Jia Q and He K. Usefulness of the neutrophil-to-lymphocyte ratio in predicting adverse events in elderly patients with chronic heart failure. Int Heart J 2016; 57: 615-621.
[18] Chinese Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology. Chinese guidelines for the diagnosis and treatment of heart failure 2014. Zhonghua Xin Xue Guan Bing Za Zhi 2014; 42: 98-122.
[19] Gao B, Zhang L, Wang H and Zhao M. Chinese cohort study of chronic kidney disease: design and methods. Chin Med J (Engl) 2014; 127: 2180-2185.
[20] Erturk M, Cakmak HA, Surgit O, Celik O, Aksu HU, Akgul O, Gurdogan M, Bulut U, Ozalp B, Akbay E and Yildirim A. Predictive value of elevated neutrophil to lymphocyte ratio for long-term cardiovascular mortality in peripheral arterial occlusive disease. J Cardiol 2014; 64: 371-376.
[21] Isaac V, Wu CY, Huang CT, Baune BT, Tseng CL and McLachlan CS. Elevated neutrophil to lymphocyte ratio predicts mortality in medical inpatients with multiple chronic conditions. Medicine (Baltimore) 2016; 95: e3832.
[22] Ma ZY, Li L, Zhong XZ, Tan HW, Wang R, Wang Y, Zhang W and Zhang Y. Cilnidipine improves left-ventricular midwall function independently of blood pressure changes in Chinese patients with hypertension. J Cardiovasc Pharmacol 2007; 49: 33-38.
[23] Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA and Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009; 22: 107-133.
[24] Neuen BL, Leather N, Greenwood AM, Gunnarsson R, Cho Y and Mantha ML. Neutrophil-lymphocyte ratio predicts cardiovascular and all-cause mortality in hemodialysis patients. Ren Fail 2016; 38: 70-76.
[25] Tokgoz S, Kayrak M, Akpinar Z, Seyithanoglu A, Guney F and Yuruten B. Neutrophil lymphocyte ratio as a predictor of stroke. J Stroke Cerebrovasc Dis 2013; 22: 1169-1174.

[26] Weidmann ZM, Breidthardt T, Twerenbold R, Zusli C, Nowak A, von Eckardstein A, Erne P, Rentsch K, de Oliveira MT Jr, Gualandro D, Maeder MT, Rubini Gimenez M, Pershyna K, Stallone F, Haas L, Jaeger C, Wildi K, Puelacher C, Honegger U, Wagener M, Wittmer S, Schumacher C, Krivoshei L, Hillinger P, Osswald S and Mueller C. Prediction of mortality using quantification of renal function in acute heart failure. Int J Cardiol 2015; 201: 650-657.

[27] Jenkins R, Mandarano L, Gugathas S, Kaski JC, Anderson L, Banerjee D. Impaired renal function affects clinical outcomes and management of patients with heart failure. ESC Heart Fail 2017; 4: 576-584.

[28] Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I and Erdogan O. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are predictors of heart failure. Arq Bras Cardiol 2015; 105: 606-613.

[29] Tatar E, Mirili C, Isikyakar T, Yaprak M, Guvercin G, Ozay E and Asci G. The association of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio with clinical outcomes in geriatric patients with stage 3-5 chronic kidney disease. Acta Clin Belg 2016; 71: 221-226.

[30] Peng T, Hu Z, Wu L, Li D and Yang X. Correlation between endothelial dysfunction and left ventricular remodeling in patients with chronic kidney disease. Kidney Blood Press Res 2014; 39: 420-426.

[31] Yilmaz H, Gurel OM, Celik HT, Sahiner E, Yildirim ME, Bilgic MA, Bavbek N and Akcay A. CA 125 levels and left ventricular function in patients with end-stage renal disease on maintenance hemodialysis. Ren Fail 2014; 36: 210-216.

[32] Wohlfahrt P, Rokosny S, Melenovsky V, Borlaug BA, Pecenkova V and Balaz P. Cardiac remodeling after reduction of high-flow arteriovenous fistulas in end-stage renal disease. Hypertens Res 2016; 39: 654-659.

[33] Mathew J, Katz R, St John Sutton M, Dixit S, Gerstenfeld EP, Ghio S, Gold MR, Linde C, Shlipak MG and Deo R. Chronic kidney disease and cardiac remodelling in patients with mild heart failure: results from the REsynchronization reVErses remodeling in systolic left ventricular dysfunction (REVERSE) study. Eur J Heart Fail 2012; 14: 1420-1428.

[34] Sharma R, Bolger AP, Li W, Davlouros PA, Volk HD, Poole-Wilson PA, Coats AJ, Gatzoulis MA and Anker SD. Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease. Am J Cardiol 2003; 92: 188-193.