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Age and sex differences in the relationship between neutrophil-to-lymphocyte ratio and chronic kidney disease among an adult population in Taiwan

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ABSTRACT

Background: This study investigated the association between systemic inflammation and chronic kidney disease (CKD), and whether this association changes with aging in adults, by using neutrophil-to-lymphocyte ratio (NLR) as an inflammation marker.

Materials and methods: A total of 2954 adults (1815 men and 1139 women) who attended a health examination at a medical center in central Taiwan were included for the final cross-sectional analysis.

Results: Compared with participants aged < 60 years, participants aged ≥60 years had a markedly higher prevalence rate of CKD in both men (7.6% vs. 37.8%, $p < .001$) and women (3.8% vs. 28.0%, $p < .001$). In men aged < 60 years, multivariable logistic regression analysis revealed that, after adjusting for conventional CKD risk factors, higher NLR (per 1 unit increment) was independently associated with higher risk of CKD [adjusted OR = 1.48 (95% C.I.: 1.10 to 1.99, $p = .009$)]. There was no such association in both men and women aged ≧60 years, and woman aged < 60 years.

Conclusions: Our study showed a differential effect that aging has on the relationship between NLR and CKD in men but not in women. Being inexpensive and readily available, NLR may potentially be used for CKD risk assessment in men younger than 60 years of age.

1. Introduction

Chronic kidney disease (CKD) is a worldwide public health problem, and epidemiological studies have shown that the prevalence of CKD is found in approximately 13.1% of the population of the United States [1], 12.9% of Japan [2], and 10.8% of China [3]. In Taiwan, the national prevalence of CKD was 11.9%, and there was a marked increase of CKD prevalence in people older than 60 years [4]. Glomerular filtration rate decline increases the risk of cardiovascular disease (CVD), speeds progression to both end-stage renal disease and mortality [4, 5], while also imposing a substantial economic burden on the patient, caregiver and society [6]. The mechanisms for the deterioration of renal function are complex, including high blood pressure, hyperglycemia, dyslipidemia, hyperuricemia, aging and male sex, all of which have been proposed as potential contributors to CKD [4, 7–9].

Several studies have reported that inflammation plays a role in the decline of kidney function [10]. Several clinical studies have shown that there are associations between CKD and certain inflammatory markers, such as C-reactive protein, and white blood cell (WBC) counts [11, 12]. Recently, serum neutrophil-to-lymphocyte ratio (NLR) has been recognized as a useful surrogate for systemic inflammation and autoimmune disease activity, and having the ability to predict

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prognosis in some cancers and CVD [13–15]. In patients with end stage renal disease, it has been shown that NLR positively correlates with vascular calcification [16, 17] and tumor necrosis factor-α (TNF-α) levels [18], and higher NLR predicts increased risk of overall mortality and cardiovascular mortality [19, 20]. However, an association between NLR and CKD in the general population was less studied [21]. Since NLR is a readily available result from complete blood count tests, studies regarding its value in predicting the risk of CKD would be of interest. Hence, this study was aimed to investigate whether NLR is associated with kidney function, and whether this association changes with aging, in an adult population in Taiwan.

2. Materials and methods

We examined participants who were undergoing a self-paid, packaged physical examination from August 2000 to April 2002 at a medical center in central Taiwan. Medical histories regarding hypertension, diabetes and CVD (including myocardial infarction and stroke), as well as lifestyle habits (including smoking and alcohol consumption), were collected using a structured questionnaire. Smoking was defined as current tobacco usage. Alcohol consumption was categorized as either nondrinker (less than one intake per week) or current drinker (at least one intake per week).

All subjects were weighed wearing light clothing without shoes, and their heights were also measured. Blood pressure (BP) at the arm was measured after 5 min of rest using standard mercury sphygmomanometers, with patients in a sitting position. After an overnight fast of at least 8 h, a venous blood sample was collected to measure plasma glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) concentrations using a photometric enzymatic method with a chemistry analyzer (Hitachi 7600, Tokyo, Japan), at the central laboratory of the hospital. Creatinine was measured using the Jaffe method (Hitachi 7600, Tokyo, Japan), which was calibrated from the isotope dilution mass spectrometry method. Uric acid was measured using the uricase method with a Hitachi 7600 analyzer. The total WBC and WBC differential count were computed using an auto-analyzer (Sysmex SE-9000, Kobe, Japan). The internal quality control and external quality assessment of all laboratory methods were deemed acceptable.

A diagnosis of hypertension was assigned if the subject reported to have been given a physician's diagnosis of hypertension, if the subject reported taking medications for hypertension, or if the systolic BP was ≥140 mmHg or diastolic BP was ≥90 mmHg. A diagnosis of diabetes mellitus was assigned if the subject reported to have been given a physician's diagnosis of diabetes, if the subject reported taking medications for diabetes, or if their fasting plasma glucose concentration was ≥7 mmol/L. Hypercholesterolemia was defined as a total cholesterol concentration ≥ 5.18 mmol/L, hypertriglyceridemia was defined as a triglyceride concentration ≥ 1.70 mmol/L, and a low HDL-C concentration was defined as a HDL-C < 1.04 mmol/L for men and < 1.29 mmol/L for women. Dyslipidemia was defined as the existence of any one of the aforementioned lipid abnormalities, or if the subject was using a lipid-lowering drug. Hyperuricemia was defined as a serum uric acid concentration ≥ 420 μmol/L in men and ≥ 360 μmol/L in women, or if the subject reported taking urate-lowering medications.

Of the 4832 participants aged ≥20 years, 696 did not fill out the questionnaire, while 727 offered incomplete responses to the questionnaire. In addition, we stepwise excluded participants with missing data on BP measurement (n = 205), serum creatinine (SCr) (n = 1), serum uric acid (n = 4), total WBC count (n = 1), and WBC differential count (n = 6). Participants with total WBC counts ≥10,000 cells/μL (n = 125) and < 3000 cells/μL (n = 6) were excluded because of possibly active infection or bone marrow disorder. Participants with analgesics usage (77) or a history of cancer (n = 30) were also excluded for nonvascular conditions associated with inflammation [16]. After these exclusions, 2954 subjects (1139 women and 1815 men) were included in the final analysis. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (protocol no: CE17066B).

2.1. Statistical analysis

Body Mass Index (BMI) was calculated by dividing body-weight in kilograms by the square of height in meters (kg/m^2). The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The estimated Glomerular Filtration Rate (eGFR) was calculated by using the CKD-Epidemiology Collaboration (CKD-EPI) equation [22]: eGFR ($mL/min/1.73\,m^2$) = $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and − 0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1. CKD was defined as eGFR < 60 $mL/min/1.73\,m^2$.

Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data, and as median (interquartile range) for non-normally distributed data (fasting glucose, AST, ALT and triglyceride), while categorical variables were presented as number (percentage). Comparisons between groups were performed by using chi-square analysis or Fisher's exact test for categorical variables, and unpaired t-test or Mann-Whitney U test for continuous variables. To investigate the relationship between NLR and kidney function in different sex- and age- groups, we stratified the participants into four groups according to sex and age (< 60 years and ≧60 years). Because NLR correlates with several atherosclerosis risk factors and NLR can be lowered by therapy with statin and some anti-hypertensive medications [16, 23], we used multivariable linear regression analysis with adjustment of the risk factors for CKD and atherosclerosis (namely, BMI, smoking, alcohol use, hyperuricemia, previous CVD, hypercholesterolemia, hypertriglyceridemia, low HDL-C, lipid-lowering medication use, diabetes, systolic blood pressure, anti-hypertensive medication use, age, and total bilirubin) to separately evaluate the independent association between eGFR and total WBC, each WBC differential count, and NLR. Multivariable logistic regression analysis was performed to separately evaluate the independent association between CKD and total WBC, each WBC differential count, and NLR, after adjusting for the aforementioned risk factors.

All statistical analyses were performed with the STATA 10 software (StataCorp LP, College Station, TX, USA), and a two-tailed p value of < 0.05 was considered statistically significant.

3. Results

Of the 2954 participants, 14.7% (266/1815) of men and 7.6% (87/1139) of women had CKD. The overall prevalence of CKD was 12.0% (353/2954). Compared with participants aged < 60 years, participants aged ≥60 years had a markedly higher prevalence rate of CKD in both men (105/1389 vs. 161/426, or 7.6% vs. 37.8%, p < .001) and women (36/957 vs. 51/182, or 3.8% vs. 28.0%, p < .001).

Compared with men without CKD, men with CKD were found to be older, with a higher blood neutrophil count, higher NLR, and lower lymphocyte count. They also showed a higher prevalence of hypertension, previous CVD, and hyperuricemia, but a lower prevalence of being current-smokers and current-drinkers. (Table 1) Compared with their counterparts, women with CKD were older, had a higher BMI, lower serum total bilirubin level, and higher blood monocyte and eosinophil counts, but showed no differences in neutrophil, lymphocyte counts and NLR. They also had a higher prevalence of hypertension, diabetes mellitus, dyslipidemia, previous CVD, and hyperuricemia. (Table 2).

To assess the relationship between eGFR and NLR, multivariable linear regression analysis showed that higher NLR (per 1 unit increment) was independently associated with lower eGFR [adjusted β = −1.06