Inflammation & Cell Signaling 2016; 3: e683. doi: 10.14800/ics.683; © 2016 by Sawako Kato, *et al*.
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MINIREVIEW

Neutrophil/lymphocyte ratio: A promising prognostic marker in patients with chronic kidney disease

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Received: March 01, 2015
Published: January 16, 2016

Chronic kidney disease (CKD), especially end-stage renal disease (ESRD), is associated with high morbidity and mortality due to cardiovascular disease (CVD) and infection, two common complications of ESRD that may be related, in part, to chronic inflammation and protein-energy wasting (PEW). Recently, in a Japanese prospective cohort study, we reported that there was significantly higher risk for CVD-related events in CKD patients with an increased neutrophil/lymphocyte ratio (NLR) at the start of their dialysis therapy. Because higher neutrophil count reflects inflammation and lower lymphocyte count may reflect malnutrition, NLR is hypothesized to be a more sensitive index than other existing inflammatory markers for detecting those at high risk for CVD-related events. This research highlight describes the potentials of NLR as a prognostic marker in patients with CKD. Although further studies are required to better understand its value as prognostic tool in clinical practice, current data suggest that NLR may be a useful and inexpensive marker for identifying CKD patients at high risk for CVD-related complications.

Keywords: chronic kidney disease; inflammation; neutrophil/lymphocyte ratio

Abbreviations: CKD, Chronic kidney disease; ESRD, end-stage renal disease; CVD, cardiovascular disease; PEW, protein-energy wasting; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; PCT, Procalcitonin; COPD, chronic obstructive pulmonary disease

To cite this article: Sawako Kato, *et al*. Neutrophil/lymphocyte ratio: A promising prognostic marker in patients with chronic kidney disease. Inflamm Cell Signal 2016; 3: e683. doi: 10.14800/ics.683.

Introduction

Reduced renal function is a significant risk factor for mortality in patients with chronic kidney disease (CKD); this risk is further increased as CKD progresses to end-stage renal disease (ESRD) [1]. The number one cause of death in patients with ESRD is cardiovascular disease (CVD) [1], while the second cause is infection [2]. Recently, in a Japanese prospective cohort study, we reported on the association between CVD and the neutrophil/lymphocyte ratio (NLR), a new index of inflammation in incident dialysis patients [3]. According to 2013 data from the Japanese Society of Dialysis Therapy, the total annual death rate in Japanese dialysis patients was 9.8%, while CVD and infection death rates were 3.8% and 1.96%, respectively [4]. The high mortality in this patient population may be related, in part, to immune dysfunction due to the uremic milieu [5].

CKD has been likened to a clinical model of premature ageing [6]. The uremic phenotype is characterized by various features of ageing, such as atherosclerosis, protein-energy wasting (PEW), oxidative stress, inflammation, sarcopenia, osteoporosis, and frailty, which all play a role in the increased risk of CVD and infection [7]. Among them, poor nutrition status and inflammation are highly prevalent and mutually entangled in patients with CKD [8]. The condition of poor nutrition status with exhausted body stores of protein and energy, now termed as PEW [9], is strongly associated with inflammation in patients with CKD [10]. In order to establish a new strategy to improve premature mortality in

patients with CKD, we started patient-oriented research called the Nagoya Immunity System in End-stage renal disease (NISE) study, a prospective cohort study of Japanese incident dialysis patients that started in 2007. In this research highlight, we introduce the backgrounds of our ongoing cohort study and discuss the potential role of NLR as an inflammatory biomarker in patients with CKD.

Chronic inflammation and infection in patients with CKD

In patients with CKD, the most widely studied biomarker associated with PEW and inflammation is C-reactive protein (CRP) [11, 12]. In CKD, inflammation may be induced by multiple causes, including *dialysis-related factors* such as membrane bioincompatibility and back-filtration of endotoxins from the dialysate [13], and *non–dialysis-related factors* such as non-access related infections and comorbidities [14]. While dialysis techniques have progressively developed to decrease dialysis-related risk factors, including inflammation [13], the rate of infections has not diminished [15]. The infectious disease depends on the individual patient's conditions, including immune dysfunction, PEW, comorbid conditions, dental illness, use of immunosuppression drugs, and, not least, presence of vascular access devices [16]. Central catheter [17, 18], periodontal disease [19], and bacterial translocation from the gastrointestinal tract [20] are often verified or suspected as a cause of chronic low-grade inflammation; however, it is likely that many unrecognized subclinical infections with opportunistic pathogens also contribute [21].

The high prevalence of infections in patients with CKD is deplorable, but especially since several kinds of infections, such as blood access-related infections and viral hepatitis, can be prevented by improving clinical practices. This vicious triad of immune dysfunction, infection, and inflammation is linked to increased risk for CVD-related morbidity and mortality [5]. Indeed, Dalrymple *et al*. reported that during the 30 days following an infection-related hospitalization, the risk for a CVD-related event in dialysis patients increased by 25% [22]. Furthermore, it was reported that cardiac complications worsen the outcomes of pneumonia in patients with CKD [23]. We believe that decreasing the incidence of infections may promise to improve CVD-related events, in part, by controlling inflammation.

Monitoring CRP level is still not routine in many dialysis centers worldwide, especially in the USA and Canada while the employment of routine measurement of CRP in Japanese dialysis center is over 70% [11, 24]. Moreover, baseline CRP levels might differ among races [25]. For example, CRP levels in Asian patients with CKD, including Japanese, seem to be much lower than those in Western patients with CKD [25]. In addition, CRP level measured by the standard technique may not detect low-grade inflammation, especially in Japanese patients with CKD [26]. Procalcitonin (PCT), a precursor of calcitonin and a polypeptide of 116 amino acids (molecular weight, 13 kDa), is a specific biomarker of bacterial infection [27]. Serum PCT (sPCT) has been reported to increase during bacterial infections in patients with CKD [28]. Based on data from the NISE cohort, we observed that PCT was positively correlated with CRP level [29]. In that paper, we also demonstrated that global DNA hypermethylation (gene expression under control by DNA methylation) was associated with inflammatory markers, including ferritin and PCT, suggesting that inflammation induced by subclinical bacterial infection promotes DNA methylation [29].

Inflammation and impaired nutrition status including PEW

In the NISE study, we are focusing on nutritional status as well as inflammation. The Subjective Global Nutritional Assessment (SGA) [30] is a reliable tool for assessing PEW. Guidelines released by the National Kidney Foundation's Kidney Disease/Dialysis Outcomes and Quality Initiative in 2000 recommended use of the SGA for assessing PEW in dialysis patients [31]. Thus, we have investigated the SGA as well as other markers of nutritional status such as serum albumin level in the NISE study.

There are other composite indices for evaluating nutrition state in patients with CKD. The Geriatric Nutritional Risk Index (GNRI) was originally developed for elderly patients, and is calculated from serum albumin level and body weight [32]. Recently, there have been some reports that the GNRI is a useful clinical nutritional marker for dialysis patients [33, 34]. Malnutrition-Inflammation Score (MIS), another increasingly employed composite index, comprises a questionnaire similar to that of SGA, as well as comorbid conditions, body mass index, albumin level, and transferrin level [35]. Amparo *et al*. reported that a worsening MIS score was associated with inflammation and increased mortality risk [10]. Whereas these indices appear to be appropriate nutritional markers, we often fail to predict outcome by using the GNRI, a modified MIS that considers albumin level, or serum albumin level alone. We speculate that one reason could be that serum albumin levels in patients undergoing dialysis therapy are confounded by volume overload and anabolic and catabolic processes.

Nutrition status and inflammation can affect concentration and differentiation of leukocytes. Because hematopoietic tissue requires a high nutrient supply, nutritional deficiencies in protein and calories may alter bone marrow function,

causing it to be insufficient to produce lymphocytes [36]. In the Dialysis Outcome and Practice Pattern Study, low lymphocyte count was significantly associated with mortality in 7700 adult hemodialysis patients [37]. Kuwae *et al*. reported that low lymphocyte percentage was associated with mortality and hospitalization, and correlated with MIS, in maintenance dialysis patients [38]. Therefore, NLR should be a suitable screening marker for patients at the start of dialysis therapy because it can be easily calculated, adds little or no cost, and can enable detection of high-risk patients who require further examination.

Potential role of NLR as an inflammatory biomarker

In 2014, based on the NISE study, we reported that a higher NLR was associated with higher risk of CVD in 86 incident dialysis patients with a median follow-up of 38.7 months [3]. The main finding of that study was that a higher NLR was associated with increased risk for CVD-related events, both in terms of shorter duration from the start of the dialysis therapy to the first CVD event and a large number of cumulative CVD events during the follow-up time. Moreover, patients with higher NLR had increased relative risk of CVD, after adjusting for age, sex, and diabetes. When comparing the prognostic power for CVD-related events among NLR, inflammatory markers (CRP and interleukin-6), and nutritional markers (serum albumin and SGA), NLR was the superior marker. According to these results, we concluded that NLR may be a useful marker for identifying patients at high risk of CVD.

As we mentioned, CKD is a premature ageing disease, a category that also includes chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, chronic heart failure, and autoimmune diseases [6]. A reliable risk prediction marker is necessary for any strategy aiming at reducing the high premature mortality in these patients, while fastness, simplicity, and low cost would be additional features requested in the clinical setting. According to our experience, NLR is a simple risk prediction marker for evaluating the combined impact of both inflammation and impaired nutritional status, without needing a special tool or technique.

NLR is being widely used to identify high-risk patients with various illnesses, including cancer [39] and CVD [39-42]. In our paper, we discussed NLR and clinical outcomes in patients with ESRD. Moreover, with regard to patients with CKD of other stages, high NLR predict worse outcomes also in patients with stage 4 CKD, and faster progression to renal replacement therapy [43]. High NLR also is related to endothelial dysfunction and increased CVD-related events [44].

Since releasing our report [3], the number of studies on NLR has been increasing in the fields of cancer, atherosclerotic disease including CVD in CKD patients. In 2004, Rifaioglu *et al*. reported that NLR was higher in patients with Beh ̧et disease compared with healthy subjects, and that increased NLR correlated with disease activity [45]. In 2005, it was reported that NLR in patients with ulcerative colitis was associated with active phase of the disease [46]. On the other hand, although obesity causes subclinical inflammation, NLR was not a good indicator of inflammation in patients with obesity and metabolic syndrome because they showed higher lymphocyte as well as leukocyte, neutrophil counts, and CRP level [47]. In addition, Salciccioli *et al*. investigated 5000 patients treated at the intensive care unit in a large clinical database, and reported that NLR was significantly associated with mortality; however, this relationship disappeared in patients with sepsis [48]. We speculate that NLR may be superior for identifying subclinical inflammation and malnutrition, but further studies are required to clarify its indication and limitations.

Conclusions

NLR has emerged as a suitable screening marker for identifying high-risk patients with chronic inflammatory disease including those with CKD. We believe that NLR has the potential to become a common biomarker in the clinical setting because it is inexpensive and easily performed.

Acknowledgments

The basic study of this research highlight was funded by the Nagoya University Graduate School of Medicine and was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research, Research on Rare and Intractable Disease, from the Ministry of Health, Labour and Welfare of Japan. The Department of Nephrology, Nagoya University Graduate School of Medicine, reports receiving research promotion grants from Kyowa Hakko Kirin Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Otsuka Phaemaceutical Co., Ltd. and Mochida Phaemaceutical Co., Ltd. However, the research topics of these donation grants are not restricted.

Conflict of interest

Bengt Lindholm is affiliated with Baxter Healthcare. Baxter Novum is the result of a grant from Baxter Healthcare to Karolinska Institutet. Other authors declare that they have no conflict of interest.

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