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Neutrophil-Lymphocyte Ratio a Potential Predictor of Inflammation Among Chronic Kidney Disease Patients

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Abstract

Chronic kidney disease is an important public health problem due to its high prevalence, morbidity, mortality, complex and long-term progressive nature. CKD progression is panic, as it affects both patient and physician. Early detection and treatment of chronic kidney disease not only reduce the progression but also narrow down the complications associated with end stage renal disease without creating an economic burden to the patient. As inflammation is closely linked with CKD and cardiovascular complications, early detection of inflammation is imperative thus can improve renal outcomes. There is a growing interest in research aimed at better understanding the disease status or predicting the prognosis of patients with simple blood tests associated with systemic inflammation. Among different approaches which monitor the inflammatory status among CKD patients, neutrophil-lymphocyte ratio (NLR) as a marker is getting much recognition as it reflects the state of systemic inflammation. However, the data regarding the association of neutrophil-lymphocyte ratio (NLR) and CKD progression is still limited. In the light of increased attention towards chronic kidney disease associated inflammation, this commentary aims to offer the better understanding of neutrophil-lymphocyte ratio (NLR) as a clinically useful indicator for inflammation and predicting the prognosis of CKD patients.

Keywords: Inflammation; Chronic kidney disease; Neutrophil-lymphocyte ratio

Abbreviations: CKD: Chronic Kidney Disease; NLR: Neutrophil-lymphocyte ratio; CRP: C Reactive Protein; ESRD: End Stage Renal Disease; HD: Hemodialysis; PD: Peritoneal Dialysis; TMAO: Trimethylamine N-oxide; eGFR: Estimated Glomerular Filtration Rate

Introduction

Chronic kidney disease (CKD) is defined, according to KDIGO guideline 2017 as "abnormalities of kidney structure or function, present for more than 3 months, with implications for health." Based on pathological cause, Classification of CKD is as follows: glomerular filtration rate category (from G1, normal, to G5, kidney failure), and albuminuria category (from A1, <30 mg/g, to A3 > 300 mg/g) [1].

Around 10-12% of the population are now affected with chronic kidney disease [2] and this will continue to rise, reflecting the increasing numbers of patients with Diabetes and Hypertension. It has been projected, if we assume CKD as a country, then it will be the third most populous country in the world. It also affects one-seventh of adults above the age of 20 years [3]. Patients suffer from this disease in many aspects. Because of its insidious nature, it is rarely diagnosed in early stages and if identified, therapy can only lessen the time for progression of the disease. Renal replacement therapy is an option, but affordability is also a concern [4]. CKD has been reported as an important cause of death and loss of disability-adjusted life-years worldwide.

Inflammation and chronic kidney disease

Normally, inflammation is a protective and physiological response to various noxious stimuli. However, in several chronic debilitating disorders, like chronic kidney disease, inflammation has proven to be maladaptive, uncontrolled and persistent [5]. This persistent, low-grade inflammation has been recognized as an important component of the CKD scenario, leading to fibrosis and loss of renal function. It's involvement in the occurring of all-cause mortality and poor quality of life is also apparent [6]. Inflammation is also reported to be correlated with coronary

heart disease [7], metabolic syndrome, diabetes [8], and aging [9].

From the last 2 decades, systemic persistent inflammation is observed as one of the major contributors to the uremic phenotype linked to cardiovascular disease, Depression, protein energy wasting, Osteoporosis and frailty.

Different studies have reported that a large proportion of CKD population from stage 3 onwards have chronic inflammation or increased level of CRP [10,11], with further increase in prevalence accompanying the decline of renal function and commencement of dialysis [12]. From the evidence received, relationship between the markers of inflammation, variation in GFR and nutrition habits in elderly individuals, conveys the notion i. e. the effect of inflammation on the progression of both CKD and cardiovascular diseases. Higher levels of inflammatory and prothrombotic markers are observed in renal insufficiency and this could be one of the explanations for the increased risk of cardiovascular disease among individuals suffering from renal insufficiency [13,14]. Another study reported that markers of inflammation and thrombosis were also associated with a subsequent rise in serum creatinine, urea and fall in estimated GFR [15]. Another finding stated that elevated plasma levels of fibrinogen, TNF-alpha and reduced serum albumin are associated with rapid loss of kidney function in CKD patients [16]. The prevalence of inflammation varies from 30 to 75% depending on numerous factors, such as residual renal function, geographic and genetic differences, dialysis therapy, comorbidities and even the cutoff point used for diagnosing inflammation by CRP [17].

To delay or retard the CKD progression which is largely caused by secondary factors that are often unrelated to the activity of the initial disease, create an urgent need to better understand the risk factors and underlying pathophysiology. Inflammation is reported to be associated with faster decline in eGFR and ESRD.

The precise mechanism through which inflammation would lead to a decline in renal function is not clear. Strong evidence over the recent years suggests that chronic inflammation represents a nontraditional risk factor in CKD population whereas gastrointestinal tract being a major player in systemic inflammation occurring in CKD [18]. Any change in the signaling pathway of the commensal flora contributes to the pathogenesis of diseases, including chronic inflammation and renal disease. Gut bacterial DNA fragments are detected in the pre-dialysis and chronic hemodialysis CKD patients [19]. A prospective, observational study reported the uremic toxins like p-cresol sulfate, indoxyl sulfate, and trimethylamine N-oxide (TMAO) were monitored in relation to kidney function (estimated GFR), and the results suggests that the elevated expression of these uremic toxins were associated with an increased risk for all-cause mortality in ESRD patients [20,21].

Among various inflammatory biomarkers like C-reactive protein, interleukin (IL)-6, 6 tumor necrosis factor and their soluble receptors, interleukin seems to be the most robust predictor of comorbidity and outcome in CKD [22]. There is growing evidence that neutrophil-lymphocyte ratio can also serve a productive and less expensive tool to assess the inflammatory status among CKD patients.

In patients with acute heart failure, neutrophilia and relative lymphocytopenia have been demonstrated to be an independent predictor of mortality [23,24]. Moreover, neutrophil-to-lymphocyte ratio (NLR) is monitored as a potential marker to assess the status of inflammation in cardiac and noncardiac disorders [25,26]. Recently, there were reports that NLR was closely associated with increased inflammation in both peritoneal dialysis (PD) and hemodialysis (HD) patients [27]. Another finding reported that ESRD patients on maintenance Hemodialysis showed higher values for NLR and PLR along with higher levels of inflammation thus revealing a significant positive correlation of both NLR and PLR with hs-CRP levels [28]. The increasing NLR ratio, which reflects inflammation, predicts the progression of CKD to dialysis. A study reported that patients with stage 4 CKD who had an NLR ≥3 showed swift progression to dialysis compared to patients with an NLR ratio <3. Duration of progression was shortened in the high NLR group [29]. A study reported by Forget et.al stated that neutrophil-lymphocyte ratio >3.53 shall be taken as indication of inflammation [30].

Another risk factor for mortality and progression of CKD is immune dysfunction. An increased total white blood cell (WBC) count often signifies inflammation and low lymphocyte counts suggests immunosuppression, Low lymphocyte count and high WBC are associated with worse prognosis in CKD patients [31]. Thus, non-microbial inflammation contributes to CKD progression and fibrosis. The increased neutrophil count reflects oxidative stress [32] and that lower lymphocyte counts indicates the status of general stress and deterioration of nutritional status [33], which in turn are associated with adverse renal outcomes.

Summary

Pertinacious low-grade inflammation has been identified as a significant component playing key roles in the pathogenesis and complications of CKD. Further research is needed to fully understand the function of inflammation in the CKD population, particularly in the early phases. Prediction of CKD progression is an important clinical issue. Early assessment of inflammation will open up better treatment options for the patients thereby delaying the progression of the CKD disease.

Several studies have defined and demonstrated many biomarkers, but excessive costs and technical factors such as advanced laboratory requirements have preclude their clinical use. In contrast, easily accessible, relatively inexpensive and simply examining the peripheral blood NLR has proven to be a clinically useful indicator for the rapid progression of CKD. Since NLR is readily derived from complete blood count tests, its

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potential as a predictor should be further investigated in a large cohort of patients with stage 1-5 CKD.

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