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Neutrophil-to-lymphocyte ratio predicts long-term all-cause mortality in patients with chronic kidney disease stage 5

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Abstract: Introduction: A high neutrophil-to-lymphocyte ratio (NLR) has been reported to be a strong biomarker of inflammation.
Aim: We sought to evaluate the impact of NLR on long-term all-cause and cardio-vascular (CV) mortality in hemodialysis (HD) patients.
Material and Methods: A total of 84 chronic kidney disease (CKD) stage 5 patients with 54 of them on HD, with a median age of 61.5 (51.3–74.8) years were enrolled. The association between NLR and clinical biomarkers was investigated. Multivariable Cox regression analysis was used to find significant predictors of all-cause and CV mortality at follow-up.
Results: The median NLR (interquartile range) was 3.0 (2.1–4.1). Patients with NLR ≥3.9 (the highest tertile) had higher five-year all-cause mortality then remaining patients (53.6% vs. 30.4%; p = 0.039). On the contrary, only a trend towards increased CV mortality was observed (25.0% vs. 42.9%; p = 0.10). NLR ≥3.9 was a significant predictor of all-cause mortality at five years [hazard ratio (95%CI): 2.23 (1.10–4.50); p = 0.025] in Cox regression model adjusted for age, gender, and diabetes status. Similarly, while using NLR as continuous variable a significant association between NLR and all-cause mortality was confirmed even after adjustment for covariates [hazard ratio per 1 unit increase (95%CI): 1.26 (1.06–1.51); p = 0.009] with the area under the receiver operating characteristic (ROC) curve of 0.64. Correlations between NLR and WBC, concentration of fibrinogen, albumin were observed.

C o n c l u s i o n s: Asymptomatic inflammation measured by NLR showed an association with long-term all-cause mortality in stage 5 CKD patients, even while white blood cell count was in the normal range.

Key words: neutrophil-to-lymphocyte ratio, CV mortality, all-cause mortality, CKD stage.

Introduction

A high neutrophil-to-lymphocyte ratio (NLR) has been reported to be a strong biomarker of acute and chronic inflammation. NLR is obtained from a complete blood count by dividing the number of neutrophils by the number of lymphocytes, therefore is inexpensive and widely accessible [1]. Not always the amount of leukocyte ratio in complete blood count is above the normal range or the modifications in percentage composition of morphotic components are changed. The extent of minimal inflammation taking part in main vessels and leading to cardiovascular disease (CVD) can be predicted by measuring NLR [2]. Interestingly, activated neutrophils are the source of neutrophil extracellular traps (NETs). The nuclear material (including DNA, citrullinated histones, and enzymes of neutrophil granule) released into extracellular space, plays a role in the nonspecific immune response and might promote inflammatory reactions and cause tissue damages [3, 4]. NLR has been studied as the independent predictor of mortality in heart failure, CVDs [5, 6], cardiothoracic surgery, neurological diseases, oncology [7–9], multimorbid medical inpatients [10] and also as the predictor of severity and mortality of patients with infectious diseases in general population [11, 12].

The prevalence of coronary artery disease (CAD) in patients with reduced kidney two times higher twice than in the general population. Also, an increased cardiovascular (CV) mortality is observed in patients with chronic kidney disease (CKD), especially those on renal replacement therapy [13, 14]. Yet, traditional risk factors for atherosclerosis such as÷ arterial hypertension, diabetes mellitus (DM), dyslipidemia, obesity, older age, and male sex are not explaining this dependence. Hence, microinflammation, especially asymptomatic, plays an important role in the development and progression of endothelial dysfunction and atherogenesis in hemodialysis (HD) patients through leukocyte adhesion and infiltration of the vascular endothelium [2, 15, 16]. Multifactorial causes of inflammation comprise of dialysis-related and unrelated components. The pathogenesis of MIA syndrome (malnutrition, inflammation, atherogenesis) may cause progressive atherosclerotic CVD. Oxidative stress leading to endothelial dysfunction and elevated plasma lipoprotein and proinflammatory cytokines (TNF-α, IL-1, and IL-6) develops chronic inflammation. Also, protein-energy wasting increases susceptibility to infection [17–24]. According to available data, the main mediators of MIA syndrome: low levels of albumin and

high levels of CRP and fibrinogen correlates with the high NLR [25, 26]. This requires further investigations. Thus, we sought to evaluate the impact of NLR on long-term all-cause and CV mortality in HD patients.

Materials and Methods

Patients

The study population included 84 patients (34 women and 50 men), including 54 patients on chronic HD. The median age was 61.5 (51.3–74.8) years and the patients were treated by HD for a median period of 11 years (range, 3.0–38.0 years). DM was diagnosed in 25 patients and arterial hypertension in 71 patients. Obesity defined as body mass index (BMI) ≥25 kg/m^2 affected 44 patients. Thirty-eight patients suffered from CAD and 18 had previous myocardial infarction. A total of 45 patients had hyperlipidemia. Patients were followed-up for five years and were stratified into tertiles according to NLR at baseline (Table 1).

Table 1. Demographic and biochemical features of the studied population. Results are presented as numbers (percentages) or median (interquartile range).

Items/Variables	Total (n = 84)	NLR <3.9 (n = 56)	NLR ≥3.9 (n = 28)	P Value
HD	54 (64.3)	38 (67.9)	16 (57.1)	0.33
HD time (HD patients only)	11.0 (3.0–38.0)	20.0 (4.0–38.0)	4.0 (1.0–12.0)	0.04
Gender (female)	34 (40.5)	23 (41.1)	11 (39.3)	0.88
Age	61.5 (51.3–74.8)	62.0 (50.0–74.5)	60.0 (53.0–74.5)	0.99
Age >61 years	42 (50.0)	29 (51.8)	13 (46.4)	0.64
BMI	25.1 (22.0–28.5)	24.9 (22.0–28.2)	25.3 (21.6–29.2)	0.87
Overweight	44 (52.4)	28 (50.)	16 (57.1)	0.54
DM	25 (29.8)	15 (26.8)	10 (35.7)	0.40
CAD	38 (45.2)	27 (48.2)	11 (39.3)	0.44
MI	18 (21.4)	14 (25.0)	4 (14.3)	0.26
DVT	21 (25.0)	13 (23.2)	8 (28.6)	0.59
Prior stroke	3 (3.6)	3 (5.4)	0 (0.0)	0.55
HA	71 (84.5)	46 (82.1)	25 (89.3)	0.53
Hyperlipidemia	45 (53.6)	31 (55.4)	14 (50.0)	0.64
Smokers	20 (23.8)	13 (23.2)	7 (25.0)	0.86
WBC	6.9 (5.5–8.1)	6.2 (5.4–7.5)	7.7 (6.3–9.5)	0.002

Table 1. Cont.

Items/Variables	Total (n = 84)	NLR <3.9 (n = 56)	NLR ≥3.9 (n = 28)	P Value
NLR	3.0 (2.1–4.1)	2.5 (1.8–3.0)	4.4 (4.1–5.3)	<0.001
Fibrinogen	5.2 (4.3–5.9)	5.2 (4.3–5.5)	5.9 (5.0–6.5)	0.020
Creatinine	445.9 (336.9–543.3)	466.4 (355.7–744.1)	410.6 (380.0–522.3)	0.79
eGFR MDRD	10.5 (8.0–14.0)	10.5 (6.0–14.0)	13.0 (10.0–15.0)	0.86
Albumin	42.0 (38.0–44.0)	41.5 (39.0–47.0)	39.0 (37.0–42.0)	0.003
CaxP	3.4 (2.9–4.1)	3.7 (2.8–4.8)	3.0 (2.8–3.7)	0.40
TGF-β1	5638.0 (4013.8–7578.3)	6090.0 (4130.5–6849.5)	5013.0 (3780.0–7702.5)	0.37
Pentraxin	1.4 (0.7–2.2)	1.2 (0.7–2.1)	1.4 (0.7–2.5)	0.82
IL-6	4.0 (2.1–7.5)	3.9 (2.1–6.9)	4.0 (2.4–7.5)	0.85
IL-18	616.0 (496.2–805.4)	609.4 (499.5–775.0)	642.0 (498.4–810.2)	0.70
hsCRP	7.4 (2.1–19.6)	5.9 (2.1–10.3)	16.2 (2.5–24.8)	0.17
MAP	103.3 (96.7–113.3)	103.3 (96.7–113.3)	105.0 (98.4–113.3)	0.16
Fe	10.9 (7.8–13.0)	11.2 (8.6–11.6)	7.9 (6.7–10.4)	0.02

HD — hemodialysis, BMI — body mass index, DM — diabetes mellitus, CAD — coronary artery disease, MI — myocardial infarction, DVT — deep vein thrombosis, HA — hypertension, WBC — white blood count, NLR — neutrophil-to-lymphocyte ratio, eGFR MDRD estimated glomerular filtration rate Modification of Diet in Renal Disease, CaxP — calcium-phosphorus products, TGFβ1 — transforming growth factor β1, IL — interleukin, hsCRP — high-sensitivity C-reactive protein, MAP — mean arterial pressure, Fe — iron.

Ethics statement

The study was conducted according to the principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonization/Good Clinical Practice regulations. The study was approved by the Bioethics Committee of the Jagiellonian University (KBET/94/B/2011) and all patients signed an informed consent for their participation. All the patients were treated at the Department of Nephrology, University Hospital in Krakow.

Laboratory tests

Complete blood cell count and serum concentrations of lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (TG), serum concentrations of albumin, high-sensitivity C-reactive protein (hsCRP), interleukins: IL-6 and IL-18, transforming growth factor-β1 (TGFβ1), Pentraxin were assessed in all patients.

On the day of blood collection, routine laboratory tests were performed using automatic biochemical analysers: Hitachi 917 (Hitachi, Japan) and Modular P (Roche Diagnostics, Mannheim, Germany). Serum hs-CRP concentration was determined by an immunonephelometric assay using Nephelometer BNII (Siemens, Healthcare Diagnostics, Germany). Serum samples for other laboratory tests were aliquoted and stored at a temperature below –70°C. The measurements of IL-6, TGF-β1 and Pentraxin were performed using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems ELISA kits, Minneapolis, United States), while IL-18 with the MBL ELISA kit (Nagoya, Japan). Hematological parameters were measured using Sysmex XE 2100 Hematological Analyzer (Sysmex Corp., Japan).

The NLR was calculated for each patient using absolute neutrophils count ($\times 10^9$/l) divided by absolute lymphocytes count ($\times 10^9$/l) from the complete blood count.

Statistical methods

The population of patients was stratified into tertiles according to NLR at baseline. Categorical variables were expressed as numbers of patients (percentages). Continuous variables were expressed as median (interquartile range). The association between NLR and other biomarkers was assessed using the Pearson's correlation coefficient (r). Survival was estimated using Kaplan–Meier method according to NLR categories. In addition, a multivariable Cox proportional hazards model was constructed to identify independent predictors of all-cause and CV mortality at follow-up. Variables entered in multivariate analysis were age, gender, DM, and hemodialysis status. Results are presented as hazard ratios with associated 95% confidence interval (CI). Receiver operating characteristic (ROC) curves analysis was used to assess the predictive ability of NLR and other biomarkers. STATISTICA version 13.3 (Tibco Software Inc., Palo Alto, CA) was used for analysis and significance was determined at P value of <0.05.

Results

The median NLR (interquartile range) was 3.0 (2.1–4.1). Patients with NLR ≥3.9 (the highest tertile) had higher five-year all-cause mortality then remaining patients: 53.6% vs. 30.4%; p = 0.039 (Fig. 1A). On the contrary, only a trend towards an increased CV mortality was observed: 25.0% vs. 42.9%; p = 0.10 (Fig. 1B).

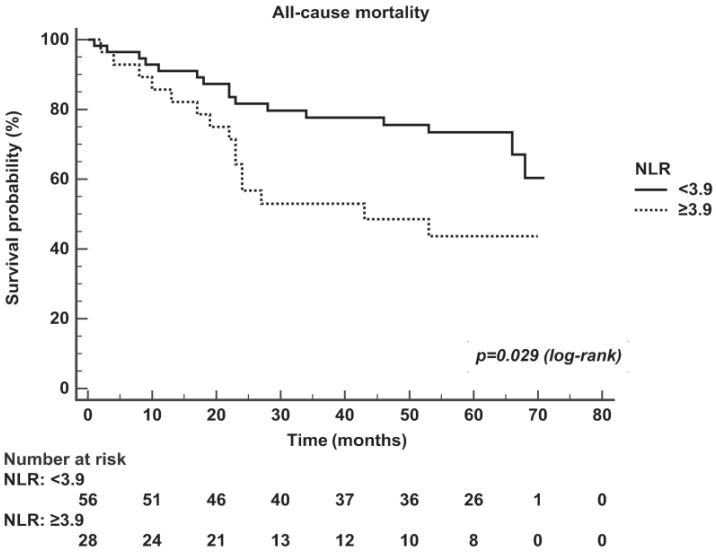

Fig. 1A. Kaplan–Meier estimates of all-cause mortality.

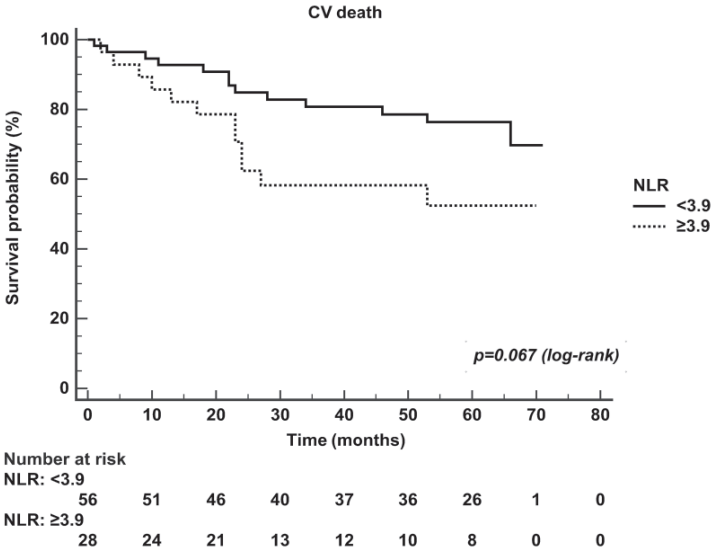

Fig. 1B. Kaplan–Meier estimates of CV mortality. Patients divided into two groups based on the neutrophil-to-lymphocyte ratio (NLR) above and below 3.9.

After adjustment for age, gender, DM, and hemodialysis status in Cox regression model, NLR ≥3.9 was a significant predictor of all-cause mortality at 5 years (hazard ratio [HR] (95%CI) 2.40 (1.17–4.92); p = 0.017). Similarly, while using NLR as continuous variable a significant association between NLR and all-cause mortality

was confirmed even after adjustment for covariates (HR per 1 unit increase (95%CI) 1.26 (1.06–1.51); p = 0.010) with an area under the ROC curve of 0.64 (Fig. 2). The optimal cut off value of NLR for prediction of all-cause death was ≥4.16 with sensitivity and specificity of 40.6% and 86.5%, respectively. For the used cut off value of ≥3.90, sensitivity and specificity was 43.8% and 80.8%, respectively.

However, there was no association between NLR and mortality due to heart failure, myocardial infarction, infections, neoplasms or stroke (Table 2). Interestingly, there were no significant correlations between serum concentration of hs-CRP, IL-6, IL-18, TGF β1 and NLR in the studied patients with CKD stage 5. Nonetheless, significant correlations were observed between NLR and WBC, as well as, serum concentration of fibrinogen and albumin (Table 3).

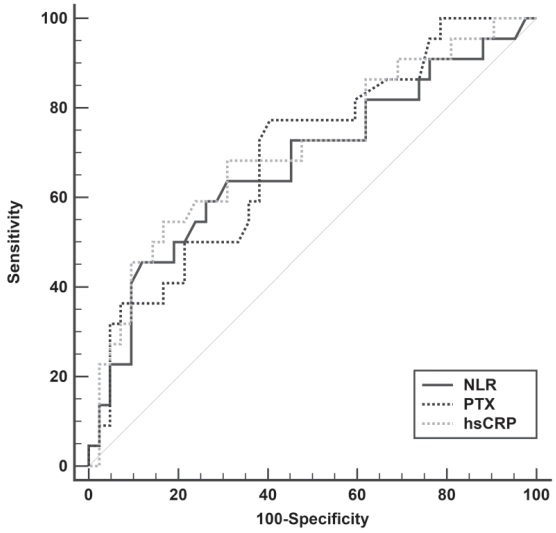

Fig. 2. Receiver operating curves for NLR, PTX, hsCRP and all-cause death.

Table 2. Five-year mortality stratified by NLR and cause of death. Results are presented as numbers (percentages).

Five-year mortality	Total (n = 84)	NLR <3.9 (n = 56)	NLR ≥3.9 (n = 28)	P Value
All	32 (38.1)	17 (30.4)	15 (53.6)	0.039
CV-related	26 (31.0)	14 (25.0)	12 (42.9)	0.10
HF-related	18 (21.4)	10 (17.9)	8 (28.6)	0.26
Infection-related	3 (3.6)	2 (3.6)	1 (3.6)	1.00
Neoplasm-related	2 (2.4)	1 (1.8)	1 (3.6)	0.99
MI-related	18 (21.4)	10 (17.9)	8 (28.6)	0.26
Stroke-related	8 (9.5)	4 (7.1)	4 (14.3)	0.43

CV — cardiovascular, HF — heart failure, MI — myocardial infarction

Table 3. Correlation between NLR and other inflammatory markers.

		NLR	IL-18	IL-6	sTNF R II	Pentraxin	hsCRP
NLR	P value	1	0.073	0.031	0.090	0.012	0.030
			0.547	0.801	0.457	0.919	0.794
IL-18	P value	0.073	1	0.203	0.425**	0.258*	0.206
		0.547		0.071	0.000	0.022	0.078
IL-6	P value	0.031	0.203	1	0.193	0.313**	0.333**
		0.801	0.071		0.087	0.005	0.004
sTNF R II	P value	0.090	0.425**	0.193	1	0.340**	0.320**
		0.457	0.000	0.087		0.002	0.005
Pentraxin	P value	0.012	0.258*	0.313**	0.340**	1	0.269*
		0.919	0.022	0.005	0.002		0.022
hsCRP	P value	0.030	0.206	0.333**	0.320**	0.269*	1
		0.794	0.078	0.004	0.005	0.022	

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
NLR — neutrophil-to-lymphocyte ratio, IL — interleukin, sTNFR II — soluble tumor necrosis factor receptor 2, hsCRP — high-sensitivity C-reactive protein

Discussion

Our study has confirmed the usefulness of NLR as a predictor of all-cause mortality in patients with CKD stage 5. NLR ≥3.9 was associated with increased long-term all-cause mortality, whereas only a trend towards an increased CV mortality was observed.

Azab *et al.* [27] conducted the study to explore the normal range of NLR and its relationship with demographics, risk factors and comorbidities in a non-institutionalised population of adults in the US. Interestingly, they found that such normal value significantly varies with race and they emphasise the necessity to adjust NLR cut-off points to racial differences. Authors suggest racial distinctions in the inflammatory response. Additionally, elevated NLR was associated with self-reported chronic conditions such as DM, CV diseases, smoking or obesity [27].

Previous studies have demonstrated the predictive value of NLR as an inflammatory marker in a variety of diseases but especially were focused on CV diseases in the general population. Among others, in few studies, correlations between NLR and short- and long-term mortality in patients with myocardial infarction and patients undergoing percutaneous coronary interventions were shown [28–31]. Moreover, in assays relating to chronic heart failure, it has been presented that NLR is a better

predictor of mortality than absolute counts of neutrophils and lymphocytes. On the contrary, we confirmed no correlation between NLR and both chronic heart failure-related mortality and myocardial infarction-related mortality [32]. Interestingly, Dong *et al.* [33] has shown not only positive association of NLR and GRACE score but also that NLR combined with GRACE score gives better predictive value than GRACE score alone in predicting CV events in Chinese patients with acute coronary syndrome.

Regardless of those studies, only a few concerned patients with CKD or on renal replacement therapy. According to Kocyigit *et al.* [34] worse prognosis and faster progression affected the ones with a high NLR in patients with stage 4 CKD. Likewise, Tatar *et al.* [35] divided geriatric patients with stage 3–5 CKD into two groups: with increased and decreased or stable delta NLR and found the basal NLR as the independent predictor of death. Moreover, NLR >3.76 and 3.72 was investigated to be a significant and independent predictor of CV events in pre-dialysis and dialysis-dependent patients, respectively [36, 37]. Though, Altunoren *et al.* [38] found in Cox-regression analysis that NLR is not an independent predictor of CKD progression except for advanced CKD stages. Interestingly, some studies showed NLR as a simple indicator of contrast induced nephropathy in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention [39]. According to Bal *et al.* [40] study, NLR is an independent predictor of the extent of coronary artery disease (CAD) in patients with end stage renal disease (ESRD). In our research no NLR correlation with myocardial infarction-related death was found.

Compellingly, Neuen *et al.* [41] in multivariate Cox regression showed NLR ≥3.3 as independently associated with all-cause mortality, as well as, with CV death marker in HD patients. Similarly to Han Li *et al.* study [42] where NLR ≥3.5 was a predictor of both all-cause and CV mortality. Correspondingly, An *et al.* [43] proved that peritoneal dialysis patients with NLR >3.5 had an increased risk of overall and CV mortality. In Chen *et al.* [44] study NLR was able to predict clinical outcomes in patients with advanced CKD and peripheral artery disease undergoing percutaneous transluminal angioplasty.

According to Afari *et al.* [24] NLR as a marker of CV diseases has a greater predictability than total white blood cell (WBC) count or neutrophil count. Some studies have demonstrated the association between NLR and inflammatory markers such as TNF-α, CRP, albumin, hemoglobin or total cholesterol [45–47], though in our study, apart from serum albumin level, such correlation has not been shown. Furthermore, Ahbap *et al.* [26] demonstrated in ESRD population on HD a significant positive correlation between NLR and hsCRP. Similar NLR and CRP positive association was found in Pineault *et al.* study [25]. However, this study showed inverse correlation with albumin in patients receiving chronic dialysis. In the cross-

sectional study of Thijssen [48], parameters such as age, access type, and variables of 3 domains: nutrition, dialysis parameters and inflammation measured by WBC, NLR, and hemoglobin, were related to serum albumin. Ozcicek *et al.* [49] found NLR as a predictor of epicardial adipose tissue in HD patients. In geriatric population elevated NLR was an independent factor to predict the malnutrition or the risk of malnutrition [50] as well as an indicator of fracture presence, risk factor and moderate predictor of postoperative myocardial injury, high inflammatory response/infection and in-hospital death [51]. In HD patients study NLR better predicted mortality in addition to demographics, comorbidities, and serum albumin [52]. In results from 2 international cohort studies increased CRP levels >10.0 mg/l was observed with the combination of high NLR and low albumin levels [53]. According to Chittawar *et al.* [54] analysis of Indian population revealed a significantly higher occurrence of diabetic nephropathy, albuminuria, retinopathy and coronary artery disease (CAD) among patients in higher quartiles of NLR. They have long standing DM and lower GFR. NLR was the best independent predictor of the occurrence of microvascular complications in patients with DM type 2. Another study showed a significant corelation between NLR and diabetic nephropathy, especially in early stages [55].

There are many studies based on cancer patients groups showing NLR/albumin ratio as an independent prognostic factor of overall survival [56–58].

Interestingly, also lymphopenia can be associated with progression of atherosclerosis [59]. Moreover, De Jager *et al.* [60] found that NLR and lymphocytopenia are better predictors of bacteriemia in adult patients admitted to Emergency Department than routine parameters like CRP level, WBC count and neutrophil count. However, in our study among HD patients, no association with infectious mortality was found.

Some studies on patients with different kinds of neoplasms have shown the composition of preoperative or pretreatment plasma fibrinogen level and NLR as a combined score called F-NLR. Marchetti *et al.* [61] divided F-NLR into 3 groups (group 0 for both low markers, group 1 for low NLR and high fibrinogen and group 2 for both high markers) and identified their prediction of prognosis and response to treatment in patients with ovarian cancer. F-NLR was investigated as the independent prognostic factor for the disease-free survival and overall survival (for patients with small cell lung cancer and hypopharyngeal squamous cell cancer [62] or advanced epithelial tumor cancer [63, 64]). Fu *et al.* [65] showed that F-NLR enhances prognostic value for hepatocellular carcinoma patients and their poor outcomes. According to Arigami *et al.* [66] study, F-NLR can be a clinical predictor of response to treatment (chemotherapy and chemoradiotherapy) in patients with gastric cancer. Moreover, in Liu *et al.* [67] study postoperative F-NLR score for outcomes in gastric cancer independently predicted overall survival, However, in similar study of lung adenosquamous cancer the combination of postoperative NLR, PLT, PLR (platelet-

to-lymphocyte ratio) and fibrinogen called CO-NPF had grater prognostic value than NLR, fibrinogen, PLT or PLR separately [68]. Interestingly, F-NLR may be used as a way to distinguish between the non muscle-invasive and muscle-invasive bladder cancer [69]. To our best knowledge, there are no investigations showing the association between NLR and fibrinogen in patients on HD. In our study we found a correlation between NLR and fibrinogen.

The relationship between NLR and atherosclerosis has several theories and explanations such us a direct role of neutrophils in early endothelial dysfunction, atherogenesis and plaque destabilization [2, 15, 16]. Recently, the NETs and its marker of formation — circulating cell-free DNA are demonstrated to promote inflammation and to predict mortality in HD patients [70, 71]. According to Jwa-Kyunget *et al.* study, blood urea nitrogen and creatinine levels were not associated with NET levels, but interestingly, whole blood WBC and neutrophil counts were significantly elevated in patients with an increased NET formation, as were NLR and hs-CRP levels. Furthermore, baseline NET formation correlated positively with CAD, peripheral neutrophil count and inflammatory markers such as NLR and hs-CRP. Moreover, multivariate analyses identified the prevalence of CAD and neutrophil counts as independent predictors of baseline NET formation [72]. Still, many facts concerned with chronic, low-grade inflammation and atherosclerosis, especially among patients with CKD treated by HD need more and deep investigations. Consequently, little is known about the interpretation of the findings of inflammatory markers in the clinical setting. Nevertheless, in practical findings, NLR above a certain value might induce changing or initiating treatment as in the cease of CRP use. Thus, low-cost and easily available measurement are the strong advantages to prompt to consider NLR as a predictor of all-cause mortality. Yet, large studies should be undertaken before a wide clinical practice acquaintance.

Study limitations

The main study limitation was the single measurement of complete blood count on admission. Therefore, the changes in NLR were not evaluated. Moreover, patients with DM should be excluded. NLR may be superior for identifying subclinical inflammation but further studies are needed to clarify its indications and limitations.

Conclusions

Asymptomatic inflammation measured by NLR showed an association with long-term all-cause mortality in CKD stage 5 patients, even while white blood cell count was in the normal range. As a cheap and convenient marker NRL can be useful in identifying CKD stage 5 patients at a high-risk of mortality at long-term follow-up.

Contribution statement

KK and KW conceived the study, were the major participants in its design, coordination, interpretation of results and statistical analysis, they also prepared draft manuscript. AD performed statistical analysis. MP, AP, MK, BS, PG and MB participated in the design of the study. PL and MAK participated in design of the study and analyzed the data. All authors were involved in data collection, draft manuscript modifications and approved the final version of the manuscript.

Disclosure statement

The manuscript has not been published elsewhere.

Conflict of interest

None declared.

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