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Journal of Nephrology and Renal Disorders

Resesarch Article

Neutrophil Lymphocyte Ratio in Acute Kidney Injury and Chronic Kidney Disease: Gender Associations. A Descriptive Comparative Study

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Citation: Peter Kehinde Uduagbamen, Adesola T Oyelese, Boladale A Alalade, Sule I Ahmed, Marion Itohan Ogunmola (2022) Neutrophil Lymphocyte Ratio in Acute Kidney Injury and Chronic Kidney Disease: Gender Associations. A Descriptive Comparative Study. J Nephrol Ren Disord 3: 101

Abstract

Introduction

The neutrophil lymphocyte ratio (NLR) is a cheap and readily available tool that is becoming increasingly recognized as a marker of pan-systemic inflammation. Gender differences have been identified in various inflammatory responses and play significant roles in the etiopathologic, epidemiological, clinical and prognostic profile of most disease entities. We assess gender association with the NLR.

Methods

One hundred and eighty-eight participants, with were studied. Data of clinical, NLR, uric acid, urine albumin creatinine ratio (UACR), electrolytes were documented and independent predictors of the association between NLR and gender were identified.

Results

The NLR was higher in CKD than AKI,P=0.04, higher in females, P<0.001 and aged, P<0.001. The NLR was positively related to the platelet-lymphocyte ratio (PLR), albumin creatinine ratio, P=0.01 and the severity of the inflammatory condition. The men had higher albumin, creatinine, uric acid and UACR. The uric acid was higher in AKI than in CKD, P=0.04. The systolic blood pressure and PLR were higher in AKI than CKD, P<0.001 and P=0.04. The serum bicarbonate was lower in AKI than CKD, P=0.04. Females were more likely to be older, P<0.001.

Aging (OR-6.20, CI-3.17-9.58), smoking (OR-5.86, CI-4.52-8.95), systolic blood pressure (OR-3.75, 95% CI-1.83-4.03) and serum creatinine (OR-5.73, 95% CI-1.65-5.89) independently predicted gender associations of the NLR.

Conclusion

The NLR is a readily available and cheap tool that marks inflammation and higher in CKD than AKI. Females had higher NLR was higher in females and was positively related to the severity of the inflammatory condition hence it can be used in prognosticating diseases and perhaps predict outcome.

Keywords: Neutrophil Lymphocyte Ratio; Inflammation; Acute Kidney Injury; Chronic Kidney Disease; Platelet Lymphocyte Ratio; Hyperuricemia; Albumin Creatinine Ratio.

Introduction

The neutrophil lymphocyte ratio (NLR), a cheap and readily available hematologic tool is becoming increasingly recognized as a marker of pan-systemic inflammation of various sources, including stress.[1] Gender differences have be identified in various inflammatory responses, from acute insults through chronic to debilitating terminal diseases. These gender difference which are mostly contributions from genetic and environmental factors have be reported to play significant roles in the etiopathologic, epidemiological, clinical and prognostic profile of most disease entities.[2] In acute inflammatory states, women show higher tissue responses associated with higher levels of inflammatory markers such as leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and in chronic illnesses, with lymphopenia.[3]

The gender differences seen in physiologic and pathologic states have largely be attributed to the differential actions of the sex hormones [4]. The heightened inflammatory cascade in chronic kidney disease (CKD) has been reported to be the main bases upon which the poor quality of life (QOL) increased morbidity and mortality are hinged, compared with disease conditions preceding CKD such as hypertension, diabetes.[5] The prevalence of hypertension and CKD (particularly predialytic) is reported to be higher in males and this has been attributed to their higher responsiveness to the sympathetic, renin angiotensin and aldosterone system (RAAS) stimulation and lesser responsiveness to sympathetic and RAAS inhibition.[6] Testosterone induces a dose-dependent apoptotic damages in the renal tubules in addition to the alteration of the glomerular microstructural and hemodynamic pattern. [7] Castration and other conditions that reduces androgenic activity are associated with a lower risk of CKD, lesser proteinuria and slowing of CKD progression.[8]

The differential immune response in acute and chronic inflammatory states tends to be related more to the leucocytes, neutrophils and monocytes. While lymphocytes are increased in many recurrent inflammatory condition, they are suppressed in chronic disease associated with debilitating course. This may explain the higher lymphocyte count in Africans compared to Caucasians as the former have higher exposure to recurrent acute antigenA positive association has been reported between estrogens and inflammatory markers.[9]

The leucocyte count, the neutrophil, neutrophil-lymphocyte ratio and progesterone are also reported to be higher peri-ovulation and through the luteal phase of the menstrual flow.[10] The reduction in the quality of sleep in the peri-menstrual period is adduced to the lower concentration of estrogens considering the suppressive role of estrogens on the pineal gland. The NLR is reported to be elevated in both AKI and CKD, having a positive relationship with both. Elevated NLR in AKI could be predictive of poor treatment outcome and death. A greater increase of NLR in AKI could be predictive of sepsis, progression to CKD and, mortality but in CKD, these increases are mostly pointer to disease severity[11]. The NLR is well reported worldwide in AKI and in CKD but the study of NLR in both conditions is rarely reported, we studied the NLR in AKI and CKD and assess gender associations in both.

Material and Methods

Study design

This was a prospective comparative study conducted at the Nephrology and Hypertension Clinics of Babcock University Teaching Hospital, Ilishan-Remo between August 2020 and July 2021. Participants were 16 years or older, with at least a monthly regular clinic attendance, gave informed consent and were consecutively recruited. Participants with AKI met the KDIGO 2012 AKI diagnostic criteria and participants with CKD met the KDOQI 2012 diagnostic criteria. All participant had renal ultrasound scan to rule out obstructive lesion. [12, 13]

Exclusion criteria

Participants with cancers, connective tissue disease, cardiorenal syndrome, hepatorenal syndrome, hematologic disorders, diabetes and blood dyscriasis. Frequent users of non-steroidal anti-inflammatory drugs (NSAIDs), those who within the previous 6 months from the time of recruitment into study, had used steroids and/or heavy metal containing soaps, creams, ointments or "eye paints", those on weight loosing regimen and participants who were taking herbal remedies were excluded.

A brief history was taken from each participant and a general physical examination was conducted. The height and weight were measure using standardized protocols and the body mass index was calculated. The blood pressure (BP) was measured in the sitting position after a five minutes rest, with participants' arm and back supported. Each participant hospital case file was retrieved to recover the demographics and rule out any exclusion criteria.

An on-the-spot microalbuminuria test was done using the Micral albustic strips which were taken and the end of each strip with the pad was inserted into the urine for 50 seconds and the value of matched color for creatinine and albumin were recorded. Two venous blood samples was collected from a peripheral vein while patient sat at room temperature, for analysis of the full blood count (hematocrit, leucocytes and differentials and platelets), erythrocyte sedimentation rate (ESR) and, serum electrolytes, urea, creatinine and uric acid. The creatinine-based glomerular filtration rate (GFR) was calculated with the CKD epidemiological collaboration (CKD-EPI) formula [14]

Definitions

Elevated NLR: >3 [15]
Elevated PLR: >160 [16]
AKI: Increase in serum creatinine by 0.3 mg/dl (26.5umol/L) within 48 hours, or increase in serum creatinine, 150% of baseline, known to have occurred within the previous 7 days, or urine output (OU): <0.5 ml/kg/hr for 6 hour.

AKI stage 1: Rise in serum creatinine of $\geq$26 umol/L $\leq$48 hours or 150-199% of baseline within 7 days or UO <0.5 ml/kg/hr for more than 6 hours.

AKI Stage 2: AKI stage 2: Serum creatinine 200–299% of baseline within 7 days or UO <0.5mls/kg per hour for more than 12 hours

AKI Stage 3: AKI Stage 3: Serum creatinine ≥ 300% of baseline within 7 days or concentration of ≥ 354 umol/L within 48 hr or ≥ 50% rise from baseline within 7 days or any requirement for RRT or OU <0.3ml/kg per hour for 24 hrs or anuria for 12 hrs.

CKD stage 1and 2: History or radiological evidence of CKD with GFR $\geq$60 [17]
CKD stage 3-4: History or radiological evidence of CKD with GFR 15-59 [17]

Hypovolemia: Fluid loss with features of dehydration and changes in the hemodynamics such as tachycardia and hypotension

Sepsis: Culture confirmed or suspected microbial infection, with at least 2 of these conditions:
temperature > 38°C or < 36°C, pulse rate >90/minute, respiratory rate > 20cycles/minute, white cell count of > 11,000cells/mm^3 or < 4000 cells/mm^3 [18]

Hypotension

Intraoperati Hypertension: BP $\geq$140/90 mmHg or physician diagnosed hypertension or using BP lowering drugs to control BP [19]

Diabetes: Fasting blood glucose ≥7.0 mmol or physician-diagnosed diabetes or using hypoglycemic agents [20]

Microalbuminuria: ACR >3.4mg/mmol [21]
Anemia: hematocrit <39% (males) and <36% (females) [22]
Hypoalbuminemia: Serum albumin <35mg/dl [23]
Hyperuricemia: uric acid (UA) >0.42mmol/l (males); 0.36mmol/l (females) [24]
Metabolic acidosis (MA): Serum bicarbonate <22 mmol/l [25]

Statistical analysis

Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Inc, NY, USA). Continuous variables are presented as means or medians and compared using paired student t-test. Categorical variables are presented as proportions and compared using the Chi-square test or Fisher's exact test when variables are less than five. Variables with a p-value <0.25 from univariate analysis were entered into a multivariate model using backward elimination to adjust for cofounders [26]. Associations between variables were considered significant for p-value <0.05.

Ethical clearance

The research followed the tents of the Declaration of Helsinki and was approved by Babcock University Human Ethics committee (BUHREC/733/19, NHREC/24/01/2018).

Results

A total of 188 participants (44 with AKI and 144 with CKD) were studied. The mean of the population was 48.2 ± 9.9 years (AKI-46.4 ± 6.2 years, 48.8 ± 15.9 years). A greater proportion of the elderly were women, P=0.001 (Table 1). Males were more likely to be hypertensive, P=0.001, and to smoke, P<0.001. AKI was commoner in males as CKD was commoner in females, P=0.04.

Variables	All participants N=188 (%)	Males N=103 (%)	Females N=85 (%)	P-value
Age, years				
16-39	52 (27.7%)	34 (33.0%)	18 (21.2%)	
40-64	108 (57.4%)	60 (58.3%)	48 (56.5%)	0.001
≥65	28 (14.9%)	9 (8.7%)	19 (22.3%)	
Smoking				
Yes	14 (7.4%)	14 (13.6%)	0 (0.0%)	<0.001*
No	174 (92.6%)	89 (86.4%)	85 (100.0%)	
BMI, kg/m^2				
<25.0	73 (38.8%)	39 (37.9%)	34 (40.0%)	0.1
≥25.0	115 (61.2%)	64 (62.1%)	51 (60.0%)	
Systolic BP, mmHg				
<140	111 (59.0%)	52 (50.5%)	59 (69.4%)	0.003
≥140	77 (41.0%)	51 (49.5%)	26 (30.6%)	
Diastolic BP, mmHg				
<90	132 (70.2%)	67 (65.0%)	65 (76.5%)	0.001
≥90	56 (29.8%)	36 (35.0%)	20 (23.5%)	
Kidney disease				
AKI (n, %)	44 (23.4%)	21 (20.4%)	23 (24.4%)	0.04
CKD (n, %)	144 (76.6%)	82 (79.6%)	62 (75.6%)	

BMI-body mass index, BP-blood pressure, AKI-acute kidney injury, CKD-chronic kidney disease

Table 1: Participants' sociodemographic, and clinical characteristics

Sepsis was the commonest cause of AKI (Table 2) Hypertension followed by chronic glomerulonephritis, was the commonest cause of CKD

Variables	Frequency	Percentage
Acute kidney Injury		
Sepsis	16	36.4
Acute blood loss	7	15.9
Exogenous nephrotoxins	7	15.9
Preeclampsia/Eclampsia	4	9.1
Others	10	22.7
Chronic Kidney Disease		
Hypertension	59	41.0
Chronic glomerulonephritis	42	29.2
Diabetes	18	12.5
Obstructive uropathy	13	9.0
Others	12	8.3

Table 2: Etiology of Acute Kidney Injury and chronic kidney disease in the participants

The mean NLR for the study was 3.8 ± 0.9, it was 3.5 ± 1.2 for AKI and 3.9 ± 1.4 for CKD. The mean NLR of participants with sepsis was higher than other causes of AKI, 4.7 ± 1.7. The mean blood pressure, uric acid and hematocrit and serum albumin of participants with AKI were higher than their CKD counterparts, P<0.001, P=0.001, P=0.04.and P=0.06 (Table 3). The mean ACR and NLR of the CKD cohorts were higher than that of AKI, P=0.03 and P=0.05. The NLR and the PLR were more likely to be elevated in females. P=0.04 and P=0.05 (Table 4). The mean serum albumin, hematocrit, uric acid and creatinine were all higher in men than women, P=0.06, P=0.04, P=0.001 and P<0.001.

From the multivariate model (Table 5), aging (OR-6.20, CI-3.17-9.58), smoking (OR-5.86, CI-4.52-8.95), systolic blood pressure (OR-3.75, 95% CI-1.83-4.03) and serum creatinine (OR-5.73, 95% CI-1.65-5.89) independently predicted gender associations.

Variables	All participants N=188 (%) Mean ± SD	AKI N=44 (%) Mean ± SD	CKD N=144 (%) Mean ± SD	P-value
Sex Males Females	 103 (54.8%) 85 (45.2%)	 21 (47.7%) 23 (52.3%)	 82 (56.9%) 62 (43.1%)	0.01
Age, years	48.2 ± 9.9	46.4 ± 6.2	48.8 ± 15.9	0.04
BMI, kg/m^2	26.6 ± 5.8	27.1 ± 6.3	26.5 ± 4.5	0.06
Systolic BP, mmHg	136.3 ± 17.7	146.8 ± 19.4	133.1 ± 17.7	<0.001
Diastolic BP, mmHg	82.4 ± 11.0	86.5 ± 14.4	81.2 ± 11.8	0.03
ACR, mg/mmoL	35.4 ± 7.1	30.3 ± 6.6	35.7 ± 8.7	0.003
NLR	3.8 ± 0.9	3.5 ± 1.2	3.9 ± 1.4	0.05
PLR	125.0 ± 11.7	128.5 ± 16.3	123.9 ± 23.5	0.04
Serum bicarbonate, mmol/L	21.1 ± 4.5	19.4 ± 4.2	21.6 ± 3.8	0.04
Anion gap, mEq	16.1 ± 4.4	17.6 ± 6.3	15.6 ± 2.9	0.03
Serum Creatinine	206.5 ± 9.7	179.5 ± 8.9	214.8 ± 11.7	<0.001
Uric acid, mmol/L	414.8 ± 14.7	452.8 ± 18.7	403.2 ± 16.5	0.001
Hematocrit, %	33.6 ± 8.2	35.3 ± 8.2	33.1 ± 6.1	0.04
Albumin, mg/dL	4.1 ± 4.6	4.4 ± 6.4	4.0 ± 4.4	0.06

Low HDL cholesterol, mg/dL	97 (51.6%)	27 (61.4%)	70 (48.6%)	<0.001
Elevated LDL cholesterol, mg/dL	89 (47.3%)	24 (54.5%)	65 (45.1%)	0.01
Elevated triglyceride, mg/dL	97 (51.6%)	32 (72.7%)	65 (45.1%)	<0.001
Reduced kidney volume, cm^3	58 (30.8%)	4 (9.1%)	54 (37.5%)	<0.001

Table 3: Relationship between duration of disease and participants' characteristics

Variables	Males N=103 (%)	Females N=85 (%)	OR	95% CI	P-value
Age, years					
<65	94 (59.5%)	64 (40.5%)	5.1	1.95-5.67	<0.001
≥65	9 (30.0%)	21 (70.0%)			
Smoking					
Yes	14 (100.0%)	0 (0.0%)	6.6	4.82-13.86	<0.001
No	89 (51.1%)	85 (48.9%)			
Kidney Disease					
AKI	21 (47.7%)	23 (52.3%)	2.2	2.16-3.04	0.04
CKD	82 (56.9%)	62 (43.1%)			
BMI, kg/m^2					
<25.0	39 (53.4%)	34 (46.6%)	1.14	0.87-1.18	0.06
≥25.0	64 (55.6%)	51 (44.4%)			
Systolic BP, mmHg					
<140	52 (46.9%)	59 (53.1%)	4.37	2.34-4.87	0.001
≥140	51 (66.2%)	26 (33.8%)			
Diastolic BP, mmHg					
<90	67 (50.8%)	65 (49.2%)	3.73	1.97-378	0.004
>90	36 (64.3%)	20 (35.7%)			
ACR, mg/mmoL					
<3.4	39 (59.1%)	27 (40.9%)	1.65	1.56-2.01	0.05
≥3.4	64 (52.5%)	58 (47.5%)			
NLR					
<3.0	74 (58.3%)	53 (41.7%)	3.13	2.63-3.92	0.04
≥3.0	29 (47.5%)	32 (52.5%)			
PLR					
<60	63 (54.3%)	53 (45.7%)	1.61	0.94-1.67	0.05
≥60	40 (47.5%)	32 (52.5%)			
Bicarbonate, mmol/L					
<22	56 (51.9%)	52 (48.1%)	1.1	0.98-1.04	0.07
≥22	33 (50.0%)	33 (50.0%)			
Serum Creatinine					
Males <130; Females <106	35 (41.7%)	49 (58.3%)	5.00	3.61-7.58	<0.001
Males ≥130; Females ≥106	68 (65.4%)	36 (34.5%)			
Uric acid, mmol/L					
M <0.42; F <0.36	13 (44.8%)	16 (55.2%)	3.09	2.88-4.04	0.04
M ≥0.42; F ≥0.36	90 (56.7%)	69 (43.3%)			

Hematocrit, %					
<39	36 (50.7%)	35 (49.3%)	2.43	1.86-2.98	0.05
≥39	66 (56.9%)	50 (43.1%)			
Albumin, mg/dL					
<35	7 (53.8%)	6 (46.2%)	1.10	074-1.18	0.08
≥35	96 (54.9%)	79 (45.1%)			
Low HDL, mmol/L					
<1.1	45 (54.9%)	37 (45.1%)	1.02	1.00-1.09	0.11
≥1.1	58 (55.2%)	47 (44.8%)			
Elevated LDL, mmol/L					
<3.4	44 (58.7%)	31 (41.3%)	1.35	1.14-1.94	0.08
≥3.4	59 (52.2%)	54 (47.8%)			
Elevated triglyceride,					
>2.2	42 (56.0%)	33 (44.0%)	1.21	0.96-1.24	0.09
≥2.2	61 (59.2%)	52 (40.8%)			
Kidney volume, cm^3					
<50	27 (46.6%)	31 (53.4%)	3.01	2.53-3.89	0.04
≥50	74 (57.8%)	54 (42.2%)			

Table 4: Participants' characteristics and gender associations

Variables	aOR	95% CI	P-value
Age	6.20	3.17-9.58	<0.001
Smoking	5.86	4.52-8.95	<0.001
Systolic blood pressure	3.76	1.83-4.03	0.03
Diastolic blood pressure	2.61	0.99-2.68	0.05
Serum creatinine	5.73	1.65-5.89	<0.001

Table 5: Multiple Regression Analysis

Discussion

We found in our study, gender differences in the pattern of NLR, been higher in females than males, a higher NLR in CKD than in AKI, and both the NLR and the PLR were found to be higher in females than males. Women were more likely to be older and to have CKD than AKI. In the AKI cohorts, participants with sepsis had higher NLR than others. Aging, smoking, elevated systolic BP and higher serum creatinine were independent predictors of gender associations.

The higher NLR in females in our study is not in agreement with many previous finding which reported lower NLR in female compared to men. [15] Estrogem mobilize neutrophils from the bone marrow hence they tend to have higher NLR in their reproductive years. This reduces peri-menopause and starts rising from about sixth years of age. We infer that the far higher proportion of elderly women in this study agrees with the matching up age, from 60 years, at which women portray higher cardiovascular risk profile, higher inflammatory biomarkers and risk of death. The reported lesser sleep in the peri-menstrual period associated with leucocyte infiltration only proved the fact that women mount and curtail inflammation faster than men. [27]

The higher NLR in the aged in our study mirrors several previous findings. Aging is known to be a pro-inflammatory state. This, coupled with the physiologic decline in kidney function with aging is associated with retention of nitrogenous wastes which further worsens the background inflammatory state that could be associated with atherosclerosis, renovascular and systolic hypertension which has been reported to increase the risk of cerebral events. [28]

The higher NLR in CKD than in AKI agrees with previous findings. [29] The inflammatory process in both AKI and CKD involve the activation of the immune system leading to increases in leucocyte count, particularly neutrophils which are mobilized in conjunction

the lysosomal lysing and killing to initial and sustain the inflammatory process. The greater ratio in CKD therefore suggest a greater reduction in the lymphocyte count. Lymphopenia, a common finding in chronic ill health would be expected.

The higher PLR in this population brings another dimension into the discussion: both platelets and lymphocytes are reduced in chronic inflammatory states. Estrogens stimulates the production and release of platelets. Also, higher ratio could entail greater reductions in lymphocytes compared to platelets. In acute inflammatory states the neutrophils recruit platelets into the vascular endothelial layers leading to platelet aggregation and consumption. [16] This results in the recruitment of more vasoconstriction inducing cytokines damages the vascular bed with a suppression of the endothelial derived nitric oxide (eNO) and the release of the inducible form (iNO). The persistence of this inflammatory cascade could lead to the laying down of fibro-fatty deposits in the vessel wall that could form atherosclerotic plaque. Azab et al [30] had reported that higher NLR predict myocardial infarction and cardiovascular mortality.

In hypovolemia, particularly when prolong, the inflammatory response that follows involve reperfusion injury characteristic by infiltration of inflammatory mediators, vasodilatation, release of cellular toxins that damages the renal tubules that can lead to AKI. The higher NLR in sepsis induced AKI in our study agrees with findings by Zarbock et al [31] who reported that in the initiating phase of the inflammatory response, AKI still develops despite the compensatory vasodilatation. Sepsis induced AKI typically involves the pre renal and the intrinsic renal components of the injury hence he higher levels of inflammatory markers due to the combined effect of shedding, sludging of tubular backflow products, consumption coagulopathy and metabolism of tubular proteins further worsening the tubular insults. Gameuro et al [32] found sepsis as the leading cause of critical illnesses in the intensive care units. This inflammatory response is less intense in chronic inflammatory course, hence less platelet consumption and higher peripheral blood availability.

The role of the NLR as an inflammatory maker is further supported in our study by the positive relation between the NLR and microalbuminuria. Higher ACR have been identified as a predictor of cardiovascular and renal risk profile and mortality. [33] However this cannot be said of uric acid in this study despite been a known inflammatory marker. A greater proportion of our CKD cohorts were receiving uric acid lowering agents unlike the AKI cohorts and this we infer accounted for this peculiar finding.

The NLR has been reported to predict several cardiovascular events and mortality as well as predict poor treatment outcome post abdominal and cardiac surgery. The low cost and readily available feature of the NLR further heightens its usefulness in low income nations (LINs) not only in AKI and CKD but in several inflammatory conditions and in terminal conditions like cancer. [34]

Limitations: Encountered included the fact that we could not rule out chronic subtle inflammation. Secondly, we could not entirely rule out the use of herbal remedies and other non-prescription drugs that could affect the hematologic profile of participants. The strength of this study is in its prospective design, the incorporation of smoking and ruling out of diabetes and frequent NSAIDs users.

Conclusion: The NLR is a cheap, readily available test that can be used in predicting the occurrence of many renal and cardiovascular diseases, prognosticate, and predict disease outcome. It has a positive relationship with the age and other makers of inflammation. The NLR is higher in CKD than AKI and is positively related to the PLR. Gender associations with the NLR could be predicted by aging, systolic blood pressure, smoking and serum creatinine.

Acknowledgement

The authors appreciate the contributions of the staffs of the medical and laboratory departments for their support for the study.

Conflict of Interest

None declared

Funding

None

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