Original Research Article

The Gender Associations of Neutrophil Lymphocyte Ratio in Acute Kidney Injury and Chronic Kidney Disease.

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. This phrase is not clear and should be edited.

Results and Discussion

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. Needs language editing!

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. It 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. Not clear, needs language editing!

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 been 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 been 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, and the gender differences seen in physiologic and pathologic states have largely be attributed to the differential actions of the sex hormones [3]. Too long sentence. Needs editing!

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 rates are hinged, compared with disease conditions preceding CKD such as hypertension, diabetes. The prevalence of hypertension and CKD (particularly predialysis~~tic~~) 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 [4] Testosterone induces a dose-dependent apoptotic damages in the renal tubules in addition to the alteration of the glomerular microstructural and hemodynamic pattern as it reported that castration and other conditions that reduces androgenic activity are associated with a lower risk of CKD, lesser proteinuria and slowing of CKD progression [5]

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 conditions, they are suppressed in chronic diseases associated with debilitating courses. This may explain the higher lymphocyte count in Africans compared to Caucasians as the former have higher exposure to recurrent acute infective and stressful stimulants. A positive association has been reported between estrogens and inflammatory markers [6]. 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. 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 [7]

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 [8, 9].

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. The aim is not clearly stated.

Material and Methods

Study design

Patients

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 mean age?, 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 [10] and participants with CKD met the KDOQI 2012 diagnostic criteria.[11] each ~~All~~ participant had renal ultrasound scan to rule out obstructive lesions.

Exclusion criteria

Participants with cancers, connective tissue disease, cardiorenal syndrome, hepatorenal syndrome, hematologic disorders, diabetes and blood dyscrasia this sentence is not completed. 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 also excluded.

Methods?

A brief ?? unclear history was taken from each participant and a general physical examination was conducted. The height and weight were measured 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 albustix 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. What kind of analytical methods are used for measuring these parameters? The creatinine-based glomerular filtration rate (GFR) was calculated with the CKD epidemiological collaboration (CKD-EPI) formula [12].

Definitions It is not clear why these definitions are given here.

Elevated NLR, greater than 3 [13].

Elevated PLR, greater than 160 [14].

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) less than 0.5 ml/kg/hr for 6 hour.

AKI stage 1, rise in serum creatinine of greater than 26 umol/L less than 150-199% of baseline within 7 days or UO less than 0.5 ml/kg/hr for more than 6 hours.

AKI stage 2, serum creatinine 200–299% of baseline within 7 days or UO less than 0.5 ml/kg/hr.

AKI Stage 3, serum creatinine 300% or more, of baseline within 7 days or concentration greater than 354 umol/L within 48 hr or a rise of 50% or more, from baseline within 7 days or any requirement for RRT or OU less than 0.3ml/kg/hr for 24 hrs or anuria for 12 hrs.

CKD stage 1and 2, history or radiological evidence of CKD with GFR 60 or higher [15].

CKD stage 3-4, history or radiological evidence of CKD with GFR 15-59 [15].

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 greater than 38°C or less than 36°C, pulse rate greater than 90/minute, a respiratory rate greater than 20cycles/minute, white cell count of greater than 11,000cells/mm^3 or less than 4000 cells/mm^3 [16].

Hypertension, BP greater than or equal to 140/90 mmHg or physician diagnosed hypertension or using BP lowering drugs [17].

Diabetes, fasting blood glucose greater than or equal to 7.0 mmoL or physician-diagnosed diabetes or using hypoglycemic agents [18]

Microalbuminuria, ACR greater than 3.4mg/mmoL [19]

Anemia, hematocrit less than 39% (males) and less than 36% (females) [20]

Hypoalbuminemia, serum albumin less than 35mg/dL [21]

Hyperuricemia, uric acid (UA) greater than 0.42mmol/L (males), 0.36mmol/L (females) [22]

Metabolic acidosis (MA), serum bicarbonate less than 22 mmol/L [23]

Statistical analysis

Data was analyzed using the IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Continuous variables are presented as means or medians and compared using paired student t-test. Why is used paired 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. 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 age 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 compared to what?. AKI was commoner in males as CKD was commoner in females, P=0.04.

Table 1: Participants' sociodemographic, and clinical characteristics, n(%)

Variables	what stands	All participants	Males	Females	P-value

	here?				
Age, years		188	144	44	
	16-39	52 (27.7%)	34 (33.0%)	18 (21.2%)	0.001
	40-64	108 (57.4%)	60 (58.3%)	48 (56.5%)	
	≥65	8 (14.9%)	9 (8.7%)	19 (22.3%)	
Smoking					
	Yes	14 (7.4%)	14 (13.6%)	0 (0.0%)	0.1
	No	174 (92.6%)	89 (86.4%)	85 (100%)	
BMI, kg/m^2					
	<25.0	73 ()	39 (37.9%)	34 (40.0%)	0.1
	≥25.0	115 ()	64 (62.1%)	51 (60.0%)	
SBP, mmHg					
	<140	111 (59.0%)	52 (50.5%)	59 (69.4%)	0.003
	≥140	77 (41.0%)	51 (49.5%)	26 (30.6%)	
DBP, 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	44 (23.4%)	21 (20.4%)	23 (24.4%)	0.04
	CKD	144 (76.6%)	82 (79.6%)	62 (75.6%)	

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

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

Table 2: Etiology of Acute Kidney Injury and Chronic Kidney Disease in the Participants, n(%)

Variables	Etiology	Frequency	Percentage
Acute kidney injury		44	100
	Sepsis	16	(36.4%)

	Acute blood loss	7	(15.9%)
	Exogenous nephrotoxins	7	(15.9%)
	Preeclampsia	4	(9.1%)
	Others	10	(22.7%)
Chronic kidney disease		144	100
	Hypertension	59	(41.0%)
	Chronic glomerulonephritis	42	(29.2%)
	Diabetes	18	(12.5%)
	Obstructive uropathy	13	(9.0%)
	Others	12	(8.3%)

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, 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).

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

Variables		Total	AKI	CKD	P-value

		n (%)/mean ± SD	n (%)/mean ± SD	n (%)/mean ± SD	
		188	44	144	
Sex					
	Males	103 (54.8%)	21 (47.7%)	82 (56.9%)	0.01
	Females	85 (45.2%)	23 (52.3%)	62 (43.1%)	
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, umol/L		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

The mean ACR and NLR of the CKD cohorts were higher than that of AKI, P=0.03 this p value is different from the value given in table 3. Which one is the correct P value? 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.

Table 4: Participants' characteristics and gender associations, n (%)

Variables		Males	Females	OR	95% CI	P-value
		103 (%)	85 (%)			
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, umol/L						
	M <130/F <106	35 (41.7%)	49 (58.3%)	5.00	3.61-7.58	<0.001
	M ≥130/F ≥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 TRG, mmol/L						
	<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						
	<50.0	27 (46.6%)	31 (53.4%)	3.01	2.53-3.89	0.04
	>50.0	74 (57.8%)	54 (42.2%)			

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.

Table 5: Multiple Regression Analysis

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

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 [13] Estrogen~~m~~ mobilize neutrophils from the bone marrow hence females tend to have higher NLR in their reproductive years. This reduces peri-menopause and starts rising from about sixth decade of life. 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 [24]. 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 [7].

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 [25]

The higher NLR in CKD than in AKI agrees with previous findings [26] 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 with lysosomal lysing and killing to initiate and sustain the inflammatory process. The greater ratio in CKD therefore suggest a greater reduction in the lymphocyte count, lymphopenia, being a common finding in chronic ill health [26]

The higher PLR in this population portrays another aspect of the inflammatory cascade: both platelets and lymphocytes are reduced in chronic inflammatory states. Estrogens stimulates the production and release of platelets. Also, higher ratio could entails 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 [14] This results in the recruitment of more vasoconstriction inducing cytokines that 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 response could lead to the laying down of fibro-fatty deposits in the vessel wall that could form atherosclerotic plaque. Azab et al [27] had reported that higher NLR predict myocardial infarction and cardiovascular mortality, events that commonly share atherosclerotic background.

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 previous findings that 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 the higher levels of inflammatory markers due to the combined effect of shedding, ~~sludging~~slugging of tubular backflow products, consumption coagulopathy and metabolism of tubular proteins further worsening the tubular insults. Gameuro et al [28] found sepsis as the leading cause of critical illnesses in the intensive care units. This inflammatory response is less

intense in chronic inflammatory conditions, hence the lesser 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 [27] 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 [13]. 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 chronic inflammatory, and terminal conditions like cancer [29]

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. It could 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, smoking and elevated systolic blood pressure and serum creatinine.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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