Suleiman *et al.*, Pan African Journal of Life Sciences (2026): 10(1): 693 –701
10.36108/pajols/6202/01.0210

Publication of Faculty of Basic Medical Sciences and Basic Clinical Sciences , Ladoke Akintola University of Technology, Ogbomoso

www.pajols.org
Online ISSN:2672-5924

RESEARCH Open Access

Utility of Derived Inflammatory indices in Gammopathies Characterisation

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Received 16th March 2026; Revised 5th April 2026; Accepted 29th April 2026

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ABSTRACT

Background: Polyclonal hypergammaglobulinemia (PHGG) and monoclonal gammopathy of undetermined significance (MGUS) represent reactive and clonal immunoglobulin disorders with divergent prognostic trajectories. Serum protein electrophoresis (SPE) and serum free light chain ratio (FLCr) are crucial for detecting monoclonal proteins, while a full blood count (FBC) is often included in the preliminary assessment of suspected gammopathies. Its ability to discriminate between the two conditions, however, remains inadequately defined. Therefore, the aim of this study was to evaluate the utility of inflammatory indices in the characterisation of gammopathies.

Methods: A cross-sectional study of MGUS subjects (n = 6), PHGG patients (n = 18), and normogammaglobulinemic control, NC (n = 48), was conducted. FBC and inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), were analysed. Group comparisons were performed using the Kruskal–Wallis test, while associations were assessed by Spearman's correlation. Firth's logistic regression (FLR) and receiver operating characteristic (ROC) analyses were employed to evaluate predictors of monoclonality.

Results: Conventional FBC parameters showed no significant differences across groups. In contrast, FLCr was significantly elevated in MGUS ($p < 0.001$). Among inflammatory indices, LMR was significantly reduced in MGUS compared to PHGG ($p = 0.049$). Correlation analysis revealed an inverse relationship between serum FLCr and blood haemoglobin concentrations. In multivariable analysis, LMR emerged as a strong inverse predictor of monoclonality (OR = 0.33, $p = 0.018$), while absolute neutrophil count was a positive predictor (OR = 2.34, $p = 0.041$). ROC analysis demonstrated modest discriminatory performance.

Conclusion: Conventional FBC have limited utility in differentiating gammopathies. However, inflammatory indices, particularly LMR, show promise as adjunctive markers. Integration of LMR into established biomarkers may improve early diagnostic accuracy, especially in resource-limited settings.

Keywords: PHGG, MGUS, FLCr, FBC and LMR

1.0 INTRODUCTION

Gammopathies comprise a heterogeneous group of haematological disorders characterised by the overproduction of either intact immunoglobulins or free light chain fractions [1]. These conditions span a clinical spectrum ranging from benign reactive immune responses to premalignant and overt malignant plasma cell dyscrasias [2]. Polyclonal hypergammaglobulinemia (PHGG) is typically associated with chronic infections, autoimmune diseases, and sustained inflammatory states, and is generally regarded as a reactive, non-clonal process [3]. In contrast, monoclonal gammopathy of undetermined significance (MGUS) represents a clonal plasma cell disorder with established potential for progression to multiple myeloma (MM) and related lymphoproliferative malignancies [4]. Despite their distinct biological origins, PHGG and MGUS may present with overlapping biochemical profiles, thereby posing diagnostic challenges, particularly in settings where advanced immunochemical testing may not be immediately accessible.

The full blood count (FBC) remains one of the most frequently requested investigations in clinical practice and is often part of the initial assessment of suspected gammopathies due to its availability, affordability, and routine use [5, 6]. However, its diagnostic value in distinguishing reactive from clonal gammopathies is uncertain. Although anaemia and other cytopenias are well-recognised features of advanced plasma cell disorders such as multiple myeloma (MM) and plasma cell leukaemia, these abnormalities are often absent in early or asymptomatic stages, including MGUS [7, 8]. Thus, evidence is limited regarding whether routine haematological parameters demonstrate significant differences between these entities or possess meaningful diagnostic relevance in differentiating them. In recent years, derived inflammatory indices calculated from routine haematological parameters, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have emerged as inexpensive biomarkers of systemic inflammation and immune dysregulation in several malignancies and hematologic disorders [9, 10]. These indices may provide additional insight into tumor–host immune interactions beyond conventional haematological parameters and could potentially improve the discriminatory evaluation of gammopathies.

Serum protein electrophoresis (SPE) and serum free light chain ratio (FLCr) assays remain established tools for the detection and characterisation of monoclonal proteins [11, 12] and were employed in this study as classification criteria for defining PHGG and MGUS groups. This study was therefore designed to evaluate the diagnostic utility of conventional haematological parameters and derived inflammatory indices in gammopathies by comparatively assessing individuals classified as PHGG or MGUS using SPE and FLCr criteria, alongside apparently healthy normogammaglobulinemic controls (NC). Specifically, the study sought to determine whether inflammatory and haematological indices differ significantly between PHGG and MGUS and whether such parameters could serve as potential adjunctive biomarkers for differentiating reactive from clonal gammopathies. By exploring the diagnostic relevance of derived inflammatory indices within routine clinical practice, this study provides insight into their potential applicability as low-cost supportive biomarkers, particularly in resource-limited settings.

2.0 METHODOLOGY

2.1 Study Design

This study was designed as a cross-sectional community-based analytical study to investigate the correlation between serum FLCs and FBC among individuals with polyclonal and monoclonal gammopathies in Ilorin metropolis. This study was carried out in three (3) local government areas (Ilorin-West, -Ilorin-East and -South) that constituted Ilorin metropolis and over one-third of the population of Kwara State.

2.2 Inclusion and Exclusion Criteria

Participants were adults (≥18 years) who provided informed consent. MGUS was defined by the presence of a monoclonal protein (M-protein) on SPE, and no evidence of myeloma-defining events or end-organ damage. PHGG was diagnosed in individuals with a broad-based γ -region elevation on SPE, negative, and proportionally elevated FLCr. Controls were age- and sex-matched individuals with normal SPE, and FLCr profiles, and no history of autoimmune, infectious, or lymphoproliferative disease.

Exclusion criteria history of recent corticosteroid or immunoglobulin therapy, blood transfusion, or major surgery within four weeks; chemotherapy, radiotherapy, or immunosuppressive therapy within the past year; pregnancy or lactation; and prior diagnosis of plasma cell dyscrasias or related haematologic malignancies. Only non-hemolyzed and analytically adequate samples were pro-

cessed, and equivocal electrophoretic findings were repeated after four weeks, with persistently indeterminate cases excluded.

2.3 Sample size Determination

The study population was derived from a larger community-based gammopathy screening survey conducted within Ilorin metropolis, Nigeria. The prevalence survey recruited 1,120 participants, exceeding the initially projected sample size of 1,000 to accommodate possible non-response and incomplete datasets while maintaining adequate statistical robustness [11].

Following screening and immunochemical characterisation, all identified MGUS cases (n = 6) were included in the present biochemical and haematological analyses using a census approach due to the low prevalence of monoclonal gammopathy within the study population. To provide comparative analytical groups, participants with PHGG and NC were subsequently selected from the larger prevalence cohort using structured ratio-based random sampling. Specifically, a 1:3 ratio of MGUS to PHGG participants was adopted, yielding 18 PHGG subjects, while a 1:2 ratio of total gammopathy cases (MGUS + PHGG) to controls yielded 48 NC participants.

Random selection of PHGG and NC participants was performed using the Research Randomiser computerised sampling tool [12] to minimise selection bias and ensure probabilistic allocation. This sampling framework was designed to optimise comparative statistical analysis while preserving representativeness within the constraints imposed by the low prevalence of MGUS. The small MGUS sample size reflects the low prevalence of MGUS identified during the population-based screening.

2.4 Sample and Data Collection

Socio-demographic and anthropometry data were obtained by questionnaire/direct interview and measurement respectively. Laboratory analysis was evaluated from blood samples taken. About 5 mL of whole blood was collected aseptically from each participant into an EDTA and plain vacutainer tubes. Samples in plain tubes were allowed to clot, centrifuged at 3,000 rpm for 10 minutes, and serum was aliquoted into cryovials. Aliquots were stored at –80 °C until analysis. Repeated freeze-thaw cycles were avoided. FBC was run within 2 hours of collection.

2.5 Serum electrophoresis analysis

Serum protein electrophoresis (SPE) was performed using cellulose acetate electrophoresis according to the method previously described by [13]. Briefly, serum specimens were applied onto cellulose acetate strips and electrophoresed in barbital buffer (pH 8.6). Following protein separation, the strips were visualised in Ponceau S, destained, and subsequently cleared for analysis. Electrophoretic patterns were independently reviewed by two of the investigators ALA & SIE; and any discrepancies were resolved by consensus. Particular attention was given to the gamma globulin region for identification of M-spikes, defined as sharp, discrete electrophoretic bands suggestive of monoclonal gammopathy.

2.6 Free Light Chain Ratio Assay

Serum free kappa (κ) and lambda (λ) light chains were measured using a commercial ELISA kit (Eldere Reagent Kit, China) following the manufacturer's protocol as described by [14]. Samples from all the selected 72 participants were analysed in duplicate. Absorbance was read at 450 nm, and concentrations were interpolated from standard curves. The free κ/λ ratio was calculated for each participant as a marker of light chain clonality.

2.7 Full Blood Count Evaluation

Full blood count (FBC) evaluation was performed using a Sysmex Haematology Analyser as previously described by [15]. Samples from all 72 participants were analysed. EDTA anticoagulated blood was processed according to the manufacturer's protocols. The analyser provided automated quantification of the following parameters: haemoglobin concentration (Hb), red blood cell count (RBC), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count (PLT). Quality control was performed daily using commercial control materials to ensure instrument accuracy and precision.

2.7 Statistical analysis

Data were analysed using SPSS version 25. Continuous variables were expressed in median (interquartile range) and tested for normality using the Shapiro-Wilk test. Comparisons between PHGG, MGUS, and NC groups were performed using the Kruskal–Wallis test for continuous variables and the Mann–Whitney U test for pairwise post-hoc comparisons. Fisher's exact test for categorical variables. Correlation analyses between parameters were assessed using Spearman correlation. Given the explora-

tory nature of the study and multiple comparisons performed, p-values (< 0.05) were interpreted cautiously without formal correction. Adjustment for infectious comorbidities (e.g., hepatitis, HIV) was not performed due to sample size constraints and risk of model overfitting.

2.8 Ethical Consideration

Ethical approval was obtained from the ethical review committee of the Kwara state Ministry of Health with reference number ERC/MOH/2024/01/180. The research was carried out in line with the ethics governing the use of human samples and in accordance with the Helsinki declaration. Ethical practices such as participant consent, confidentiality and safety laboratory practice were observed during the study. A structured questionnaire was used to gather socio-demographic data such as age, gender, marital status, and family type.

3.0 RESULTS

3.1 Demographic and Clinical Characteristics of Study Participants

Table 1 shows the socio-demographic and economic characteristics of the cohort across the three groups. The age distribution was the only significant factor, the data further indicate that most participants were aged 60 years and above, particularly within the NC (43.8%) and MGUS (33.3%) groups. Thus, reflecting the age-related predisposition to gammopathies. A mild male predominance was observed in both PHGG and MGUS groups compared with the controls. Males constituted a higher proportion in the PHGG (61.1%) and MGUS (66.7%) groups compared with NC (39.6%).

3.2 Comparative analysis of Haematological parameters in gammopathies

Table 2 presents the comparison of haematological parameters and inflammatory indices across study groups. Conventional FBC parameters, including WBC, Hb, RBC indices, and platelet parameters, showed no statistically significant differences. In contrast, FLCr was significantly elevated in MGUS ($p = 0.001$), with post hoc analysis confirming differences between PHGG and MGUS. Among inflammatory indices, only LMR showed a significant difference ($p = 0.049$), with lower values observed in MGUS.

3.3 Correlation of haematological indices with FLCr

Table 3 shows the pooled Spearman correlation analysis among key haematological variables. Significant positive correlations were observed between WBC and ANC ($r = 0.794$, $p < 0.01$) and between ALC and MPV ($r = 0.636$, $p < 0.01$). Haemoglobin correlated positively with RBC ($r = 0.774$, $p < 0.01$) and negatively with ANC ($r = -0.528$, $p < 0.05$). Platelet count demonstrated a strong inverse correlation with ANC ($r = -0.721$, $p < 0.01$). FLCr showed no statistically significant correlations with the evaluated haematological parameters.

Table 1. Demographic and clinical characteristics of study participants

Variable	NC (n=48)	PHGG (n=18)	MGUS (n =6)	p-value
Mean Age (years)	60.8 ± 24.2	69.3 ± 25.4	64.3 ± 9.8	0.725
Age group				
< 40	9 (18.8)	8 (44.4)	0	0.035*
40 – 59	9 (18.8)	2 (11.1)	1 (16.7)	
60 – 69	21 (43.8)	6 (33.3)	2 (33.3)	
> 70	9 (18.8)	2 (11.1)	3 (50)	
Sex				
Male	19 (39.6)	11 (61.1)	4 (66.7)	0.493
Female	21 (43.8)	7 (38.9)	2 (33.3)	
eGFR (mL/min/1.7 m^2)	103.8 (93.1 - 110.3)	80.9 (76.5 - 87.3)	72.5 (72.8 - 78.3)	0.039*
Serum Ca^{2+} (mmol/L)	2.43 (1.93 - 2.74)	2.41 (2.18 - 2.59)	2.38 (2.27 - 2.44)	0.436
Other Haematology dxs	Nil	Nil	Nil	NA
γ globulin band	Normal	Broadly stained	M-spike	NA
Immunomodulatory drugs	Nil	Nil	Nil	NA
History of DM	8 (16.7)	3 (16.7)	1 (16.7)	--
HIV infections n (%)	4 (8.3)	3 (16.7)	0	--
Hepatitis infections n (%)	10 (20.8)	12 (66.7)	2 (33.3)	--

Values are presented as mean ± standard deviation or number (%), Fisher's Exact test was adopted for the comparison, NC = Normo-gammaglobulinemic control, PHGG = polyclonal hypergammaglobulinemia, MGUS = monoclonal gammopathy of undetermined significance, eGFR = estimated glomerular filtration rate, DM = diabetes mellitus, dxs. = diseases, HIV = human immunodeficiency virus, NA = not applicable.

Table 2. Comparative analysis of Conventional haematologic and derived inflammatory indices between study groups

Variables	NGC	PHGG	MG	p-value	P. hoc
FLCr	0.83 (0.55 - 1.36)	1.24 (0.78 - 2.07)	2.5 (2.08 - 3.00)	0.001*	< 0.001
WBC (x 10^9/L)	5.09 (4.83-5.40)	5.98 (5.30 - 6.28)	6.17 (4.16 - 8.17)	0.572	-
Neutrophils (%)	44.85 (43.80-48.60)	54.50 (53.40 - 58.70)	59.75 (49.95 - 70.30)	0.742	-
Lymphocytes (%)	43.45 (40.90 - 43.70)	38.50(35.40 - 39.31)	24.10 (17.35 - 34.70)	0.183	-
Monocytes (%)	7.85 (5.70 - 8.10)	4.69 (3.29 - 5.23)	9.15 (6.98 - 11.85)	0.262	-
Basophils (%)	0.40 (0.30 - 0.40)	0.53 (0.49 - 0.55)	0.60 (0.25 - 1.25)	0.809	-
Eosinophils (%)	2.00 (1.10 - 3.20)	2.98 (2.50 - 3.03)	1.90 (0.90 - 3.25)	0.663	-
Heamoglobin (g/dL)	12.90 (12.30 - 14.10)	11.02 (11.02 - 12.00)	10.80 (8.60 - 11.50)	0.856	-
Hematocrit (%)	40.75 (37.10 - 44.50)	34.87 (33.60 - 35.88)	31.35 (29.15 - 35.05)	0.629	-
RBC (x10^{12}/L)	4.87 (4.36 - 5.43)	4.17 (3.89 - 4.32)	4.01 (3.70 - 4.01)	0.919	-
MCH (Pg)	27.85 (25.90 - 29.40)	26.90 (25.98 - 27.60)	27.70 (22.65 - 30.40)	0.638	-
MCV (fL)	85.55 (79.70 - 89.90)	83.10 (79.51 - 83.60)	84.80 (75.60 - 86.45)	0.894	-
MCHC (g/dL)	32.20 (31.80 - 32.60)	32.97 (32.50 - 33.00)	32.80 (32.30 - 34.65)	0.637	-
ANC (x10^9/L)	2.28 (2.20 - 2.62)	3.02 (2.95 - 3.46)	3.09 (2.46 - 4.98)	0.892	-
ALC (x10^9/L)	2.12 (2.04 - 2.68)	2.22 (2.04 - 2.22)	1.36 (1.04 - 2.24)	0.113	-
PLT (x 10^9/L)	271.50 (232.00 - 310.00)	203.72(199.63 - 223.01)	229.00 (187.50 - 280.00)	0.539	-
MPV (fL)	8.90 (8.20 - 9.30)	9.08 (8.93 - 9.11)	8.40 (8.25 - 10.60)	0.519	-
PDW (fL)	10.60 (9.60 - 14.20)	11.39 (9.55 - 11.40)	11.00 (9.60 - 13.50)	0.407	-
PLC-R (%)	26.30 (22.30 - 31.70)	29.03 (27.72 - 31.10)	24.05 (20.60 - 25.55)	0.757	-
PLC-C (%)	74.00 (58.00 - 94.00)	58.38 (55.00 - 59.11)	50.00 (46.50 - 74.00)	0.106	-
PLR	6.37 (5.25 - 6.54)	6.21 (5.45 - 6.23)	10.64 (5.61 - 16.37)	0.260	-
NLR	1.04 (0.90 - 1.27)	1.48 (1.37 - 1.56)	2.51 (1.51 - 4.14)	0.211	-
NPR	0.12 (0.11 - 0.14)	0.17 (0.16 - 0.18)	0.15 (0.12 - 0.18)	0.827	-
LMR	5.33 (5.14 - 8.74)	10.82 (5.58 - 12.40)	2.19 (1.83 - 4.27)	0.049*	< 0.001
ELR	0.04 (0.03 - 0.07)	0.06 (0.05 - 0.08)	0.10 (0.04 - 0.14)	0.329	-

The values are median (IQR), Kruskal-Wallis test was used to compare the means at p = 0.05, Post hoc comparison was between PHGG and MGUS. PLR = Platelet/lymphocytes, NLR= Neutrophil/lymphocytes, NPR = Neutrophil/platelet, LMR = Lymphocyte/monocytes, ELR = Eosinophil/lymphocytes

Table 3. Pooled Spearman rho correlation analysis of the parameters in the study group

Correlation		FLCr	WBC	ANC	ALC	HBG	RBC	PLT	MPV	LMR
FLCr	r	1	0.176	0.267	-0.277	-0.427	-0.161	-0.205	-0.016	-0.279
	p	.	0.498	0.3	0.282	0.087	0.538	0.43	0.951	0.277
WBC	r	0.176	1	.794**	.498*	-0.16	-0.097	-.498*	0.446	0.152
	p	0.498	.	0	0.042	0.541	0.711	0.042	0.072	0.56
ANC	r	0.267	.794**	1	0.282	-.528*	-0.314	-.721**	0.421	0.194
	p	0.3	0	.	0.273	0.03	0.22	0.001	0.093	0.456
ALC	r	-0.277	.498*	0.282	1	0.298	-0.021	-0.34	.636**	0.407
	p	0.282	0.042	0.273	.	0.245	0.937	0.182	0.006	0.105
HBG	r	-0.427	-0.16	-.528*	0.298	1	.774**	0.318	0.121	0.123
	p	0.087	0.541	0.03	0.245	.	0	0.214	0.643	0.639
RBC	r	-0.161	-0.097	-0.314	-0.021	.774**	1	0.244	0.085	0.233
	p	0.538	0.711	0.22	0.937	0	.	0.346	0.746	0.368
PLT	r	-0.205	-.498*	-.721**	-0.34	0.318	0.244	1	-0.476	-0.173
	p	0.43	0.042	0.001	0.182	0.214	0.346	.	0.053	0.507
MPV	r	-0.016	0.446	0.421	.636**	0.121	0.085	-0.476	1	.538*
	p	0.951	0.072	0.093	0.006	0.643	0.746	0.053	.	0.026
LMR	r	-0.279	0.152	0.194	0.407	0.123	0.233	-0.173	.538*	1
	p	0.277	0.56	0.456	0.105	0.639	0.368	0.507	0.026	.

FLCr = free light chain ratio, WBC = white blood cells count, ANC = absolute neutrophil count, ALC = absolute lymphocytes count, PLT = platelet count, MPV = mean platelet volume, r = Spearman's rank correlation coefficient, p = * = Correlation is significant at the 0.05 level. ** = Correlation is significant at the 0.01 level (2-tailed)

3.4 Predictors of FLCr in Firth Logistic Regression Analysis

Table 4 presents the Firth logistic regression model assessing predictors of monoclonality. LMR emerged as a significant inverse predictor (OR = 0.33, p = 0.018), while ANC was identified as a significant positive predictor (OR = 2.34, p = 0.041). Other parameters, including Hb, RBC, platelet count, MPV, and WBC, were not statistically significant predictors, although some demonstrated weak trends.

3.5 Diagnostic Performance of Selected Predictors

Table 5 summarises the diagnostic performance of selected predictors using ROC analysis. ANC demonstrated modest discriminatory ability (AUC = 0.635), although not statistically significant. LMR showed a statistically significant result (p = 0.024) but with a low AUC (0.115), indicating poor standalone diagnostic performance, possibly due to inverse scaling or sample size limitations.

Table 4. Firth Binary Logistic Regression Analysis of Haematological Predictors of Monoclonality

Variable	β (Coefficient)	OR (Exp β)	95% CI (Approx.)	p-value	Interpretation
LMR	-1.12	0.33	0.12 – 0.78	0.018	Strong inverse predictor
ANC	+0.85	2.34	1.05 – 6.90	0.041	Positive predictor
ALC	-0.48	0.62	0.21 – 1.80	0.29	Not significant
HBG	-0.27	0.76	0.48 – 1.15	0.21	Weak inverse trend
RBC	-0.39	0.68	0.31 – 1.40	0.26	Not significant
PLT	+0.002	1.00	~1.00 – 1.01	0.18	Minimal effect
MPV	+0.31	1.36	0.78 – 2.80	0.17	Weak trend
WBC	+0.22	1.25	0.80 – 2.10	0.19	Not significant

ALC = absolute lymphocytes count, ANC = absolute neutrophil count, LMR = Lymphocyte/monocytes, PLT = platelet count, MPV = mean platelet volume.

Table 5.Table 5: Comparative ROC Analysis of ANC and LMR, Including Directionally Corrected LMR, for Predicting Monoclonality

Variable	AUC	Interpretation
ANC	0.714	Modest discrimination
LMR	0.200	Inverse discrimination
LMR (directional corrected)	0.800	Good discriminatory ability

Initial ROC analysis of LMR yielded an AUC below 0.5, indicating inverse discrimination. Directional correction was subsequently applied by defining lower LMR values as predictive of monoclonality.

Figure 1 illustrates the receiver operating characteristic (ROC) curves evaluating the diagnostic performance of selected haematological predictors of monoclonality. ANC demonstrated modest discriminatory ability, with an area under the curve (AUC) of 0.714, indicating limited but appreciable capacity to distinguish MGUS from PHGG. In contrast, LMR showed a statistically significant and demonstrated inverse discrimination on initial ROC analysis AUC (0.20); however, directional correction revealed improved discriminatory performance AUC of 0.80

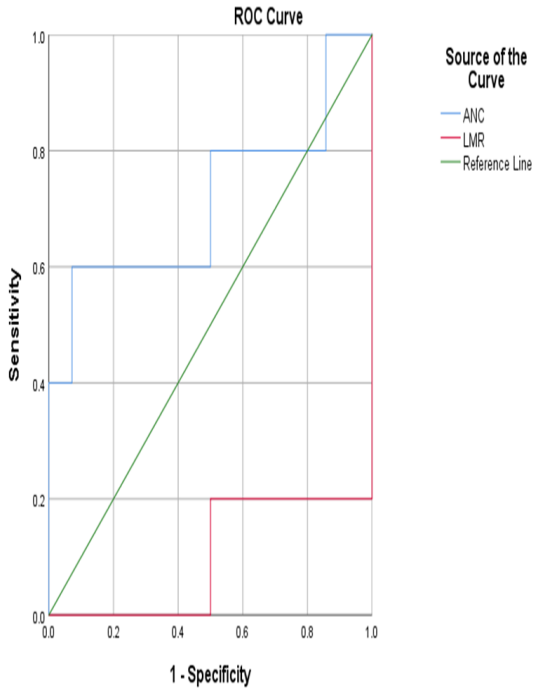

Figure 1. ROC Curve Analysis of Derived Inflammatory Indices in Differentiating Monoclonal and Polyclonal Gammopathies

4.0 DISCUSSION

A preliminary study was performed to determine the prevalence of gammopathies among 1,120 participants where PHGG, MGUS, and NC were identified. A comparative evaluation of haematological index, SPE, and FLCr among individuals with PHGG, MGUS, and NC was performed in Ilorin metropolis, Nigeria. The progressive increase in FLCr concentrations from NC through PHGG to MGUS reflects clonal plasma cell expansion and immunoglobulin light chain imbalance. This observation is consistent with established diagnostic criteria, where abnormal FLCr is a central biomarker for detecting monoclonal gammopathies and assessing the risk of disease progression [2, 5]. Previous studies have demonstrated that abnormal FLCr independently predicts progression from MGUS to MM, further supporting its clinical relevance [5].

The demographic distribution of the participants in this study (Table 1) revealed a higher proportion of elderly individuals in both PHGG and MGUS groups, consistent with the established age-related risk of clonal and reactive gammopathies [16, 17]. Male predominance, particularly in the PHGG and MGUS cohorts, aligns with prior reports that suggest sex-related differences in immune dysregulation and gammopathy prevalence [18]. Mean calcium values across MGUS, PHGG, and NC groups remained within the normal clinical reference suggesting preserved calcium homeostatic functions in these cohorts [19]. Though a significant reduction was reported in eGFR in both PHGG and MGUS groups. However, the values are within the clinical reference range, confirming the absence of overt renal impairment and supporting the classification of MGUS participants as non-myeloma [20].

A key observation in our findings is the lack of statistically significant differences in core FBC parameters, including WBC count, Hb concentration, RBC indices, and platelet count across the study groups (Table 2). Although trends toward anaemia and reduced hematocrit were noted in MGUS and PHGG, these did not reach statistical significance ($p > 0.05$). This aligns with previous studies demonstrating that MGUS is typically characterised by minimal bone marrow infiltration and preserved hematologic function, with cytopenias usually manifesting only upon progression to overt plasma cell malignancies such as MM [16, 17]. Consequently, these findings underline the limited diagnostic utility of conventional haematological parameters in distinguishing

MGUS from PHGG at early stages.

Importantly, this study identified derived inflammatory indices (NLR, PLR, LMR, NPR, and ELR) as potential adjunctive biomarkers in differentiating the two conditions. Among these, LMR was the only parameter that demonstrated statistical significance ($p = 0.049$), with markedly lower values observed in MGUS compared to PHGG (Table 2). Although NLR and PLR did not achieve statistical significance, their relative elevation in MGUS aligns with previous reports linking systemic inflammatory indices with tumour-associated immune dysregulation and hematologic malignancies [21, 22]. The absence of statistical significance for other indices may be attributable to the relatively small MGUS sample size. Nevertheless, the observed patterns support the emerging role of inflammatory biomarkers as indicators of tumor–host immune interactions in plasma cell dyscrasias.

The reduction in LMR observed in MGUS likely reflects a combination of relative lymphopenia and monocytosis, indicative of impaired immune surveillance and a tumour -supportive inflammatory microenvironment [23]. Monocytes are known precursors of tumour-associated macrophages, which contribute to immune evasion, angiogenesis, and disease progression, whereas lymphopenia reflects compromised antitumor immune activity [24]. These findings are consistent with previous studies demonstrating the prognostic relevance of reduced LMR across several hematologic malignancies, including MM and lymphoproliferative disorders [25, 26]. Collectively, the findings suggest that alterations in monocyte–lymphocyte balance may occur early during MGUS development, even before overt malignant transformation.

The correlation analysis further revealed evidence of subtle immune-haematologic interplay (Table 3). The inverse relationship between FLCr and Hb suggests early suppression of erythropoiesis, potentially mediated by inflammatory cytokines or alterations in the bone marrow microenvironment, consistent with mechanisms described in anaemia of chronic disease [26]. Additionally, the strong negative correlation between ANC and PLT count may reflect inflammatory redistribution or underlying marrow regulatory dynamics. The observed association between MPV and lymphocyte count further supports the role of platelets in modulating immune responses [24]. Although several correlations did not reach statistical significance, likely due to limited sample size, the overall pattern suggests early subclinical hematologic perturbations in MGUS.

Multivariable analysis using Firth logistic regression (Table 4) identified LMR as an inverse predictor of monoclonality ($\beta = -1.12$, $p = 0.018$) and ANC as a positive predictor ($\beta = +0.85$, $p = 0.041$). These findings reinforce the contribution of systemic inflammation and immune dysregulation in monoclonal gammopathies. Previous studies have similarly demonstrated the prognostic and biological significance of neutrophil- and monocyte-related inflammatory indices across various malignancies and plasma cell disorders [21, 27]. Notably, conventional haematological parameters did not emerge as significant predictors, supporting the premise that derived inflammatory indices may better capture subtle immunologic perturbations associated with early monoclonal plasma cell disorders.

The ROC analysis provided additional insight into the discriminatory performance of the evaluated inflammatory markers (Figure 1). ANC demonstrated modest discriminatory ability (AUC = 0.714), indicating limited standalone clinical utility. The initial ROC analysis for LMR yielded an AUC below 0.5, reflecting inverse discrimination rather than true diagnostic failure. This indicated that lower, rather than higher, LMR values were associated with monoclonality. Following directional correction of the ROC analysis, LMR demonstrated improved discriminatory performance (corrected AUC = 0.800), consistent with both the regression findings and the observed biological reduction of LMR in MGUS. This observation highlights the importance of appropriate directional specification when evaluating biomarkers inversely associated with disease states [28].

Importantly, the corrected ROC findings suggest that LMR possesses appreciable discriminatory ability in dif-

ferentiating MGUS from PHGG. Beyond its statistical performance, LMR also demonstrated biological relevance as a marker of immune dysregulation and inflammatory imbalance. These observations align with accumulating evidence that inflammatory indices reflect tumor–host immune interactions in hematologic disorders [21, 22]. Nevertheless, despite the improved discriminatory performance, the findings should still be interpreted cautiously due to the relatively small MGUS sample size and the potential confounding influence of chronic infections, particularly hepatitis and HIV within the PHGG group. Therefore, the clinical utility of LMR may be best considered as a complementary biomarker alongside established markers such as FLCr rather than an indepen-

-dently definitive diagnostic tool. Collectively, these findings support the potential integration of derived inflammatory indices into multimarker approaches for gammopathy evaluation, particularly in resource-limited settings where access to advanced diagnostic modalities may be limited.

However, this study is not without limitations. The relatively small sample size, particularly within the MGUS group, may have reduced statistical power and contributed to instability of effect estimates and wide confidence intervals. The cross-sectional design also limits causal inference. Additionally, the absence of comprehensive inflammatory biomarkers and the potential confounding effects of chronic infections, particularly the high prevalence of hepatitis and HIV within the PHGG group, should be considered when interpreting the findings. Although directional correction improved the discriminatory performance of LMR, the results remain exploratory and require validation in larger, well-controlled studies before broader clinical application.

Derived inflammatory indices demonstrated greater discriminatory relevance than conventional haematological parameters in differentiating MGUS from PHGG. In particular, LMR showed appreciable diagnostic performance following directional correction of ROC analysis, suggesting potential utility as a low-cost biomarker of immune dysregulation in monoclonal gammopathies. Nevertheless, the findings should be interpreted cautiously due to the small MGUS sample size, potential confounding effects of chronic infections, and the exploratory nature of the study. Therefore, inflammatory indices may serve as complementary biomarkers alongside established laboratory parameters such as FLCr, while larger and well-controlled studies are needed to validate their diagnostic utility and clinical applicability.

Conflicts of Interest

The authors declare that there is no conflict of interests.

Authors' Contributions

IES performed data collected, contributed to contributed to data analysis tools, analysis of data, and manuscript writing. **OGA** conceived and designed the study, and proofread the manuscript. **FBO** Contributed to data analysis tools and proofread the manuscript. **ALA** contributed to study design, data analysis tools and proofread the manuscript. All authors approved the final version of the manuscript.

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