RESEARCH ARTICLE

Elevated Serum Netrin-1, Platelet-to-Lymphocyte Ratio, and Monocyte-to-Lymphocyte Ratio are Associated with Impaired Fasting Glucose in Adults with Central Obesity

Brian Eka Putera[1], Meita Hendrianingtyas[2,*], Nyoman Suci Widyastiti[2], Dwi Retnoningrum[2], Purwanto Adipireno[2]

[1]Clinical Pathology Specialist Doctor Education Program, Faculty of Medicine, Universitas Diponegoro, Jl. Prof. Mr. Sunario, Semarang 50275, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Diponegoro, Jl. Prof. Mr. Sunario, Semarang 50275, Indonesia

*Corresponding author. Email: meitanote2015@gmail.com

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Abstract

BACKGROUND: Adults with central obesity may develop impaired fasting glucose (IFG) due to chronic low-grade inflammation. Although C-reactive protein (CRP) is a common marker of systemic inflammation, it is nonspecific and cannot fully capture obesity-related inflammatory pathways. Netrin-1 promotes macrophage retention in visceral adipose tissue, thereby sustaining inflammation and insulin resistance, while platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) reflect complementary inflammatory pathways; however, their discriminatory performance and associations with IFG remain uncertain. Therefore, this study was conducted to evaluate these markers in adults with central obesity.

METHODS: Blood samples from 88 adults with central obesity were obtained, and fasting glucose concentration was measured using hexokinase method to determine IFG status. Serum Netrin-1 was measured using an enzyme-linked immunosorbent assay (ELISA), serum CRP was measured using fluorescence immunoassay (FIA); PLR and MLR were calculated from complete blood counts. Receiver operating characteristic (ROC) analysis assessed discriminatory performance, while exploratory logistic regression adjusted for age, sex, and BMI to examine biomarker associations with IFG.

RESULTS: Among 88 participants, 54.5% had IFG. The AUCs were 0.694, 0.627, 0.689, and 0.532 for Netrin-1, PLR, MLR, and CRP, respectively. In crude prevalence-ratio (PR) analysis, Netrin-1 ≥315.35 pg/mL (PR=1.742; p=0.006), PLR ≥132.43 (PR=1.593; p=0.019), and MLR ≥0.20 (PR=2.119; p<0.001) were associated with IFG, whereas CRP was not. In separate ROC analysis, MLR had an AUC of 0.689 (p=0.002). After adjustment for age, sex, and BMI; MLR ≥0.20 remained associated with IFG (adjusted OR=7.516; p<0.001).

CONCLUSION: Elevated serum Netrin-1, PLR, and MLR were associated with IFG in adults with central obesity. MLR showed the strongest crude association and was the only evaluated inflammatory biomarker retained in the exploratory adjusted logistic regression model. As an inexpensive index derived from a routine complete blood count, MLR may complement fasting-glucose assessment by helping characterize the inflammatory phenotype of adults with central obesity.

KEYWORDS: central obesity, C-reactive protein, impaired fasting glucose, netrin-1, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio

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Introduction

Central obesity is a major global health concern and is a major threat for cardio-metabolic health.(1,2) Central obesity is a metabolically adverse pattern of fat accumulation that is strongly associated with insulin resistance, prediabetes, type 2 diabetes mellitus (T2DM), and cardiovascular disease. Visceral adipose tissue functions as both an endocrine and immune organ. Its expansion increases free fatty acid flux, oxidative stress, cytokine release, and inflammatory-cell recruitment, all of which can disrupt insulin signaling before overt diabetes develops.(2-9)

Impaired fasting glucose (IFG) is an early dysglycemic state characterized mainly by hepatic insulin resistance and impaired basal insulin secretion. Although fasting glucose provides a direct and practical means of identifying IFG, a single measurement does not capture the inflammatory milieu that may influence metabolic progression. C-reactive protein (CRP) is a conventional marker of systemic inflammation, but it is nonspecific and may be affected by adiposity, intercurrent inflammation, medication use, and other factors.(10-13) Biomarkers that reflect distinct components of obesity-related inflammation may therefore complement, rather than replace, fasting glucose.

Netrin-1 is a laminin-related guidance molecule with context-dependent roles in leukocyte migration, tissue repair, and inflammation. In adipose tissue, macrophage-derived Netrin-1 can inhibit macrophage egress, promote macrophage retention, and sustain insulin resistance. Human studies have reported altered circulating Netrin-1 concentrations in IFG and diabetes, although findings vary across metabolic phenotypes and assay platforms.(14-18) Hematological inflammatory ratios are also of interest because they can be derived from a routine complete blood count. Platelet-to-lymphocyte ratio (PLR) integrates platelet-related thrombo-inflammatory activity with relative lymphocyte status, whereas monocyte-to-lymphocyte ratio (MLR) reflects the balance between circulating monocytes, which can differentiate into adipose-tissue macrophages, and lymphocyte-mediated immune regulation. Previous studies have linked these ratios to prediabetes, diabetes, insulin resistance, and metabolic complications, although results have varied across populations.(19-26)

Few studies have simultaneously compared Netrin-1, PLR, MLR, and CRP in adults with central obesity or examined whether their associations with IFG persist after accounting for age, sex, and the degree of obesity. Evaluating these markers is clinically relevant because they may help characterize an inflammatory phenotype that warrants closer metabolic follow-up, although they are not stand-alone diagnostic tests. This study therefore was conducted to compare their discriminatory performance and crude associations with IFG and explored whether these associations persisted after adjustment for age, sex, and body mass index (BMI).

Methods

Study Design and Subjects Recruitment

A cross-sectional analytical study was conducted at Diponegoro National Hospital, Semarang, Indonesia, from July to October 2025. Eligible subjects were adults aged 30-60 years with central obesity, defined in the archived study dataset as a waist circumference >90 cm in men and >80 cm in women. Exclusion criteria included a known history of diabetes mellitus, malignancy, chronic liver disease, hematological disorders, acute infection, inflammatory disease, or pregnancy. Diabetes exclusion was based on documented medical history, interviews, and available supporting clinical information. Repeat fasting glucose measurements, oral glucose tolerance testing, and confirmatory hemoglobin A1c (HbA1c)-based classification were unavailable. Accordingly, the analytical outcome was fasting-glucose-defined IFG rather than a comprehensive diagnosis of prediabetes or diabetes. Subjects were recruited consecutively, and all provided written informed consent. Of 103 individuals screened, 15 were excluded, leaving 88 subjects for analysis.

Clinical Assessment and Specimen Collection

Subjects' waist circumference was measured at the end of normal expiration, positioning the tape horizontally midway between the lower rib margin and the iliac crest. After an overnight fast of 8-10 hours, study staff collected 5 mL of venous blood. Two milliliters were transferred to an ethylenediaminetetraacetic acid (EDTA) tube for complete blood count analysis, and 3 mL were collected in a tube without anticoagulant. After clotting, the serum was separated by centrifugation.

Fasting Glucose Measurement

Fasting glucose was measured in serum using the hexokinase method on an Indiko Clinical Chemistry System (Thermo Fisher Scientific, Waltham, MA, USA). Subjects were classified as having IFG when fasting glucose was 100-125 mg/dL and as non-IFG when fasting glucose was <100 mg/

dL. No participant had a fasting glucose concentration ≥126 mg/dL. Therefore, the terms IFG and non-IFG refer only to the prespecified fasting-glucose categories used in this study.

Calculation of PLR and MLR

A Sysmex XN-350 automated hematology analyzer (Sysmex Corporation, Kobe, Japan) measured complete blood counts in EDTA-anticoagulated blood. PLR was calculated by dividing the platelet count by the absolute lymphocyte count, and MLR by dividing the absolute monocyte count by the absolute lymphocyte count.

Netrin-1 Measurement

Serum Netrin-1 was measured at The GAKI Laboratory, Faculty of Medicine, Universitas Diponegoro using the Human Ntn1 ELISA Kit (Catalog No. RE2374H; Reed Biotech Ltd, Wuhan, China), which is based on a sandwich enzyme-linked immunosorbent assay (ELISA) principle. According to the manufacturer, the assay has an analytical sensitivity of 18.75 pg/mL, a measurement range of 31.25-2,000 pg/mL, and an overall repeatability coefficient of variation <10%. Optical density was read at 450 nm with a 620-nm reference wavelength, and concentrations were calculated from the standard curve.

CRP Measurement

Serum CRP was measured using the VivaDiag™ Whole C-Reactive Protein Test Kit (FIA) (REF VID01-01-011; VivaChek Biotech, Hangzhou, China) on a VivaDiag™ POCT Analyzer (REF VIM1000-00-011; VivaChek Biotech), according to the manufacturer's instructions. The assay used fluorescence-based sandwich immunodetection. For each measurement, 10 µL of serum was mixed with the supplied buffer, 75 µL of the diluted sample was applied to the test device, and the analyzer read the result after a 3-minute reaction. Most results were reported tbelow the laboratory reporting threshold (<5 mg/L); therefore, the continuous receiver operating characteristic (ROC) result for CRP was interpreted cautiously, and the categorical threshold was treated as a study-derived cut-off rather than a clinical reference limit.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics version 26 (IBM Corporation, Armonk, NY, USA) and verified the results against the archived dataset. Data were descriptively presented, and statistical analyses were performed accordingly. ROC analysis was used to evaluate the ability of Netrin-1, PLR, MLR, and CRP to distinguish IFG from non-IFG. The Youden index identified optimal thresholds, and 2×2 tables yielded crude PRs with 95% CIs.

All exploratory logistic regression models retained age, sex, and BMI as a priori adjustment variables. The initial backward likelihood-ratio model included Netrin-1, PLR, and MLR categories, and backward elimination was applied only to these biomarker categories. Adjusted associations are reported as adjusted odds ratios (ORs) with 95% CIs. Because IFG was common (54.5%), the adjusted ORs may be farther from the null than the corresponding adjusted PRs and were not interpreted as adjusted prevalence ratios (PRs). Statistical significance was defined as $p<0.05$.

Results

The final study population included 88 adults with central obesity, consisting of 31 men (35.2%) and 57 women (64.8%). Forty-eight subjects (54.5%) had IFG (Table 1).

Subjects with IFG had higher body weight and BMI than those without IFG. Netrin-1, PLR, and MLR values were also significantly higher in the IFG group. Age, waist circumference, platelet count, absolute monocyte count,

Table 1. Baseline characteristics of the study subjects.

Parameters	Mean±SD	Median (Min–Max)
Age (years)	39.42±7.66	38 (30–60)
Height (cm)	159.70±8.50	159.50 (143.00–179.50)
Weight (kg)	78.12±15.48	73.70 (54.40–115.80)
BMI (kg/m^2)	30.50±4.73	29.60 (22.80–44.20)
WC (cm)		
Male	109.85±8.92	110.00 (95.00–125.00)
Female	109.69±9.06	108.50 (95.00–135.00)
Platelets (/µL)	312,341±62,311	307,000 (163,000–551,000)
ALC (/µL)	2,406.56±610.09	2,241.00 (1,456.00–4,142.00)
AMC (/µL)	516.10±158.01	486 (280–981)
FG (mg/dL)	100.81±9.09	100.50 (79.00–125.00)
PLR	136.86±40.33	132.65 (70.33–240.00)
MLR	0.22±0.07	0.20 (0.11–0.43)
Netrin-1 (pg/mL)	395.27±210.19	327.11 (153.39–1,230.80)
CRP (mg/L)	5.47±2.08	5.00 (5.00–22.60)

WC: waist circumference; BMI: body mass index; FG: fasting glucose; ALC: absolute lymphocyte count; AMC: absolute monocyte count; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; CRP: C-reactive protein. CRP results <5 mg/L were reported as 5.0 mg/L.

Table 2. Clinical and laboratory characteristics according to IFG status.

Parameters	IFG (n=48)		Non-IFG (n=40)		*p*-value
	Mean±SD	Median	Mean±SD	Median	
Age (years)	40.71±7.56	38.00 (31.00–60.00)	37.88±6.18	36.05 (30.00–55.00)	0.205[b]
Height (cm)	160.82±9.00	161.50 (145.60–179.50)	158.40±7.83	158.75 (143.00–178.50)	0.186[a]
Weight (kg)	82.48±16.94	76.65 (55.10–115.80)	72.89±11.71	69.20 (54.40–109.00)	0.006[b,*]
BMI (kg/m²)	32.01±5.18	30.85 (24.50–44.20)	28.79±3.43	27.95 (22.80–35.70)	0.003[b,*]
WC (cm)	111.06±9.41	110.00 (95.00–135.00)	108.18±8.22	107.00 (95.00–128.00)	0.133[a]
Platelets (×10³/µL)	320.27±65.72	321.50 (163.00–551.00)	302.83±57.33	293.50 (199.00–437.00)	0.188[a]
ALC (/µL)	2,339.93±624.16	2,150 (1,456–4,142)	2,486.52±590.61	2,367 (1,512–3,920)	0.157[b]
AMC (/µL)	540.63±163.45	509 (312–981)	486.67±147.90	448 (280–903)	0.081[b]
Serum Netrin-1 (pg/mL)	452.30±231.89	396.29 (300.03–534.70)	326.83±157.93	291.77 (222.37–372.31)	0.002[b,*]
PLR	145.93±46.24	137.27 (112.77–179.63)	125.99±28.82	129.01 (102.79–140.45)	0.041[b,*]
MLR	0.238±0.066	0.237 (0.193–0.276)	0.201±0.062	0.185 (0.170–0.232)	0.002[b,*]
CRP, n (%)					0.364[c]
<5.10 mg/L	40 (83.3%)		36 (90.0%)		
≥5.10 mg/L	8 (16.7%)		4 (10.0%)		

Continuous variables are presented as both mean±SD and median values. Medians are reported with minimum-maximum for age, height, body weight, BMI, waist circumference, platelet count, ALC, and AMC and as median (IQR) for Netrin-1, PLR, and MLR; CRP is presented as n (%). [a]Tested with Independent-samples t test; [b]Tested with Mann-Whitney U test; [c]Tested with Pearson chi-square test. ALC: absolute lymphocyte count; AMC: absolute monocyte count; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; CRP: C-reactive protein. CRP results <5 mg/L were reported as 5.0 mg/L; 76 of 88 observations (86.4%) were left-censored at this value.

and absolute lymphocyte count did not differ significantly between groups. The proportion of participants with CRP ≥5.10 mg/L was also similar between groups (Table 2).

Among the evaluated markers, Netrin-1 had the highest AUC (0.694), followed closely by MLR (0.689). PLR showed modest but statistically significant discrimination, whereas CRP did not distinguish participants with IFG from those without IFG. At the selected thresholds, MLR had the highest sensitivity and overall accuracy. The MLR p=0.002 in Table 3 indicated whether the ROC AUC differs from 0.5 and was not the p-value for the PR (Table 3, Figure 1).

At the ROC-derived thresholds, IFG was more prevalent among participants with elevated Netrin-1, PLR, or MLR. MLR showed the strongest crude association. For MLR, p<0.001 in Table 4 refers to the crude PR. Because these p-values arise from different analyses, they were not inconsistent. CRP was not significantly associated with IFG (Table 4, Figure 2).

There were three parameters that were retained in all exploratory logistic regression models: age, sex, and BMI. Netrin-1, PLR, and MLR were included in Model 1; but Netrin-1 was removed in the backward elimination of Model 2, while PLR was removed in the backward elimination of Model 3. In the final model, MLR ≥0.20 remained associated with IFG after adjustment for age, sex, and BMI and had the largest adjusted OR (Table 5). However, this OR should not be interpreted as an adjusted PR.

Table 3. ROC characteristics and discriminatory performance.

Markers	Cut-off	AUC (95% CI)	*p*-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Netrin-1	315.35 pg/mL	0.694 (0.583-0.805)	0.002*	64.6	65.0	68.9	60.5	64.8
PLR	132.43	0.627 (0.510-0.744)	0.041*	62.5	62.5	66.7	58.1	62.5
MLR	0.20	0.689 (0.574-0.803)	0.002*	70.8	67.5	72.3	65.9	69.3
CRP	5.10 mg/L	0.532 (0.411-0.653)	0.609	16.7	90.0	66.7	47.4	50.0

AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value. The p-values indicate null hypothesis that AUC=0.5 and do not represent the p-values for PRs.

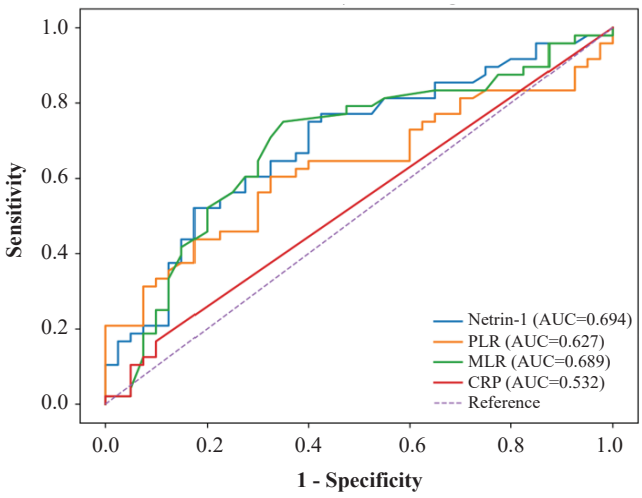

Figure 1. ROC curves for Netrin-1, PLR, MLR, and CRP for distinguishing IFG from non-IFG.

Discussion

In this cross-sectional study of adults with central obesity, more than half of the participants had IFG. Netrin-1, PLR, and MLR were associated with IFG in crude analyses, whereas CRP was not. In the exploratory logistic regression models, which retained age, sex, and BMI throughout, MLR was the only inflammatory biomarker retained in the final model. These findings suggest that cellular inflammatory indices may capture aspects of early metabolic dysregulation that are not reflected by a conventional acute-phase marker alone. However, the adjusted OR does not represent an adjusted PR.

Fasting glucose remains the direct measure used to identify IFG. Netrin-1, PLR, and MLR are therefore not intended to replace glucose measurement but may provide complementary information about the inflammatory phenotype of adults with central obesity. These markers may help distinguish individuals with similar fasting-glucose values but different inflammatory burdens, thereby identifying a subgroup that may benefit from closer metabolic surveillance and more intensive lifestyle-risk management. But these markers are not proposed as diagnostic substitutes, and their incremental value beyond established clinical risk factors requires prospective confirmation. No combined biomarker score or incremental-performance model was prespecified or analyzed; therefore, the present data do not show that combining these markers improves diagnostic accuracy or risk stratification.

The overall median Netrin-1 concentration was 327.11 pg/mL, whereas 315.35 pg/mL was the ROC-derived threshold. A previous study reported a circulating Netrin-1 concentration of approximately 275.9 pg/mL in healthy controls and higher concentrations in participants with IFG or newly diagnosed diabetes.(16) The somewhat higher concentration in the present cohort of adults with central obesity is biologically plausible, although direct comparisons require caution because study populations and assay platforms differ. Netrin-1 can retain macrophages in visceral adipose tissue and sustain local inflammation and insulin resistance.(14,15) Its exclusion from the final logistic regression model may reflect overlap with BMI and other inflammatory pathways, as well as the modest sample size.

The median PLR in this cohort was 132.65. Published reference intervals for healthy Chinese adults range from 36.63 to 149.13 in men and from 43.36 to 172.68 in women. Thus, the cohort median fell within these reported population ranges, although the ROC threshold of 132.43 was associated with IFG in this cohort of adults with central obesity.(27) These thresholds should therefore be considered population-specific rather than universal. MLR showed the strongest crude association and remained associated with IFG after adjustment for age, sex, and BMI.(28) This association is biologically plausible because circulating monocytes can migrate into adipose tissue and differentiate into macrophages, whereas lymphocytes contribute to immune regulation. The lack of standardized reference limits for MLR further supports external validation before clinical adoption.

Table 4. Crude PR for IFG (*p*-values refer to crude PR comparisons).

Exposure	IFG in Exposed	IFG in Reference	PR	95% CI	*p*-value
Netrin-1 ≥315.35 pg/mL	31/45 (68.9%)	17/43 (39.5%)	1.742	1.147-2.648	0.006*
PLR ≥132.43	30/45 (66.7%)	18/43 (41.9%)	1.593	1.059-2.396	0.019*
MLR ≥0.20	34/47 (72.3%)	14/41 (34.1%)	2.119	1.337-3.357	<0.001*
CRP ≥5.10 mg/L	8/12 (66.7%)	40/76 (52.6%)	1.267	0.805-1.993	0.364

Reference categories were as follow: Netrin-1 <315.35 pg/mL, PLR <132.43, MLR <0.20, and CRP <5.10 mg/L.
PR: prevalence ratio; CI: confidence interval.

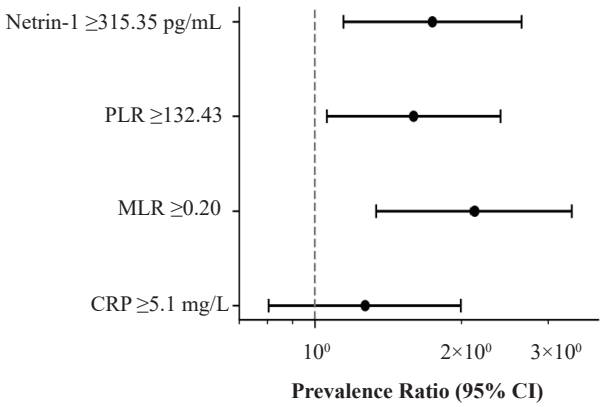

Figure 2. PRs for Netrin-1, PLR, MLR, and CRP in relation to IFG.

CRP showed poor discrimination and no significant crude association with IFG. In the archived analytical dataset, 76 of 88 CRP observations (86.4%) were stored as 5.0 mg/L after laboratory results had been reported as <5 mg/L. This left-censoring compressed variability within the low-concentration range relevant to obesity and likely reduced the ability of CRP to distinguish participants with IFG from those without IFG. The ROC-derived threshold of 5.10 mg/L separated the cluster of observations stored at 5.0 mg/L from the next observed value of 5.2 mg/L; therefore, it should not be interpreted as a clinical reference limit. CRP reflects generalized hepatic acute-phase activity and is influenced by adiposity, acute inflammation, medication use, smoking, and other factors. The negative finding therefore does not exclude low-grade inflammation; rather, the archived reporting and coding format limited differentiation among participants near the lower end of the CRP distribution.

The adjusted analysis also underscores the importance of age and BMI. Greater adiposity contributes to insulin resistance and may confound associations between inflammatory biomarkers and IFG. Sex was retained as an a priori adjustment variable because sex-related differences in adipose distribution and metabolic risk may influence these associations, although sex was not statistically significant in the final model.(29) The logistic regression was used for the available adjusted analysis. Because IFG was common, the adjusted ORs may overstate the magnitude of the corresponding PRs. Future confirmatory analyses should use log-binomial or robust Poisson regression to estimate adjusted PRs directly.

This study has several limitations. The cross-sectional design precludes causal and temporal inferences. Recruitment from a single center and the modest sample size limit generalizability and model precision. The absence of

Table 5. Exploratory adjusted association models using backward likelihood-ratio logistic regression.

Model	Parameter	Reference	Adjusted OR	95% CI	*p*-value
Model 1	Age, per year	Continuous	1.078	1.002-1.160	0.044*
	Female sex	Male	0.661	0.211-2.073	0.477
	BMI, per kg/m²	Continuous	1.244	1.075-1.439	0.003*
	Netrin-1 ≥315.35 pg/mL	Netrin-1 <315.35 pg/mL	2.394	0.805-7.119	0.116
	PLR ≥132.43	PLR <132.43	2.909	0.927-9.131	0.067
	MLR ≥0.20	MLR <0.20	5.698	1.783-18.206	0.003*
Model 2	Age, per year	Continuous	1.088	1.012-1.170	0.023*
	Female sex	Male	0.679	0.222-2.084	0.499
	BMI, per kg/m²	Continuous	1.264	1.099-1.455	0.001*
	PLR ≥132.43	PLR <132.43	2.533	0.835-7.687	0.101
	MLR ≥0.20	MLR <0.20	6.205	1.959-19.658	0.002*
Model 3	Age, per year	Continuous	1.100	1.024-1.182	0.009*
	Female sex	Male	0.734	0.247-2.186	0.579
	BMI, per kg/m²	Continuous	1.238	1.086-1.412	0.001*
	MLR ≥0.20	MLR <0.20	7.516	2.465-22.911	<0.001*

All models retained age, sex, and BMI. Model 1 included Netrin-1, PLR, and MLR; Netrin-1 was removed in Model 2, and PLR was removed in Model 3. The final model (Model 3) had a -2 log likelihood of 89.033, a Nagelkerke R^2 of 0.410, and a classification accuracy of 73.9%. OR: odds ratio; CI: confidence interval. Because IFG was common, ORs should not be interpreted as PRs.

a healthy, non-obese control group limits comparison with normal physiology. Diabetes exclusion relied on previously diagnosed disease, and IFG classification relied on fasting glucose. Because repeat fasting glucose measurements, oral glucose tolerance testing, and confirmatory HbA1c-based classification were unavailable, diabetes defined by other glycemic criteria could not be completely excluded. The multivariable analysis was exploratory, categorized the biomarker values, produced wide confidence intervals, and did not estimate adjusted PRs. Renal function, which can influence circulating Netrin-1, was not assessed.(30) Cardiovascular disease, smoking, medication use, diet, and physical activity were also not comprehensively evaluated. The Netrin-1 manufacturer did not provide separate intra-assay and inter-assay precision estimates. In addition, 76 of 88 CRP observations (86.4%) were left-censored below 5 mg/L and coded as 5.0 mg/L in the archived analytical dataset. This coding compressed low-range variability and made the ROC-derived 5.10 mg/L threshold strongly dependent on the observed data distribution. Prospective multicenter studies using standardized quantitative reporting across the full hsCRP range and adjusted PR models should validate these thresholds and determine whether the biomarkers add value beyond established clinical risk factors.

Conclusion

Elevated serum Netrin-1, PLR, and MLR were associated with IFG in adults with central obesity. MLR showed the strongest crude association and was the only evaluated inflammatory biomarker retained in the exploratory adjusted logistic regression model. Because it can be calculated inexpensively from a routine complete blood count, MLR may complement fasting-glucose assessment by helping characterize the inflammatory phenotype of adults with central obesity. However, it should not be used as a diagnostic substitute.

Authors Contribution

BEP conceived and designed the study, supervised data collection, analyzed the data, prepared the tables and figures, and drafted the manuscript. MH supervised the study, contributed critical intellectual content, and critically revised the manuscript. NSW supervised and reviewed the statistical analysis and methodological interpretation. DR and PA contributed critical intellectual content and reviewed the manuscript. All authors have agreed with the final draft of the manuscript.

Ethical Statement

The Health Research Ethics Committee of the Faculty of Medicine, Universitas Diponegoro, approved the study protocol (No. 243/EC/KEPK/FK-UNDIP/IX/2025). All participants provided written informed consent.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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