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Determinants of Insulin Resistance Beyond Adiposity: A Multivariable Analysis in Normal-Weight Adults

Adipozite Dışındaki İnsülin Direnci Belirleyicileri: Normal Ağırlıktaki Yetişkinlerde Çok Değişkenli Bir Analiz

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Abstract: Insulin resistance (IR) is a key pathogenic mechanism in Type 2 Diabetes Mellitus, often linked to obesity-related inflammation. However, IR can also occur in individuals with normal weight, a condition known as the metabolically obese normal-weight phenotype. This study assesses the predictive value of routine hematological parameters compared to combined inflammation indices for detecting IR in non-obese populations. This retrospective cross-sectional study included 305 normal-weight adults (body mass index < 25 kg/m²). IR was defined by a Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) threshold of 2.5. Parameters were analyzed using univariate and hierarchical multivariable logistic regression. Parallel models, adjusted for age, sex, and body mass index (BMI), were used to assess individual leukocyte subtypes. Discriminatory performance was evaluated through Receiver Operating Characteristic (ROC) curve analysis. IR was found in 93 (30.5%) participants. The IR+ group exhibited significantly higher BMI, glucose, triglycerides, HbA1c, and white blood cell (WBC) counts ($p < 0.05$). Multivariable analysis identified WBC count as the only independent predictor of inflammation (OR = 1.946, $p < 0.001$). WBC count showed better explanatory power (Nagelkerke R2 = 0.196) and discriminatory ability (AUC = 0.725) compared to individual subtypes and composite indices, like the panimmune inflammation value (AUC = 0.510). The final multivariable model achieved an AUC of 0.736. In normal-weight adults, IR appears to exhibit a more pronounced association with generalized systemic inflammation reflected by absolute WBC counts rather than ratio-based indices. WBC count serves as a practical marker for early metabolic risk identification in non-obese individuals.

Keywords: Insulin resistance, White blood cell count, Inflammation, Systemic immune indices, Panimmune inflammation value.

Ethics Committee Approval: The study was approved by Kutahya Saglık Bilimleri University Non-Interventional Clinical Research Ethics Committee (Decision No:2025/14, Date:16.12.2025).

Informed Consent: Given the retrospective design of this study, the requirement for written informed consent was waived.

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Özet: İnsülin direnci (IR), Tip 2 diabetes mellitusun patogenezinin merkezinde bulunan önemli bir mekanizmadır ve genellikle obeziteye bağlı inflamasyonla bağlantılıdır. Ancak IR, normal kilolu bireylerde de görülebilir; bu durum metabolik obez normal kilolu fenotipi olarak bilinir. Bu çalışmanın amacı, obez olmayan popülasyonlarda IR'yi tespit etmek için rutin hematolojik parametrelerin, kombine inflamasyon indekslerine kıyasla öngörü değerini belirlemektir. Bu retrospektif kesitsel çalışmaya 305 normal kilolu yetişkin (vücut kitle indeksi < 25 kg/m²) dahil edildi. Çalışmada IR için kesim değeri olarak 2,5 kullanılmıştır. Parametreler, tek değişkenli ve hiyerarşik çok değişkenli lojistik regresyon kullanılarak analiz edildi. Yaş, cinsiyet ve vücut kitle indeksi (VKİ) için ayarlanmış paralel modeller, bireysel lökosit alt tiplerini değerlendirmek için kullanıldı. Ayırt edici performans, alıcı çalışma karakteristiği (ROC) eğrisi analizi ile değerlendirildi. IR, 93 (%30,5) katılımcıda saptandı. IR olan grupta, VKİ, glikoz, trigliseritler, HbA1c ve beyaz kan hücresi (WBC) sayılarında anlamlı olarak daha yüksek değerler saptandı ($p < 0,05$). Çok değişkenli analizde, WBC sayısı inflamasyonun tek bağımsız belirleyicisi olarak saptandı (OR = 1,946, $p < 0,001$). WBC sayısı, panimmün inflamasyon değeri (AUC = 0,510) gibi bireysel alt tiplere ve bileşik indekslere kıyasla daha iyi açıklayıcı güç (Nagelkerke R2 = 0,196) ve ayırt edici performans (AUC = 0,725) gösterdi. Nihai çok değişkenli model 0,736 AUC değerine ulaştı. Normal kilolu yetişkinlerde, IR, oran bazlı indekslerden ziyade mutlak WBC sayılarının yansıttığı genel sistemik inflamasyon ile daha belirgin bir ilişki sergilemektedir. WBC sayısının günlük pratikte obez olmayan bireylerde erken metabolik risk tanımlaması için ucuz, pratik bir biyobelirteç olarak akılda tutulması faydalı bir yaklaşımdır.

Anahtar Kelimeler: İnsülin direnci, Beyaz kan hücresi sayısı, Enflamasyon, Sistemik bağışıklık indeksleri, Panimmün inflamasyon değeri.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a major global health concern because of its strong link to morbidity and mortality (1) . Central to the pathophysiology of T2DM is insulin resistance (IR), defined as the reduced responsiveness of insulin-targeting tissues to normal levels of insulin (2, 3). IR is closely linked to obesity, which promotes a chronic, low-grade inflammatory state known as metabolic inflammation . This ongoing inflammation disrupts insulin signaling pathways, highlighting the crucial need for early identification of IR, as it often precedes the development of T2DM and its complications by years (2, 3).

Due to the complexity and high cost of the gold standard method (hyperinsulinemic-euglycemic clamp), practical surrogate indices derived from routine clinical parameters are widely adopted (4). Key examples include the homeostasis model assessment of insulin resistance (HOMA-IR) and the triglyceride-glucose (TyG) Index (1) . Despite the utility of these established indices, their precise cut-off points for defining IR exhibit significant variability across diverse populations (5, 6). Furthermore, traditional measures of obesity, such as Body Mass Index (BMI), are insufficient because they fail to accurately differentiate between fat, muscle, and bone mass (7). This limitation is particularly pronounced because IR is not confined strictly to obese individuals; it also manifests in patients categorized as non-obese, a condition often referred to as metabolically obese normal weight (MONW)(8) .

Consequently, there is a need for reliable inflammatory markers that can predict IR in non-obese adults. While hematological indices like the systemic immune-inflammation index (SII) and pan immune value (PIV) have shown promise in obese and diabetic cohorts, their usefulness in non-obese populations remains unclear (9, 10). This study aims to evaluate the predictive utility of accessible inflammatory markers and composite indices in non-obese adults, determining whether absolute cell counts or derived ratios better predict metabolic risk in this specific population.

2. Material And Methods

2.1. Study Population and Patient Selection

This cross-sectional study was conducted between January 2024 and October 2025 in the internal medicine outpatient clinics of a tertiary care hospital following approval from the Institutional Ethics Committee (Decision No: 2025/14-32; Date: December 16, 2025).

A total of 305 adult outpatients were screened. Inclusion criteria were: being between 18 and 60 years of age, having a BMI < 25 kg/m² (classified as non-obese according to World Health Organization criteria) (11), and having complete clinical and laboratory data. Exclusion criteria were: BMI ≥ 25 kg/m², acute infection, chronic inflammatory disease, pregnancy, use of anti-inflammatory drugs (steroids or NSAIDs), use of antiobesity drugs, history of malignancy, and C-reactive protein (CRP) ≥ 5 mg/dL.

2.2. Data Collection

Demographic and anthropometric data including age, sex, height, weight, body mass index, and waist circumference were collected. Biochemical parameters, including fasting glucose, insulin, lipid profile such as triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), creatinine, estimated glomerular filtration rate (eGFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid, white blood cell count (WBC) and other hemogram parameters, were retrieved from the hospital information system.

2.2.1. Calculation of Insulin Resistance and Indices

Insulin resistance was calculated using the HOMA-IR formula: (Fasting Glucose (mg/dL) × Fasting Insulin (μU/mL)) / 405. A HOMA-IR threshold of 2.5 was used to classify patients into Insulin Resistant (IR+) and Non-Insulin Resistant (IR-) groups (12).

Inflammatory indices were computed as follows:

- **SII:** (Neutrophil count × Platelet count) / Lymphocyte count
- **PIV:** (Neutrophil count × Platelet count × Monocyte count) / Lymphocyte count
- **NLR** (Neutrophil/Lymphocyte ratio): Neutrophil count / Lymphocyte count

2.3. Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 31.0 (IBM Corp., Armonk, NY, USA). The

normality of continuous variables was assessed through visual inspection of histograms and confirmed with the Shapiro–Wilk test. All continuous variables exhibited non-normal distribution on Shapiro–Wilk testing; between-group comparisons were therefore performed using the Mann–Whitney U test, and continuous variables are reported as median [interquartile range, IQR]. Categorical variables were analyzed using the Chi-square test.

Univariate binary logistic regression analyses were conducted to evaluate factors associated with insulin resistance. Variables demonstrating collinearity were not entered simultaneously into multivariate models. Hierarchical multivariate logistic regression models were constructed by sequentially adjusting for demographic variables and inflammatory parameters. In addition to the hierarchical models, parallel multivariable logistic regression analyses were performed to evaluate the independent associations of individual leukocyte subsets with insulin resistance. Separate models were constructed in which total white blood cell count, neutrophil count, lymphocyte count, and monocyte count were entered individually, each adjusted for age, sex, and body mass index, to avoid collinearity among inflammatory parameters. Model performance was assessed using the Hosmer–Lemeshow goodness-of-fit test, −2 log likelihood, and Nagelkerke R^2. Given the recognised tendency of the Hosmer–Lemeshow test to over-reject otherwise well-fitting models in moderate-to-large samples, model adequacy was not interpreted solely on the basis of this test (13). Calibration was therefore appraised jointly with the discrimination performance reflected by the area under the receiver operating characteristic curve (AUC), in line with current recommendations for predictive logistic regression models.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory performance of individual inflammatory parameters and the predicted probability derived from the multivariable logistic regression model. The area under the ROC curve with 95% confidence intervals was calculated for each parameter. Optimal cut-off values were determined using the Youden index, and corresponding sensitivity and specificity values were reported. A two-sided *p* value < 0.05 was considered statistically significant.

3. Results

A total of 305 normal-weight adults were included in the study, of whom 93 were classified as insulin-resistant (IR+) and 212 as non-insulin-resistant (IR−). Comparisons of demographic, metabolic, and inflammatory characteristics between groups are presented in Table 1. The IR(+) group demonstrated higher BMI, fasting glucose, triglyceride, insulin, HbA1c, and white blood cell counts compared with the IR(−) group.

In univariate logistic regression analyses (Table 2), BMI, fasting glucose, triglycerides, HbA1c, white blood cell count, neutrophil count, lymphocyte count, monocyte count, and PIV were associated with insulin resistance. Due to collinearity among inflammatory parameters, hierarchical multivariate models were constructed (Table 3).

Receiver operating characteristic curve analysis was conducted to assess the discriminatory performance of the multivariate model and selected individual variables (Table 4). The predicted probability derived from Model 2 yielded an AUC of 0.736 (95% CI: 0.679–0.793, $p < 0.001$). At an optimal cut-off value of 0.30, sensitivity and specificity were 86.0% and 69.8%, respectively. White blood cell (WBC) count demonstrated an AUC of 0.725 (95% CI: 0.663–0.786, $p < 0.001$), whereas BMI showed lower discriminatory ability (AUC = 0.597, 95% CI: 0.528–0.667, $p = 0.006$). The panimmune inflammation value did not show significant discrimination for insulin resistance (AUC = 0.510, $p = 0.800$).

ROC curve analysis demonstrated that the predicted probability from the final multivariate model had an AUC of 0.736 (95% CI, 0.679–0.793; $p < 0.001$). The optimal cut-off value was 0.30, yielding a sensitivity of 86.0% and specificity of 69.8% (Table 4, Figure 1). Among individual parameters, white blood cell count demonstrated an AUC of 0.725, whereas BMI (AUC = 0.597) and panimmune inflammation value (AUC = 0.510) showed limited discriminatory performance (Figure 2).

In addition to the hierarchical multivariate models, parallel multivariable logistic regression analyses were performed to evaluate the independent associations of individual leukocyte subsets with insulin resistance (Table 5). In Model A, white blood cell count remained independently associated with insulin resistance after adjustment for age, sex, and BMI (OR = 1.946, 95% CI: 1.540–2.459; $p < 0.001$; Nagelkerke $R^2 = 0.196$). Similarly, neutrophil count (Model B; OR = 2.092, 95% CI: 1.546–2.832; $p < 0.001$; Nagelkerke $R^2 = 0.150$), lymphocyte count (Model C; OR = 2.836, 95% CI: 1.771–4.541; $p < 0.001$; Nagelkerke $R^2 = 0.131$), and monocyte count (Model D; OR = 8.792, 95% CI: 1.164–

66.383; p = 0.035; Nagelkerke R^2 = 0.059) were each independently associated with insulin resistance when entered into separate multivariable models.

Receiver operating characteristic curve analysis was further conducted to assess the discriminatory performance of absolute leukocyte parameters for insulin resistance (Table 6, Figure 3). White blood cell count demonstrated the highest discriminatory ability, with an area under the curve (AUC) of 0.725 (95% CI: 0.663–0.786; p < 0.001). Neutrophil count showed an AUC of 0.660 (95% CI: 0.591–0.728; p < 0.001), lymphocyte count an AUC of 0.689 (95% CI: 0.625–0.752; p < 0.001), and monocyte count an AUC of 0.597 (95% CI: 0.528–0.665; p = 0.006). The corresponding ROC curves demonstrated overlapping but distinct discriminatory profiles across leukocyte subtypes (Figure 3).

Table 1. Comparison of the Clinical and Demographic Characteristics of Patients with and without Insulin Resistance

	All patients (n=305)	**Insulin Resistance (+) (n=93)**	**Insulin Resistance (-) (n=212)**	***p* value**
Age (year)	25.00 [23.00–29.00]	26.00 [24.00–28.00]	24.00 [23.00–29.00]	*0.076*
Gender, male (%) *	80(26.2)	28(35)	52(65)	*0.308*
BMI (kg/m^2)	22.50 [20.68–23.71]	22.86 [21.22–23.94]	22.35 [20.58–23.57]	***0.007***
Waist circumference (cm)	76.00 [71.00–82.00]	78.00 [71.00–85.00]	75.00 [71.00–80.00]	*0.140*
IR	1.96 [1.41–2.87]	3.36 [2.92–4.23]	1.62 [1.30–2.00]	***<0.001***
Glucose (mg/dL)	90.00 [84.00–96.00]	95.00 [91.00–99.00]	88.00 [83.00–92.00]	***<0.001***
Creatinine (mg/dL)	0.70 [0.60–0.80]	0.70 [0.60–0.80]	0.70 [0.64–0.80]	*0.454*
eGFR (mL/min/1.73m^2)	116.00 [107.00–125.00]	112.00 [102.00–124.00]	116.00 [108.00–125.00]	*0.281*
ALT (U/L)	12.10 [10.00–18.00]	13.40 [8.30–21.00]	12.10 [10.00–16.00]	*0.928*
AST (U/L)	16.20 [14.00–20.00]	18.00 [12.30–21.00]	16.00 [14.00–19.50]	*0.431*
Uric acid (mg/dL)	4.45 [3.70–5.20]	4.40 [3.60–5.40]	4.60 [3.70–5.20]	*0.898*
T. Cholesterol	163.60 [143.00–189.00]	160.00 [147.00–189.00]	163.60 [137.00–190.00]	*0.353*
Triglyceride (mg/dL)	71.00 [54.20–93.00]	77.00 [70.00–116.00]	65.50 [52.00–91.40]	***<0.001***
HDL (mg/dL)	57.00 [48.00–66.00]	53.00 [46.00–67.00]	58.00 [49.00–65.00]	*0.319*
LDL (mg/dL)	89.00 [73.00–113.00]	93.00 [78.00–114.00]	87.00 [69.00–108.00]	*0.136*
HbA1c (%)	5.20 [5.00–5.30]	5.20 [5.10–5.40]	5.10 [4.90–5.30]	***<0.001***
TSH (mU/L)	1.90 [1.28–2.40]	1.67 [1.19–2.72]	1.92 [1.30–2.33]	*0.886*
WBC (x10^3/μL)	6.54 [5.79–7.52]	7.31 [6.54–8.23]	6.22 [5.74–7.11]	***<0.001***
Neutrophil count (x10^3/μL)	3.54 [3.03–4.39]	4.24 [3.34–4.84]	3.46 [2.94–3.90]	***<0.001***
Lymphocyte count (x10^3/μL)	2.21 [1.89–2.67]	2.57 [2.24–2.93]	2.11 [1.80–2.46]	***<0.001***
Monocyte(x10^3/μL)	0.51 [0.43–0.61]	0.54 [0.44–0.64]	0.49 [0.43–0.59]	***0.007***
Platelet (x10^3/μL)	265.00 [234.00–305.00]	260.00 [229.00–328.00]	268.00 [238.00–303.00]	*0.908*
SII	430.17 [306.47–525.93]	377.73 [293.63–542.88]	443.52 [336.52–523.25]	*0.598*
PIV	212.66 [164.17–283.65]	200.74 [157.98–395.72]	217.88 [165.66–277.55]	*0.798*
Neutrophil/Lymphocyte	1.56 [1.36–1.93]	1.50 [1.27–2.11]	1.62 [1.41–1.92]	*0.333*
C- Reactive Protein (mg/L)	1.00 [1.00–1.70]	1.00 [1.00–1.71]	1.00 [0.92–1.56]	*0.053*

Data are presented as median [interquartile range, IQR] for continuous variables and as n (%) for categorical variables.

*Comparisons between groups were made using the *Chi-Square Test, Mann-Whitney U Test. Abbreviations: BMI: Body mass index, IR: Insulin resistance, eGFR: Estimated glomerular filtration rate, HbA1c: Hemoglobin A1c, TSH: Thyroid-stimulating hormone, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SII: Systemic inflammatory index, PIV: Pan immune inflammation value, HDL: High-Density Lipoprotein, Waist circum: Waist circumference.*

Table 2. Univariate Regression Analyses of Patients with Insulin Resistance

Variable	OR	95% CI	p
Unıvariate Analysıs			
Age (year)	1.024	0.984–1.065	0.247
Gender, male (%)	0.754	0.439–1.298	0.309
BMI (kg/m²)	1.186	1.035–1.358	***0.014***
Waist circum. (cm)	1.016	0.986–1.048	0.301
Glucose (mg/dL)	1.131	1.088–1.176	***<0.001***
Creatinine (mg/dL)	0.649	0.104–4.047	0.644
eGFR (mL/min/1.73m²)	0.977	0.955–1.000	0.053
ALT (U/L)	0.986	0.958–1.015	0.344
AST (U/L)	0.987	0.959–1.016	0.369
Uric acid (mg/dL)	0.963	0.764–1.213	0.748
Total cholesterol (mg/dL)	1.003	0.996–1.010	0.374
Triglyceride (mg/dL)	1.015	1.008–1.022	***<0.001***
HDL (mg/dL)	1.002	0.985–1.019	0.814
LDL (mg/dL)	1.005	0.997–1.013	0.238
HbA1c (%)	7.228	2.594–20.139	***<0.001***
TSH (mU/L)	1.111	0.862–1.431	0.417
WBC (×10³/L)	1.879	1.511–2.336	***<0.001***
Neutrophil count (×10³/L)	1.973	1.488–2.616	***<0.001***
Lymphocyte count (×10³/L)	2.915	1.870–4.545	***<0.001***
Monocyte (×10³/L)	12.667	1.973–81.339	***0.007***
Platelet (×10³/L)	1.002	0.997–1.007	0.375
SII	1.001	0.999–1.002	0.337
PIV	1.002	1.000–1.005	***0.022***
Neutrophil/Lymphocyte	0.983	0.651–1.483	0.933
C-Reactive Protein (mg/L)	1.208	0.983–1.485	0.072

Abbreviations: BMI: Body mass index, IR: Insulin resistance, eGFR: Estimated glomerular filtration rate, HbA1c: Hemoglobin A1c, TSH: Thyroid-stimulating hormone, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SII: Systemic inflammatory index, PIV: Panimmune Inflammation Value, HDL: High-Density Lipoprotein, Waist circum: Waist circumference. Model fit statistics: Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=28.277$, Nagelkerke $R^2=0.229$; −2 log likelihood=321.289.

Table 3. Hierarchical Multivariate Logistic Regression Models of Patients with Insulin Resistance

Variable	β	SE	Wald	OR	95% CI	p
Model 1						
Age (year)	0.006	0.021	0.075	1.006	0.965-1.048	0.784
Gender, male (%)	-0.404	0.292	1.917	0.667	0.377-1.183	0.166
BMI (kg/m²)	0.185	1.600	9.062	1.203	1.039-1.393	***0.013***
Constant	-4.816	1.600	9.062	0.008		***0.003***
Model 2						
Age (year)	-0.017	0.023	0.519	0.983	0.940-1.029	0.471
Gender, male (%)	-0.748	0.317	5.578	0.474	0.255-0.881	0.076
BMI (kg/m²)	0.156	0.080	3.780	1.169	0.999-1.369	0.052
WBC ($x10^3$/μL)	0.666	0.119	31.074	1.946	1.540-2.459	***<0.001***
Constant	-7.916	1.833	18.660	<0.001		***<0.001***
Model 3						
Age (year)	0.005	0.021	0.061	1.005	0.964-1.048	0.805
Gender, male (%)	-0.499	0.297	2.827	0.607	0.339-1.086	0.093
BMI (kg/m²)	0.171	0.076	5.135	1.187	1.023-1.376	***0.023***
PIV	0.002	0.001	4.795	1.002	1.000-1.005	***0.029***
Constant	-5.024	1.616	9.669	0.007		***0.002***
Model 4						
Age (year)	-0.018	0.023	0.604	0.982	0.938-1.028	0.437
Gender, male (%)	-0.736	0.318	5.372	0.479	0.257-0.893	0.058
BMI (kg/m²)	0.160	0.081	3.928	1.174	1.002-1.375	***0.047***
PIV	-0.001	0.001	0.308	0.999	0.997-1.002	0.579
WBC ($x10^3$/μL)	0.696	0.131	28.017	2.005	1.550-2.595	***<0.001***

Constant	-7.998	1.844	18.810	<0.001	***<0.001***

Model 1: Base Model; Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=32.533$, $p<0.001$, Nagelkerke $R^2=0.039$; −2 log likelihood=336.552.

Model 2: Base + WBC- adjusted Model; Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=61.930$, $p<0.001$, Nagelkerke $R^2=0.196$; −2 log likelihood=329.502.

Model 3: Base + PIV- adjusted Model : Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=28.406$, $p<0.001$, Nagelkerke $R^2=0.061$; −2 log likelihood=361.722.

Model 4: Combined Model: Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=46.857$, $p<0.001$, Nagelkerke $R^2=0.198$; −2 log likelihood=329.191

Table 4. ROC Analysis of the Multivariate Model and Selected Predictors of Insulin Resistance

Variable	**Cut-off**	**Sensitivity**	**Specificity**	**AUC**	**95% CI (AUC)**	***p*-value**
Model 2 (Predicted probability)	0.30	0.860	0.698	0.736	0.679-0.793	***<0.001***
BMI (kg/m²)	22.52	0.409	0.344	0.597	0.528-0.667	***0.006***
WBC (x10^3/μL)	7.11	0.731	0.755	0.725	0.663-0.786	***<0.001***
PIV	389.55	0.60	0.74	0.510	0.435-0.584	0.800

Abbreviations:BMI: Body mass index, WBC: White blood cell count, PIV: Pan-immune inflammation value, ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval

Table 5. Parallel Multivariable Logistic Regression Models of Leukocyte Subtypes and Insulin Resistance

Model	Variable	OR	95% CI	p value	Nagelkerke R^2
Model–A	Age (year)	0.983	0.940 – 1.029	0.471	0.196
	Gender, male	0.474	0.255 – 0.881	0.185	
	BMI (kg/m²)	1.169	0.999 – 1.369	0.052	
	WBC (x10^3/μL)	1.946	1.540 – 2.459	***<0.001***	
Model-B	Age (year)	1.004	0.961 – 1.048	0.873	0.150
	Gender, male	0.498	0.272 – 0.912	0.204	
	BMI (kg/m²)	1.192	1.025 – 1.386	***0.022***	
	Neutrophil (x10^3/μL)	2.092	1.546 – 2.832	***<0.001***	
Model–C	Age (year)	0.986	0.942 – 1.031	0.527	0.131
	Gender, male	0.611	0.336 – 1.112	0.107	
	BMI (kg/m²)	1.149	0.981 – 1.346	0.085	
	Lymphocyte (x10^3/μL)	2.836	1.771 – 4.541	***<0.001***	
Model–D	Age (year)	0.991	0.949 – 1.036	0.701	0.059
	Gender, male	0.691	0.388 – 1.230	0.209	
	BMI (kg/m²)	1.1186	1.020 – 1.378	***0.027***	

Monocyte (x10^3/μL)	8.792	1.164 – 66.383	***0.035***

Abbreviations:*BMI: Body mass index, WBC: White blood cell count, AUC: Area under the curve, CI: Confidence interval*

Model A: Age, gender(male), BMI, WBC; Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=61.930$, $p<0.001$, Nagelkerke $R^2=0.196$; −2 log likelihood=329.502

Model B: Age, gender(male), BMI, neutrophil; Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=27.000$, $p<0.001$, Nagelkerke $R^2=0.150$; −2 log likelihood=340.793

Model C: Age, gender(male), BMI, lymphocyte; Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=28.413$, $p<0.001$, Nagelkerke $R^2=0.131$; −2 log likelihood=345.569

Model D: Age, gender(male), BMI, monocyte; Hosmer–Lemeshow goodness-of-fit test $\chi^2(8)=23.688$, $p<0.001$, Nagelkerke $R^2=0.039$; −2 log likelihood=362.093

Table 6. Diagnostic Performance of White Blood Cell Count and Leukocyte Subtypes in Identifying Insulin Resistance

Variable	**Cut-off**	**Sensitivity**	**Specificity**	**AUC**	**95% CI (AUC)**	***p*-value**
WBC (x10^3/μL)	7.11	0.73	0.75	0.725	0.663-0.786	***<0.001***
Neutrophil (x10^3/μL)	3.92	0.62	0.75	0.660	0.591-0.728	***<0.001***
Lymphocyte (x10^3/μL)	2.23	0.77	0.64	0.689	0.625-0.752	***<0.001***
Monocyte (x10^3/μL)	0.52	0.61	0.62	0.597	0.528-0.665	***0.006***

Abbreviations: *WBC: White blood cell count, AUC: Area under the curve, CI: Confidence interval*

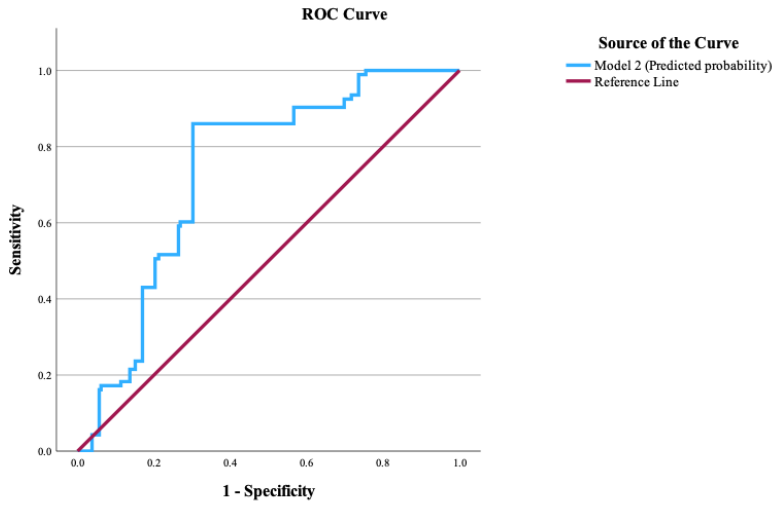

Figure1. ROC curve demonstrating the discriminatory performance of the multivariate logistic regression model (Model 2) based on predicted probability

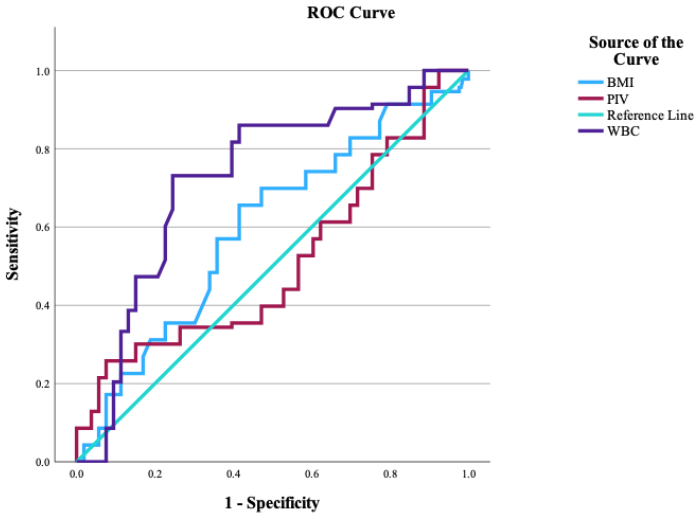

Figure 2. Receiver operating characteristic curves comparing the discriminatory performance of BMI, white blood cell count, and panimmune inflammation value for insulin resistance

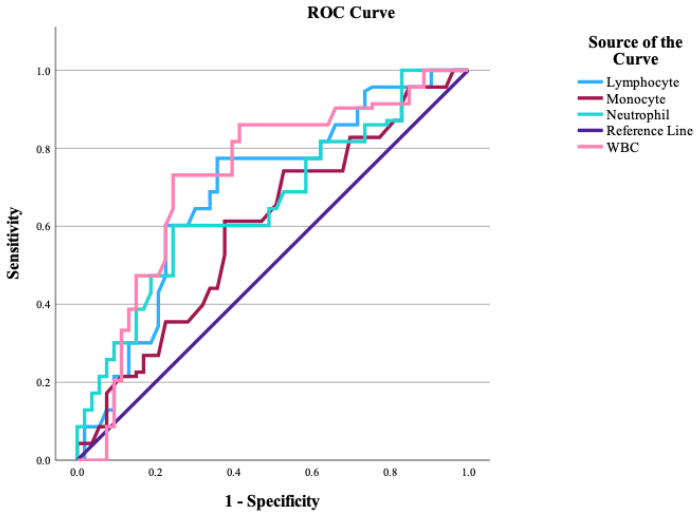

Figure 3. Comparative ROC analysis of white blood cell count, lymphocyte, monocyte, and neutrophil levels in identifying insulin resistance.

4. Discussion

The present study demonstrates that even within a strictly normal-weight population, insulin resistance is closely associated with a generalized increase in absolute leukocyte counts, independent of body mass index**.** Among all evaluated inflammatory markers, total white blood cell count consistently emerged as the strongest and most robust correlate of insulin resistance across multiple analytical approaches, including hierarchical multivariable modeling and receiver operating characteristic analysis. Importantly, this association was observed in the absence of overt obesity or clinically significant systemic inflammation, suggesting that subtle immune activation may precede traditional

anthropometric or biochemical manifestations of metabolic dysfunction (8, 14).

Body mass index is widely used to assess obesity-related metabolic risk; however, it inadequately reflects body composition and adipose tissue distribution (15). Consistent with previous studies, we observed that BMI within the non-obese range was not independently associated with IR after multivariate adjustment (1, 6). This observation highlights the limitations of relying solely on anthropometric indices to identify metabolically at-risk individuals in normal-weight populations and emphasizes the importance of using additional biological markers.

We observed a strong correlation between elevated WBC count and insulin resistance. The continued presence of this correlation across hierarchical multivariate models indicates that widespread systemic immune activation is an early sign of metabolic distress. Elevated WBC count has previously been associated with metabolic syndrome and cardiovascular risk in various populations (16-19). Our findings extend these observations to a strictly non-obese cohort, suggesting that inflammatory activation can occur before overt adiposity [4]. Additional multivariable and discriminatory analyses further confirmed the robustness of this association. Parallel multivariable analyses showed that neutrophil, lymphocyte, and monocyte counts had effect sizes similar to that of total WBC count when examined separately. Notably, the neutrophil-based model produced an association magnitude comparable to the WBC-based model. However, total WBC count offered the greatest overall explanatory power and serves as a more comprehensive marker of generalized leukocytosis, indicating simultaneous activation across multiple leukocyte lineages rather than just a single immune cell type subset. Consistently, ROC analysis showed that WBC count achieved the highest area under the curve among all evaluated leukocyte parameters, indicating superior discriminatory performance for insulin resistance. Although neutrophil, lymphocyte, and monocyte counts also demonstrated statistically significant discrimination, their individual AUC values remained lower than that of total WBC.

In contrast to the majority of previous studies reporting strong associations between hematological inflammation indices (SII, PIV) and insulin resistance, our findings revealed that these complex ratios showed no statistically significant association with IR in the non-obese cohort (9, 10). Indices like SII and NLR are often validated in populations with overt obesity, cancer, or advanced diabetes, where physiological stress leads to neutrophilia and concurrent lymphopenia, significantly altering the ratio (17-21). However, in our non-obese study population, we observed a simultaneous increase in neutrophils, monocytes, and lymphocytes (generalized leukocytosis). This proportional increase in both the numerator and denominator of the formulas probably concealed the statistical significance of the ratios. The comparative ROC results further support this interpretation by demonstrating that all absolute leukocyte subsets played a role in distinguishing insulin resistance to varying extents. This pattern aligns with a diffuse, low-grade immune activation rather than a stress-related redistribution of leukocytes, reinforcing the idea of early metabolic immune pan-activation. Supporting this interpretation, a recent meta-analysis indicated that absolute leukocyte parameters, particularly total WBC and absolute neutrophil count, are more reliable markers of chronic metabolic inflammation than ratio-based indices (7). The clinical significance of our findings is further supported by receiver operating characteristic analysis. While WBC alone demonstrated acceptable discriminative ability for IR, the predicted probability from the final multivariate model showed slightly better performance. Together, these results suggest that metabolic risk assessment is improved when incorporating demographic factors with inflammatory markers, whereas models focusing solely on individual leukocyte subtypes may underestimate the overall inflammatory burden in non-obese individuals populations.

Our observations are further reinforced by contemporary literature on metabolically obese normal-weight and normal-weight obesity phenotypes. A recent systematic review and meta-analysis by Khonsari et al. reported that individuals with a normal-weight obesity phenotype display significantly higher concentrations of inflammatory mediators including CRP, interleukin-6 and circulating white blood cell counts than their metabolically healthy normal-weight counterparts, supporting the concept that subclinical immune activation contributes to the pathogenesis of insulin resistance in apparently lean individuals (22). In parallel, He et al. demonstrated in a paediatric cross-sectional study that elevated absolute white blood cell and neutrophil counts were independently associated with HOMA-IR after adjustment for age and sex, mirroring the leukocyte-based pattern observed in our adult non-obese cohort (23). Taken together with our findings, these reports converge on the view that absolute leukocyte counts may represent an early, lineage-non-specific signature of

metabolic immune pan-activation that precedes both overt adiposity and conventional dyslipidaemic markers, and that this signature is captured more reliably by total WBC than by composite ratio-based indices in non-obese populations.

Our study has several limitations. First, its retrospective and cross-sectional design prevents establishing causality between inflammatory markers and insulin resistance. Because leukocyte parameters and insulin resistance were measured concurrently, the directionality of the association cannot be determined; the present findings should therefore be interpreted as associative rather than causal. Second, all data were collected from a single center, which may limit the applicability of the findings to broader or more diverse populations. Third, unmeasured confounders such as dietary habits, physical activity, or subclinical infections could not be fully controlled due to the retrospective nature of data collection. Fourth, although the Hosmer–Lemeshow goodness-of-fit test yielded statistically significant deviation from perfect calibration in the multivariable models, this finding should be interpreted cautiously. The Hosmer–Lemeshow test is well known to be overly sensitive in moderate-to-large samples and frequently rejects clinically acceptable models on the basis of practically irrelevant miscalibration (13). Because the discrimination performance of our final multivariable model remained adequate (AUC = 0.736, 95% CI: 0.679–0.793), and because Nagelkerke R^2 values were comparable to those reported in analogous studies, the joint appraisal of calibration and discrimination supports the practical utility of the model rather than indicating clinically meaningful misfit. Additionally, although HOMA-IR is a widely used and practical surrogate marker of insulin resistance, there is currently no universally accepted cutoff value specific to this population. Therefore, the threshold used in this analysis was based on prior literature and may not fully reflect population-specific metabolic characteristics. Furthermore, despite its widespread clinical and epidemiological use, HOMA-IR may not capture the complex, tissue-specific aspects of insulin resistance as accurately as direct methods like the hyperinsulinemic–euglycemic clamp. Finally, although the study involved a relatively large sample of non-obese adults, prospective multicenter studies with longitudinal follow-up are needed to better confirm these associations and clarify the temporal relationships.

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5. Conclusion

In conclusion, our findings suggest that even among non-obese adults, low-grade systemic inflammation is associated with the development of insulin resistance. Unlike the evaluated composite inflammation indices, routine test parameters such as white blood cell count appeared to be independent and reliable predictors of IR. Monitoring WBC can offer an accessible and cost-effective way to screen non-obese individuals for early metabolic risk.

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