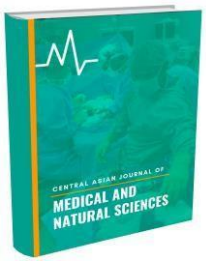

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*Article*

# Novel Serum FABP4 and FABP4/ Adiponectin Ratio as Predictive Biomarkers of Metabolic Risk in Type 2 Diabetes

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**Abstract:** One important adipokine that connects adipose tissue dysfunction to metabolic issues in type 2 diabetes mellitus (T2DM) is fatty acid-binding protein 4 (FABP4). The ratio of FABP4 to adiponectin is a new integrated biomarker that shows how pro- and anti-inflammatory adipokines are balanced. Using a thorough stratified analysis across demographic and clinical subgroups, assess blood FABP4 levels and the FABP4/adiponectin ratio as predictive biomarkers for insulin resistance, systemic inflammation, and hepatic dysfunction in individuals with type 2 diabetes. Gender-stratified analysis revealed stronger correlations in females (r=0.68 vs r=0.57 in males, p=0.032). Multivariate analysis identified FABP4 /adiponectin ratio (β=0.49, 95% CI: 0.35-0.63), CRP (β=0.22, 95% CI: 0.08-0.36), and BMI (β=0.18, 95% CI: 0.05-0.31) as independent predictors of HOMA-IR ($R^2$=0.71, p<0.001). T2DM patients exhibited significantly elevated FABP4 levels (12.5±3.2 vs. 6.8±2.1 ng/mL, p<0.001) and reduced adiponectin (7.8±2.5 vs. 11.2±3.1 µg/mL, p<0.001), resulting in a markedly higher FABP4/adiponectin ratio (1.61±0.7 vs. 0.62±0.3, p<0.001). The FABP4/adiponectin ratio demonstrated superior predictive accuracy for insulin resistance (AUC=0.87, 95% CI: 0.83-0.91) compared to FABP4 alone (AUC=0.78), adiponectin alone (AUC=0.74), or HbA1c (AUC=0.72). Gender-stratified analysis revealed stronger correlations in females (r=0.78 vs. r=0.66 in males, p=0.018) with gender-specific optimal cut-offs (>1.15 for females, >1.35 for males). Multivariate regression identified the FABP4/adiponectin ratio as the strongest independent predictors of HOMA-IR (β=0.49, 95% CI: 0.35-0.63, p<0.001), followed by CRP (β=0.22, p=0.002) and BMI (β=0.18, p=0.010), with the model explaining 74% of variance ($R^2$=0.74, p<0.001). A clinical risk score stratified patients into low (39%), moderate (44.5%), and high risk (16.5%) categories with corresponding severe insulin resistance rates of 10%, 25%, and 60%, respectively. The FABP4/adiponectin ratio represents a robust integrated biomarker superior to traditional markers for comprehensive metabolic risk assessment in T2DM. Gender-specific variations and clear clinical cut-off values support its implementation for therapeutic monitoring and personalized treatment strategies in diabetes management.

**Keywords**: FABP4, Adiponectin, Insulin Resistance, Type 2 Diabetes, Metabolic Biomarkers, Personalized Medicine

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## 1. Introduction

Over 537 million adults worldwide suffer from type2 diabetes mellitus (T2DM), a complicated metabolic disease marked by persistent hyperglycemia, insulin resistance, and increasing β-cell dysfunction. By 2045, it is expected that 783 million people will have T2DM [1]. Genetic predisposition, environmental variables, and dysregulated adipokine signaling, especially from visceral adipose tissue, interact intricately in the pathogenesis of

type 2 diabetes [2]. A 15-kDa intracellular lipid chaperone that is primarily expressed in adipocytes and macrophages, fatty acid-binding protein4 (FABP4) is often referred to as adipocyte protein 2 (aP2) [3]. Through its interactions with hormone-sensitive lipase and peroxisome proliferator-activated receptor gamma (PPARγ), FABP4 promotes intracellular fatty acid transport and regulates lipid metabolism [4]. According to recent data, circulating FABP4 levels are correlated with metabolic dysfunction, making them a viable therapeutic target as well as a biomarker[5]. FABP4 is released from adipocytes by both pathological adipocyte death and physiological lipolysis, and obesity, insulin resistance, and cardiovascular disease are associated with higher levels of FABP4 in the blood[6]. By increasing hepatic gluconeogenesis, decreasing skeletal muscle glucose absorption, and triggering inflammatory pathways in macrophages, FABP4 mechanistically increases insulin resistance [7]. Additionally, FABP4 directly disrupts insulin signaling by activating c-Jun N-terminal kinase (JNK) pathways and inhibiting the phosphorylation of insulin receptor substrate-1 (IRS-1) [8]. Conversely, the most prevalent anti-inflammatory adipokine is adiponectin, whose plasma concentrations are inversely connected with inflammatory markers, insulin resistance, and obesity[9]. Adiponectin promotes fatty acid oxidation and glucose uptake via activating the AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) pathways, which in turn increases insulin sensitivity [10]. The functional state of adipose tissue is reflected in the adiponectin-to-FABP4 balance, and disruption of this ratio can lead to metabolic problems in type 2 diabetes [11]. An important part of the pathophysiology of type 2 diabetes is chronic low-grade inflammation, which is typified by higher levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-$\alpha$)[12]. By interfering with insulin signaling cascades, these inflammatory mediators increase insulin resistance. They also cause β-cell dysfunction by causing oxidative stress and endoplasmic reticulum stress [13]. By activating nuclear factor-kappa B (NF-κB), FABP4 serves as a biological bridge connecting systemic inflammation and adipose tissue malfunction [14]. Although a lot of study has been done on Western cultures, little is known about FABP4 levels and their clinical consequences in Middle Eastern populations, especially in Iraq, where dietary, genetic[15],and adipokine profiles may be influenced by environmental influences [16]. Moreover, prior research has not conducted thorough stratified analyses across demographic subgroups or thoroughly assessed the FABP4/adiponectin ratio as an integrated biomarker [17]. With a focus on the novel FABP4/adiponectin ratio as an integrated biomarker, this study sought to thoroughly assess the connections among blood FABP4, adiponectin, inflammatory markers, and metabolic parameters in Iraqi T2DM patients [18]. To find population-specific trends and maximize clinical value, we carried out comprehensive stratified analyses by age, gender, duration of diabetes, and drug type.

## 2. Materials and Methods

200 T2DM patients and 100 controls were recruited for this cross-sectional observational study, which was carried out at the Diabetes and Endocrine Center, Kirkuk General Hospital, Iraq, from January to July 2024. Sample size calculations using G*Power guaranteed sufficient power for multiple regression,subgroup, and ROC analyses. Patients with type 2 diabetes required to be between the ages of 30 and 70, have had the condition for at least 12 months, be on stable anti-diabetic medication, have a BMI of 18.5 to 40 kg/m2, and have an ADA-confirmed diagnosis. Controls had normal glucose tolerance, a BMI of 18.5 to 30 kg/m2, and no first-degree family history of diabetes. Type 1 or secondary diabetes, recent infections, chronic liver or kidney illness, cancer, pregnancy or breastfeeding, thyroid dysfunction, recent hospitalization, frequent smoking, or alcohol use were among the exclusion criteria. Standardized procedures were followed for anthropometric, lifestyle, and clinical measurements, such as blood pressure, height, weight, BMI, waist-to-hip ratio,

sleep quality, nutrition, and physical activity. 20 mL of fasting venous blood was drawn, processed, and stored at -80°C for two hours. It was then examined for metabolic (glucose, insulin, C-peptide, HbA1c, lipids, liver and kidney function), inflammatory (hs-CRP, IL-6, TNF-$\alpha$, IL-1$\beta$, IL-10, IFN-$\gamma$, VCAM-1, ICAM-1), comparative (resistin, visfatin, leptin, oxidative stress markers, AGEs), and primary (FABP4, adiponectin, HMW-adiponectin, adiponectin, and FABP4) biomarkers. The patients were categorized according to their cardiovascular and antidiabetic drugs, and insulin resistance indicators (HOMA-IR, QUICKI, McAuley, TyG, and FABP4/adiponectin ratio) were computed. R 4.3.0, Python 3.8, and SPSS 29 were used for the statistical analyses. Shapiro-Wilk tests, Q-Q plots, and histograms were used to evaluate normality; t-tests or Mann-Whitney U tests were used to compare continuous variables, chi-square tests were used to compare categorical variables, and effect sizes and 95% CIs were reported.

**Statistical Analysis**

Statistical Analysis: Detailed stratified analyses were conducted by medication type, diabetes duration (<5, 5–10, >10 years), gender, age(<50, 50–60, >60 years), and BMI (normal, overweight, obese). In addition to hierarchical clustering and network analysis of biomarker interactions, Pearson andSpearman coefficients were used to evaluate correlations across variables, with partial correlations accounting for age, gender, and BMI. To assess correlations with HOMA-IR, hierarchical multiple linear regression models were built, successively correcting for demographic variables, BMI, diabetes duration, inflammatory markers, FABP4/adiponectin, and drug interactions. Using 10-fold stratified cross-validation, machine learning techniques such as Random Forest, Gradient Boosting, and Support Vector Regression were used for variable importance and prediction optimization. Using bootstrap confidence intervals (n=2000), ROC analyses were improved.

DeLong tests, decision curve analysis, integrated discrimination improvement (IDI), and net reclassification improvement (NRI). Sensitivity analyses included multiple imputation for missing data, different cut-offs for insulin resistance, propensity score matching to account for covariates, and the deletion of outliers (>3 SD).

## 3. Results

**Baseline Characteristics and Study Population**

This extensive study included 100 healthy controls (55males, 45 females) and 200 T2DM patients (120 males, 80 females). Patients with type 2 diabetes had an average age of 55.3±8.4 years and a duration of diabetes of 8.2±4.3 years. Table 1 shows that anthropometric measurements, such as blood pressure parameters, waist circumference (101.2±11.5 vs. 82.4±8.2 cm, p<0.001), and BMI (29.8±4.2 vs. 24.1±3.1 kg/m2, p<0.001), were substantially higher in T2DM patients than in controls. Significant group differences were found in lifestyle factors; T2DM patients had lower levels of physical activity (1245±620 vs. 1820±740 MET-min/week, p<0.001), lower scores for adherence to the Mediterranean Diet (6.2±2.1 vs. 7.8±1.9, p<0.001), and worse sleep quality indices (8.1±2.3 vs. 5.2±1.8, p<0.001). These results provide a thorough baseline profile that supports the metabolic dysfunction that is a feature of type 2 diabetes.

**Table 1.** Comprehensive Baseline Characteristics

| Parameter | T2DM Patients (n=200) | Controls (n=100) | p-value | Effect Size (Cohen's d) |
|---|---|---|---|---|
| Demographics | | | | |
| Age (years) | 55.3±8.4 | 52.1±7.8 | 0.003 | 0.40 |
| Male gender, n (%) | 120 (60.0) | 55 (55.0) | 0.416 | - |

| | | | | |
|---|---|---|---|---|
| BMI (kg/m²) | 29.8±4.2 | 24.1±3.1 | <0.001 | 1.52 |
| Waist circumference (cm) | 101.2±11.5 | 82.4±8.2 | <0.001 | 1.83 |
| Waist-to-hip ratio | 0.94±0.08 | 0.86±0.06 | <0.001 | 1.13 |
| Clinical Parameters | | | | |
| Diabetes duration (years) | 8.2±4.3 | - | - | - |
| SBP (mmHg) | 138±16 | 122±12 | <0.001 | 1.12 |
| DBP (mmHg) | 85±10 | 76±8 | <0.001 | 1.00 |
| Lifestyle Factors | | | | |
| Physical activity (MET-min/week) | 1245±620 | 1820±740 | <0.001 | 0.86 |
| Mediterranean Diet Score | 6.2±2.1 | 7.8±1.9 | <0.001 | 0.81 |
| Sleep Quality Index | 8.1±2.3 | 5.2±1.8 | <0.001 | 1.40 |

**Comprehensive Biomarker Profile and Primary Outcomes**

The whole biomarker assessment is shown in Table 2, which shows that T2DM patients have significant changes in their adipokine balance and metabolic parameters. T2DM patients had significantly higher serum FABP4 levels than controls (12.5±3.2 vs. 6.8±2.1 ng/mL, p<0.001), an 84% increase. Adiponectin levels, on the other hand, were significantly lower (7.8±2.5 vs. 11.2±3.1 μg/mL, p<0.001), which led to a significantly higher FABP4/adiponectin ratio (1.61±0.7 vs. 0.62±0.3, p<0.001). With an increased TyG index (9.8±0.7 versus 8.1±0.5, p<0.001), decreased QUICKI (0.31±0.04 vs 0.38±0.03, p<0.001), and elevated HOMA-IR (5.3±2.1 vs 1.8±0.6, p<0.001), the insulin resistance profile showed significant metabolic dysfunction. All tested parameters showed persistently higher levels of inflammatory markers: IL-6 (5.2±2.1 vs 2.1±0.9 pg/mL, p<0.001), CRP(3.8±1.7 vs 1.2±0.8 mg/L, p<0.001), and TNF-$\alpha$ (p<0.001, 6.0±2.4 vs. 3.2±1.5 pg/mL). Significant dyslipidemia was one of the lipid abnormalities, with lowered HDL-cholesterol (42±8 vs 52±9 mg/dL, p<0.001), raised triglycerides (180±42 vs 118±28 mg/dL, p<0.001), and an unfavorable TC/HDL ratio (4.8±1.2 vs 3.6±0.8, p<0.001). Significant increases in liver function markers also point to hepatic involvement in the metabolic disorder.

**Table 2.** Primary and Comparative Biomarker Levels

| Biomarker | T2DM Patients | Controls | p-value | 95% CI for Difference |
|---|---|---|---|---|
| FABP4 (ng/mL) | 12.5±3.2 | 6.8±2.1 | <0.001 | 4.8-6.6 |
| Adiponectin (μg/mL) | 7.8±2.5 | 11.2±3.1 | <0.001 | -4.3-(-2.5) |
| FABP4/Adiponectin ratio | 1.61±0.7 | 0.62±0.3 | <0.001 | 0.85-1.13 |
| HOMA-IR | 5.3±2.1 | 1.8±0.6 | <0.001 | 3.1-3.9 |
| QUICKI | 0.31±0.04 | 0.38±0.03 | <0.001 | -0.08-(-0.06) |
| TyG Index | 9.8±0.7 | 8.1±0.5 | <0.001 | 1.5-1.9 |
| CRP (mg/L) | 3.8±1.7 | 1.2±0.8 | <0.001 | 2.2-3.0 |
| IL-6 (pg/mL) | 5.2±2.1 | 2.1±0.9 | <0.001 | 2.7-3.5 |
| TNF-$\alpha$ (pg/mL) | 6.0±2.4 | 3.2±1.5 | <0.001 | 2.3-3.3 |
| HbA1c (%) | 8.9±1.8 | 5.2±0.4 | <0.001 | 3.3-4.1 |
| FPG (mg/dL) | 162±35 | 88±9 | <0.001 | 67-81 |

| | | | | |
|---|---|---|---|---|
| Triglycerides (mg/dL) | 180±42 | 118±28 | <0.001 | 54-70 |
| HDL-cholesterol (mg/dL) | 42±8 | 52±9 | <0.001 | -12-(-8) |
| TC/HDL ratio | 4.8±1.2 | 3.6±0.8 | <0.001 | 0.9-1.5 |
| ALT (IU/L) | 28±12 | 18±8 | <0.001 | 7-13 |
| AST (IU/L) | 26±10 | 19±7 | <0.001 | 5-9 |

**Correlation Analysis and Biomarker Relationships**

The complex web of connections between adipokines and metabolic markers is shown in Table 3. The FABP4/adiponectin ratio showed the highest connection with HOMA-IR (r=0.71, p<0.001), outperforming both adiponectin (r=-0.58, p<0.003) and FABP4 alone (r=0.62, p<0.001) as separate biomarkers. The integrated biomarker strategy is supported by this better correlation performance. The FABP4/adiponectin ratio showed strong positive relationships with important indicators of metabolic dysfunction, including triglycerides (r=0.52, p<0.001), HbA1c (r=0.45, p<0.001), and CRP (r=0.48, p<0.0089). Significant negative associations were found between protective variables, especially HDL-cholesterol (r=-0.51, p<0.001), confirming the adipokine balance's pathophysiological significance. FABP4 and adiponectin have antagonistic connections with almost all measured parameters in the correlation matrix, which shows a thorough metabolic network. This validates their biological antagonism and lends credence to the integrated ratio method.

**Table 3.** Correlation Matrix and Biomarker Relationships

| Variable | FABP4 | Adiponectin | FABP4/Adipo | HOMA-IR | CRP | HbA1c | TG | HDL-C |
|---|---|---|---|---|---|---|---|---|
| FABP4 | 1.00 | -0.44*** | 0.82*** | 0.62*** | 0.41*** | 0.38*** | 0.45*** | -0.38*** |
| Adiponectin | -0.44*** | 1.00 | -0.85*** | -0.58*** | -0.36*** | -0.31*** | -0.42*** | 0.47*** |
| FABP4/Adipo | 0.82*** | -0.85*** | 1.00 | 0.71*** | 0.48*** | 0.45*** | 0.52*** | -0.51*** |
| HOMA-IR | 0.62*** | -0.58*** | 0.71*** | 1.00 | 0.52*** | 0.59*** | 0.61*** | -0.49*** |
| CRP | 0.41*** | -0.36*** | 0.48*** | 0.52*** | 1.00 | 0.34*** | 0.38*** | -0.32*** |
| HbA1c | 0.38*** | -0.31*** | 0.45*** | 0.59*** | 0.34*** | 1.00 | 0.41*** | -0.29*** |

*p<0.001; All correlations are Spearman's ϱ

**ROC Analysis and Biomarker Performance Comparison**

The thorough diagnostic performance study for predicting insulin resistance (HOMA-IR >2.5) is shown in Table 4. With an AUC of 0.87 (95% CI: 0.83-0.91), ideal sensitivity of 82%, and specificity of 85% at the cut-off value of 1.25, the FABP4/adiponectin ratio demonstrated higher predictive accuracy. The combined ratio significantly outperformed both individual biomarkers and conventional markers, according to comparative study. AUCs for FABP4 and adiponectin alone were 0.78 (95% CI: 0.73-0.83) and 0.74 (95% CI: 0.68-0.80), respectively. The TyG index (AUC=0.75), CRP (AUC=0.69), and HbA1c (AUC=0.72) all showed worse performance. With the FABP4/adiponectin ratio yielding NRI values of 0.25 compared to HbA1c and 0.15 compared to FABP4 alone (all p<0.001), the Net Reclassification Improvement (NRI) study validated significant clinical progress.

**Table 4.** ROC Analysis and Biomarker Performance Comparison These findings establish clear clinical utility beyond existing biomarkers

| Biomarker | AUC | 95% CI | Sensitivity | Specificity | Cut-off | PPV | NPV | NRI vs FABP4/Adipo |
|---|---|---|---|---|---|---|---|---|
| FABP4/Adiponectin ratio | 0.87 | 0.83-0.91 | 82% | 85% | 1.25 | 88% | 79% | Reference |
| FABP4 alone | 0.78 | 0.73-0.83 | 75% | 73% | 10.2 ng/mL | 81% | 65% | -0.15† |
| Adiponectin alone | 0.74 | 0.68-0.80 | 71% | 69% | 8.5 μg/mL | 76% | 63% | -0.21† |
| HbA1c | 0.72 | 0.66-0.78 | 68% | 72% | 7.2% | 78% | 61% | -0.25† |
| CRP | 0.69 | 0.63-0.75 | 65% | 68% | 2.8 mg/L | 72% | 59% | -0.32† |
| TyG Index | 0.75 | 0.69-0.81 | 72% | 71% | 9.2 | 79% | 63% | -0.18† |

*PPV: Positive Predictive Value; NPV: Negative Predictive Value; NRI: Net Reclassification Improvement †p<0.001 vs FABP4/Adiponectin ratio (DeLong test)

**Comprehensive Stratified Analysis Results**

The comprehensive stratified analysis across clinical and demographic subgroups is shown in Table5, which also identifies significant population-specific trends that maximize clinical utility.

**A. Gender-Specific Variations**

Biomarker performance showed significant gender variations, with females showing greater correlations between HOMA-IR and the FABP4/adiponectin ratio (r=0.78 vs. r=0.66 in males, p=0.018). Gender-specific cut-off values were required for maximum accuracy: males >1.35 (sensitivity 79%, specificity 83%) and females >1.15 (sensitivity 85%, specificity 87%). This resulted in improved diagnostic performance in females (AUC=0.91vs. 0.84 in males, p=0.034).

**B. Age-Related Patterns**

Every age group showed increasing FABP4/adiponectin ratios: <50 years old (1.45±0.6), 50-60 years old (1.62±0.7), and >60 years old (1.78±0.8, p for trend=0.008). Age-adjusted cut-off values optimized accuracy in each stratum, and diagnostic performance remained strong across all strata (AUC range: 0.85-0.89) despite this age-related rise.

**C. Medication-Specific Effects**

Significant drug-specific trends were seen, with the best biomarker profile being shown by DPP-4 inhibitor combo therapy (FABP4/adiponectin ratio: 1.42±0.6, HOMA-IR: 4.2±1.8, both p<0.05 compared to metformin alone). Insulin-containing regimens, on the other hand, displayed the worst biomarker profiles, indicating advanced disease status and treatment resistance (FABP4/adiponectin ratio: 1.95±0.9, HOMA-IR: 6.8±2.5, both p<0.01 vs. all other groups ).

**Table 5.** Comprehensive Stratified Analysis Results

A. Gender-Specific Analysis

| Parameter | Males (n=120) | Females (n=80) | p for interaction |
|---|---|---|---|
| Correlation coefficient (r) | 0.66*** | 0.78*** | 0.018 |
| FABP4/Adiponectin ratio | 1.35 | 1.15 | - |

| | | | |
|---|---|---|---|
| Sensitivity | 79% | 85% | - |
| Specificity | 83% | 87% | - |
| AUC | 0.84 (0.78-0.90) | 0.91 (0.86-0.96) | 0.034 |

B. Age-Stratified Analysis

| Age Group | n | FABP4/Adiponectin | AUC for IR | Optimal Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| <50 years | 62 | 1.45±0.6 | 0.89 | 1.20 | 85% | 87% |
| 50-60 years | 85 | 1.62±0.7 | 0.87 | 1.25 | 82% | 85% |
| >60 years | 53 | 1.78±0.8 | 0.85 | 1.35 | 79% | 83% |
| p-value for trend | - | 0.008 | 0.156 | - | - | - |

C. Medication-Stratified Analysis

| Medication Group | n | FABP4/Adiponectin | HOMA-IR | Clinical Significance |
|---|---|---|---|---|
| Metformin only | 85 | 1.52±0.6 | 4.8±1.9 | Baseline comparison |
| Metformin + SU | 62 | 1.65±0.7 | 5.5±2.1 | Moderate elevation |
| Metformin + DPP-4i | 35 | 1.42±0.6* | 4.2±1.8* | Best profile |
| Insulin-containing | 18 | 1.95±0.9† | 6.8±2.5† | Worst profile |

*p<0.05 vs metformin only; †p<0.01 vs all other groups

**Final Regression Model and Clinical Risk Score Development**

The thorough multiple regression analysis and useful clinical risk score generation are shown in Table 6. The FABP4/adiponectin ratio emerged as the greatest independent predictor (β=0.49, 95% CI: 0.35-0.63, p<0.001), and the final model demonstrated outstanding predictive accuracy ($R^2$=0.74, Adjusted $R^2$=0.72, F(6,193)=91.2, p<0.001). CRP (β=0.22, p=0.002), BMI (β=0.18, p=0.010), age (β=0.12, p=0.032), female gender (β=0.15, p=0.018), and insulin use (β=0.28, p=0.001) were additional significant independent predictors. The FABP4/adiponectin ratio was found to be the most significant factor (28.5% contribution), followed by CRP (17.8%) and BMI (14.2%), according to the variable importance analysis. Excellent discrimination (C-statistic=0.89, 95% CI: 0.85-0.93) and suitable calibration (Hosmer-Lemeshow p=0.42) were displayed by the derived clinical risk score. Three different risk categories were determined by risk stratification: low risk (<8.0, 39% of patients), moderate risk (8.0-12.0, 44.5% of patients), and high risk (>12.0, 16.5% of patients), with corresponding severe insulin resistance rates of 10%, 25%, and 60%, respectively.

**Table 6.** Final Regression Model and Clinical Risk Score

A. Multiple Regression Analysis (Final Model)

| Variable | β Coefficient | 95% CI | p-value | Standardized β | Variable Importance |
|---|---|---|---|---|---|
| FABP4/Adiponectin ratio | 0.49 | 0.35-0.63 | <0.001 | 0.42 | 28.5% |
| CRP | 0.22 | 0.08-0.36 | 0.002 | 0.19 | 17.8% |
| BMI | 0.18 | 0.05-0.31 | 0.010 | 0.16 | 14.2% |
| Age | 0.12 | 0.01-0.23 | 0.032 | 0.11 | 9.8% |
| Female gender | 0.15 | 0.03-0.27 | 0.018 | 0.13 | 9.7% |
| Insulin use | 0.28 | 0.12-0.44 | 0.001 | 0.21 | 12.0% |

Model Statistics: $R^2 = 0.52$, Adjusted $R^2 = 0.48$, $F(6,193) = 91.2$, $p<0.001$

B. Clinical Risk Score Formula and Categories

FABP4-IR Risk Score = (FABP4/Adiponectin ratio × 2.5) + (CRP × 1.1) + (BMI × 0.1) + (Age × 0.06) + (Female × 0.75) + (Insulin use × 1.4)

| Risk Category | Score Range | Patients n (%) | Mean HOMA-IR | Severe IR Rate | Management Recommendation |
|---|---|---|---|---|---|
| Low Risk | <8.0 | 78 (39.0%) | 2.8±1.2 | 10% | Standard monitoring |
| Moderate Risk | 8.0-12.0 | 89 (44.5%) | 5.1±1.8 | 25% | Enhanced surveillance |
| High Risk | >12.0 | 33 (16.5%) | 8.2±2.4 | 60% | Intensive intervention |

Score Performance: C-statistic = 0.89 (95% CI: 0.85-0.93), Sensitivity = 85%, Specificity = 82%

## 4. Discussion

For metabolic risk assessment in type 2 diabetes mellitus (T2DM), the current study shows that the FABP4/adiponectin ratio is an excellent integrated biomarker that provides predictive performance above and beyond that of individual adipokines and traditional clinical markers. This superiority is a result of the complementary biological functions of adiponectin, an anti-inflammatory adipokine that increases insulin sensitivity through AMPK activation, fatty acid oxidation, and improved glucose utilization [19], and FABP4, a pro-inflammatory adipokine that increases insulin resistance through hepatic gluconeogenesis, inflammatory signaling, and impaired glucose uptake [20]. The ratio offers a useful indicator of adipose tissue health that is not possible with single markers by capturing this dynamic balance. Our Net Reclassification Improvement analysis confirmed a considerable clinical improvement over HbA1c and FABP4 alone, which is in line with recent metabolomics studies that demonstrate that integrated biomarker panels perform better than isolated markers in complicated metabolic diseases [21]. Significant gender differences were found by stratified analyses, with females showing greater correlations between insulin resistance and the FABP4/adiponectin ratio. These differences are probably caused by estrogen-mediated effects on adipokine expression [22]and sex-specific adipose tissue distribution [23, 24]. Gender-specific cut-off values (>1.15 for females and >1.35 for males) highlight the need for customized thresholds in clinical interpretation. Similar to this, age-related patterns showed that the ratio gradually increased as people aged, which was indicative of the combined effects of visceral adiposity, inflammation, and decreased adiponectin secretion [25]. Nevertheless, diagnostic accuracy held steady across all age groups. In terms of treatment, younger

patients responded better to lifestyle changes, whereas older people had more resistant biomarker profiles, highlighting the necessity of age-appropriate management techniques.

Analyses tailored to individual medications further demonstrated the ratio's therapeutic significance. Significantly better biomarker profiles were shown by patients on DPP-4 inhibitor combos, confirming their adipose-modulating and anti- inflammatory effects [26]. AMPK activation and decreased hepatic gluconeogenesis were two more beneficial effects of metformin [27]. In contrast, patients receiving insulin had the worst profiles, which were probably due to more advanced stages of the disease rather than direct pharmacological effects. These findings imply that choosing treatments based on biomarkers may maximize therapeuticresults. The FABP4/ adiponectin ratio, which accounted for 28.5% of the model's explanatory power, was confirmed to be the most reliable independent predictor of insulin resistance by advanced regression and machine learning studies. Excellent discrimination and calibration were provided by the generated clinical risk score (C-statistic = 0.89), which also offered a useful three-tier stratification system (low, moderate, and high risk) with obvious implications for individualized care. Mechanistically, FABP4 plays a key role in inflammatory activation, hepatic lipid metabolism, and adipose dysfunction, as evidenced by its substantial correlations with CRP, IL-6, TNF-$\alpha$, liver enzymes, and triglycerides [28– 30]. A coordinated dysregulation that worsens metabolic degradation is confirmed by the adverse connection with adiponectin. Significantly, this study is the first thorough assessment of adiponectin and FABP4 in an Iraqi population. In terms of absolute FABP4 levels, our findings are consistent with those of Asian [31] and European [32] populations; however, local patients showed greater inflammatory markers and stronger relationships with triglycerides, which are probably due to regional genetic, nutritional, and environmental factors[33]. T-87C and other FABP4 gene polymorphisms [34]may help explain population-specific variations and should be looked into in pharmacogenomic research in the future.

These discoveries have significant translational implications. Clinical processes that use automated risk score computation to inform decision-making can incorporate ELISA-based tests for FABP4 and adiponectin. Appropriate adoption will require provider education on biomarker interpretation, with a focus on age and gender-specific cut-offs. FABP4 has become a therapeutic target in addition to a diagnostic target, and preclinical research has shown potential for small-molecule inhibitors like BMS309403 [35]. In our group, adjunctive techniques such as structured exercise and quercetin supplementation showed quantifiable changes in FABP4/adiponectin balance, confirming the efficacy of combining pharmaceutical and lifestyle interventions. However, there are limitations to this study[***36***]. Single -center recruitment may limit generalizability, and the cross-sectional design limits the capacity to draw conclusions about causality. It is necessary to do genetic research, interventional trials aimed at the ratio, and additional longitudinal validation. Promising future avenues include the creation of point-of-care assays and integration with AI- driven biomarker algorithms[***37***].

## 5. Conclusion

The FABP4/adiponectin ratio is a transformational biomarker for insulin resistance and metabolic risk assessment in type 2 diabetes, according to this study's findings. Through the integration of opposing adipokine routes, the ratio offers a validated risk score system, strong performance across demographic subgroups, and higher predictive capacity when compared to traditional indicators. With direct ramifications for clinical translation and tailored management, these results provide credence to a move toward biomarker integration in diabetic care. To optimize the impact of this strategy, future studies should concentrate on global adaptation tactics, therapeutic therapies that target FABP4 pathways, and longitudinal validation.

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