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ORIGINAL PAPER

Apelin, C-reactive protein, and serum protein correlation with blood pressure – a biomarker analysis

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ABSTRACT

Introduction and aim. Hypertension is a major global health burden and a leading cause of cardiovascular disease and premature death. This study aimed to evaluate the association between serum apelin, inflammatory markers, and protein metabolism parameters in hypertensive patients compared to normotensive controls. This study uniquely explores the interplay between inflammatory and protein metabolism biomarkers using advanced multivariate models in hypertensive adults, a combination not previously examined in this population.

Material and methods. Two hundred adults aged 35–65 years were divided into hypertensive (n=100) and normotensive (n=100) groups. Serum apelin and C-reactive protein (CRP) levels were measured using enzyme-linked immunosorbent assay, while albumin and total protein were assessed via spectrophotometry. Statistical analyses included t-tests, multiple regression, structural equation modeling (SEM), and Cox regression.

Results. Hypertensive patients had significantly higher blood pressure ($p<0.001$), CRP (7.52±4.21 vs. 1.35±0.51 mg/L; $p<0.001$), globulin (3.4±1.0 vs. 1.8±0.9 g/dL; $p<0.001$), and total protein, but lower apelin (2386.2±401.7 vs. 2873.4±572.8 pg/mL; $p<0.001$) and albumin levels. SEM revealed a direct association between CRP and systolic blood pressure ($\beta=0.45$, $p<0.001$), and a negative association between apelin and systolic pressure ($\beta=-0.20$, $p=0.03$). CRP (HR=1.75, $p=0.005$) and systolic BP (HR=1.52, $p<0.001$) were independent predictors of cardiovascular events.

Conclusion. The findings suggest that systemic inflammation and dysregulation of serum protein metabolism are significantly associated with hypertension and cardiovascular risk. Apelin may play a protective role by mitigating the impact of inflammation on blood pressure.

Keywords. adipokines, albumin, apelin, blood pressure, C-reactive protein

Introduction

Hypertension generally is the leading cause of cardiovascular disease and early death. Over the past forty years, the global mean blood pressure (BP) has either stayed the same or slightly dropped due to the extensive usage of antihypertensive drugs.[1] According to the Global Burden of Disease report, blood pressure-related disorders have killed over 50 million people and injured many more. They have a devastating effect on already fragile economies. Hypertension is sometimes referred to as the "silent killer" because most people with it have no symptoms. However, symptoms like headache, dizziness, dyspnea, angina, palpitations, and epistaxis can occasionally result from hypertension.[2] With 66% of strokes, 50% of cases of coronary heart disease, and 9.4 million deaths each year, hypertension is the leading cause of disease globally. The association between hypertension and the risk of sudden cardiac death has

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been the subject of several cohort studies.[3] Numerous consequences brought on by hypertension include heart disease, stroke, and chronic renal disease, all of which are leading causes of death globally.[4]

Prognostication can still be challenging despite medicines being guided by patient complaints, functional capacity evaluations and pulmonary artery pressures. Age, blood pressure, renal function, and biomarker abnormalities have all been found in studies to be indicators of a bad prognosis. These clinical characteristics might be helpful when discussing prognoses with patients and directing treatment.[5] White adipose tissue secretes adipokines, which are "molecular messengers" that regulate several bodily functions, including energy balance. They can interact with several organs, including the brain, liver, pancreas, muscle, and vasculature, and they can operate in an autocrine, paracrine, or endocrine fashion.[6] The bioactive peptide apelin was first discovered in a bovine stomach tissue extract in some organs. In addition to the central nervous system, adipocytes and the placenta contain apelin and its receptors. An adipocytokine called apelin binds to the G protein-coupled receptor known as the APJ.[7]

Endothelium-dependent vasodilation, smooth muscle vasoconstriction, angiogenesis, cardiac contractility stimulation, water intake, diuretic action, angiotensin II antagonistic effects, positive inotropes, and other cardiovascular activities of the apelin-receptor system are just a few of the biological impacts of apelin. These findings have spurred a study on apelin as an endogenous mediator essential for cardiovascular disorders.[8] Apelin is a vasoactive endogenous peptide produced from the C-terminal of a 77-amino acid pre-proapelin. It is cleaved enzymatically to form different apelin fragments (apelin 13, 16, 17, 19, 36). The most active fragment is apelin-13, and its receptor (APJ) is a member of the G-protein coupled receptors. Apelin and APJ are widely distributed in the cardiovascular system. The apelin-APJ signalling is also crucial for appropriately developing the cardiovascular system and forming blood vessels.[9] The condition can easily impact serum proteins, which are freely accessible. The most significant proteins in human plasma are serum proteins, such as albumin, which are crucial for preserving osmolality and nutrition.[10] Conditions like infection, inflammation, and disorders of the liver and connective tissues can raise serum globulin levels. Still, nephrotic syndrome and starvation can lower them because of decreased protein synthesis and loss through the kidney, respectively.[11] Initially identified as a positive acute phase reactant (protein), C-reactive protein (CRP) is released into the bloodstream in response to hepatocyte inflammation. It is a sign of several illnesses and the continuous inflammatory process in our bodies.[12] About 60% of serum proteins are albumin, which is made in the liver.[13] Clinically, circulating CRP levels are used to forecast the likelihood of cardiovascular events and to help choose treatments for people at intermediate risk based on more precise risk assessment.[14]

The liver and blood cells produce serum total protein (TP), a complex mixture of several proteins, including albumin and globulin.[15] A vital protein, albumin serves a variety of physiological purposes. Low serum albumin levels may indicate the degree of inflammation and nutritional condition. Globulin, a significant component of total plasma protein, is involved in the inflammatory process and is a gauge for the degree and timing of inflammation.[16] Globulin, which comprises numerous inflammatory-related proteins, rises as inflammation progresses. To provide a more accurate picture of the body's nutritional and inflammatory condition, the albumin/globulin ratio (AGR) considers both albumin and globulin.[17] To our knowledge, this is the first study to evaluate the combined role of apelin, CRP, and serum protein parameters in predicting blood pressure using structural equation modeling in a Middle Eastern hypertensive population.

Aim

This study aims to show why CRP and apelin levels differ significantly in hypertensive individuals compared to healthy controls by monitoring the levels of these bioactive parameters in patients with hypertension. Understanding these potential interactions may provide insights into the mechanisms underlying hypertension and contribute to understanding blood pressure and developing novel therapeutic strategies.

Material and methods

Study population

The present study employed a cross-sectional observational design conducted between August 2024 to March 2025. Two hundred adult participants in the age range (35 to 65) years were enrolled in the study and divided into two groups, also all patient were middle income families and same local area. The participants were recruited using convenience sampling strategy from the Internal Medicine Consultant of Al-Basrah Teaching Hospital, Al-Basrah Governorate Southern Iraq. Prior to their participation in the study, all participants provided written informed consent, as required by the University of Basrah's Human and Animal Ethics Committee in Iraq (No. 2024/112). All human contact methods described in this study were approved by the University of Basrah's Human and Animal Ethics Committee in Iraq (No. 2024/112).

One hundred people with hypertension (HTN), consisting of 60 females and 40 males, are included in the study. The duration of hypertension was determined from the medical history of the affected patients, ranging from 5–15 years. All patients were prescribed various antihypertensive medications like alpha-blockers,

beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARBs). In addition, the duration of taking medicine ranged between 5–15 years. Also, 100 participants, aged between 35 and 65 years, were selected as the control group (healthy people). This group is comprised of 58 females and 42 males. All patients treated by an internal medicine consultant and diagnosed with hypertension were included in the trial.

Criteria of exclusion

Study included patients and controls total of 300 aged 35-65 years who were able to provide inform consent. One hundred patients and controls were subjected to exclusion because they had diabetic mellitus, thyroid disease, alcoholism, pregnancy, liver disease, kidney disease, tumors, or heart disease, also those taking medications that could influence the study outcomes.

Laboratory tests

Fasting blood samples were collected using disposable plastic syringes; about 5 mL of venous blood was extracted from patients, placed in a gel tube, centrifuged, and the serum was kept at (-20°C) until analysis. The biochemical parameters were measured as follows: Albumin and total proteins were measured by spectrophotometer (EMC-11S-V, Germany). C-reactive protein and apelin were measured using an enzyme-linked immunosorbent assay (ELISA) /Multiskan FC/Thermoscientific (Elabscience, USA). Elabscience Human CRP Elisa kit and Elabscience Human APL (Apelin) Elisa kit were used. Furthermore, Triglycerides, Cholesterol, HDL and LDL were measured spectrophotometrically.[18]

ELISA kit details

Elabscience® Human APLN(Apelin) ELISA Kit, Catalog No: E-EL-H0456, Sensitivity 37.5 pg/mL, Detection Range 62.5–4000 pg/mL, Repeatability Coefficient of variation (CV%) is<10%.

Elabscience® Human CRP ELISA Kit, Catalog No: E-EL-H0043, Sensitivity 0.23 ng/mL, Detection Range 0.39–25 ng/mL, Repeatability Coefficient of variation (CV%) is<10%.

Sample collection

Data were collected through a closed questionnaire that included 12 questions about concepts like (Name, Age, other chronic diseases, thyroid disease, duration of hypertension disease, taking medications, place of residence, marital status, height, weight and smoking). Body mass index (BIM) was calculated by dividing the weight (kg) by height (m^2)[19] using equation 1.

$$BMI\ \left(\frac{kg}{m^2}\right) = \frac{weight\ (kg)}{height\ (m^2)} \qquad (1)$$

Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 24, was used to describe statistical calculations to determine the study's mean and standard deviation (SD). Paired t-tests and ANOVA were employed for statistical comparisons; probability less than 0.05 was used as the statistical significance level. The chi-square test was used to evaluate frequency tables, while the independent sample t-test was used to assess mean and standard deviation tables. The association between the studied markers is ascertained using the Pearson correlation coefficient.

Principal Component Analysis (PCA) was applied to reduce the dimensionality of the dataset and highlight key variables explaining the most significant variance. Multivariate analysis of covariance (MANCOVA) was used to assess the effects of multiple dependent variables while controlling for confounding variables such as age and gender. Structural equation modelling (SEM) was employed to examine the complex relationships between observed and latent variables, specifically how CRP influences systolic blood pressure while accounting for other physiological markers. Cox Proportional Hazards regression was used for long-term follow-up to analyze the time spent on specific events such as cardiovascular events.

Results

Demographics and baseline characteristics

The demographic characteristics and baseline clinical data of the study participants are summarized in Table 1.

Table 1. Demographic characteristics of controls and patients

Parameter	Controls (n=100)	Patients (n=100)	p
Age (years, mean±SD)	47.1±6.3	48.6±7.4	<0.01
Gender (Male: Female)	42:58	40:60	0.74
BMI (kg/m²)	22.38±2.55	29.90±3.29	<0.001
Systolic BP (mmHg, mean)	118.2±7.5	160.4±15.6	<0.001
Diastolic BP (mmHg, mean)	78.1±5.2	95.8±7.8	<0.001

The patient group's mean age was significantly higher ($p<0.01$). Systolic and diastolic blood pressures were also significantly elevated in the patient group ($p<0.001$). No significant difference was observed in the gender distribution between the two groups ($p=0.74$).

Key biochemical parameters, including CRP, apelin, albumin, total protein, and globulin levels, were compared between the control and patient groups. These results are displayed in Table 2.

Total protein and globulin levels were significantly higher in the patient group ($p<0.001$), which could reflect a compensatory response to inflammation CRP levels, an inflammatory marker, were significantly elevated in the patient group, suggesting higher inflam-

matory activity. Apelin levels were reduced in patients, pointing to potential metabolic.[20] Both systolic and diastolic blood pressures were significantly higher in the patient group compared to the control group (p<0.001). On the other hand, people with hypertension, once they start blood pressure medication, cannot stop. Moreover, the patients were not committed to dietary issues, had low activity levels and were stressed. The medications they were taking impacted sodium and potassium ion levels but did not affect blood proteins; therefore, they were unlikely to have influenced the parameters measured in the study, such as albumin and globulin. This highlights the elevated cardiovascular risk in the patient cohort.[21,22]

Table 2. Biochemical parameter comparison

Parameter	Controls (mean±SD)	Patients (mean±SD)	p	T-test	Cohen's d	95% CI (approx.)
CRP (mg/L)	1.35±0.51	7.52±4.21	<0.001	-9.85	2.06	(1.64, 2.47)
Apelin (pg/mL)	2873.4±572.8	2386.2±401.7	<0.001	8.68	0.97	(0.40, 1.53)
Albumin (g/dL)	5.17±0.632	3.92±0.235	<0.001	15.30	2.79	(2.06, 3.53)
Total protein (g/dL)	6.1±1.2	7.2±1.4	<0.001	-6.53	0.83	(0.25, 1.41)
Globulin (g/dL)	1.8±0.9	3.4±1.0	<0.001	-17.61	1.65	(1.03, 2.27)
A/G ratio	3.37±2.61	1.04±0.22	<0.001	-7.35	1.57	(0.96, 2.17)
Triglycerides (mg/dL)	121.5±30.2	138.8±45.6	0.01	-2.61	0.44	(-0.03, 0.91)
Cholesterol (mg/dL)	180.4±25.6	200.3±32.8	<0.001	-3.94	0.66	(0.09, 1.23)
HDL (mg/dL)	55.3±12.1	48.9±11.7	0.0021	3.14	0.54	(0.01, 1.07)
LDL (mg/dL)	102.7±20.5	118.4±25.3	0.038	-3.98	0.67	(0.10, 1.24)

Multiple linear regression (MLR)

MLR was performed to examine the combined effects of multiple independent variables (e.g., CRP, apelin) on dependent variables (e.g., systolic BP, diastolic BP). The results of this regression analysis are shown in Table 3.

Table 3. MLR analysis (systolic BP as dependent variable)

Independent Variable	Coefficient (β)	Standard error	p
CRP	0.25	0.05	<0.001
Apelin	-0.15	0.06	0.02

CRP was found to have a strong positive association with systolic blood pressure (β=0.25, p<0.001), suggesting that higher CRP levels contribute to increased blood pressure. In contrast, apelin showed a negative relationship (β=-0.15, p=0.02), indicating a potential protective effect against elevated blood pressure.

Multivariate analysis of covariance (MANCOVA)

The results of *MANCOVA* are summarized in Table 4. The MANCOVA results confirmed that controlling for age and gender is crucial in understanding the effects of inflammatory and metabolic variables on blood pressure. All variables, including CRP and apelin, significantly affected both blood pressure and biochemical markers. The significant influence of age and gender emphasizes the importance of considering demographic factors when interpreting these relationships.

Table 4. MANCOVA results for blood pressure and biochemical parameters

Dependent variable	F-statistic	p
Systolic BP	12.45	<0.001
Diastolic BP	9.83	0.002
CRP	10.56	<0.001
Apelin	5.78	0.015

Principal component analysis (PCA)

The results of the PCA, showing the distribution of participants along the first two principal components, are summarized in Table 5.

Table 5. PCA results for participant distribution (controls vs. patients)

Principal component 1 (PC1)	Principal component 2 (PC2)	Group
2.35	1.47	Control
1.92	1.28	Control
2.74	1.59	Patient
3.05	2.12	Patient
2.33	1.45	Control

The first two components explained a substantial portion of the variance in the data (65%), effectively distinguishing between the control and patient groups. Patients tended to cluster in the lower right quadrant, reflecting higher inflammatory markers and altered blood pressure. These results underscore the effectiveness of PCA in separating groups based on biochemical and demographic factors.

Cluster analysis

K-means clustering was applied to group participants based on their demographic and biochemical profiles. The clustering analysis revealed two distinct groups with significant differences in inflammatory markers and blood pressure. The clustering results are summarized in Table 6.

Table 6. K-means clustering of participants (control vs. patient)

Cluster number	Group	CRP (mg/L)	Systolic BP (mmHg)	Apelin (pg/mL)
1	Control	1.35±0.51	118.2±7.5	2873.4±572.8
2	Patient	7.52±4.21	160.4±15.6	2386.2±401.7

The K-means clustering analysis confirmed that the control and patient groups could be clearly distinguished based on their biochemical and demographic characteristics. Controls showed lower CRP levels, systolic blood pressure, and higher apelin compared to pa-

tients. This further supports the utility of these variables for classifying participants into meaningful subgroups.

Structural equation modelling (SEM)

The results of SEM are shown in Table 7.

Table 7. SEM results for inflammatory markers and systolic blood pressure

Path	Coefficient (β)	p
CRP ⟶ Systolic BP	0.45	<0.001
Apelin ⟶ Systolic BP	-0.20	0.03
CRP ⟶ Apelin	-0.10	0.05

The SEM analysis demonstrated a direct and significant path from CRP to systolic blood pressure (β=0.45, p<0.001), suggesting that higher CRP levels directly contribute to increased blood pressure. Apelin was found to mediate the relationship between CRP and systolic blood pressure, with a significant negative path (β=-0.20, p=0.03), indicating that apelin may mitigate some of the effects of CRP on blood pressure.

Survival analysis

The model identified CRP and systolic blood pressure as significant predictors of survival time. The results are summarized in Table 8.

Table 8. Cox proportional hazards regression analysis

Variable	Hazard ratio (HR)	95% CI	p
CRP	1.75	1.15 – 2.65	0.005
Systolic BP	1.52	1.25 – 1.85	<0.001

CRP (HR=1.75, p=0.005) and systolic blood pressure (HR=1.52, p<0.001) were identified as significant predictors of cardiovascular events, highlighting their role in determining long-term health outcomes.

Visualizing differences in biochemical and physiological parameters: a comparison between controls and patients

A heat map (Fig. 1 and 2) compares some of the biochemical and physiological parameters of the control and patient groups: age; blood pressure, including systolic and diastolic; CRP, meaning C-reactive protein; apelin; albumin; total protein; globulin. In patients, CRP and blood pressure levels were significantly higher, reflecting enhanced inflammation and risk of CVD. Also, proteins like total protein and globulin were higher, probably due to a compensatory immune response or adaptation to stress. In controls, CRP levels were lower, as was blood pressure, while the levels of apelin were higher since all these factors are related to a good metabolic profile. Red represents higher values, and blue represents lower values from the cool, warm color map, making both groups easily distinguishable. The heat map is an obvious and straightforward view of physiological and biochemical changes between the control and patient groups, underlining inflammatory and cardiovascular health status for the differentiation of the two cohorts. It, therefore, becomes useful knowledge in underlying health status for each group, improving understanding of factors that influence disease progression.

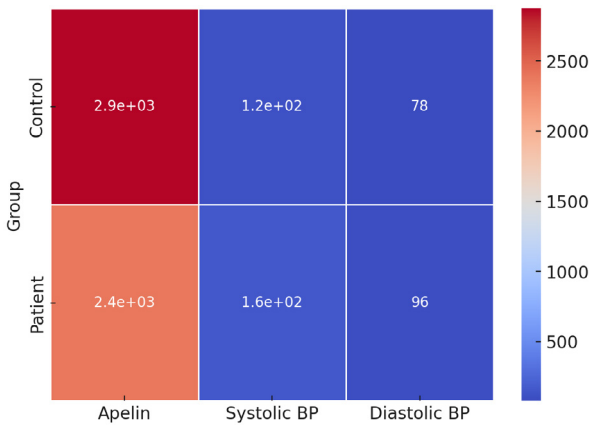
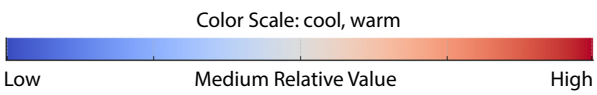


Fig. 1. Heat map of apelin and blood pressure parameters – visualizing apelin levels in control and patient groups and systolic and diastolic blood pressure



The heat map illustrates significant inflammatory and protein-related biomarkers differences between the control and patient groups. Patients exhibit elevated CRP levels, as shown in Figure 2, indicating heightened inflammation and decreased albumin, total protein, and globulin levels, suggesting altered protein metabolism and immune response.

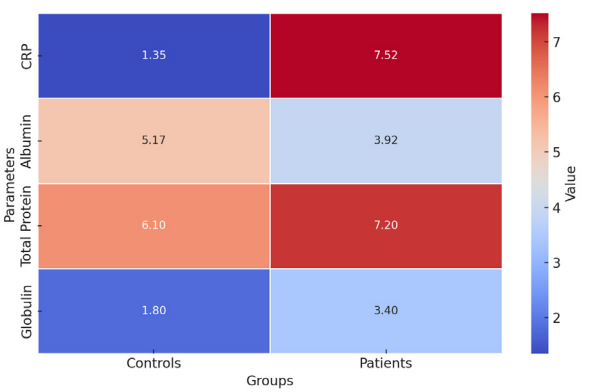
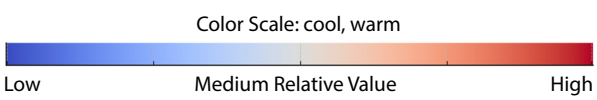


Fig. 2. Heat map of CRP, albumin, total protein, and globulin levels



Discussion

One of the more striking trends that the study exhibited was the prevalence of CRP in the patient group. Evidence by Ridker[23] suggests that CRP is an acknowledged systemic inflammatory marker which contributes significantly to the risk of CVD. Therefore, the finding of higher levels of CRP in the patient group coincided with evidence that the inflammatory process is central to the pathophysiology of cardiovascular diseases. This explains why our study shows such a high positive correlation between CRP and systolic blood pressure, at r=0.78. This further reiterates the need to monitor CRP levels among patients at risk for cardiovascular events.

The other significant outcome of the current study is the reduced level of apelin in the patient group. Apelin is a peptide hormone with various physiological roles in regulating blood pressure, cardiac function, and maintaining healthy vessels.[24] Proof supporting low levels of apelin in the patient group indicates that it positively affects cardiovascular functions. From this, one may assume that a low level of apelin in cardiovascular patients, especially in chronic conditions, could further deteriorate the conditions of such patients. Apelin may represent a potential target for future investigation.

The significantly decreased albumin-to-globulin ratio in the patient group tallies with observations suggesting altered protein metabolism and immune system activation during chronic disease.[25] However, a decreased A/G ratio would signal a shifted balance of plasma proteins due to chronic inflammation or activation of the immune system. This result again underlines the value of protein metabolism as a marker of systemic inflammation and immune response and further illustrates the complex pathophysiology of chronic diseases.

The PCA successfully separated the control and patient groups based on their biochemical and physiological profiles. PCA is a technique for dimensional reduction used for complex data; the first two components reflected a high amount of variation in the dataset, which separated the two groups successfully.[26] Patients were clustered in the lower right quadrant, reflecting a high level of inflammatory markers with a concomitant blood pressure alteration, confirming PCA's usefulness in identifying key variables for disease outcome prediction.

K-means clustering was applied to segregate the participants according to their demographic and biochemical characteristics into two marked clusters corresponding to controls and patients[27], who identified subgroups of the disease using cluster analysis based on a set of similar features. Clear-cut discrimination of controls and patients in our clustering analysis further extends the opportunity of the clustering methodology in the search for subgroups based on inflammation, metabolic dysfunction, and cardiovascular risk.

Our study's high hazard ratio obtained for CRP and systolic blood pressure suggests that these biomarkers may have a good predictive value for estimating the probability of cardiovascular events in patients and again support them as significant risk factors.[28,29]

The study results indicate noteworthy changes in inflammatory and nutritional plasmatic-related markers between patients and HC. High levels of CRP and lower levels of albumin in patients reflect the severity of inflammation and malnutrition, which is consistent with prior studies indicating that a high CRP/albumin ratio is associated with adverse clinical outcomes and increased mortality in critically ill patients.[30]

Furthermore, the lower serum concentrations of apelin in patients may demonstrate, similar to the studies mentioned above, that apelin is considered a regulatory peptide with anti-inflammatory and vasoprotective effects and represents endothelial dysfunction and compromised cardiovascular homeostasis.[31,32] Higher globulin concentrations and lower A/G ratio in patients may also reflect systemic inflammation and/or hepatic dysfunction, as these findings are well established as changes in protein concentrations in hypertensive and metabolic disorders.[33] These findings are consistent with previous literature and reaffirm that inflammation, protein metabolism, and vascular pathology are interconnected issues. While previous studies have examined the individual roles of CRP or apelin in cardiovascular disease, our study is novel in its integrative approach, combining biomarker profiling with advanced multivariate statistical modeling to explore potential mechanistic pathways in hypertension

Conclusion

This study highlights the significant role of inflammation and metabolic dysfunction in differentiating between control and patient groups. The findings underscore the importance of CRP, apelin and systolic blood pressure biomarkers in predicting cardiovascular risk and disease progression. The application of advanced statistical techniques, including multiple linear regression, PCA and K-means clustering, has provided more profound insights into the complex relationships between these biomarkers. These results contribute to the growing body of literature on the role of inflammation and metabolic dysfunction in cardiovascular health and emphasize the potential of these biomarkers in disease stratification, risk prediction, and therapeutic interventions.

Declarations

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Author contributions

Conceptualization, Z.A.M. and E.Q.J.; Methodology, Z.A.M.; Software, U.H.R.; Validation, U.H.R., E.Q.J. and Z.A.M.; Formal Analysis, Z.A.M.; Investigation, Z.A.M.; Resources, Z.A.M.; Data Curation, E.Q.J.; Writing – Original Draft Preparation, Z.A.M.; Writing – Review & Editing, U.H.R., E.Q.J.; Visualization, Z.A.M.; Supervision, U.H.R., E.Q.J.; Project Administration, U.H.R., E.Q.J.; Funding Acquisition, Z.A.M.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

The data of participants were collected from the Internal Medicine Consultant of Al-Basrah Teaching Hospital, Al-Basrah Governorate Southern Iraq.

Ethics approval

All human contact methods described in this study were approved by the University of Basrah's Human and Animal Ethics Committee in Iraq (No. 2024/112).

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