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ORIGINAL PAPER

Serum ATP1A1 and epinephrine as potential biomarkers for essential hypertension – a case-control study

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ABSTRACT

Introduction and aim. Essential hypertension is a leading cause of global morbidity driven by complex genetic and physiological interactions. The roles of the Na^+/K^+-ATPase pump, sympathetic nervous system, and electrolyte balance are critical, yet their simultaneous interaction remains unexplored. This study aimed to investigate the serum levels of Na^+/K^+-ATPase alpha-1 subunit (ATP1A1), epinephrine, and key electrolytes (sodium, potassium, chloride, and calcium) in hypertensive patients, providing a novel multi-marker approach to evaluate their potential as diagnostic biomarkers.

Material and methods. We enrolled 80 hypertensive patients and 40 normotensive controls in this cross-sectional study. Serum ATP1A1 and epinephrine levels were measured by ELISA, and electrolytes were analyzed using an ion-selective electrode analyzer.

Results. Hypertensive patients exhibited significantly higher serum levels of ATP1A1 (430±190 vs. 161±71.16 ng/L), epinephrine (339±188 vs. 116.5±38.6 ng/L), sodium, chloride, and calcium, with significantly lower potassium (all $p<0.001$ ROC analysis demonstrated a promising discriminatory ability for ATP1A1 (AUC=0.92) and epinephrine (AUC=0.94). Multiple regression analysis identified ATP1A1, epinephrine, and chloride levels as significant independent predictors of systolic blood pressure.

Conclusion. Patients with essential hypertension display a distinct biochemical signature of elevated serum ATP1A1 and epinephrine levels coupled with significant electrolyte disturbances. These preliminary findings suggest potential value as biomarkers for essential hypertension, although extensive validation in larger, independent cohorts is required before clinical application can be considered.

Keywords. blood pressure, catecholamines, electrolytes, sodium-potassium-exchanging ATPase

Introduction

Hypertension, a medical condition characterized by persistently elevated arterial blood pressure, remains one of the most significant global health challenges of the 21st century.[1] It affects approximately 15–20% of the adult population globally and is a leading risk factor for numerous serious health outcomes, including cardiovascular disease, stroke, chronic kidney disease, and dementia.[2,3] It is frequently asymptomatic at onset; however, uncontrolled hypertension leads to early death in many parts of the world. This disorder is generally divided into two types: essential (or primary) and secondary hypertension. Essential hypertension, which represents 90–95% of cases, is idiopathic and is the consequence of a mix of genetic predispositions and unspecific lifestyle conditions, including high dietary salt consumption, obesity, and physical inactivity.[4] The remaining 5–10% of cases are classified as secondary hypertension, high blood pressure with an identifiable cause such as chronic kidney disease, endocrine disorders, or use of birth control pills.[5]

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The complex control of blood pressure results from a tenuous interaction between hemodynamic and neurohormonal effects. Of these, electrolyte balance has been a major focus of research for many years.[6] In the 1970s and the 1980s, preliminary research of early work initiated a direct correlation between dietary electrolyte intake and blood pressure.[7] Disturbances in major electrolytes, such as sodium and potassium, may interfere with homeostatic mechanisms that regulate vascular tone and fluid status.[8] These early observations have been subsequently elaborated, as recent studies have suggested that the ratio of sodium to potassium intake might be a better predictor of blood pressure levels than the intake of any one mineral in isolation.[9] Since electrolyte disturbances are common and have been associated with increased morbidity and mortality, their role in the pathophysiology of hypertension is highly clinically relevant.[10]

The sodium-potassium pump Na^+/K^+-ATPase alpha-1 subunit (ATP1A1) plays a central role in the regulation of cellular electrolyte homeostasis. Its discovery in 1957 by Danish researchers Jens Christian Skou (this work was also honored with the Nobel Prize for Chemistry, in 1997) has been fundamental to modern physiology.[11] This enzyme facilitates the active transport of sodium ions out of the cell and potassium ions into the cell, operating against their respective concentration gradients, a mechanism that is driven by the hydrolysis of ATP. This function is essential for the preservation of resting membrane potential, the regulation of cell volume, and the facilitation of secondary transport processes for various solutes.[9] The alpha subunit is the catalytic subunit and ATP1A1 is a key isoform in both vascular and renal tissues.

Growing evidence has implicated Na^+/K^+-ATPase dysfunction in the pathogenesis of essential hypertension. The pump is an important modulator of the contractile response in muscle cells. Inhibiting it would result in a higher intracellular sodium level, impact calcium handling, and cause vasoconstriction with an increase in blood pressure.[12] Changes in the expression and/or function of the ATP1A1 subunit are associated with modification of vascular tone and blood pressure control. While traditionally studied as a membrane-bound protein, emerging evidence suggests that ATP1A1 can be detected in the circulation and may have a role as a biomarker in various pathological conditions. The circulating ATP1A1 protein is found in various locations throughout the body, including neurons and glial cells in the brain. Mammals have three auxiliary β subunits, identified as β1 to β3. The β1 subunit, encoded by ATP1B1, is present in nearly all tissues and cells, while β2 and β3 have more limited patterns of tissue expression. The β subunit plays a crucial role in positioning the Na^+/K^+ ATPase at the cell membrane. Additionally, it serves as a protein for intracellular adhesion by associating with adjacent β subunits from nearby cells. A functional pump is established through the assembly of one α subunit, one β subunit, and optionally one from a group of seven regulatory FXYD subunits. Among these, α1 and β1 are the most prevalent components that are believed to contribute to the formation of the essential Na^+/K^+ ATPase isozymes.[13] For instance, studies have shown that ATP1A1 is overexpressed in certain tumor cells and can be released into the circulation. While the exact mechanisms of its release into the serum in the context of hypertension are not fully elucidated, we hypothesize that it may be shed from the cell membrane of vascular endothelial cells, smooth muscle cells, or renal tubular cells in response to the pathophysiological changes associated with hypertension, such as increased shear stress or neurohormonal activation. In addition, the sympathetic nervous system, an important controller of the cardiovascular system, can also have a large effect on blood pressure, which is mediated by epinephrine (adrenaline) release. Many years ago, early investigators reported that hypertensive subjects displayed increased plasma catecholamine levels and a state of sympathetic hyperactivity.[14,15] Epinephrine, when released from the adrenal medulla during stress, directly augments the heart rate and cardiac output and has long been recognized to play a role in maintaining the hypertensive state.[16]

Despite extensive research focusing individually on genetic aspects of Na^+/K^+-ATPase, electrolyte imbalances, or catecholamines, the exact interaction between electrolyte balance, Na^+/K^+-ATPase activity, and sympathetic nervous system overactivity in hypertension remains a critical gap in the literature. While previous studies have examined these components in isolation, their simultaneous assessment has not been conducted. This study was conducted to address this gap by determining the serum ATP1A1 and epinephrine levels alongside key electrolytes (Na^+, K^+, Cl^-, Ca^{2+}) in hypertensive patients compared with healthy normotensive controls. This integrated multi-marker approach is highly novel, as it captures the complex interplay between different physiological systems implicated in hypertension. By simultaneously examining these interconnected biochemical pathways, we sought to clarify their roles in the pathophysiology of hypertension and assess their added value as integrated biomarkers for the disease, potentially offering a more comprehensive diagnostic window than single-parameter assessments.

Material and methods

Study design and population

A 120-subject case-control study was conducted (case control design). The study group included 80 hypertensive patients with an established diagnosis and 40 normotensive controls. Recruitment was performed in

three medical centers at Najaf, Iraq, Al-Sadar General Hospital, Al-Hakeem General Hospital, and Al-Najaf General Hospital from September to December 2025. The study protocol was approved by the local ethics committee of the Najaf Health Department (No. 35083, dated 28.9.2025) and all participants provided informed consent prior to their inclusion.

Inclusion and exclusion criteria

Subjects were eligible if they were 30–65 years old. Hypertensive patients were then classified into two groups: newly diagnosed hypertension (blood pressure ≥130/80 mmHg) without receiving drug therapy and patients with a history of hypertension under regular medication treatment drag include (Beta-blockers, also referred to as beta-adrenergic blockers, are medications prescribed to address heart-related ailments, including high blood pressure, angina, irregular heartbeats, and heart failure. They function by obstructing the effects of adrenaline, resulting in a decreased heart rate and lower blood pressure. These drugs are also beneficial for treating migraines, tremors, and anxiety disorders. Commonly prescribed types of these medications include atenolol, metoprolol, and propranolol. Candesartan is utilized either by itself or in combination with other drugs to manage hypertension in both adults and children aged between 1 and 16 years. Elevated blood pressure increases the strain on the heart and arterial system. Captopril is a medication approved by the FDA that is crucial for controlling high blood pressure, managing left ventricular dysfunction following a heart attack, and treating diabetic kidney damage. Its effectiveness is largely due to its ability to inhibit the renin-angiotensin-aldosterone system (RAAS), which makes it essential for the treatment of these cardiovascular issues.

Amlodipine is categorized as a calcium channel blocker that is employed to manage high blood pressure. For individuals suffering from hypertension, amlodipine can be instrumental in reducing the risk of future heart disease, heart attacks, and strokes.

Diuretics, often referred to as "water pills," are medications that assist the body in removing excess salt and water by promoting increased urination. They are mainly prescribed to manage hypertension, heart failure, kidney disorders, and conditions involving fluid accumulation) for at least more than six months. Normotensive individuals without a prior history of cardiovascular disease served as controls.

The exclusion criteria for all patients were secondary hypertension, chronic kidney disease, diabetes mellitus, and other endocrinopathies. Pregnant women and individuals taking medications known to affect electrolyte balance or sympathetic nervous system activity, such as corticosteroids or beta-agonists, were also excluded from the study.

Sample collection and processing

Venous blood samples, each measuring 5 mL, were collected from all participants. The blood was gathered in sterile gel tubes and permitted to coagulate at room temperature for a duration of 30 minutes prior to undergoing centrifugation at 3000 rpm for 10 minutes to facilitate the separation of the serum. The serum was subsequently divided into three Eppendorf tubes for each subject and preserved at -80°C until analysis to maintain the stability of the analytes.

Biochemical analysis

Serum concentrations of ATP1A1 (cat. no. E437hu) and epinephrine (cat. no. EA0033Hu) were quantified using two different ELISA kits (Bioassay Laboratory, China), following the instructions of manufacturer's. The assay procedure was performed as follows:

1. Standards were diluted according to the manufacturer's protocol to generate a standard curve.
2. Serum samples were added in duplicate to the respective wells.
3. After incubation and washing steps, the specific antibodies were added.
4. The absorbance was read at the specified wavelength.

The ATP1A1 ELISA kit had an assay range of 10-3000 ng/L and a sensitivity of 5.12 ng/L. The intra-assay and inter-assay CV were <8% and <10%, respectively. The epinephrine ELISA kit had an assay range of 15–3000 ng/L and a sensitivity of 7.5 ng/L. The intra-assay and inter-assay CVs were <8% and <10%, respectively. Serum electrolyte levels (Na^+, K^+, Cl^-, and Ca^{2+}) were measured using a Seamaty SE1 electrolyte analyzer (Seamaty, China). Laboratory personnel performing the biochemical assays were blinded to the clinical status (case vs. control) of the samples.

Statistical analysis

All statistical analyses were conducted using GraphPad Prism software (version 9.0). The Shapiro-Wilk test was utilized to evaluate the normality of data distribution prior to the implementation of parametric tests. For normally distributed variables, the independent t-test was used to compare mean values between hypertensive and control groups, after confirming the homogeneity of variance using Levene's test. Continuous variables are expressed as mean±SD (range), and categorical variables are shown as frequency and percentage. Multicollinearity among predictor variables (ATP1A1, epinephrine, and electrolytes) was assessed using the Variance Inflation Factor (VIF) in the context of multiple regression analysis; a VIF value<10 was interpreted as indicative of no significant multicollinearity. Bonferroni correction was applied to adjust the threshold for statistical significance when performing multiple comparisons across

the different electrolyte and biomarker subgroups, setting the corrected significance level at p<0.05.

Results

Demographic, clinical, and biochemical profiles of the participants are presented in Table 1. Age and sex differences between the groups were not statistically significant (p=0.31, p=0.9, respectively). As anticipated, systolic and diastolic blood pressures were significantly higher in the patient group (150.12±10.85 mmHg and 90.00±6.94 mmHg, respectively) than in the control group (115.00±5.07 mmHg and 74.00±4.96 mmHg, respectively). The serum electrolyte profile was markedly deranged among hypertensive patients. In particular, serum levels of sodium (142.16±3.49 mmol/L), chloride (102.33±4.21 mmol/L), and calcium (1.16±0.07 mmol/L) were significantly higher than in the control group (p<0.0001, p<0.0001, and p=0.0004; respectively). In contrast, serum potassium was significantly lower in the patients (4.25±0.48 mmol/L) than the controls (4.66±0.21 mmol/L; p<0.0001). In addition, the mean concentration of ATP1A1 was significantly higher in patients (430±190 ng/L) than in controls (161±71.16 ng/L). Blood epinephrine was also significantly increased in patients (339±188 ng/L) vs. healthy subjects (116.5±38.6 ng/L). These differences were statistically significant (p<0.0001 for both biomarkers).

Table 1. Comparative analysis of demographic, clinical, and biochemical profiles in hypertensive patients and normotensive controls*

Characteristic	Patients (n=80)	Control (n=40)	p
Demographic and clinical data			
Age (years), mean±SD	49.8±11.6	44.5±6.7	0.31
Gender, male, n (%)	40 (50%)	20 (50%)	0.9
Gender, female, n (%)	40 (50%)	20 (50%)	
Systolic BP (mmHg), mean±SD	150.12±10.85	115.00±5.07	<0.0001
Diastolic BP (mmHg), mean±SD	90.00±6.94	74.00±4.96	<0.0001
Serum electrolytes			
Sodium (mmol/L), mean±SD	142.16±3.49	138.43±1.03	<0.0001
Potassium (mmol/L),mean±SD	4.25±0.48	4.66±0.21	<0.0001
Chloride (mmol/L), mean±SD	102.33±4.21	97.10±1.01	<0.0001
Calcium (mmol/L), mean±SD	1.16±0.07	1.12±0.03	0.0004
Biomarkers			
ATP1A1 (ng/L), mean±SD	430±190	161±71.16	<0.0001
Epinephrine (ng/L), mean±SD	339±188	116.5±38.6	<0.0001

* data are presented as the mean±SD, p-value from Chi-square/independent samples t-test

Table 2 presents a comparison of biomarker levels between patients with hypertension receiving pharmacological treatment and those not receiving medication. Patients undergoing drug treatment exhibited significantly elevated levels of ATP1A1 (508.3±143 ng/L vs. 352±200 ng/L, p<0.0001), and epinephrine (384.3±175.5 ng/L vs. 295±192 ng/L, p=0.0338) compared to untreated patients. Similarly, electrolyte concentrations were higher in the treatment group for sodium (143.54±3.10 mmol/L vs. 140.77±3.33 mmol/L, p=0.0002) and chloride (104.11±3.60 mmol/L vs. 100.55±4.06 mmol/L, p<0.0001), while potassium was significantly lower (4.08±0.49 mmol/L vs. 4.42±0.42 mmol/L, p=0.0014). Serum calcium levels showed a trend toward elevation in the treatment group but did not reach statistical significance (1.18±0.07 mmol/L vs. 1.15±0.06 mmol/L, p=0.0582).

Table 2. Biomarkers in patients stratified by drug treatment*

Biomarker	Drug treatment (n=40)	No drug (n=40)	p
ATP1A1	508.3±143	352±200	<0.0001
Epinephrine	384.3±175.5	295±192	0.0338
Sodium	143.54±3.10	140.77±3.33	0.0002
Potassium	4.08±0.49	4.42±0.42	0.0014
Chloride	104.11±3.60	100.55±4.06	<0.0001
Calcium	1.18±0.07	1.15±0.06	0.0582

* data are presented as the mean±SD, p-value from the independent samples t-test

The discriminatory ability of ATP1A1 and epinephrine for HTN patients compared to normotensive controls was estimated using the ROC curve. Figure 1 shows the discriminatory abilities of both biomarkers. For ATP1A1, the Area Under the Curve (AUC) was 0.92 (95% CI: 0.85 to 0.96; p<0.001). A cutoff value of >218 ng/L was identified to achieve a sensitivity of 80% and a specificity of 92%. The Youden's index for overall diagnostic accuracy was 0.74 for ATP1A1. Epinephrine performed similarly, with an AUC of 0.94 (95% CI: 0.90–0.98; p<0.001). A cutoff value of >162 ng/L yielded a sensitivity of 88% and specificity of 90%. This resulted in a Youden index of 0.78, indicating a high level of discriminatory ability in this study population.

A Pearson's correlation analysis was also performed. The associations documented in the correlation matrix (Table 3) revealed various significant correlations that highlight the multifaceted pathophysiology of hypertension. There was a good correlation between systemic sodium and chloride (r=0.824, p<0.001) as physiological phenomenon, and ATP1A1 was also significantly positively associated with sodium (r=0.793, p<0.001) and chloride (r=0.682, p<0.001). In contrast, serum potassium levels were strongly and significantly negatively correlated with sodium (r=-0.846, p<0.001), chloride (r=-0.727, p<0-001) and ATP1A1 (r=-0.710, p < 0.001) levels. Systolic blood pressure was strongly positive correlated with several critical variables such as ATP1A1 (r=0.431, p=0.001), sodium (r=0.406, p=0.002), and chloride

(r=0.364, p<0.009). However, diastolic BP had a less robust yet still significant positive correlation with SBP (r=0.421, p=0.001) and did not correlate significantly with the majority of electrolytes measured. Epinephrine showed no significant association with primary electrolytes or blood pressure.

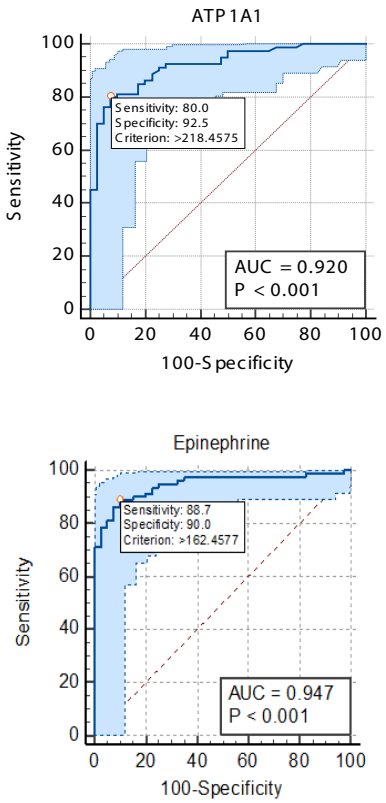

Fig. 1. Receiver operating characteristic curve for ATP1A1 and epinephrine in predicting hypertension

Table 3. Correlations analysis of biochemical and hemodynamic parameters

	Cl^- (mmol/L)	Na^+ (mmol/L)	ATP1A1	Ca^{2+} (mg/dL)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Epinephrine
Cl^- (mmol/L)	1						
Na^+ (mmol/L)	0.824 P<0.001	1					
ATP1A1	0.682 p<0.001	0.793 p<0.001	1				
Ca^{2+} (mg/dL)	0.639 p<0.001	0.697 p<0.001	0.551 p<0.001	1			
Systolic BP (mmHg)	0.364 p=0.009	0.406 p=0.002	0.431 p=0.001	0.343 p=0.001	1		
Diastolic BP (mmHg)	0.150 p=0.182	0.097 p=0.390	0.131 p=0.245	-0.073 p=0.520	0.421 p=0.001	1	
Epinephrine	0.072 p=0.526	0.020 p=0.858	0.148 p=0.188	-0.036 p=0.744	0.117 p=0.302	-0.174 p=0.12	1
K^+ (mmol/L)	-0.727 p<0.001	-0.846 p<0.001	-0.710 p<0.001	-0.519 p<0.001	-0.448 p<0.001	-0.184 p=0.10	-0.046 p=0.65

Multiple linear regression analysis was conducted to identify the significant biochemical and hormonal predictors of systolic blood pressure (Table 4). The model explained a substantial proportion of the variance in SBP (R^2=0.59; adjusted R^2=0.57; F=41.86; p<0.001). Significant positive associations were observed for plasma ATP1A1 (β=0.038, p=0.0009), epinephrine (β=0.002, p=0.0004). Variables, such as sodium, potassium, and calcium levels, were not statistically significant in the final model. The VIF values for all variables were below 5, suggesting that multicollinearity did not pose a significant issue.

Table 4. Analysis of multiple linear regression concerning predictors of systolic blood pressure*

Predictor	Beta (β) Coefficient	Std. Error	T-Value	VIF	p
Intercept	2.78				
ATP1A1	0.037637	0.0009	3.39	2.88	0.0009
Epinephrine	0.002499	0.0006	3.67	1.27	0.0004
R-squared	0.59				
Adjusted R-squared	0.57				

* dependent variable: systolic BP, model summary: F=41.86, p<0.001

Discussion

This study provides a comprehensive analysis of the interplay between serum ATP1A1, epinephrine, and electrolytes in patients with essential hypertension. Our findings reveal a distinct biochemical signature in hypertensive individuals, characterized by elevated serum ATP1A1 and epinephrine levels, alongside significant electrolyte imbalances. These results, while preliminary, suggest that these markers warrant further investigation regarding their potential role in the clinical assessment of hypertension.

To our knowledge, this is one of the first studies to simultaneously investigate the circulating levels of ATP1A1, epinephrine, and a panel of electrolytes in essential hypertension. While previous research has extensively focused on the genetic and tissue-specific aspects of the Na^+/K^+-ATPase,[17] our work extends these findings by quantifying the circulating protein itself, offering a potential window into systemic pathophysiology. The integrated multi-marker approach employed here is a key novelty, aiming to capture the complex interplay between different physiological systems implicated in hypertension.[18,19]

The most striking finding of this study was the pronounced elevation of ATP1A1 levels in the hypertensive cohort. Our observation of almost a three-fold increase in ATP1A1 levels in patients compared to controls strongly supports the growing body of evidence implicating ATP1A1 gene and its protein product as key molecules in blood pressure regulation. While many studies have focused on genetic mutations lead-

ing to conditions such as primary aldosteronism,[17] our estimation of the circulating protein per se provides an indirect observation of its pathogenic upregulation in hypertensive patients. This aligns with recent reviews that confirmed that the Na^+/K^+-ATPase contributes to hypertension through mechanisms in multiple organ systems, including the vasculature and kidneys.[20] Research indicates that variations in the abundance and activity of ATP1A1 significantly influence renal Na reabsorption, Na balance, and blood pressure.[21] Furthermore, an earlier investigation indicated that models of polygenic hypertension are associated with ATP1A1 in relation to salt-sensitive hypertension.[22] The high positive correlations between ATP1A1 and serum sodium and chloride found in the full model also supports a mechanistic relationship, suggesting that down-regulation or overexpression of the pump may occur to counteract or induce changes in sodium balance, which may be related to compensatory machinery due to disturbed Na^+ homeostasis, a characteristic feature of the hypertensive state and supported by recent models of Na^+/K^+-ATPase signaling.[23]

The precise mechanism for the elevated circulating ATP1A1 levels observed in our study remains to be fully elucidated. One possibility is the shedding of the ectodomain of the protein from vascular endothelial or smooth muscle cells in response to hypertensive stimuli.[24] Another potential mechanism is the release of ATP1A1 in extracellular vesicles, which are known to carry membrane proteins and have been implicated in various cardiovascular diseases.[25,26] The observed correlation with epinephrine also suggests a potential crosstalk between the sympathetic nervous system and the regulation of Na^+/K^+-ATPase expression and activity.[27] Further research is warranted to explore these potential mechanisms.

Our findings regarding serum electrolyte levels are consistent with the current understanding of the pathophysiology of hypertension. The observed distribution of increased sodium and chloride with reduced potassium supports the wealth of epidemiologic data over recent years, highlighting the importance of the sodium-to-potassium ratio as a stronger predictor of BP than either ion alone.[28,29] Large-scale analysis, including the KNHANES, consistently shows a strong relationship between a high urinary Na/K ratio and poor blood pressure control.[30] Multiple regression analysis in our study underscored the significance of chloride and revealed it to be an independent predictor of systolic blood pressure. This supports recent research indicating that chloride is more than a passive follower of sodium, and has an independent role in the regulation of blood pressure and cardiovascular disease progression.[31] Similarly, the mild but significant increase in serum calcium is consistent with the hypothesis that perturbed intracellular calcium handling contributes to increased vascular smooth muscle tone and peripheral resistance in essential hypertension.

Additionally, the present investigation of hypertensive subjects demonstrated a state of marked sympathetic nervous system overactivity, as reflected by significantly increased plasma epinephrine concentrations. This result is consistent with the influential review by Grassi et al., who highlighted arterial epinephrine as a predictor of future hypertension.[32] This finding was further supported by our regression analysis, which demonstrated that epinephrine was a significant independent risk factor for SBP. This underscores the importance of the sympathoadrenal axis in the rate-limiting progression of hypertensive disease, an idea that has been continuously revised by a recent meta-analysis of sympathetic nerve traffic.[33] Moreover, identification of genetic mutations resulting in autonomous epinephrine production with consequent hypertension provides additional evidence for the causal association between catecholamines and elevation in blood pressure.[34] This finding is consistent with earlier research that primes the body to release energy stores and triggers a host of changes, referred to as the fight-or-flight response. Epinephrine acts on alpha-1 adrenergic receptors, resulting in higher PVR and BP.[35]

A particularly noteworthy, though exploratory, finding of our study is the observed discriminatory ability of ATP1A1 and epinephrine. The mean AUC values from the ROC analysis for ATP1A1 (0.92) and epinephrine (0.94) suggest a strong discriminative ability in this study population. While these results are promising, it is crucial to interpret them with caution. The high sensitivity and specificity observed at the optimal cutoff values in our cohort suggest that these markers warrant further investigation as potential tools for risk stratification. However, extensive validation in larger, independent, and more diverse populations is required before any clinical utility can be considered.[36,37]

Patients receiving antihypertensive therapy had even higher ATP1A1 and epinephrine levels and more severe electrolyte disruptions, which is an interesting finding. Although this may be counterintuitive, it is possible that these patients had a worse hypertensive phenotype (that required pharmacological therapy). However, some recent guidelines and studies emphasize that some of these antihypertensive medications may in turn cause electrolyte disturbances, thus contributing to the complex biochemical picture.[38] This intricate relationship calls for more longitudinal studies to distinguish diseases from their treatment effects.

The results show that patients with essential hypertension had higher ATP1A1 and epinephrine.[39] This study also describes how FXYD2, signaling from cardiotonic steroids, and hormones including angiotensin II, dopamine, insulin, and catecholamines influence the

control of Na^+/K^+-ATPase. Additionally, this review underscores the significance of Na^+/K^+-ATPase in conditions like hypertension.[40]

Study limitations

This research presents several significant limitations that should be taken into account when analyzing the results. Initially, the ROC curve analyses were performed in the same cohort from which the data were derived, without an independent validation set. This approach is prone to overfitting and may substantially overestimate the true diagnostic performance of these biomarkers. Second, our single-center design limits the generalizability of our findings. Third, the cross-sectional design precludes the establishment of temporal relationships or causality

Conclusion

In conclusion, this study provides preliminary evidence for a concurrent dysregulation of serum ATP1A1, epinephrine, and electrolytes in patients with essential hypertension. These findings contribute to our understanding of the complex pathophysiology of the disease and suggest that a multi-marker approach may warrant further investigation. The results should be interpreted as hypothesis-generating, and extensive validation in larger, prospective, multi-center cohorts is essential before these biomarkers can be considered for any clinical application.

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Declarations

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Author contributions

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

Conflicts of interest

The authors have nothing to disclose.

Data availability

The datasets that were generated or analyzed during the current study are not publicly available due to concerns about participant privacy and confidentiality but are available from the corresponding author on reasonable request.

Ethics approval

Ethical approval for this study was obtained from the Medicine Department Ethical Committee of Medical Laboratories College of Health and Medical Technologies/Kufa-Iraq, with reference (35083) on (28.9.2025).

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