



Strong Ion Difference: A Promising Biomarker for Differential Diagnosis of Hypertensive Disorders in Pregnancy

Güçlü İyon Farkı: Gebelikte Hipertansif Bozuklukların Ayırıcı Tanısında Umut Vadeden Bir Biyobelirteç

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ABSTRACT

Aim: Hypertensive disorders of pregnancy (HDP), including gestational hypertension (GHT) and preeclampsia, are significant causes of maternal and neonatal morbidity. Early differentiation is crucial, especially in severe cases. This study evaluated venous blood gas parameters, specifically Strong Ion Difference (SID) and Apparent Strong Ion Difference (SIDa), to distinguish GHT from preeclampsia and severe preeclampsia.

Material and Method: This retrospective, single-center study analyzed 94 pregnant patients with hypertension of unknown origin beyond 20 weeks' gestation (October 2021–2022). Patients were categorized as GHT (n=39) or preeclampsia spectrum (n=55), with subgroup analysis in 74 patients without chronic diseases. Proteinuria was assessed via 24-hour urine collection or protein/creatinine ratio. Statistical methods included t-tests, chi-square, Mann-Whitney U, Kappa, and ROC analysis.

Results: Significant differences were found between GHT and preeclampsia groups in dipstick protein $\geq 2+$, protein/creatinine ratio, SID, and SIDa ($p < 0.001$). In the subgroup analysis, significant differences were noted for dipstick protein $\geq 1+$ and $\geq 2+$, protein/creatinine ratio, SID, and SIDa ($p = 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.015$, $p = 0.012$). Kappa analysis showed poor agreement between SID and proteinuria in the total cohort ($\kappa = -0.166$, $p = 0.092$) and slight agreement in the subgroup analysis ($\kappa = 0.190$, $p = 0.020$), suggesting a weak concordance between these two parameters. SID showed moderate discriminatory power (AUC: 0.672 overall, 0.668 in the subgroup).

Conclusion: SID and SIDa are promising biomarkers for distinguishing GHT from preeclampsia. Further extensive cohort studies are needed to establish accurate cut-off values for routine clinical use.

Key words: gestational hypertension, preeclampsia, severe preeclampsia, SID, strong ion difference

ÖZET

Amaç: Gestasyonel hipertansiyon (GHT) ve preeklampsi dâhil olmak üzere gebeliğin hipertansif bozuklukları (HDP), maternal ve neonatal morbiditenin başlıca nedenlerindedir. Özellikle ağır vakalarda, erken ayırt edilmesi hayati önem taşımaktadır. Bu çalışma, GHT'yi preeklampside ve ağır preeklampside ayırt etmek amacıyla venöz kan gazı parametrelerini, özellikle Güçlü İyon Farkı (SID) ve Görünür Güçlü İyon Farkı'nı (SIDa) değerlendirmiştir.

Materyal ve Metot: Bu retrospektif, tek merkezli çalışmada, 20. gebelik haftasını geçmiş ve nedeni bilinmeyen hipertansiyonu olan 94 gebe hasta (Ekim 2021–2022) analiz edilmiştir. Hastalar GHT (n=39) ve preeklampsi spektrumu (n=55) olarak sınıflandırılmıştır. Kronik hastalığı olmayan 74 hasta üzerinde alt grup analizi yapılmıştır. Proteinüri, 24 saatlik idrar toplama veya protein/kreatinin oranı ile değerlendirilmiştir. İstatistiksel yöntemler arasında t-testi, ki-kare, Mann-Whitney U, Kappa ve ROC analizi yer almıştır.

Bulgular: GHT ve preeklampsi grupları arasında idrar çubuğunda protein $\geq 2+$, protein/kreatinin oranı, SID ve SIDa açısından anlamlı farklılıklar saptanmıştır ($p < 0,001$). Alt grup analizinde, idrar çubuğunda protein $\geq 1+$ ve $\geq 2+$, protein/kreatinin oranı, SID ve SIDa açısından anlamlı farklılıklar tespit edilmiştir ($p = 0,001$, $p < 0,001$, $p < 0,001$, $p = 0,015$, $p = 0,012$). Kappa analizi, toplam kohortta SID ile proteinüri arasında zayıf bir uyum olduğunu ($\kappa = -0,166$, $p = 0,092$) ve alt grup analizinde hafif bir uyum bulunduğunu ($\kappa = 0,190$, $p = 0,020$) göstermiştir. Bu durum, bu iki parametre arasında zayıf bir korelasyon olduğunu düşündürmektedir. SID, orta düzeyde ayırt edici güce sahip bulunmuştur (AUC: 0,672 genel kohort, 0,668 alt grup).

Sonuç: SID ve SIDa, GHT'yi preeklampside ayırt etmede umut vadeden biyobelirteçlerdir. Rutin klinik kullanım için kesin eşik değerlerin belirlenmesi amacıyla daha geniş kohort çalışmalarına ihtiyaç vardır.

Anahtar kelimeler: gestasyonel hipertansiyon; preeklampsi; ağır preeklampsi; SID; güçlü iyon farkı

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Introduction

Background

Hypertensive disorders of pregnancy (HDP), despite significant scientific advancements, remain a leading cause of maternal mortality and morbidity. Hypertensive disorders of pregnancy accounts for approximately 16% of maternal deaths in developing countries and 25% in developed countries, complicating 2–8% of pregnancies worldwide^{1,2}. The differential diagnosis of new-onset hypertension after 20 weeks of gestation includes gestational hypertension (GHT), preeclampsia, superimposed preeclampsia, and preeclampsia with severe features. Gestational hypertension is defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or both, measured on at least two occasions four hours apart, arising after 20 weeks of gestation in women without prior hypertension and without proteinuria.

Preeclampsia, typically occurring after 20 weeks and often near term, involves new-onset hypertension with proteinuria, defined as >300 mg/dL protein in a 24-hour urine collection or a protein/creatinine ratio >0.3 ^{3,4}. When quantitative methods are unavailable or rapid decisions are needed, spot urine protein testing is acceptable. However, dipstick urinalysis may overdiagnose proteinuria in 53% and 23% of cases with 1+ and 2+ results, respectively, with accuracies of 70% and 82% compared to gold-standard methods⁵.

Recent cadaver studies and case series using electron microscopy have revealed that chronic inflammation and secondary endothelial dysfunction are fundamental to the microangiopathy seen in preeclampsia. This microangiopathy contributes to a range of complications, including edema, end-organ damage, and, notably, proteinuria^{6,7}. The pathogenesis of preeclampsia is closely linked to abnormal placentation, where inadequate trophoblastic invasion into the spiral arterioles of the decidua basalis leads to defective myometrial invasion⁸. A variety of factors are implicated in this abnormal process, including maternal and environmental factors such as defective trophoblast differentiation, placental hypoperfusion, hypoxia, ischemia, exaggerated inflammatory response, excessive complement activation and genetic predispositions⁹. Regardless of the cause, these factors converge on a common pathway of microangiopathy, endothelial dysfunction, and the diverse end-organ damage that defines the severity of clinical spectrums of preeclampsia^{10,11}.

Blood gas analysis is a widely used and rapid method for evaluating complex metabolic conditions in critically

ill patients, such as those with sepsis, trauma, or major surgery. Various approaches for interpreting blood gas results are described in the literature. Unlike the classical approach for acid-base analysis, Stewart's theory, published in 1983, mathematically formulates acid-base balance based on the principles of mass conservation, dissociation curves, and the conservation of electrical neutrality in fluids. Maintaining normal membrane function is critical for preserving this balance, which can be disrupted in pathological conditions like microangiopathy¹². According to Stewart's theory, the independent variables determining acid-base status are the partial pressure of carbon dioxide (PaCO₂) in arterial blood, the total concentration of non-volatile weak acids in plasma (A_{tot}), and the strong ion difference (SID) between the concentrations of fully dissociated cations and anions in plasma. Typically, membranes separating body fluids are impermeable to proteins, making A_{tot} interactions negligible. However, in pathological conditions, alterations in A_{tot} can significantly impact pH balance. SID, defined as the difference between the concentrations of strong cations (Na⁺, K⁺, Ca²⁺, Mg²⁺) and strong anions (Cl⁻, lactate⁻, SO₄²⁻, and other strong anions), is a key concept in Stewart's theory. SID, simplified as $[(Na^+) - (Cl^-)]$, directly influences blood pH; a high SID is associated with alkalosis, while a low SID is associated with acidosis¹³. Changes in SID provide insights into acid-base disorders that traditional bicarbonate analysis might miss, allowing clinicians to conduct a more comprehensive assessment of acid-base balance in complex clinical scenarios¹⁴.

Objectives

This study aims to retrospectively evaluate blood gas parameters at initial presentation in patients with HDP. The primary objective is to compare SID values between patients diagnosed with GHT, preeclampsia and preeclampsia with severe features. The secondary aim is to investigate whether SID values in blood gas analyses can serve as an additional biomarker in the diagnosis of HDP.

Material and Method

Study Design

This retrospective, single-center observational study aimed to analyze venous blood gas (VBG) parameters in pregnant individuals beyond 20 weeks of gestation who presented with hypertension of unknown origin. Demographic data, including age, gravidity, parity, and

number of abortions, gestational age week at initial presentation, recorded highest systolic and diastolic blood pressure at presentation, laboratory findings, presence of additional chronic diseases, and VBG results, were collected and analyzed (Additional file 1). According to our clinical protocol, the 24-hour urine collection was accepted as the gold standard for proteinuria diagnosis, and in cases where it was available, its results were prioritized. Otherwise, the protein/creatinine ratio was used as the diagnostic test. These parameters were evaluated in relation to the final diagnosis, which was determined based on clinical findings, laboratory, and quantitative urinalysis results.

Setting and Participants

A total of 232 pregnant patients admitted to our tertiary referral hospital's Obstetrics and Gynecology Emergency Department and undergoing VBG analysis from October 1, 2021, to October 1, 2022, were initially considered. Of these, 103 were excluded for non-hypertensive indications, 27 for pre-gestational chronic hypertension, and 7 for VBG analysis post-magnesium sulfate therapy. This left a study cohort of 94 patients. Proteinuria was assessed by 24-hour urine collection in 23 patients, while all 94 had protein/creatinine ratios and dipstick tests. Within the cohort, 39 had GHT, and 55 had preeclampsia-related conditions: 42 with preeclampsia, 9 with severe preeclampsia, and 4 with superimposed preeclampsia (Fig. 1, Table 1).

Variables

The parameters analyzed in this study included calculated SID $[(Na^+ - Cl^-)]$ and apparent SID (SIDa) $[(Na^+) - (Cl^- + Lac^-)]$ from VBG analysis (Table 2). Urinalysis parameters included dipstick urinalysis protein readings, spot urine protein/creatinine ratio, and 24-hour urine protein excretion rate. Additionally, the presence of chronic diseases that could potentially cause electrolyte imbalances was meticulously assessed and treated as confounding variables. To address this, a subgroup analysis was performed on a cohort without these additional chronic conditions ($n=74$).

Data sources/Measurement

The accuracy of these parameters in differentiating diagnostic outcomes across HDP groups and within the subgroup analysis without additional chronic conditions ($n=74$) is detailed in Table 2, offering insights into their relevance to diagnostic efficacy.

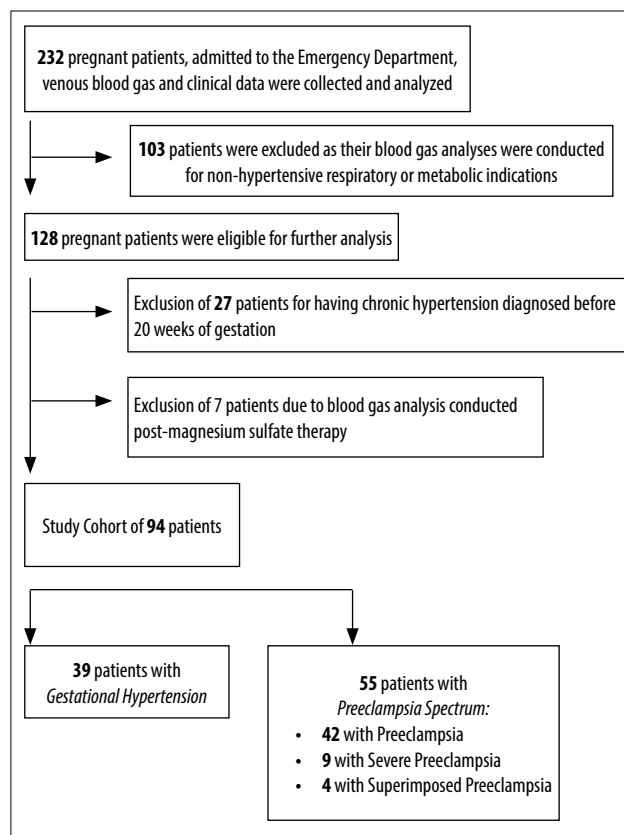


Figure 1. Flowchart of patient exclusion criteria and formation of the total study cohort (AUC: Area Under the ROC Curve; Sensitivity, and Specificity at Optimized Cutoff Point for Predicting Differential Diagnosis of Hypertensive Disorders in Pregnancy; Total Study Cohort).

Bias

Bias was minimized by excluding patients whose blood gas analysis was conducted after magnesium sulfate therapy and by conducting thorough assessments of all variables through subgroup analysis. Additionally, deliberate efforts were made to identify and mitigate any inherent biases in the study design and analytical processes.

Study Size

The sample size for this study was calculated based on prior research that identified significant hyperchloremic acidosis differences between healthy pregnancies and those diagnosed with severe preeclampsia¹⁵. Using the G*Power program, and assuming an alpha level of 0.05 and an effect size of 0.8, we aimed for a minimum power of 80%¹⁶. This calculation indicated that a sample size of 26 participants per group was required to ensure the study's ability to detect meaningful effects with statistical reliability.

Quantitative Variables

Proteinuria was quantified according to standard definitions, with a threshold set at 300 mg/dL of protein or more in a 24-hour urine collection, or a protein/creatinine ratio of 0.3 or higher¹. The SID is measured, with a normal value defined as 38 mEq/L¹³.

Ethical Considerations

This retrospective observational study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Clinical Research Ethics Committee on December 14, 2022 (approval number: 2022.12.400). Written informed consent specific to this study was not obtained as the data were collected retrospectively from patients' medical records. However, all patients had previously provided general written consent during their clinical admission, agreeing to the use of their anonymized data for scientific research, as approved by the ethics committee.

Statistical Methods

Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) program version 26.0. The Kolmogorov-Smirnov test was employed to assess the normality of continuous variables. Data that followed a normal distribution are presented as mean \pm standard deviation, with comparisons made using the independent t-test. For data not normally distributed, results are presented as median (25th–75th percentile) and analyzed using the Mann-Whitney U test. Categorical variables are reported as numbers and percentages, with statistical significance determined by the chi-square test. The receiver-operating characteristic (ROC) curve was utilized to evaluate the sensitivity and specificity of diagnostic tests based on optimized cutoff points. Kappa statistics were used to assess the agreement between SID and proteinuria in both the total study cohort and the subgroup without additional diseases affecting electrolyte balance. Statistical significance was set at $p < 0.05$.

Results

Participants

The study included 94 pregnant individuals diagnosed with hypertensive disorders of pregnancy (HDP), divided into two groups: 39 with GHT and 55 with a spectrum of preeclampsia-related conditions. The subgroup study cohort without additional chronic diseases for electrolyte imbalance ($n=74$) consists of 31 GHT patients and 43 patients with preeclampsia spectrum of diseases (Table 1).

Descriptive Data

Demographically, there were no statistically significant differences between the two groups in terms of age, gravidity, parity, abortion numbers, or gestational week at the time of diagnosis. Additionally, there was no significant difference in the prevalence of chronic diseases that could contribute to electrolyte imbalance ($p=0.88$). The preeclampsia group demonstrated statistically significant but clinically insignificant elevations in creatinine ($p=0.03$) and AST levels ($p=0.04$) compared to the GHT group, while ALT levels were comparable between the groups ($p=0.41$). Blood pressure measurements revealed significant differences, with the preeclampsia spectrum group showing higher systolic and diastolic pressures ($p<0.001$ and $p=0.02$, respectively). In a subgroup analysis excluding patients with additional chronic conditions that could influence electrolyte balance ($n=74$), similar trends persisted. The preeclampsia spectrum group ($n=43$) continued to exhibit significantly higher systolic and diastolic blood pressure levels ($p=0.001$ and $p=0.004$, respectively) compared to the GHT group ($n=31$). Kappa analysis revealed poor agreement between SID and proteinuria in the total cohort ($\kappa=-0.166$, $p=0.092$). In contrast, a slight but statistically significant agreement was observed in the subgroup without electrolyte-altering conditions ($\kappa=0.190$, $p=0.020$). These findings suggest that while SID and proteinuria are both associated with preeclampsia, they may reflect different pathophysiological mechanisms.

Outcome Data

Blood gas and electrolyte parameters were analyzed between the GHT and preeclampsia spectrum groups; the comparison showed no statistically significant differences in pH, lactate, Na⁺, K⁺, and base excess values across both the study cohort ($n=94$) and subgroup cohort without additional electrolyte imbalance ($n=74$) ($p>0.05$ for all). However, a statistically significant difference was observed in the HCO₃⁻ levels ($p=0.03$), and Ca⁺ levels ($p=0.04$), with the GHT group presenting higher levels compared to the preeclampsia spectrum group in the whole study cohort; while Cl⁻ levels were marginally higher in the preeclampsia group ($p=0.06$) in the study cohort without additional chronic diseases for electrolyte imbalance ($n=74$). By implying Stewart approach and calculating SID [(Na⁺) - (Cl⁻)], a remarkable hyperchloremic acidosis can be observed in all 4 study cohorts ($SID \leq 38$ mEq/L)¹³.

In the total study cohort, there was no statistically significant difference in dipstick urinalysis protein readings $\geq 1+$ between GHT and preeclampsia spectrum

patients ($p=0.78$). However, for dipstick urinalysis protein reading $\geq 2+$, spot urine protein/creatinine ratio, SID, and SIDa measurements, statistically significant results were observed between the two groups ($p<0.001$, $p<0.001$, $p=0.005$, and $p=0.005$, respectively). In the study cohort without additional chronic

diseases for electrolyte imbalance, both GHT and preeclampsia spectrum groups had statistically significant differences for dipstick urinalysis protein reading $\geq 1+$ and $\geq 2+$, spot urine protein/creatinine ratio, SID, and SIDa measurements ($p=0.001$, $p<0.001$, $p<0.001$, $p=0.015$, and $p=0.012$, respectively) (Table 2).

Table 1. Comparative analysis of clinical findings and demographic data between patients diagnosed with gestational hypertension and preeclampsia spectrum with and without additional chronic diseases for electrolyte imbalance

Parameter	Study cohort (n=94)			Study cohort without additional chronic diseases for electrolyte imbalance (n=74)		
	Gestational hypertension (n=39)	Preeclampsia spectrum (n=55)	P value	Gestational hypertension (n=31)	Preeclampsia spectrum (n=43)	P value
Age (years)	29.26±5.98	31.65±7.05	0.12	28.71±5.84	30.35±7.18	0.29
Gravidity (n)	2.49 (1,00–3,00)	2.65 (1,00–3,00)	0.12	1.00 (1,00–4,00)	2.37 (1,00–3,00)	0.54
Parity (n)	0.85 (0,00–2,00)	1.13 (0,00–2,00)	0.13	0.00 (0,00–2,00)	1.00 (0,00–2,00)	0.32
Abortus (n)	0.62 (0,00–1,00)	0.53 (0,00–1,00)	0.94	0.55 (0,00–1,00)	0.37 (0,00–0,00)	0.47
Gestation (weeks)	34.82 (34,00–38,00)	34.64 (34,00–37,00)	0.24	34.71±5.20	34.84±3.33	0.24
Systolic b. p. (mmHg)	141.28 (138,00–150,00)	152.36 (144,00–159,00)	<0.001	142.19±13.41	152.26±12.54	0.001
Diastolic b. p. (mmHg)	84.59±10.02	90.35±10.80	0.02	83.68±10.64	90.84±9.83	0.004
Platelets (x 1.000/mm ³)	269±78	247±87	0.18	276±79	245±87	0.12
Creatinine (mg/dl)	0.53 (0,49–0,62)	0.59 (0,53–0,77)	0.03	0.55 (0,48–0,62)	0.58 (0,50–0,67)	0.16
ALT (IU/l)	12.0 (9,0–14,0)	12.0 (9,0–19,0)	0.41	13.26±8.78	22.35±30.90	0.07
AST (IU/l)	18.00 (16,00–24,00)	22.00 (17,00–32,00)	0.04	21.35±9.18	31.35±42.01	0.19
Add. Chr. Renal D. (n)	0 (0%)	3 (5.45%)	0.88	0 (0%)	0 (0%)	-
Add. Chr. Diabetes (n)	2 (5.12%)	8 (14.54%)		0 (0%)	0 (0%)	
Add. Chr. Thyroid D. (n)	6 (15.38%)	1 (1.81%)		0 (0%)	0 (0%)	

Results were presented as mean (SD) for normally distributed data, median (25–75 percentile) was used for non-normally distributed data, and number (percentage) for categorical variables. To compare independent categorical variables, the chi-square test was applied, and the results were reported as numbers and percentages. b. p.: Blood pressure; Add. Chr.: Additional chronic; d.: Disease; n.: Number

Table 2. Comparative analysis of urinalysis and venous blood gas analysis between patients diagnosed with gestational hypertension and preeclampsia spectrum with and without additional chronic diseases for electrolyte imbalance

Parameter	Study cohort (n=94)			Study cohort without additional chronic diseases for electrolyte imbalance (n=74)		
	Gestational hypertension (n=39)	Preeclampsia spectrum (n=55)	P value	Gestational hypertension (n=31)	Preeclampsia spectrum (n=43)	P value
pH	7.38±0.03	7.39±0.03	0.89	7.39±0.03	7.39±0.02	0.87
HCO ₃	23.31±1.76	22.5±1.79	0.03	23.23±1.93	22.5±1.85	0.10
Lactate	1.28±0.55	1.29±0.52	0.93	1.26±0.56	1.30±0.55	0.73
Na	138.38±1.74	137.76±2.26	0.15	138.39±1.80	137.91±2.22	0.32
K	4.10±0.39	4.12±0.44	0.84	4.13±0.42	4.09±0.48	0.73
Ca	1.19±0.05	1.15±0.08	0.04	1.18±0.06	1.15±0.09	0.11
Cl	106.46±2.11	107.27±2.01	0.06	106.52±2.18	107.56±1.81	0.02
Base excess	-1.58±1.9	-2.38±1.8	0.03	-1.64±2.10	-2.35±1.86	0.13
Dipstick Ur. Prot. $\geq 1+$ (n)	23 (59.0%)	34 (61.8%)	0.78	9 (29.0%)	29 (67.4%)	0.001
Dipstick Ur. Prot. $\geq 2+$ (n)	0 (0%)	20 (36.4%)	<0.001	0 (0.00%)	14 (32.6%)	<0.001
Sp. Ur. Prot/Cre Ratio	0 (0%)	53 (96.4%)	<0.001	0 (0.00%)	41 (95.3%)	<0.001
SID (Na-Cl)	31.92±1.99	30.49±2.65	0.005	31.87±2.17	30.35±2.84	0.015
SIDa (Na-Cl-Lactate)	30.64±2.02	29.20±2.63	0.005	30.60±2.18	29.04±2.84	0.012

Results were presented as mean (SD) for normally distributed data, and number (percentage) for categorical variables. To compare independent categorical variables, the chi-square test was applied, and the results were reported as numbers and percentages. Dipstick Ur. Prot.: Dipstick Urinalysis Protein Reading; Sp. Ur. Prot/Cre Ratio: Spot Urine Protein/Creatinine Ratio; SID: Strong Ion Difference; SIDa: Apparent Strong Ion Difference

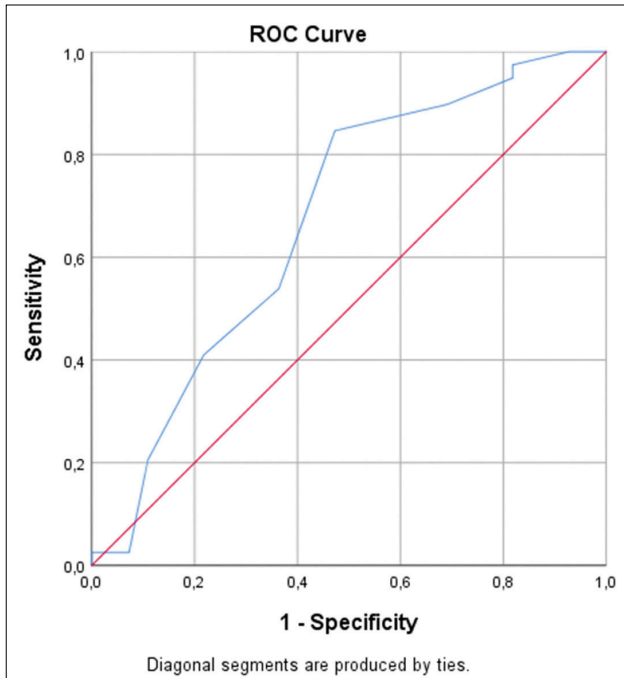


Figure 2. Area under the receiver operating characteristic (ROC) analysis (total study cohort) (AUC: Area Under the ROC Curve; Sensitivity, and Specificity at Optimized Cutoff Point for Predicting Differential Diagnosis of Hypertensive Disorders in Pregnancy; Study cohort without additional chronic diseases for electrolyte imbalance).

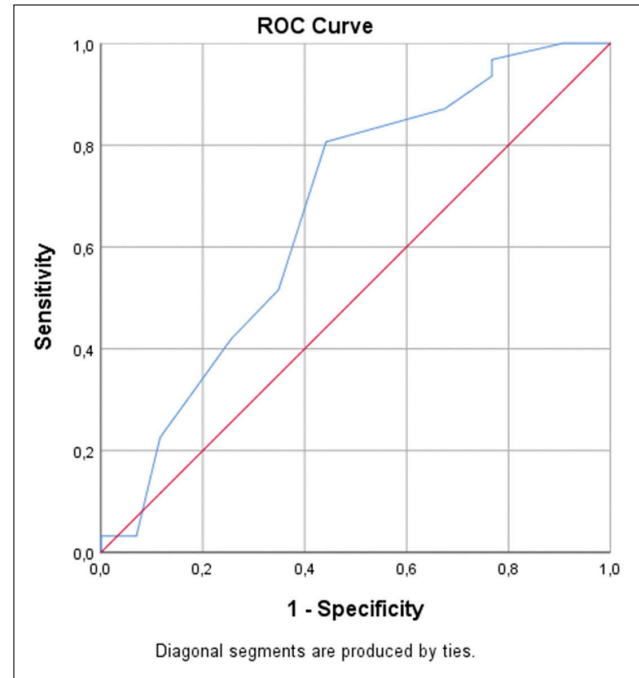


Figure 3. Area under the receiver operating characteristic (ROC) analysis (study cohort without additional chronic diseases for electrolyte imbalance). Results were presented as median (25–75 percentile) was used for non-normally distributed data.

Table 3. Strong ion difference and predictive performance metrics for differential diagnosis of hypertensive disorders in pregnancy

Study cohort (n=94)				
AUC (95% CI)	Cutoff according to Youden index	Sensitivity (%)	Specificity (%)	p value
0.672 (0.564 – 0.781)	31.5	53.8	46.2	0.005
	32.5	41.0	59.0	0.005
	33.5	20.5	79.5	0.005
Study cohort without additional chronic diseases for electrolyte imbalance (n=74)				
AUC (% 95% CI)	Cutoff according to Youden Index	Sensitivity (%)	Specificity (%)	p value
0.668 (0.545–0.791)	31.5	51.6	65.1	0.014
	32.5	41.9	74.4	0.014
	33.5	22.6	88.4	0.014

CI: Confidence Interval; AUC: Area Under Curve

Main Results

Analyzing the acid-base imbalance by Stewart approach that differs from the traditional bicarbonate-centered approach, SID and SIDa were evaluated for their diagnostic performance in distinguishing between hypertensive disorders in pregnancy. The SID values demonstrated moderate discriminative power with an AUC of 0.672 (95% CI: 0.564–0.781) for the overall study cohort (n=94) and an AUC of 0.668

(95% CI: 0.545–0.791) for the subgroup excluding chronic diseases (n=74) (Table 3, Fig. 2, Fig. 3). The most balanced cutoff values according to the Youden Index were 31.5 for both cohorts, with sensitivity and specificity reflecting moderate accuracy.

When comparing SID and SIDa between the pre-eclampsia group and those with severe features, no statistically significant differences were found (p=0.178 and p=0.190 respectively), suggesting that these

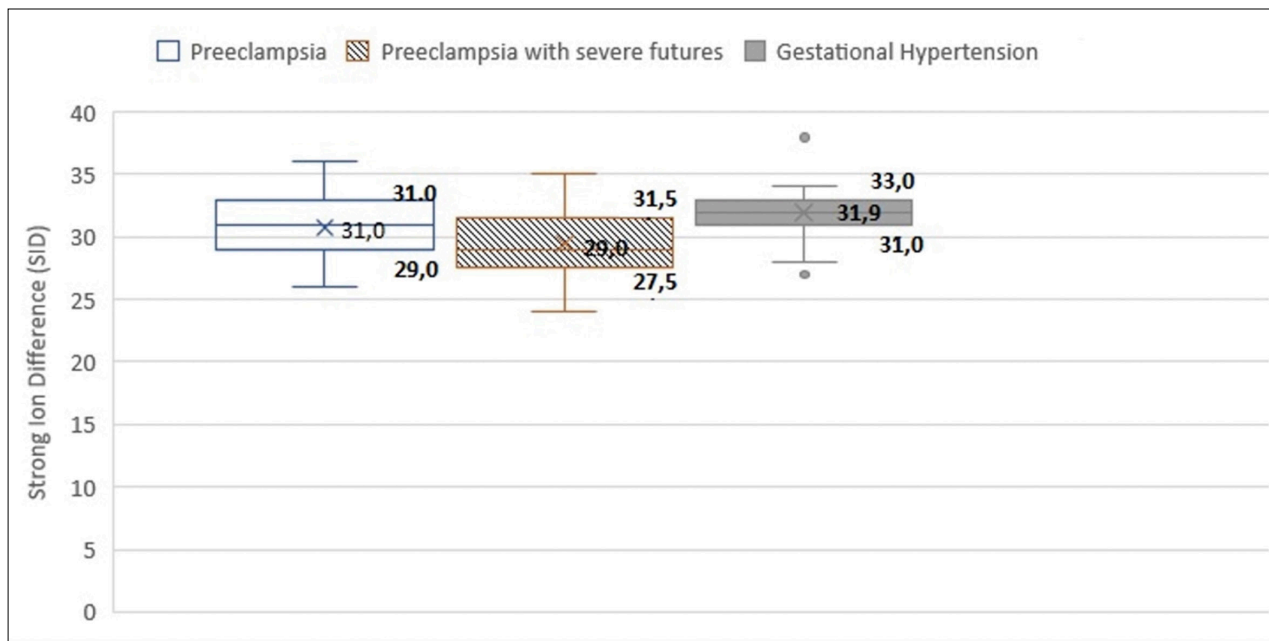


Figure 4. Graphical illustration of SID between gestational hypertension group and preeclampsia patients and preeclampsia patients with severe features in preeclampsia spectrum.

Table 4. Comparative analysis of strong ion difference and apparent strong ion difference between the preeclampsia group and the preeclampsia with severe features group

Parameter	Patient cohort (n=51)		
	Preeclampsia (n=42)	Preeclampsia with severe features (n=9)	P value
SID	31.00 (29,00–31,00)	29.00 (27,50–31,50)	0.178
SIDa	29.60 (28,12–31,32)	28.10 (26,35–30,50)	0.190

Results were presented as median (25–75 percentile), which was used for non-normally distributed data.

parameters may not vary significantly between different severities within the preeclampsia spectrum. However, the SID and SIDa were slightly lower in the severe preeclampsia (Table 4, Fig. 4).

Discussion

This study suggests that SID provides additional diagnostic information independent of proteinuria, reinforcing its potential role in evaluating hypertensive disorders of pregnancy.

Principle Findings

Dipstick urinalysis (protein $\geq 1+$) did not significantly differentiate between GHT and preeclampsia in the total cohort ($p=0.78$; sensitivity 59.6%, specificity 43.2%). In contrast, significance improved in patients without confounding electrolyte-affecting conditions ($p=0.001$; sensitivity 76.3%, specificity 61.1%).

SID, with a cutoff of 31.5, showed statistically significant diagnostic value in both groups ($p<0.001$), and remained moderately accurate regardless of comorbidities. Kappa analysis revealed poor concordance between SID and proteinuria overall, and only slight agreement in patients without chronic disease.

Severe preeclampsia, a more critical form within the preeclampsia spectrum, may occur with or without proteinuria and is characterized by end-organ damage. It can manifest through thrombocytopenia, elevated liver enzymes, right upper quadrant pain from liver capsule distension, new-onset renal insufficiency, pulmonary edema, persistent headaches unresponsive to acetaminophen, and visual disturbances^{1,17}. Although the definitions of these conditions are clear, in a clinical setting, symptoms often overlap, complicating accurate diagnosis, especially in emergent cases and patients with additional chronic diseases. Moreover, routine laboratory findings do not

always reflect the severity of the disease. For instance, right upper quadrant pain due to hepatic cell edema, parenchymal necrosis, and distention of Glisson's capsule, or headaches resulting from endothelial cell instability and periventricular edema, are non-specific symptoms. Therefore, in patient management algorithms, the sensitivity, specificity, and rapid turnaround of diagnostic tests are crucial for timely and accurate diagnosis^{18–21}.

Results

Despite various studies on blood gas analysis in HDP, classical approaches have limited clinical adoption, highlighting the value of the Stewart method^{22–25}. Ortner et al.¹⁵, found no significant SID differences post-magnesium sulfate, initially viewed as a limitation. However, aligned with our findings, this suggests that SID may serve not only as a diagnostic marker but also as a tool to monitor treatment efficacy.

Clinical Implications

An ideal biomarker should be affordable, accessible, accurate, and yield rapid results. Venous blood gas analysis offers a reliable and practical alternative to arterial blood gas testing for electrolyte assessment^{26,27}. Additionally, calculating the SID from VBG results is straightforward, further enhancing its utility in managing complex clinical conditions.

Although Stewart's theory and SID may initially seem unrelated to the preeclampsia spectrum of diseases, understanding the physiology of normal membrane function –impermeable to proteins– is crucial for maintaining quantitative acid-base balance in Stewart's world²⁸. SID, as an independent variable, is notably affected in conditions like sepsis, where normal membrane functions are compromised is well-documented in the literature^{29,30}. Recognizing the shared pathophysiological mechanisms underlying both sepsis and preeclampsia –including endothelial dysfunction, coagulation abnormalities, micro-circulatory dysfunction, and end-organ damage– underpins our methodology. Thus, while the etiologies of sepsis and preeclampsia differ, it can be expected that the metabolic alterations in blood gas parameters and electrolyte concentrations result in comparable changes in SID.

Research Implications

Larger prospective studies are needed to validate SID cut-off values and confirm its clinical utility. Future research should compare SIDa values across the HDP spectrum to refine its diagnostic and monitoring roles.

Strengths and Limitations

This study highlights SID's diagnostic potential in distinguishing preeclampsia from gestational hypertension and its role in monitoring severe cases. Its retrospective design and small sample size limit causal inference and statistical power, especially between preeclampsia subgroups. Nonetheless, the findings suggest clinical value, warranting further investigation.

Conclusion

In conclusion, traditional bicarbonate-based analyses may not fully capture the complexities of acid-base disturbances observed in hypertensive disorders of pregnancy. Stewart's theory, incorporating SID and SIDa, offers a more comprehensive approach to understanding these imbalances. By integrating these advanced diagnostic methods, clinicians can achieve a more precise assessment of the patient's acid-base status, leading to more effective treatment strategies. This study contributes valuable insights by retrospectively analyzing blood gas parameters alongside clinical data, based on microangiopathy and its role in the preeclampsia spectrum of diseases. Identifying novel biomarkers such as SID may enhance risk stratification, enable early detection, and support personalized management approaches, ultimately reducing maternal morbidity and mortality. While this study lays a solid foundation, further research is necessary to address its limitations and expand upon these findings.

Declarations

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None.

Conflict of Interest

The authors declare no conflict of interest.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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