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Article

The Levels and Significance of Serum Sex Hormones, BMP-7, and RBP in Adult Male Patients With Primary Nephrotic Syndrome

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Abstract

Aims/Background: There remain significant challenges in assessing the risk of primary nephrotic syndrome (PNS) and concomitant acute kidney injury (AKI) in adult males. AKI is characterized by decreased glomerular filtration rate. This study investigates the levels of serum sex hormones, bone morphogenetic protein-7 (BMP-7), and retinol-binding protein (RBP) and their significance in adult male patients with PNS and concomitant AKI. **Methods**: This retrospective analysis enrolled 86 adult male PNS patients admitted to Wuxi No.2 People's Hospital between January 2020 and November 2023 as the PNS group, and 80 healthy adult males as the healthy group. Serum levels of sex hormones—estradiol (E2), testosterone (T), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)—as well as bone morphogenetic protein-7 (BMP-7) and RBP were compared between the two groups. Furthermore, PNS patients were stratified into PNS groups with or without AKI cohorts based on glomerular filtration rate. Additionally, the levels of these parameters were compared between the subgroups. **Results**: In the PNS group, the levels of E2 and RBP were 66.67 $\pm$ 18.87 pg/mL and 56.65 $\pm$ 17.23 mg/L, respectively, both significantly higher than those in the healthy group ($p < 0.05$). Conversely, FSH and BMP-7 levels were 3.84 $\pm$ 1.02 IU/L and 1.83 $\pm$ 0.44 ng/mL, respectively, both significantly lower than those in the healthy group ($p < 0.05$). Within the PNS group, patients with AKI demonstrated significantly higher E2 levels of 69.93 $\pm$ 9.95 pg/mL than non-AKI patients ($p < 0.05$). FSH and BMP-7 levels were substantially lower (3.45 $\pm$ 0.96 IU/L and 1.57 $\pm$ 0.35 ng/mL) than in non-AKI patients ($p < 0.05$). However, RBP level was considerably higher (62.23 $\pm$ 12.01 mg/L) in those with AKI ($p < 0.05$). Furthermore, serum creatinine (Scr), blood urea nitrogen (BUN), and cystatin C (Cys C) levels were 167.23 $\pm$ 34.43 µmol/L, 11.14 $\pm$ 2.23 mmol/L, and 2.02 $\pm$ 0.72 mg/L, respectively, all significantly higher in patients with AKI than in non-AKI ($p < 0.05$). Regression analysis identified E2, BMP-7, and RBP as independent predictors for assessing AKI risk in PNS patients, with corresponding odds ratios (ORs) (95% confidence interval (CI)) values of 1.092 (1.016–1.175), 0.021 (0.002–0.184), and 1.095 (1.032–1.162), respectively ($p < 0.05$). **Conclusion**: Male patients with PNS exhibit abnormal serum sex hormone, BMP-7, and RBP levels, which are associated with AKI. E2, BMP-7, and RBP levels demonstrate significant predictive potential in assessing AKI risk in PNS.

Keywords: nephrotic syndrome; males; gonadal hormones; bone morphogenetic protein-7; retinol-binding protein

1. Introduction

Primary nephrotic syndrome (PNS) is a clinical condition in which various factors increase glomerular capillary permeability, resulting in significant urinary loss of plasma proteins [1,2]. PNS incidence is higher in males than in females [3]. Patients with PNS are at risk of acute kidney injury (AKI), characterized by a decline in glomerular filtration rate, which poses a substantial challenge to its clinical management [4].

Currently, clinical diagnosis of PNS-related AKI relies mainly on kidney biopsy and assessment of serum creatinine levels. Although a kidney biopsy provides detailed pathological information, its invasive nature limits its widespread application [5]. On the other hand, the elevation of serum creatinine is often delayed and therefore cannot predict early kidney damage, making it suboptimal as an early warning indicator for PNS and AKI in adult males [6].

Previous studies have shown that estradiol (E2) and follicle-stimulating hormone (FSH) are associated with mesangial cell proliferation, podocyte apoptosis, immune activation, and renal interstitial fibrosis [7,8]. Similarly, bone morphogenetic protein-7 (BMP-7) exerts anti-fibrotic effects in the renal interstitium, promotes podocyte repair, and has anti-inflammatory properties. However, its expression is negatively correlated with the severity of kidney injury [9,10]. Retinol-binding protein (RBP), synthesized in the liver, is freely filtered at the glomerulus, with approximately 95% reabsorbed by the proximal tubules, and its expression level is positively correlated with the degree of renal tubular injury [11,12]. Although the evidence provides partial insights into the pathogenesis of PNS and AKI, systematic investigations into the associations between biomarkers such as E2, FSH, BMP-7, and RBP and PNS in adult males, and their application in assessing AKI risk in this population, remain limited.

Therefore, this study aims to compare the levels of these biomarkers in adult males with PNS and healthy adult males, as well as between PNS with and without AKI. By rigorously evaluating their relationships with AKI complicating PNS, the study seeks to provide more precise and reliable evidence to enhance clinical diagnosis and management.

2. Methods

2.1 Study Design and Recruitment of the Study Participants

This study adopted a retrospective analysis design, and the required sample size was calculated using the following formula.

$$n = \frac{2 \times \left(Z_{1-\alpha/2} + Z_{\beta}\right)^2 \times \sigma^2}{\left(\mu_1 - \mu_2\right)^2}$$

Where n represents the required sample size for each group, $Z_{1-\alpha/2}$ is the Z-score corresponding to the significance level α; in this study, $\alpha = 0.05$, so $Z_{1-\alpha/2} = 1.96$. Z_{β} is the Z-score corresponding to the type II error probability β; here, $\beta = 0.1$, so $Z_{\beta} = 1.28$. The μ_1 and μ_2 are the mean values of the core observation indicator in the two groups, and σ is the standard deviation of the core observation indicator between the two groups [13].

Using BMP-7 as the core observation indicator, a preliminary sample of 15 adult males with PNS and 15 healthy males was collected. The mean BMP-7 levels were 2.08 $\pm$ 0.48 and 4.42 $\pm$ 1.09, respectively, with a pooled standard deviation of 1.27. According to the sample size formula, the required number of individuals per group (PNS and control groups) was calculated as 6.18, which was rounded to 6 cases per group. Similarly, using BMP-7 as the core indicator, a preliminary cohort of 15 male PNS patients with AKI and 15 without AKI was collected. The mean BMP-7 levels were 1.52 $\pm$ 0.35 and 2.08 $\pm$ 0.48 in the AKI and non-AKI groups, respectively, with a pooled standard deviation of 0.62. The calculated sample size for each AKI and non-AKI PNS group was 25.7, which was rounded to 26 cases. According to preliminary test data, approximately 33% of male PNS patients had concurrent AKI. Therefore, at least 79 PNS male patients were planned to be enrolled in the study.

This retrospective study included 86 adult male patients with PNS who received treatment at Wuxi No.2 People's Hospital, China, between January 2020 and November 2023 as the PNS group.

Inclusion criteria for patient selection were as follows: (1) age $\geq$18 years; (2) diagnosis of PNS and AKI based on the criteria outlined in the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases [14]; (3) first-time diagnosis; (4) no previous treatment with glucocorticoids or immunosuppressive agents; and (5) availability of complete clinical data. However, the exclusion criteria included (1) presence of acute or chronic infectious diseases, malignancies, or autoimmune disorders; (2) history of alcohol or drug abuse; and (3) concomitant diabetes, hypertension, or hyperlipidemia.

Additionally, to control unnecessary research costs, 80 of 107 eligible healthy adult males were enrolled as the healthy group. The inclusion criteria for control individuals were: (1) age $\geq$18 years; (2) 24-hour urinary protein excretion $<$3.5 g, urine protein-to-creatinine ratio $<$2.0 mg/mg, and serum albumin $>$30 g/L; (3) no prior use of glucocorticoids or immunosuppressive agents. The exclusion criteria were similar for both cases and control groups. Selection process for the study participants is outlined in Fig. 1.

2.2 Experimental Method

A 3 mL fasting venous blood sample was collected from each participant and centrifuged at 3000 rpm for 5 minutes to obtain serum. Serum levels of E2, testosterone (T), FSH, luteinizing hormone (LH), and cystatin C (Cys C) were measured using an ADVIA Centaur XP automated chemiluminescence immunoassay system (version 3.2, Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA) with the following reagent kits: E2 kit (Beckman Coulter, Inc., Brea, CA, USA; Cat. No. HM2093), T kit (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA; Cat. No. 02789602), FSH kit (Suzhou Changguang Huayi Biomedical Engineering Co., Ltd., Suzhou, China; Cat. No. AE-480), LH kit (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA; Cat. No. LH-110758), and Cys C kit (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA; Cat. No. PH32953).

Furthermore, RBP and BMP-7 levels were determined using an HZ-96A enzyme-linked immunosorbent assay (ELISA) platform, with assay kits obtained by Siemens Healthcare Diagnostics Products GmbH (Marburg, Germany; RBP: Cat. No. CB455351; BMP-7: Cat. No. CHE0182-048). Blood urea nitrogen (BUN) and serum creatinine (Scr) levels were measured using a DxC 700 AU automated biochemical analyzer (Beckman Coulter, Inc., Brea, CA, USA) with BUN and Scr reagent kits (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA; BUN: Cat. No. BC1535; Scr: Cat. No. ZC100258). Estimated glomerular filtration rate (eGFR) was calculated from serum Scr using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [15]. eGFR = 141 $\times$ min (Scr/κ, 1)$^{\alpha}$ $\times$ max (Scr/κ, 1)$^{-1.209}$ $\times$ 0.993$^{\text{age}}$ $\times$ race coefficient. Where κ is 0.7 for females and 0.9 for males; α is –0.329 for females and –0.411 for males; the race coefficient is 1.159 for African Americans and 1.0 for other populations.

2.3 Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (International Business Machines Corporation,

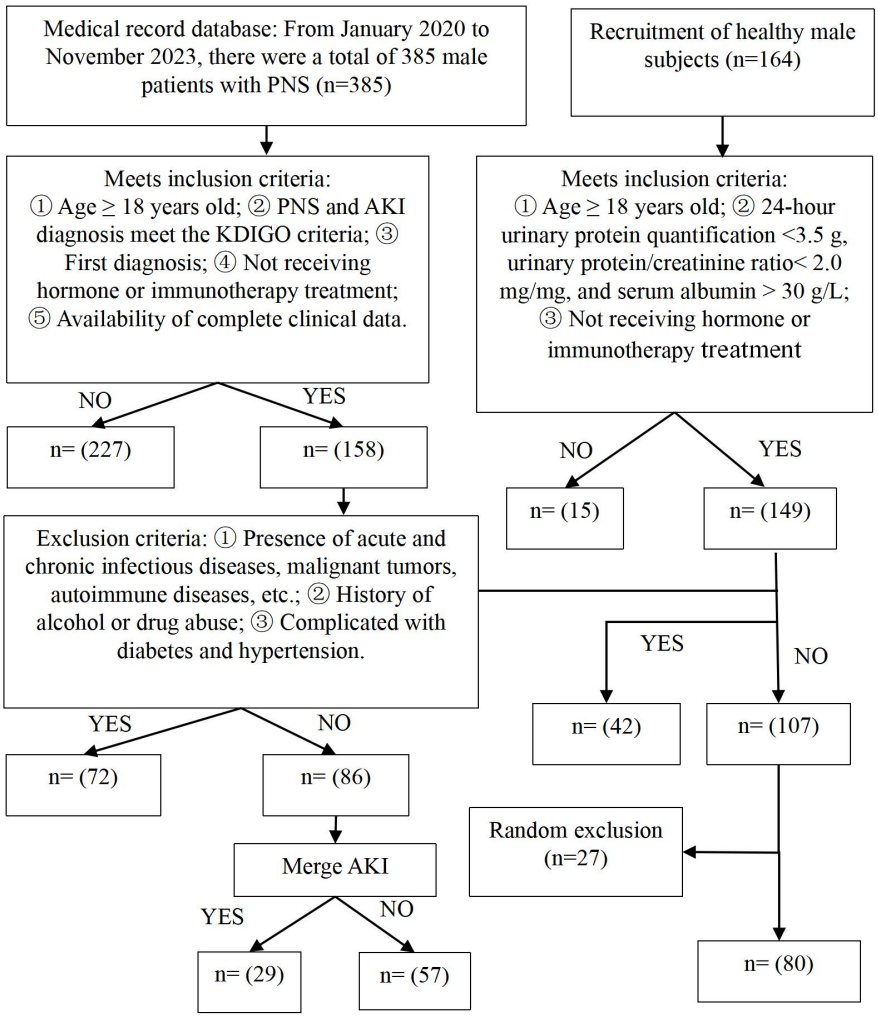

Fig. 1. A flowchart of the study participants' selection. PNS, primary nephrotic syndrome; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

Armonk, NY, USA). Measurement data were evaluated for normality using the Shapiro-Wilk test and were all confirmed to follow a normal distribution. These variables were presented as mean ± standard deviation ($\bar{x}$ ± s), and intergroup differences were analyzed using the independent-samples *t*-test. However, categorical variables were expressed as n (%), with intergroup differences analyzed using the chi-square test. Within the PNS groups, serum levels of E2, FSH, LH, T, BMP-7, and RBP were compared across subgroups with different clinical characteristics. Moreover, Scr, BUN, Cys C, and eGFR levels were assessed in PNS patients with acute kidney injury.

Furthermore, partial Pearson correlation analysis was conducted after adjusting for potential confounding factors, including age, body mass index (BMI), smoking history, and alcohol consumption. Variables with statistically significant differences in univariate analysis ($p < 0.05$) were included in the multivariable logistic regression model. Multicollinearity was assessed using the variance inflation factor (VIF), with VIF <5 indicating no severe multicollinearity. After excluding variables with collinearity, logistic regression analysis was used to determine the independent predictive value of each parameter for the occurrence of AKI in patients with PNS.

Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the performance of each parameter in assessing the risk of AKI in PNS patients, and optimal cutoff values were determined using the Youden index [16]. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Comparison of Baseline Characteristics Between the Two Groups

There were no statistically significant differences in age, body mass index, smoking history, or alcohol consumption between the PNS and healthy groups ($p > 0.05$, Table 1).

Table 1. Comparison of baseline characteristics between the two groups.

Group	Number of cases	Age (years)	Body mass index (kg/m^2)	Smoking (%)	Drinking (%)
PNS group	86	39.93 ± 9.92	21.82 ± 2.01	37 (43.02)	44 (51.16)
Healthy group	80	40.45 ± 9.17	22.04 ± 2.17	31 (38.75)	47 (58.75)
t/χ^2		–0.350	–0.678	0.313	0.963
p-value		0.727	0.499	0.576	0.326

Note: Measurement data were evaluated for normality using the Shapiro-Wilk test and were expressed as $\bar{x} \pm s$. Intergroup comparisons were performed using the independent-samples *t*-test. Categorical data were expressed as frequency (%), with intergroup comparisons performed using the chi-square test. A $p < 0.05$ was considered statistically significant.

Table 2. Comparison of serum sex hormones, BMP-7, and RBP levels between the two groups.

Group	Number of cases	E2 (pg/mL)	FSH (IU/L)	LH (IU/L)	T (ng/mL)	BMP-7 (ng/mL)	RBP (mg/L)
PNS group	86	66.67 ± 18.87	3.84 ± 1.02	5.22 ± 1.43	5.26 ± 1.03	1.83 ± 0.44	56.65 ± 17.23
Healthy group	80	35.54 ± 10.20	6.65 ± 1.14	4.81 ± 1.28	5.02 ± 1.11	5.12 ± 0.99	31.14 ± 9.92
t		13.083	–16.759	1.941	1.399	–27.925	11.576
p-value		<0.001	<0.001	0.054	0.164	<0.001	<0.001

Note: Measurement data were assessed for normality using the Shapiro-Wilk test and were expressed as $\bar{x} \pm s$. Intergroup comparisons were performed using the independent-samples *t*-test. A $p < 0.05$ was considered statistically significant. BMP-7, bone morphogenetic protein-7; RBP, retinol-binding protein; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; T, testosterone.

Table 3. Comparison of serum sex hormone levels in PNS patients stratified by age, BMI, pathological type, and AKI status.

Clinical characteristic	Number of cases	E2 (pg/mL)	FSH (IU/L)	LH (IU/L)	T (ng/mL)
Age					
<40 years	43	65.82 ± 10.20	3.86 ± 0.92	5.18 ± 1.02	5.30 ± 0.99
≥40 years	43	67.40 ± 11.43	3.82 ± 0.99	5.25 ± 1.06	5.22 ± 1.00
t		–0.676	0.194	–0.312	0.390
p-value		0.501	0.847	0.756	0.698
Body mass index					
<22 kg/m^2	48	66.45 ± 9.93	3.80 ± 0.97	5.29 ± 1.00	5.30 ± 1.05
≥22 kg/m^2	38	66.91 ± 10.04	3.88 ± 0.98	5.14 ± 0.99	5.20 ± 1.13
t		–0.212	–0.378	0.694	0.427
p-value		0.832	0.706	0.490	0.670
Pathological type					
Membranous nephropathy	58	66.31 ± 10.54	3.79 ± 0.92	5.26 ± 0.93	5.35 ± 1.00
Other	28	67.34 ± 11.15	3.93 ± 0.97	5.15 ± 0.96	5.09 ± 1.04
t		–0.417	–0.650	0.509	1.091
p-value		0.678	0.518	0.612	0.278
Acute kidney injury					
Yes	29	69.93 ± 9.95	3.45 ± 0.96	5.26 ± 1.05	5.28 ± 0.99
No	57	64.82 ± 10.00	4.06 ± 0.98	5.20 ± 1.01	5.25 ± 1.00
t		2.244	–2.747	0.257	0.136
p-value		0.027	0.007	0.798	0.892

Note: In the "Pathological type" category, "other" includes pathological types such as minimal change disease and focal segmental glomerulosclerosis, excluding membranous nephropathy. Measurement data were evaluated for normality using the Shapiro-Wilk test and were expressed as $\bar{x} \pm s$. Intergroup comparisons were performed using the independent-samples *t*-test. A $p < 0.05$ was considered statistically significant. BMI, body mass index.

3.2 Comparison of Serum Sex Hormones, BMP-7, and RBP Levels Between the Two Groups

E2, FSH, BMP-7, and RBP levels showed statistically significant differences between the PNS and healthy groups ($p < 0.05$). Specifically, E2 and RBP levels were substantially higher in the PNS group than in the healthy group ($p < 0.05$), whereas FSH and BMP-7 levels were lower in the PNS group ($p < 0.05$). Conversely, there were no considerable differences in LH and T levels between groups ($p > 0.05$, Table 2).

Table 4. Comparison of serum BMP-7 and RBP levels among PNS patients stratified by age, BMI, pathological type, and AKI status.

Clinical characteristics	Number of cases	BMP-7 (ng/mL)	RBP (mg/L)
Age			
<40 years	43	1.85 ± 0.35	57.03 ± 11.65
≥40 years	43	1.81 ± 0.36	56.32 ± 12.54
t		0.416	0.272
p-value		0.678	0.786
Body mass index			
<22 kg/m^2	48	1.84 ± 0.36	56.15 ± 12.25
≥22 kg/m^2	38	1.82 ± 0.37	57.20 ± 11.83
t		0.290	–0.401
p-value		0.772	0.690
Pathological type			
Membranous nephropathy	58	1.81 ± 0.37	55.34 ± 10.54
Other	28	1.86 ± 0.39	59.08 ± 11.16
t		–0.531	–1.513
p-value		0.597	0.134
Acute kidney injury			
Yes	29	1.57 ± 0.35	62.23 ± 12.01
No	57	1.98 ± 0.37	53.48 ± 11.82
t		–5.001	3.228
p-value		<0.001	0.002

Note: Measurement data were evaluated for normality using the Shapiro-Wilk test and were expressed as $\bar{x} \pm s$. Intergroup comparisons were performed using the independent-samples *t*-test. A $p < 0.05$ was considered statistically significant.

3.3 Comparison of Serum Sex Hormones Across Subgroups of Patients With Different Clinical Characteristics Within the PNS Group

There were no statistically significant differences in serum E2, FSH, LH, and T levels among PNS patients stratified by age, body mass index, or pathological type ($p > 0.05$). Within the PNS group, patients with AKI had higher E2 levels than those without AKI ($p < 0.05$), whereas FSH levels were lower in patients with AKI compared with those without ($p < 0.05$). Differences in LH and T levels between PNS patients with and without AKI were not significant ($p > 0.05$, Table 3).

3.4 Comparison of Serum BMP-7 and RBP Levels Across Subgroups of Patients With Different Clinical Characteristics Within the PNS Group

There was no significant difference in serum BMP-7 and RBP levels among PNS patients when stratified by age, body mass index, and pathological subtype ($p > 0.05$). However, within the PNS group, patients with AKI had substantially lower BMP-7 levels than those without AKI ($p < 0.05$), whereas RBP levels were higher in patients with AKI than in those without ($p < 0.05$, Table 4).

3.5 Comparison of Scr, BUN, Cys C, and eGFR Levels in Patients With and Without AKI Within the PNS Group

Within the PNS group, patients with AKI had higher Scr, BUN, eGFR and Cys C levels than those without AKI ($p < 0.05$, Table 5).

3.6 Correlation Between Serum Sex Hormones, BMP-7, RBP, and Renal Function Indices

After adjusting for potential confounding factors, including age, BMI, smoking history, and alcohol consumption, partial Pearson correlation analysis revealed that BMP-7 was negatively correlated with Scr, BUN, and Cys C, and positively correlated with eGFR ($p < 0.05$). In contrast, E2 and RBP were positively correlated with Scr, BUN, and Cys C, and negatively correlated with eGFR ($p < 0.05$). However, no significant associations were observed for the remaining variables ($p > 0.05$, Table 6).

3.7 The Role of Serum Sex Hormones, BMP-7, and RBP as Independent Factors Associated With AKI Risk in PNS Patients

The four indicators that demonstrated statistically significant differences between PNS patients with and without AKI in the univariate analysis (E2, FSH, BMP-7, and RBP) were included in further modeling. Multicollinearity analysis showed that these four indicators had VIF values <5.0, indicating no serious multicollinearity; therefore, they were included in the multivariable logistic regression analysis.

Multivariable logistic regression analysis revealed that E2, BMP-7, and RBP levels were independently associated with the risk of AKI in PNS patients ($p < 0.05$), with odds ratios (ORs) (95% confidence interval (CI)) of 1.092 (1.016–1.175), 0.021 (0.002–0.184), and 1.095 (1.032–1.162), respectively. FSH was not an independent indicator

Table 5. Comparison of Scr, BUN, Cys C, and eGFR levels among PNS patients stratified by AKI status.

Acute kidney injury	Number of cases	Scr (μmol/L)	BUN (mmol/L)	Cys C (mg/L)	eGFR (mL/min/1.73 m^2)
Yes	29	167.23 ± 34.43	11.14 ± 2.23	2.02 ± 0.72	52.75 ± 17.83
No	57	89.92 ± 11.12	5.76 ± 1.01	0.89 ± 0.22	87.54 ± 22.76
t		15.510	15.427	10.940	–6.826
p-value		<0.001	<0.001	<0.001	<0.001

Note: Measurement data were assessed for normality using the Shapiro-Wilk test and were expressed as $\bar{x} \pm s$. Intergroup comparisons were performed using the independent-samples *t*-test. A $p < 0.05$ was considered statistically significant. Scr, serum creatinine; BUN, blood urea nitrogen; Cys C, cystatin C; eGFR, estimated glomerular filtration rate.

Table 6. Correlation between serum sex hormones, BMP-7, RBP, and renal function indices.

	Scr	BUN	Cys C	eGFR
E2	0.270[a]	0.213[a]	0.294[a]	–0.252[a]
FSH	–0.084	–0.138	–0.154	0.042
LH	0.038	0.100	0.016	0.115
T	–0.056	–0.025	0.003	–0.047
BMP-7	–0.328[a]	–0.289[a]	–0.265[a]	0.319[a]
RBP	0.264[a]	0.313[a]	0.254[a]	–0.196[a]

Note: Pearson correlation analysis was performed with age, BMI, smoking history, and alcohol consumption as control variables; [a], the correlation analysis showed $p < 0.05$.

of AKI risk in PNS patients ($p > 0.05$), with an OR (95% CI) of 0.511 (0.248–1.051). Findings from logistic regression analysis are summarized in Table 7.

3.8 The Role of Serum Sex Hormones, BMP-7, and RBP in the Differential Diagnosis of AKI

Receiver operating characteristic (ROC) curve analysis showed that the areas under the curve (AUC, 95% CI) for E2, BMP-7, and RBP in assessing AKI risk were 0.829 (0.733–0.926), 0.900 (0.833–0.966), and 0.725 (0.609–0.841), respectively ($p < 0.05$) (Fig. 2 and Table 8).

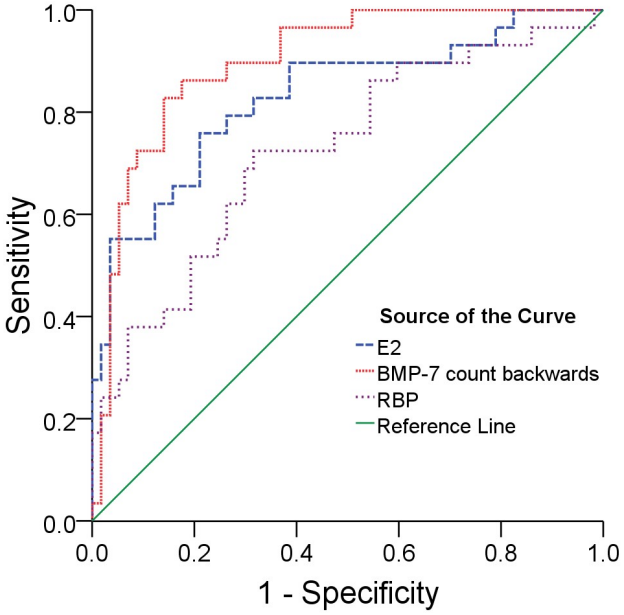

Fig. 2. ROC curve parameters of E2, BMP-7, and RBP in the diagnosis of AKI. Note: The BMP-7 count backwards calculation method is 1/BMP-7.

4. Discussion

PNS is an immune-inflammatory kidney disease in adults, often complicated by infections, which can reduce glomerular filtration rate or impair tubular reabsorption, thereby affecting life [17]. In this study, we analyzed serum sex hormone levels in adult males with PNS and found significantly higher E2 levels and substantially lower FSH levels than in the healthy group. These findings indicate a pronounced disruption of sex hormone homeostasis in PNS patients, characterized by elevated E2 and reduced FSH levels. This imbalance has been reported to have a profound impact on kidney disease on the sex hormone secretion system [18].

The findings of this study are consistent with previous research reporting altered sex hormone levels in patients with nephrotic syndrome [19]. E2, through its interaction with estrogen receptors, regulates the activity of multiple organ systems. In the context of PNS, elevated E2 levels may represent a feedback protective mechanism, reversing renal fibrosis and preserving kidney function by downregulating the expression of mesangial cell adhesion molecules and inhibiting the activity of transforming growth factor-β [20,21].

Additionally, the onset of PNS can disrupt the regulation of the hypothalamic-pituitary-gonadal axis, leading to decreased FSH secretion [22]. Current evidence suggests that PNS may also alter LH and T levels by affecting gonadal axis function [23]. In contrast, the present study did not find statistically significant differences in LH and T levels between adult males with PNS and healthy controls. This result may reflect the impact of PNS on specific components of the gonadal axis, suggesting that its effects on LH and T are relatively limited [24].

This study revealed that RBP levels in adult male PNS patients were higher than in healthy controls, whereas BMP-7 levels were significantly lower. Under physiological conditions, this low-molecular-weight protein is

Table 7. Multivariable logistic regression analysis of serum sex hormones, BMP-7, and RBP in PNS complicated by AKI.

	β	SE	Wald	p-value	OR (95% CI)
E2	0.088	0.037	5.722	0.017	1.092 (1.016–1.175)
FSH	–0.672	0.368	3.330	0.068	0.511 (0.248–1.051)
BMP-7	–3.843	1.098	12.260	<0.001	0.021 (0.002–0.184)
RBP	0.091	0.030	8.907	0.003	1.095 (1.032–1.162)
Constant	–1.450	3.954	0.134	0.714	

Note: Multivariate logistic regression analysis was used; A $p < 0.05$ was considered statistically significant. OR, odds ratio; CI, confidence interval; SE, standard error.

Table 8. ROC curve analysis of E2, BMP-7, and RBP in the diagnosis of AKI.

Indicator	Areas under the curve (95% CI)	p-value	Cutoff value	Sensitivity	Specificity
E2	0.829 (0.733–0.926)	<0.001	68.67 pg/mL	0.759	0.782
BMP-7	0.900 (0.833–0.966)	<0.001	1.73 ng/mL	0.828	0.861
RBP	0.725 (0.609–0.841)	<0.001	59.59 mg/L	0.725	0.685

Note: Cutoff values were determined by maximizing the Youden index. A $p < 0.05$ was considered statistically significant. ROC, receiver operating characteristic.

mainly reabsorbed by proximal tubular epithelial cells; elevated RBP levels indicate impaired glomerular filtration and tubular reabsorption and may contribute to the onset of primary nephrotic syndrome [25]. Previous research has shown that increased RBP is a predictor of disrupted renal filtration and reabsorption, and the present study further supports its role as a sensitive indicator of tubular function in PNS patients [26].

BMP-7 is predominantly expressed in podocytes, distal renal tubules, and collecting ducts [27]. Reduced BMP-7 expression promotes epithelial-to-mesenchymal transition in tubular epithelial cells and exacerbates podocyte injury, thereby accelerating renal fibrosis, a key pathogenic mechanism in PNS. The decreased BMP-7 levels observed in this study are consistent with these pathological characteristics and suggest that changes in BMP-7 may serve as an important diagnostic biomarker for PNS.

In male patients with PNS complicated by AKI, E2 levels were significantly higher, and FSH levels were substantially lower than in those without AKI. One underlying mechanism may be that E2 enhances immune defence by activating lymphocytes and promoting immunoglobulin production against exogenous pathogens; however, an excessive immune activation may exacerbate renal inflammation, trigger glomerulonephritis and related lesions, and thereby promote the onset of AKI in PNS [28]. Although E2 exerts renoprotective effects, such as inhibiting mesangial cell adhesion molecule expression and alleviating fibrosis, these beneficial effects may be disrupted in PNS patients who develop AKI, resulting in aggravated kidney injury [29].

Furthermore, decreased FSH levels may be a key contributor to the development of AKI. FSH plays a crucial role in maintaining testicular function and sex hormone balance, and its reduction may impair androgen synthesis and secretion, thereby disrupting normal regulation of cellular proliferation and apoptosis [30]. This disruption can diminish anti-fibrotic capability and weaken renal self-repair mechanisms, further accelerating AKI progression.

Our study findings found that BMP-7 levels were significantly decreased in adult male PNS patients complicated by AKI. This reduction is directly associated with tubular epithelial-mesenchymal transition (EMT) and podocyte injury, indicating impairment of the kidney's intrinsic protective barrier, loss of functional homeostasis, accelerated renal fibrosis, and exacerbated PNS pathology [31]. Concurrently, RBP levels were markedly elevated in these patients, reflecting compromised reabsorptive capacity of injured renal tubules and supporting the potential of RBP as a sensitive early warning biomarker for AKI in this cohort.

Additionally, we observed that compared with PNS patients without AKI, those with concurrent AKI exhibited significantly higher serum Scr, BUN, and Cys C levels, along with a substantially lower eGFR. These observations confirm significant renal dysfunction in PNS patients who develop AKI. The elevations in Scr, BUN, and Cys C directly reflect reduced renal capability to remove metabolic wastes, while the significant decline in eGFR largely reflects AKI-induced reductions in renal blood flow, dysfunction of the glomerular filtration membrane, and potential tubular obstruction, collectively leading to a sharp decrease in nephron function. Notably, correlation analysis revealed that BMP-7 levels were negatively associated with Scr, BUN, and Cys C, whereas E2 and RBP levels were positively linked to these renal function parameters. A decrease in BMP-7 indicates impaired renal protective mechanisms, facilitating the accumulation of metabolic waste products such as Scr, BUN, and Cys C. In contrast, elevated RBP levels directly reflect diminished renal excretory function, showing a trend consistent with the accumulation

of metabolic waste products [32,33]. The positive correlation between E2 levels and markers of renal dysfunction observed in this study may reflect an inadequate compensatory response to renal injury, wherein the protective mechanisms of E2 become overwhelmed in the setting of severe tubular damage and oxidative stress—a phenomenon described as hormonal resistance in other inflammatory conditions [34,35].

Regression analysis revealed that E2, BMP-7, and RBP were significantly associated with the onset of AKI in patients with PNS. Elevated E2 and RBP levels, along with reduced BMP-7 levels, were all linked to an increased risk of AKI in PNS patients. In contrast, FSH, LH, and T showed no statistically significant associations with PNS complicated by AKI, suggesting that E2, BMP-7, and RBP may serve as key indicators for assessing AKI risk in PNS patients, whereas FSH, LH, and T may have comparatively weaker associations. Similarly, ROC curve analysis further demonstrated that the AUC (95% CI) for E2, BMP-7, and RBP in diagnosing PNS complicated by AKI were 0.829 (0.733–0.926), 0.900 (0.833–0.966), and 0.725 (0.609–0.841), respectively. These findings indicate that all three markers have high potential for evaluating AKI risk in PNS and may offer new insights into understanding the mechanisms of acute kidney injury in adult male patients with PNS.

However, as this was a retrospective study, longitudinal time-series data and interventional evidence were not available to explore in depth the causal relationships and underlying mechanisms linking serum sex hormones, BMP-7, and RBP with the onset and progression of PNS, as well as with PNS complicated by AKI. Our findings can therefore only confirm that these parameters differ between male PNS patients with AKI, those without AKI, and healthy males, and that E2, BMP-7, and RBP are associated with the onset of AKI in PNS. Moreover, although the sample size was formally determined, the estimation was based solely on BMP-7 as the core parameter, which may have resulted in insufficient statistical power for other indicators. Furthermore, all participants were obtained from a single hospital, potentially limiting the generalizability of these results to broader patient populations in other regions. Future studies should include larger sample sizes and adopt a multicenter, prospective observational study design and interventional trials to further elucidate the relationships between serum sex hormones, BMP-7, and RBP, and the development and progression of PNS and its complications with AKI.

5. Conclusion

In conclusion, adult male PNS patients demonstrate significantly abnormal levels of serum sex hormones, BMP-7, and RBP, and these changes are closely related to the occurrence of AKI. E2, BMP-7, and RBP serve as reference indicators for assessing AKI risk in patients with PNS. In clinical practice, managing these biomarkers and implementing early intervention approaches based on their levels may reduce the risk of AKI in patients with PNS.

Key Points

• Compared with healthy adult males, those with PNS exhibited elevated levels of E2 and RBP but lower levels of FSH and BMP-7.

• Compared with PNS adult male patients without AKI, those with AKI had higher E2 and RBP levels and lower BMP-7 and FSH levels.

• E2, BMP-7, and RBP are independent predictors of AKI in adult male PNS patients. Combining these parameters can enhance risk assessment.

• Future studies should expand the sample size and examine whether the correlations of E2, BMP-7, and RBP with disease progression and AKI in adult male patients with PNS in different regions and ethnic groups.

• We recommend routine monitoring of E2, BMP-7, and RBP levels in these patients to enable timely assessment of AKI risk.

Abbreviations

PNS, primary nephrotic syndrome; AKI, acute kidney injury; E2, estradiol; FSH, follicle-stimulating hormone; BMP-7, bone morphogenetic protein-7; RBP, retinol-binding protein; T, testosterone; LH, luteinizing hormone; Cys C, cystatin C; BUN, blood urea nitrogen; Scr, serum creatinine; eGFR, estimated glomerular filtration rate.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

YZ and LZ designed the research study and wrote the first draft. YZ and LZ performed the research. YZ and LZ analyzed the data. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Review Committee of Wuxi No.2 People's Hospital (Approval No.: 2020-Y-7) and was conducted in accordance with the principles of the Declaration of Helsinki. All patients participated voluntarily and provided written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Li X, Liu Z, Guo Y. Primary nephrotic syndrome presenting initially as severe abdominal pain. International Urology and Nephrology. 2023; 55: 1647–1648. https://doi.org/10.1007/s11255-023-03486-4.

[2] Nagai K. Immunosuppressive Agent Options for Primary Nephrotic Syndrome: A Review of Network Meta-Analyses and Cost-Effectiveness Analysis. Medicina. 2023; 59: 601. https://doi.org/10.3390/medicina59030601.

[3] Li Y, Yu X, Zhang W, Lv J, Lan P, Wang Z, *et al*. Epidemiological characteristics and pathological changes of primary glomerular diseases. PLoS ONE. 2022; 17: e0272237. https://doi.org/10.1371/journal.pone.0272237.

[4] Lionaki S, Liapis G, Boletis JN. Pathogenesis and Management of Acute Kidney Injury in Patients with Nephrotic Syndrome Due to Primary Glomerulopathies. Medicina (Kaunas). 2019; 55: 365. http://doi.org/10.3390/medicina55070365.

[5] Wada T, Shimizu S, Koizumi M, Sofue T, Nishiwaki H, Sasaki S, *et al*. Japanese clinical practice patterns of primary nephrotic syndrome 2021: a web-based questionnaire survey of certified nephrologists. Clinical and Experimental Nephrology. 2023; 27: 767–775. https://doi.org/10.1007/s10157-023-02366-6.

[6] Ostermann M, Legrand M, Meersch M, Srisawat N, Zarbock A, Kellum JA. Biomarkers in acute kidney injury. Annals of Intensive Care. 2024; 14: 145–153. https://doi.org/10.1186/s13613-024-01360-9.

[7] Zhang K, Xia F, Chen Y, Zhang W, Wang C, Wang N, *et al*. MON-226 FSH Promotes Renal Tubulointerstitial Fibrosis Via AKT/GSK-3beta/beta-catenin Pathway. Journal of the Endocrine Society. 2019; 3: MON-226. https://doi.org/10.1210/js.2019-MON-226.

[8] Doublier S, Lupia E, Catanuto P, Periera-Simon S, Xia X, Korach K, *et al*. Testosterone and 17β-estradiol have opposite effects on podocyte apoptosis that precedes glomerulosclerosis in female estrogen receptor knockout mice. Kidney International. 2011; 79: 404–413. https://doi.org/10.1038/ki.2010.398.

[9] Peng W, Zhou X, Xu T, Mao Y, Zhang X, Liu H, *et al*. BMP-7 ameliorates partial epithelial-mesenchymal transition by restoring SnoN protein level via Smad1/5 pathway in diabetic kidney disease. Cell Death & Disease. 2022; 13: 254. https://doi.org/10.1038/s41419-022-04529-x.

[10] Manson SR, Song JB, Guo Q, Liapis H, Austin PF. Cell type specific changes in BMP-7 expression contribute to the progression of kidney disease in patients with obstructive uropathy. The Journal of Urology. 2015; 193: 1860–1869. https://doi.org/10.1016/j.juro.2014.10.117.

[11] Araumi A, Osaki T, Ichikawa K, Kudo K, Suzuki N, Watanabe S, *et al*. Urinary and plasma proteomics to discover biomarkers for diagnosing between diabetic nephropathy and minimal change nephrotic syndrome or membranous nephropathy. Biochemistry and Biophysics Reports. 2021; 27: 101102. https://doi.org/10.1016/j.bbrep.2021.101102.

[12] Vinogradov AA, Chebotareva NV, Bugrova AE, Brzhozovskiy AG, Krasnova TN, Nasibullina KZ, *et al*. Study of urinary markers of different podocytopathies by proteomic analysis. Terapevticheskii Arkhiv. 2023; 95: 457–461. https://doi.org/10.26442/00403660.2023.06.202266.

[13] Kim HY. Statistical notes for clinical researchers: Sample size calculation 1. comparison of two independent sample means. Restorative Dentistry & Endodontics. 2016; 41: 74–78. https://doi.org/10.5395/rde.2016.41.1.74.

[14] Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, *et al*. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. Kidney International. 2021; 100: 753–779. https://doi.org/10.1016/j.kint.2021.05.015.

[15] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, *et al.* A new equation to estimate glomerular filtration rate. Annals of Internal Medicine. 2009; 150: 604–616. https://doi.org/10.7326/0003-4819-150-9-200905050-00006.

[16] Samawi H, Chen DG, Yin J, Alsharman M. Performance of diagnostic tests based on continuous bivariate markers. Journal of Applied Statistics. 2022; 51: 497–514. https://doi.org/10.1080/02664763.2022.2137478.

[17] von Groote TC, Williams G, Au EH, Chen Y, Mathew AT, Hodson EM, *et al*. Immunosuppressive treatment for primary membranous nephropathy in adults with nephrotic syndrome. The Cochrane Database of Systematic Reviews. 2021; 11: CD004293. https://doi.org/10.1002/14651858.CD004293.pub4.

[18] Fang Y, Gu Q, Jia J, Yan T. A Mendelian Randomization Study on the Association Between Sex Hormone-Binding Globulin and Membranous Nephropathy Risk. Nephrology. 2025; 30: e70049. https://doi.org/10.1111/nep.70049.

[19] Turgut M, Hatemi HH. Hormone-binding proteins and their associated hormones in patients with nephrotic syndrome. Annals of Clinical and Analytical Medicine. 2024; 15: 536–539. http://doi.org/10.4328/ACAM.22074.

[20] Jog NR, Caricchio R. 17β estradiol regulates adhesion molecule expression in mesangial cells during glomerulonephritis. Clinical Immunology. 2015; 159: 13–22. http://doi.org/10.1016/j.clim.2015.04.009.

[21] Ren L, Li F, Di Z, Xiong Y, Zhang S, Ma Q, *et al*. Estradiol Ameliorates Acute Kidney Ischemia-Reperfusion Injury by Inhibiting the TGF-βRI-SMAD Pathway. Frontiers in Immunology. 2022; 13: 822604. https://doi.org/10.3389/fimmu.2022.822604.

[22] Mizdrak M, Smajic B, Mizdrak I, Ticinovic Kurir T, Kumric M, Paladin I, *et al*. Endocrine Disorders in Nephrotic Syndrome-A Comprehensive Review. Biomedicines. 2024; 12: 1860. https://doi.org/10.3390/biomedicines12081860.

[23] Bhaduri M, Sarris I, Hysi P, Nicolaides K, Baird F, Bramham K. Impact of CKD on Female Reproductive Hormones. Kidney International Reports. 2025; 10: 2178–2188. https://doi.org/10.1016/j.ekir.2025.05.003.

[24] Li G, Xu Z, Yang H, Zhang D, Liu B, Song Y, *et al*. Sex-specific mechanisms in the pathogenesis and progression of chronic kidney disease. Autoimmunity Reviews. 2026; 25: 103938. https://doi.org/10.1016/j.autrev.2025.103938.

[25] Lin L, Wang WM, Pan XX, Xu J, Gao CN, Zhang W, *et al*. Biomarkers to detect membranous nephropathy in Chinese patients. Oncotarget. 2016; 7: 67868–67879. https://doi.org/10.18632/oncotarget.12014.

[26] Chen Q, Xu J, Liu L, Ye Q, Lin W, Liao Y, *et al*. Proteomic Analysis of Idiopathic Nephrotic Syndrome Triggered by Primary Podocytopathies in Adults: Regulatory Mechanisms and Diagnostic Implications. Journal of Proteome Research. 2024; 23: 2090–2099. https://doi.org/10.1021/acs.jproteome.4c00074.

[27] Wetzel P, Haag J, Câmpean V, Goldschmeding R, Atalla A, Amann K, *et al*. Bone morphogenetic protein-7 expression and activity in the human adult normal kidney is predominantly localized to the distal nephron. Kidney International. 2006; 70: 717–723. https://doi.org/10.1038/sj.ki.5001653.

[28] Foresto-Neto O, Menezes-Silva L, Leite JA, Andrade-Silva M, Câmara NOS. Immunology of Kidney Disease. Annual Review of Immunology. 2024; 42: 207–233. https://doi.org/10.1146/an

nurev-immunol-090122-045843.
[29] Nasr MK, Schurmann C, Böttinger EP, Teumer A. Mendelian randomization indicates causal effects of estradiol levels on kidney function in males. Frontiers in Endocrinology. 2023; 14: 1232266. https://doi.org/10.3389/fendo.2023.1232266.
[30] Sawaied A, Levy BE, Arazi E, Lunenfeld E, Shi Q, Huleihel M. Follicle-Stimulating Hormone and Testosterone Play a Role in the Regulation of Sertoli Cell Functions Following Germ Cell Depletion In Vitro. International Journal of Molecular Sciences. 2025; 26: 2702. https://doi.org/10.3390/ijms260627022
[31] Manzano-Lista FJ, Sanz-Gómez M, González-Moreno D, Vega-Martín E, Gil-Ortega M, Schulz A, *et al*. Imbalance in Bone Morphogenic Proteins 2 and 7 Is Associated with Renal and Cardiovascular Damage in Chronic Kidney Disease. International Journal of Molecular Sciences. 2022; 24: 40. https://doi.org/10.3390/ijms24010040.
[32] Jeon HJ, Shin DH, Oh J, Kee YK, Park JY, Ko K, *et al*. Urinary Retinol-Binding Protein 4 is Associated With Renal Function and Rapid Renal Function Decline in Kidney Transplant Recipients. Transplantation Proceedings. 2022; 54: 362–366. https://doi.org/10.1016/j.transproceed.2021.10.028.
[33] Huang J, Liu J, Liu W. Correlations of Serum Retinol-Binding Protein and Stromal Cell-Derived Factor-1 with Renal Function in Patients with Diabetic Kidney Disease. Clinical Laboratory. 2024; 70: 10.7754/Clin.Lab.2023.211254. https://doi.org/10.7754/Clin.Lab.2023.211254.
[34] Wu S, Zhuang L, Gan B. Oestradiol-mediated ferroptosis defense shapes sex differences in acute kidney injury. Cell Death & Differentiation. 2026; 33: 428–430. https://doi.org/10.1038/s41418-025-01573-w.
[35] Ural Z. Sexual Dimorphism in Renal Progenitors: Do Immunosuppressants Erase the Female Advantage? Transplant International. 2026; 39: 16092. https://doi.org/10.3389/ti.2026.16092.