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Urology Research

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Clinical Study on Delaying the Progression of Diabetic Kidney Disease by Inhibiting Excessive Reactive Oxygen Species Production through Alleviating Renal Inflammation and Fibrosis

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Abstract: *Objective:* To investigate the intervention effect of inhibiting excessive reactive oxygen species (ROS) production on renal inflammation, fibrosis, and disease progression in patients with diabetic kidney disease (DKD). *Methods:* Thirty DKD patients treated at the Department of Nephrology, Hebei University Affiliated Hospital from April 2025 to April 2026 were enrolled as the DKD group. Thirty non-DKD patients from the same period served as the control group. General characteristics and clinical indicators were collected for both groups, including complete blood count, liver and kidney function, electrolytes, blood glucose, and 24-hour urine protein quantification. Serum NLRP3 inflammasome and inflammatory factors (IL-1 β , IL-18, TNF- α , IL-6) were measured using ELISA. Transforming growth factor- β (TGF- β) was assessed to evaluate fibrosis severity. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. Differences in indicators between groups were compared, and correlations between ROS-related pathway markers and renal function/disease progression endpoints were analyzed. Primary endpoint: eGFR decline $\geq 40\%$ or initiation of dialysis. Secondary endpoints: doubling of random urine albumin-to-creatinine ratio (UACR) or occurrence of cardiovascular events. *Results:* Patients in the DKD group exhibited significantly higher serum levels of NLRP3, IL-1 β , IL-18, TNF- α , IL-6, and TGF- β compared to the control group ($p < 0.05$). Their eGFR was significantly lower than the control group ($p < 0.05$), while 24-hour urine protein quantification and UACR were significantly higher than the control group ($p < 0.05$). Correlation analysis revealed that NLRP3 and TGF- β levels were negatively correlated with eGFR ($r = -0.682, -0.715, p < 0.05$) and positively correlated with 24-hour urine protein quantification ($r = 0.654, 0.691, p < 0.05$). During follow-up, the incidence of primary endpoint events in the DKD group was 26.67% (8/30), and that of secondary endpoint events was 36.67% (11/30), both significantly higher than in the control group ($p < 0.05$). *Conclusion:* Excessive ROS production may promote renal inflammation and fibrosis by activating the NLRP3 inflammasome pathway. Inhibiting excessive ROS production holds promise as an effective intervention target for delaying DKD progression.

Keywords: Diabetic kidney disease; Reactive oxygen species; Inflammatory response; Renal fibrosis; NLRP3 inflammasome

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1. Introduction

Diabetic kidney disease (DKD) is the most common microvascular complication of diabetes and the leading cause of end-stage renal disease (ESRD) globally ^[1]. According to 2024 data from the International Diabetes Federation (IDF), there are over 530 million people with diabetes worldwide, with approximately 30–40% of these patients progressing to DKD ^[2]. Pathologically, DKD is characterized by thickening of the glomerular basement membrane, mesangial matrix proliferation, glomerulosclerosis, and renal interstitial fibrosis. Clinically, it commonly manifests as proteinuria and progressive renal function decline, ultimately requiring dialysis or kidney transplantation for survival. This imposes a heavy burden on patients' families and the healthcare system ^[3].

Reactive oxygen species (ROS) are highly active oxygen derivatives generated during cellular metabolism, including superoxide anion, hydrogen peroxide, hydroxyl radical, and others ^[4]. Under physiological conditions, ROS participate in normal processes such as cellular signaling and immune regulation, with their production and clearance maintaining a dynamic equilibrium. However, in pathological states, oxidative stress resulting from excessive ROS production or impaired clearance represents a key mechanism in DKD pathogenesis ^[5]. Basic research has demonstrated that a high-glucose environment induces excessive ROS production in renal cells through multiple pathways, including mitochondrial electron transport chain dysfunction, activation of the polyol pathway, and accumulation of advanced glycation end products ^[6]. Excessive ROS production not only directly damages renal cell DNA, proteins, and lipids but also activates various inflammatory and fibrosis-related signaling pathways, exacerbating renal injury ^[7]. The NLRP3 inflammasome, a crucial inflammatory regulatory complex discovered in recent years, plays a central role in renal inflammatory responses by mediating the maturation and release of proinflammatory cytokines such as IL-1 β and IL-18 upon activation ^[8]. Studies indicate that ROS can activate the NLRP3 inflammasome through oxidative stress responses, promoting cytokine release and exacerbating renal inflammatory injury. simultaneously, ROS can also upregulate the expression of fibrosis-related factors such as transforming growth factor- β (TGF- β), accelerating the process of renal interstitial fibrosis ^[9]. However, clinical research on the correlation between excessive ROS production and clinical inflammatory markers, fibrosis severity, and disease progression prognosis in DKD patients remains limited. Whether inhibiting excessive ROS production can delay DKD progression by regulating inflammatory and fibrotic pathways requires further clinical evidence.

2. Research objectives and significance

This study compared serum levels of ROS-related inflammatory factors (NLRP3, IL-1 β , IL-18, etc.) and fibrotic factors (TGF- β) in serum between DKD and non-DKD patients, analyze their correlation with renal function indicators and disease progression endpoints, and explore the intervention value of inhibiting excessive ROS production on renal inflammation, fibrosis, and disease progression in DKD patients. This study aims to provide new theoretical basis and potential therapeutic targets for the clinical prevention and treatment of DKD.

3. Materials and methods

3.1. Study population and inclusion criteria

Thirty DKD patients diagnosed at the Department of Nephrology, Hebei University Affiliated Hospital, between April 2025 and April 2026 were enrolled as the DKD group. Thirty non-DKD patients undergoing health examinations or hospitalized for non-renal diseases during the same period served as the control group.

3.1.1. Diagnostic criteria

DKD diagnosis met the 2023 American Diabetes Association (ADA) criteria for diabetes and clinical DKD diagnostic standards, meeting any of the following criteria ^[10].

- (1) Random urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g or urinary albumin excretion rate (UAER) ≥ 30 mg/24 h, with 2 out of 3 repeat tests within 3–6 months reaching or exceeding the threshold, excluding confounding factors such as infection
- (2) Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² persisting for ≥ 3 months;
- (3) Renal biopsy pathology demonstrating characteristic DKD changes (e.g., glomerular basement membrane thickening, mesangial matrix proliferation).

3.1.2. Inclusion criteria

DKD group

- (1) Meets the above DKD diagnostic criteria
- (2) Age > 18 years
- (3) History of diabetes ≥ 3 months with clear causal relationship between diabetes and changes in proteinuria/renal function
- (4) Exclusion of other primary/secondary glomerular diseases and systemic disorders

Control group

- (1) Age > 18 years
- (2) eGFR ≥ 90 mL/min/1.73 m²
- (3) UACR < 30 mg/g
- (4) No history of diabetes, hypertension, kidney disease, or other chronic conditions

3.1.3. Exclusion criteria

Both groups excluded the following subjects

- (1) Severe hepatic impairment (ALT/AST > 3 times the upper limit of normal)
- (2) Acute complications such as diabetic ketoacidosis or hyperosmolar coma
- (3) Malignant tumors
- (4) Congestive heart failure (NYHA class III–IV)
- (5) Pregnant or lactating women
- (6) Urinary tract infection, acute kidney injury, or other acute infectious diseases within the past month
- (7) Use of immunosuppressants, glucocorticoids, or antioxidants (e.g., vitamin E, glutathione) within the past 3 months
- (8) Incomplete clinical data or inability to complete follow-up

3.2. Research methods

3.2.1. General data collection

General data for both groups were collected via electronic medical records and questionnaires, including name, age, gender, marital status, contact information, diabetes duration (DKD group), blood pressure, and body mass index (BMI).

3.2.2. Specimen collection and indicator detection

All subjects provided 5 mL of venous blood in the morning on an empty stomach. Serum was separated by

centrifugation and stored at -80 °C for subsequent testing. A fully automated biochemical analyzer (Model: [Add instrument model]) was used to measure: - Complete blood count (CBC) parameters (white blood cell count, neutrophil count, lymphocyte count, etc.) - Liver function (ALT, AST, total protein, albumin, etc.) - Kidney function (serum creatinine, blood urea nitrogen, uric acid) electrolytes (serum potassium, sodium, chloride), and fasting blood glucose (FBG) levels. Quantitative 24-hour urinary protein was measured using immunoturbidimetry. Serum NLRP3, IL-1 β , IL-18, TNF- α , IL-6, and TGF- β levels were measured using ELISA kits purchased from [Supplement Reagent Manufacturer], strictly following the kit instructions. Renal function was assessed using the CKD-EPI formula to calculate eGFR: $eGFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{(-1.209)} \times 0.993^{(age)} \times 1.018$ (female) $\times 1.159$ (Black), where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, and α is -0.329 for females and -0.411 for males.

3.2.3. Follow-up protocol

All subjects underwent a 12-month follow-up period. Endpoint events were collected through outpatient visits and telephone follow-ups. Primary endpoint: $\geq 40\%$ decline in eGFR or initiation of maintenance dialysis (hemodialysis or peritoneal dialysis). Secondary endpoints: doubling of UACR or occurrence of cardiovascular events (including acute myocardial infarction, cerebral infarction, hospitalization for heart failure, etc.).

3.2.4. Statistical analysis methods

Data analysis was performed using SPSS 26.0 statistical software. Quantitative data are expressed as mean \pm standard deviation ($\bar{x} \pm s$), with intergroup comparisons conducted using the independent samples *t*-test. Qualitative data are presented as case numbers (percentages) [n (%)], with intergroup comparisons performed using the chi-square (χ^2) test. Correlation analysis employed Pearson or Spearman correlation analysis. The incidence of endpoint events was calculated using the Kaplan-Meier method, with intergroup comparisons performed using the log-rank test. $p < 0.05$ was considered statistically significant.

4. Results

4.1. Comparison of general characteristics between groups

There were no statistically significant differences between the two groups in age, gender, marital status, BMI, and other general characteristics ($p > 0.05$). The DKD group had a diabetes duration of (8.2 ± 3.5) years, and their systolic blood pressure, diastolic blood pressure, and fasting blood glucose levels were significantly higher than those in the control group ($p < 0.05$). Specific data are shown in **Table 1**.

Table 1. Specific data between study group

Indicator	DKD group (n = 30)	Control group (n = 30)	<i>t</i> / χ^2 value	<i>p</i> -value
Age (years, $\bar{x} \pm s$)	56.8 \pm 10.2	55.3 \pm 9.8	0.582	0.563
Gender (Male/Female, n)	17/13	16/14	0.068	0.794
BMI (kg/m ² , $\bar{x} \pm s$)	25.3 \pm 3.1	24.8 \pm 2.9	0.654	0.516
Systolic blood pressure (mmHg, $\bar{x} \pm s$)	145.2 \pm 15.6	120.5 \pm 10.3	7.682	< 0.001
Diastolic blood pressure (mmHg, $\bar{x} \pm s$)	88.6 \pm 10.5	75.3 \pm 8.2	5.871	< 0.001
Fasting blood glucose (mmol/L, $\bar{x} \pm s$)	9.2 \pm 2.3	5.6 \pm 1.1	8.763	< 0.001

Note: BMI = Body Mass Index; DKD = Diabetic Kidney Disease

4.2. Comparison of clinical and laboratory indicators between the two groups

Patients in the DKD group exhibited significantly higher levels of serum creatinine, blood urea nitrogen, uric acid, 24-hour urine protein, and UACR compared to the control group ($p < 0.05$), while eGFR was significantly lower ($p < 0.05$). Serum NLRP3, IL-1 β , IL-18, TNF- α , IL-6, and TGF- β levels were significantly higher in the DKD group than in the control group ($p < 0.05$). No statistically significant differences were observed between the two groups in blood counts, liver function, or electrolyte levels ($p > 0.05$). Detailed data are presented in **Table 2**.

Table 2. Clinical and laboratory indicators between study group

Indicator	DKD group (n = 30)	Control group (n = 30)	t-value	p value
Serum creatinine ($\mu\text{mol/L}$, $\bar{X} \pm s$)	135.6 \pm 42.8	78.3 \pm 15.6	6.872	< 0.001
Urea nitrogen (mmol/L, $\bar{X} \pm s$)	9.8 \pm 3.2	5.2 \pm 1.5	7.654	< 0.001
eGFR (mL/min/1.73 m ² , $\bar{X} \pm s$)	52.3 \pm 15.6	105.8 \pm 18.2	-12.345	< 0.001
24-hour Urinary Protein Quantification (g/24 h, $\bar{X} \pm s$)	2.8 \pm 1.5	0.18 \pm 0.06	8.976	< 0.001
UACR (mg/g, $\bar{X} \pm s$)	325.6 \pm 156.8	18.3 \pm 6.5	10.234	< 0.001
NLRP3 (ng/L, $\bar{X} \pm s$)	185.6 \pm 68.3	65.8 \pm 20.5	9.872	< 0.001
IL-1 β (pg/mL, $\bar{X} \pm s$)	25.6 \pm 8.3	8.9 \pm 3.2	9.234	< 0.001
IL-18 (pg/mL, $\bar{X} \pm s$)	156.8 \pm 45.2	68.3 \pm 21.5	9.654	< 0.001
TNF- α (pg/mL, $\bar{X} \pm s$)	32.5 \pm 10.6	12.8 \pm 4.3	9.876	< 0.001
IL-6 (pg/mL, $\bar{X} \pm s$)	45.6 \pm 15.3	15.8 \pm 5.2	9.456	< 0.001
TGF- β (ng/mL, $\bar{X} \pm s$)	8.9 \pm 2.6	3.2 \pm 1.1	10.234	< 0.001

Note: eGFR denotes estimated glomerular filtration rate; UACR denotes urinary albumin-to-creatinine ratio; NLRP3 denotes NLRP3 inflammasome; IL-1 β denotes interleukin-1 β ; IL-18 denotes interleukin-18; TNF- α denotes tumor necrosis factor- α ; IL-6 denotes interleukin-6; TGF- β denotes transforming growth factor- β ; DKD denotes diabetic kidney disease

4.3. Correlation analysis results

Pearson correlation analysis revealed that serum NLRP3 levels in the DKD group were positively correlated with IL-1 β , IL-18, TNF- α , IL-6, and TGF- β levels ($r = 0.723, 0.756, 0.689, 0.712, 0.734$, respectively; $p < 0.05$ for all correlations). Serum NLRP3 and TGF- β levels were negatively correlated with eGFR ($r = -0.682, -0.715, p < 0.05$ each) and positively correlated with 24-hour urine protein quantification ($r = 0.654, 0.691, p < 0.05$ each).

4.4. Comparison of endpoint event occurrence between study groups

The 12-month follow-up results showed that 8 patients (26.67%) in the DKD group reached the primary endpoint, including 6 patients with an eGFR decline $\geq 40\%$ and 2 patients who initiated maintenance dialysis. Eleven patients (36.67%) reached secondary endpoints, including 7 with a doubling of UACR and 4 with cardiovascular events (2 acute myocardial infarctions, 2 heart failure hospitalizations). No patients in the control group reached either primary or secondary endpoints. Comparisons of primary and secondary endpoint event rates between groups showed statistically significant differences ($\chi^2 = 8.763, 11.234; p < 0.01$ for both). Detailed data are presented in **Table 3**.

Table 3. Endpoint events between study groups

Endpoint events	DKD group (n = 30) n (%)	Control group (n = 30) n (%)	χ^2 Value	p-value
Primary endpoint	8 (26.67)	0 (0.00)	8.763	0.003
eGFR decrease \geq 40%	6 (20.00)	0 (0.00)	6.667	0.010
Progression to dialysis	2(6.67)	0(0.00)	2.069	0.150
Secondary endpoint	11(36.67)	0 (0.00)	11.234	0.001
UACR doubling	7 (23.33)	0(0.00)	7.778	0.005
Cardiovascular events	4(13.33)	0 (0.00)	4.286	0.038

Note: eGFR denotes estimated glomerular filtration rate; UACR denotes urinary albumin-to-creatinine ratio; DKD denotes diabetic kidney disease

5. Discussion

The pathogenesis of DKD is complex, involving multiple factors such as oxidative stress, inflammatory response, fibrosis, and genetic factors. Among these, oxidative stress-mediated inflammation and fibrosis are central to DKD progression. By comparing clinical and laboratory indicators between DKD and non-DKD patients, this study investigated the role of excessive ROS production in DKD inflammation, fibrosis, and disease progression. Results demonstrated significantly elevated serum levels of ROS-related inflammatory and fibrotic factors in DKD patients, closely associated with renal impairment and poor prognosis, providing clinical evidence for inhibiting excessive ROS production to intervene in DKD progression. As crucial intracellular signaling molecules, ROS activate inflammatory responses through multiple pathways during DKD pathogenesis. The NLRP3 inflammasome, a multiprotein complex comprising NLRP3, apoptosis-related speck-like protein (ASC), and pro-caspase-1 precursor, mediates the maturation and secretion of pro-inflammatory factors such as pro-IL-1 β and pro-IL-18 upon activation. It serves as a pivotal molecular link between oxidative stress and inflammatory responses. Our findings reveal significantly elevated serum NLRP3 levels in the DKD group compared to controls, positively correlated with pro-inflammatory factors including IL-1 β , IL-18, TNF- α , and IL-6. This suggests that excessive ROS production may exacerbate renal inflammation by activating the NLRP3 inflammasome pathway. This aligns with previous basic research findings. For instance, Li et al. observed in a DKD animal model that a high-glucose environment induces excessive ROS production in glomerular mesangial cells, thereby activating NLRP3 inflammasomes, promoting IL-1 β release, and exacerbating glomerular inflammatory damage. Conversely, treatment with ROS scavengers suppressed NLRP3 inflammasome activation and markedly reduced renal inflammatory responses. Furthermore, this study revealed significantly elevated serum TNF- α and IL-6 levels in the DKD group, potentially linked to ROS-mediated activation of the nuclear factor- κ B (NF- κ B) pathway. ROS can oxidatively modify I κ B kinase (IKK), leading to its phosphorylation and degradation. This releases NF- κ B, allowing it to enter the nucleus and regulate the transcription and expression of proinflammatory factors such as TNF- α and IL-6. This further amplifies the inflammatory response, forming a vicious cycle of “oxidative stress-inflammation” that accelerates renal injury. Renal fibrosis represents the ultimate common pathway for DKD progression to ESRD, primarily manifested as activation of renal interstitial fibroblasts, collagen fiber deposition, and glomerulosclerosis. TGF- β is a recognized core fibrogenic factor that promotes fibroblast-to-myofibroblast transdifferentiation by activating the Smad signaling pathway, upregulates expression

of extracellular matrix proteins such as collagen I and collagen III, and accelerates renal interstitial fibrosis. Our findings reveal significantly elevated serum TGF- β levels in the DKD group compared to controls, positively correlated with NLRP3 expression, negatively correlated with eGFR, and positively correlated with 24-hour urine protein quantification. This suggests that excessive ROS production may indirectly promote TGF- β expression by regulating the NLRP3 inflammasome pathway, thereby exacerbating renal fibrosis. Mechanistic studies indicate that proinflammatory cytokines released upon NLRP3 inflammasome activation, such as IL-1 β and IL-18, can upregulate TGF- β transcription and expression by activating the MAPK signaling pathway. Concurrently, ROS can directly oxidatively modify TGF- β receptors, enhancing their binding affinity to ligands and amplifying the fibrogenic effects of the TGF- β /Smad signaling pathway. Furthermore, ROS can inhibit the activity of matrix metalloproteinases (MMPs), reduce extracellular matrix degradation and thereby promoting collagen fiber deposition, which exacerbates renal fibrosis.

6. Conclusion

In summary, excessive ROS production contributes to renal inflammation and fibrosis in diabetic kidney disease through activation of the NLRP3 inflammasome pathway. Targeting and inhibiting excessive ROS generation therefore represents a promising therapeutic strategy to delay the progression of DKD.

Disclosure statement

The authors declare no conflict of interest.

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Primary Leiomyosarcoma of the Inferior Vena Cava: A Case Report and Literature Review

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Abstract: *Objective:* To investigate the diagnosis and treatment methods for primary leiomyosarcoma of the inferior vena cava. *Methods:* The clinical course of a patient with primary inferior vena cava leiomyosarcoma admitted to our department in September 2022 was retrospectively analyzed. Combined with a literature review, the clinical characteristics of inferior vena cava leiomyosarcoma were summarized. *Results:* The patient recovered smoothly after radical resection. However, follow-up examination at six months postoperatively revealed local tumor recurrence and hepatic metastasis. Following a multidisciplinary discussion, the patient promptly commenced treatment at the oncology center with epirubicin (50 mg/m²) and ifosfamide (2500 mg/m²). Nevertheless, severe side effects, such as hepatotoxicity, hindered timely drug administration, and the patient was lost to follow-up after the third cycle of chemotherapy. *Conclusion:* Radical surgical resection remains the only potentially curative treatment for patients with inferior vena cava leiomyosarcoma. However, for tumor recurrence and metastasis, a comprehensive treatment approach incorporating chemotherapy may be more effective in improving patient survival rates.

Keywords: Inferior vena cava leiomyosarcoma; Surgical procedures; Vascular reconstruction; Chemotherapy

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1. Introduction

Primary leiomyosarcoma of the inferior vena cava (PIVCLMS) is a rare malignant tumor originating from the smooth muscle of the venous wall. This disease was first reported by Perl in 1871 ^[1]. Radical surgical resection is the only potentially curative treatment for patients with PIVCLMS. However, the prognosis for these patients is generally poor due to the high malignant potential of the tumor itself, frequent delays in diagnosis, and the technical challenges associated with the surgical procedure ^[2]. This paper reports the diagnosis and treatment process of one case of PIVCLMS admitted to our department.

2. Clinical data

The patient was a 56-year-old female admitted due to upper abdominal pain persisting for three months. Her

medical history included uterine fibroids, for which she had undergone a hysterectomy. Physical examination revealed mild tenderness in the right upper abdomen. The abdomen was soft, no masses were palpable, and there was no edema in the lower extremities. Laboratory tests showed no significant abnormalities, and multiple tumor markers were within normal ranges. Abdominal ultrasound indicated a widened lumen in the retrohepatic segment of the inferior vena cava (maximum diameter approximately 31 mm), within which a heterogeneous, predominantly hypoechoic mass measuring about $68 \times 32 \times 30$ mm was detected. The mass had relatively clear borders and exhibited longitudinal growth along the inferior vena cava. Whole abdominal CT and inferior vena cava CT venography (CTV) revealed an ovoid, slightly hypodense lesion protruding extraluminally from the suprarenal segment of the inferior vena cava. On its largest cross-section, it measured approximately 44×41 mm. Contrast-enhanced CT showed marked heterogeneous enhancement with small patchy areas of necrotic tissue exhibiting less enhancement. The lesion also involved the right renal vein as shown in **Figure 1a**. MRI demonstrated a mass both within and anterior to the inferior vena cava, appearing hyperintense on T2-weighted imaging (T2WI), hypointense on T1-weighted imaging (T1WI), and showing no signal change on fat-suppressed T1WI. The largest cross-sectional dimension was approximately 51×32 mm, involving a segment of the inferior vena cava about 59 mm in length. Additionally, an ovoid, slightly hyperintense focus on T2WI with relatively marked enhancement was found in segment IV of the liver (see **Figure 1b**). Radionuclide renal dynamic imaging indicated good bilateral renal function.

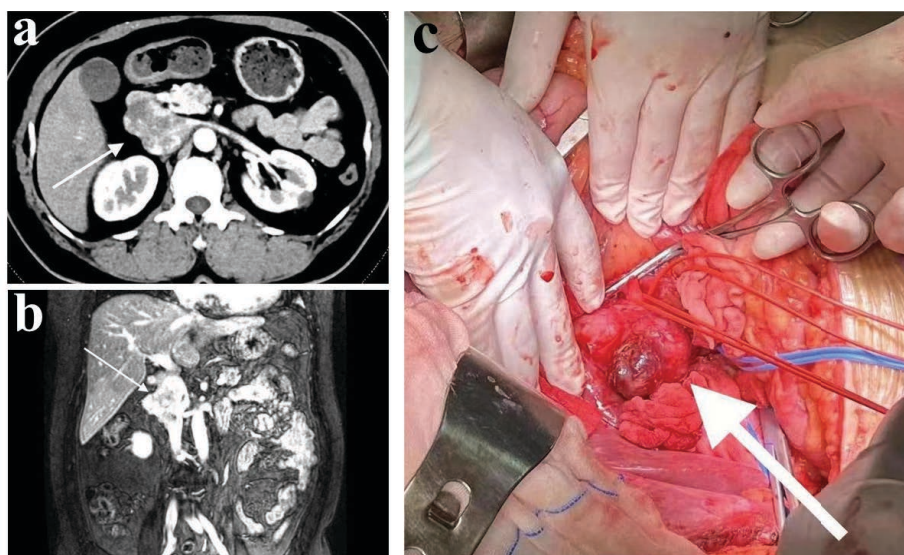


Figure 1. Preoperative imaging findings and gross appearance of the tumor.

(a) Preoperative CTV demonstrates a space-occupying lesion in the inferior vena cava, which exhibits heterogeneous enhancement on contrast-enhanced imaging. (b) MRI shows the lesion primarily involving segment II of the inferior vena cava, protruding from the lumen and extending superiorly to the inferior edge of the hepatic segment of the vessel. (c) Grossly, the tumor appears as an irregular, nodular mass with adhesion to surrounding tissues and a firm consistency.

The preoperative clinical diagnosis was inferior vena cava leiomyosarcoma (mixed intra- and extraluminal growth type). After excluding surgical contraindications, the patient underwent radical resection on September 22, 2022. Intraoperatively, the tumor appeared irregular in shape with lobulated growth, and part of the tumor tissue protruded significantly from the vessel lumen, measuring approximately $7 \times 6 \times 5$ cm with a hard texture (see **Figure 1c**). During dissection of the mass, two nodular lesions, each about 10 mm in diameter, were identified in

the caudate lobe and the right posterior hepatic lobe, respectively, and were resected along with the primary tumor. An F18 Dacron prosthetic graft was used to reconstruct the inferior vena cava defect (refer **Figure 2**). The total operative time was 390 minutes, with a cumulative vascular ischemia time of 78 minutes, and the estimated blood loss was approximately 200 mL.

Postoperative pathological examination confirmed the diagnosis of moderately to poorly differentiated leiomyosarcoma with negative resection margins. The resected hepatic nodules also contained leiomyosarcoma. Immunohistochemical staining results were as follows: Desmin (+), SMA (+), Ki-67 (75% positive), S-100 (-), CD34 (-), CD117 (-).



Figure 2. Intraoperative reconstruction of the inferior vena cava and postoperative follow-up findings.

Following complete resection of the tumor, the inferior vena cava was reconstructed using a prosthetic graft (a). Postoperative follow-up CT demonstrates patency of the inferior vena cava (b, c).

The patient recovered smoothly during the postoperative hospital stay and was discharged on the 11th day after surgery. However, a follow-up CT scan six months postoperatively revealed local tumor recurrence and hepatic metastasis **Figure 3**). Following a multidisciplinary expert discussion, the patient promptly commenced treatment at the oncology center with epirubicin (50 mg/m²) and ifosfamide (2500 mg/m²). Nevertheless, severe side effects, such as hepatotoxicity, hindered timely administration of the chemotherapy, and the patient was lost to follow-up after the third cycle.

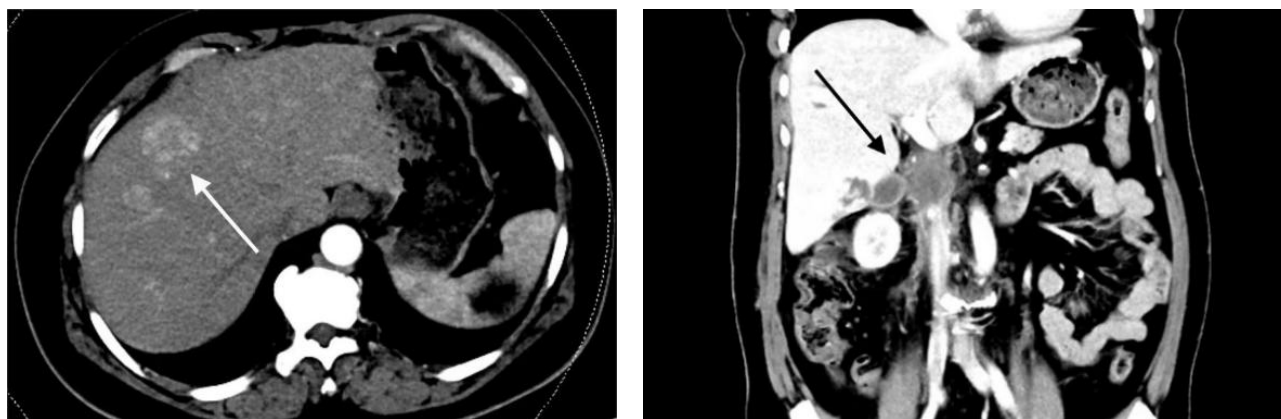


Figure 3. Local tumor recurrence and hepatic metastasis detected during follow-up examination at six months postoperatively.

3. Discussion

Primary leiomyosarcoma of the inferior vena cava (PIVCLMS) commonly occurs in middle-aged and elderly

women, with approximately 80% of patients being women aged 50–60 years. The prognosis is generally poor, with a high rate of recurrence ^[3]. Due to its occult location and slow growth, PIVCLMS is often not detected early, and clinical symptoms in its mid-to-late stages are also non-specific. Clinically, the inferior vena cava is segmented based on its anatomical relationship to the renal veins and hepatic veins. Leiomyosarcomas most frequently occur in segment II of the inferior vena cava. The majority of patients present with non-specific abdominal or back pain. Precisely because of these atypical symptoms, coupled with the significantly higher incidence in women compared to men, consulting physicians may initially consider gynecological conditions rather than vascular diseases, which can impede an accurate diagnosis.

Leiomyosarcoma of the inferior vena cava typically originates from the tunica media of the vessel wall. In its early stages, it is confined to the venous wall, subsequently invading adjacent tissues extraluminally or expanding intraluminally in a thrombus-like manner. Its growth patterns are classified as intraluminal, extraluminal, or mixed ^[4]. If the tumor exhibits intraluminal growth, preoperative diagnosis is often straightforward. However, when the growth pattern is extraluminal or mixed, and particularly when the tumor is large and causes displacement of surrounding vessels by compression, it can be difficult to determine its exact origin preoperatively. Computed tomography angiography (CTV) clearly demonstrates the tumor's size, morphology, extent of invasion, and its relationship with adjacent vessels and organs. The lesion primarily grows longitudinally along the course of the inferior vena cava. On non-contrast CT, it appears as a soft tissue density, showing heterogeneous enhancement after contrast administration. Large lesions may exhibit central necrotic areas, and the vena cava may display filling defects or local non-opacification. Magnetic resonance imaging (MRI) typically reveals a slightly hypointense signal on T1-weighted imaging and iso- to hyperintense mixed signals on T2-weighted imaging. MRI can display the entire tumor mass and the extent of collateral circulation formation. However, definitive diagnosis still requires histopathological examination, which provides conclusive evidence of the tumor's nature and aids in formulating an appropriate postoperative treatment plan when necessary.

Although extensive research has been conducted on treatment strategies for PIVCLMS, radical surgical resection appears to be the only potentially curative approach ^[2]. However, the complex adjacent anatomy of the inferior vena cava, and the potential for tumor extension into the right atrium, pose significant clinical challenges. Furthermore, management of the inferior vena cava following tumor resection is crucial and depends on factors such as tumor location and involvement of hepatic or renal veins. Unfortunately, even radical resection does not guarantee long-term survival, with reported 5-year and 10-year survival rates of approximately 40–70% and 20–40%, respectively ^[3,5].

For PIVCLMS in segment III, the inferior vena cava in this segment has a rich collateral circulation. If the common iliac vein bifurcation is not involved, venous return from the lower limbs can be ensured via anastomoses between the internal iliac veins and the pelvic venous plexus. In such cases, direct ligation of the inferior vena cava is associated with almost no complications such as lower limb edema ^[6]. Simple ligation can not only eliminate the need for complex vascular reconstruction procedures, thereby shortening operative time, but also avoid a series of complications associated with vascular reconstruction and the use of prosthetic grafts. For segment I PIVCLMS, when the tumor involves the hepatic veins or right atrium, patients often present with massive ascites due to Budd-Chiari syndrome, frequently losing the opportunity for surgical intervention. Even if surgery is performed, it must be conducted under conditions of hypothermia and cardiopulmonary bypass with cardiac arrest. Regarding segment II PIVCLMS, which often involves the renal veins, treatment becomes more complex when the tumor involves the right renal vein. Due to the short length of the right renal vein, which primarily receives drainage

from the right ureteric vein and lacks sufficient collateral circulation, preserving renal venous outflow during tumor resection is challenging. Renal vein ligation, or even nephrectomy, was previously often unavoidable in the treatment of inferior vena cava leiomyosarcoma, consequently leading to frequent occurrences of renal failure. Therefore, once a decrease in urine output is detected postoperatively, early plasma filtration should be initiated [7]. Existing literature suggests that performing a venorenal ostioplasty (VRO) during tumor resection can preserve part of the connection between the renal vein and the inferior vena cava. This technique helps prevent stenosis during anastomosis with an inferior vena cava graft and is an effective method for reconstructing renal outflow, with reported patency rates reaching 90% [8].

Following tumor resection, particularly after removal of segment II PIVCLMS, the question arises of whether reconstruction of the inferior vena cava and renal veins is necessary. If a patient's renal vein is involved, especially if chronically and completely occluded, a collateral venous circulation will form through shunt vessels [9]. Tumor resection without reconstructing the inferior vena cava or renal veins is a viable option for patients with well-developed collateral circulation. However, for patients with only partial renal vein occlusion and insufficient collateral circulation, simple surgical tumor removal is inadequate, and vascular reconstruction becomes essential [10]. In a series of cases reported by Yoshidome et al. where inferior vena cava reconstruction was not performed, 5 out of 10 patients underwent right nephrectomy due to venous outflow obstruction [11]. Reconstruction methods such as simple suture, patch repair, and graft replacement have all proven feasible to varying degrees, but the optimal management approach remains controversial [12]. In the case reported here, the inferior vena cava mass also involved the right renal vein. Therefore, reconstruction of both the inferior vena cava and the renal vein was performed using a Dacron prosthetic graft. This approach aligns with normal anatomical and physiological principles, successfully establishing a renal venous outflow tract, effectively preserving renal function. The patient recovered well on postoperative follow-up. Dacron material offers excellent mechanical properties and chemical stability, effectively resisting intra-abdominal pressure, demonstrating low thrombogenicity, and possessing notable advantages in longitudinal elasticity, allowing for better estimation of vascular defect length [13,14]. Practices regarding anticoagulant therapy after inferior vena cava reconstruction vary in the literature [15]. Given its high-flow nature, this patient did not receive postoperative anticoagulation, and no graft thrombosis was observed on follow-up examinations. Notably, thrombotic occlusion is often caused by graft deformation. During surgery, the liver is often rotated to facilitate anastomosis between the graft and the inferior vena cava, at which point the graft is patent. However, when the liver is returned to its normal anatomical position, the graft lumen can become twisted and deformed. Therefore, during inferior vena cava anastomosis, special attention should be paid to the degree of liver rotation to ensure the prosthetic graft and the inferior vena cava lie in the same plane.

Given the rarity of this disease, it is challenging to conduct large-scale controlled studies to evaluate the role of adjuvant chemotherapy in the treatment of inferior vena cava leiomyosarcoma. Currently, most treatment regimens are based on standard oncological principles and extrapolated from studies on soft tissue sarcomas. A meta-analysis indicates that combination therapy based on doxorubicin yields higher response rates and overall survival compared to doxorubicin monotherapy. Furthermore, anthracycline analogs can reduce certain side effects; for instance, epirubicin has lower cardiotoxicity while maintaining efficacy comparable to doxorubicin [16,17]. In this reported case, local recurrence and hepatic metastasis were detected during a follow-up examination six months postoperatively. Following a multidisciplinary discussion, the patient promptly commenced treatment at the oncology center with epirubicin (50 mg/m²) and ifosfamide (2500 mg/m²). Unfortunately, the patient was lost to follow-up after the third chemotherapy cycle due to adverse effects, which also implies that the efficacy

and outcomes of chemotherapy remain controversial. In Japan, when anthracycline-based chemotherapy fails, recently approved agents such as pazopanib, trabectedin, and eribulin are utilized as second-line or subsequent chemotherapy options^[18].

4. Conclusion

In summary, primary inferior vena cava leiomyosarcoma is a rare disease. Due to its occult location, it is often diagnosed at an advanced stage. Early detection can significantly increase the feasibility of surgical intervention. Until more effective preoperative and postoperative adjuvant treatments are established, radical surgical resection remains the only potentially curative treatment option. Despite the challenges, ongoing research continues to explore multimodal strategies to improve outcomes for patients with this aggressive tumor.

Disclosure statement

The authors declare no conflict of interest.

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Analysis of Differences in Urine Concentration Function and Erythrocyte Membrane Permeability among Different Animal Species

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Abstract: Through comparative studies on renal structure and urine concentration function, this research aims to observe and analyze the differential mechanisms among different animal species. Using rats as the research subjects and employing a high-protein feeding method, the study explores the mechanism of urea's effect on urine concentration function from multiple levels, including gene expression regulation and protein levels. Erythrocyte membrane permeability tests are conducted to compare the degree of differences among various animal species. This study utilized experimental techniques such as RT-PCR, Western-blot, Stopped-flow, and immunohistochemistry to investigate the urine concentration mechanism at the cellular, tissue, and whole-organism levels, laying a foundation for further screening and preparing animal models for studying the urine concentration mechanism.

Keywords: Urine concentrating function; Erythrocyte membrane permeability; Different species; Differential analysis

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1. Introduction

The kidneys are the largest excretory organs in the human body, playing a crucial role in regulating water volume and the excretion of various components^[1]. This study intends to employ a variety of research methods, including comparative physiology and molecular biology, to comparatively analyze differences in renal physiology, body fluid and metabolic ion content, erythrocyte membrane permeability to water and urea, and renal urea channels. The aim is to explore the relationship between these factors and urine concentrating function, thereby further elucidating the mechanism of urine concentration in mammalian kidneys.

2. Materials and methods

2.1. Experimental materials and instruments

2.1.1. Materials

(1) Experimental animals

All animals used in this study were bred in-house, totaling six species. These include the following: rodents (mice, rabbits), herbivores (sheep, cattle), and carnivores (cats, dogs). The experimental animal grades were as follows: rabbits, dogs, and mice all meet the national standards for second-grade experimental animals, while the other experimental animals have undergone a two-week isolation observation period to confirm their health status and absence of diseases.

(2) Reagents

4% paraformaldehyde, disposable vacuum coagulation-promoting blood collection tubes, Sumianxin, urea detection kits, PBS buffer solution, urea, urea channel protein inhibitors, and other conventional reagents were all of analytical grade purity.

2.1.2. Instruments

Vernier calipers, electronic platform scales, precision electronic balances, pH meters, clean benches, refrigerators, fully automatic electrolyte analyzers, high-speed centrifuges, photometers, spectrometer reactors, blood analyzers, cryogenic centrifuges, clean benches, etc.

2.2. Methods

2.2.1. Comparison of structural characteristics of kidneys in animals of different species

Among the six experimental breeds, three animals were included in each group for a 30-day quarantine period. Daily monitoring of their food and water intake, physical condition, and excretions was conducted, while maintaining a constant temperature (20 °C) in the animal housing. After dissection, morphological observations were made on the organs of rats in each group. The kidneys were harvested, rinsed with TBS, dried, weighed, and longitudinally sectioned for counting. The kidneys of the experimental animals were measured using vernier calipers in the following order of parameters: absolute length, width, and thickness of the kidney were determined, then the kidney was bisected along its long axis with a double-edged blade along the median plane, and the thickness of each layer was directly measured on the cross-section using vernier calipers. Finally, tissue sections of the renal cortex and medulla from the rat kidneys were prepared, washed with TBS, longitudinally sectioned to 3 mm, and stored in liquid nitrogen; subsequently, different renal tissues were eluted with chloroform, fixed with formalin solution, and subjected to further immunohistochemical detection ^[2,3].

2.2.2. Comparison of ion and urea content in animal urine and serum ion content in animals

Before handling the experimental animals, they were fasted for 24 hours and deprived of water for 2 hours. Morning urine samples were collected from each mouse, with strict recording of their volume and state, and stored at 4 °C. Meanwhile, the concentrations of ions such as Na, K, Cl, and urea in the urine were measured. A 100 g sample from each part of the kidney was weighed, ground, dissolved in distilled water, and then centrifuged to determine the content of sodium, potassium, chlorine, other ions, and urea nitrogen. The content of ions such as Na, K, and Cl in rat urine, serum, and various renal tissues was detected using high-performance liquid chromatography ^[4,5].

2.2.3. Comparative study on the difference in permeability of animal erythrocyte membranes to water and urea

A blood analyzer was used to examine erythrocytes from different species, measuring their hematocrit, erythrocyte count, and erythrocyte volume to conveniently understand the hemorheological properties of erythrocytes. Centrifugation was performed at room temperature at 1000 r/min for 10 minutes to separate the erythrocytes, which were then washed three times with PBS and the blood discarded. Subsequently, using PBS buffer solution, the permeability of erythrocytes to urea and water was measured separately using a stopped-flow assay. Urea permeability assay: The prepared erythrocyte suspension (0.5% hematocrit) was mixed with 250 mM urea, and the dynamic changes in cell volume were measured at 530 nm with 90-degree light scattering. Each erythrocyte sample was repeated five times, and the light scattering time curve was calculated by computer to obtain the osmotic urea permeability (Purea). Water permeability assay: The freshly prepared erythrocyte suspension (0.5% hematocrit) was placed in a 250 mM sucrose solution, and the same procedure as above was followed, comparing it with the measurement method for water permeability (Pf) ^[6].

2.3. Statistical analysis

All collected numerical data were entered into SPSS 20.00 software for statistical analysis. Measurement data were recorded as mean and standard deviation.

3. Results and analysis

3.1. Comparison of structural characteristics of kidneys in different animal species

The study revealed significant differences in the relative thickness of the medulla among various species, with carnivorous animals exhibiting significantly thicker renal medullae compared to herbivores. Research on the proportion of different anatomical regions of the kidneys indicated that herbivores had the highest proportion of cortex, while rodents had the highest proportion of medulla (see **Table 1**).

Table 1. Comparison of kidney weight and structural characteristics among different animals

Species	Sheep	Cattle	Cat	Dog	Rabbit	Mouse
Body weight (kg)	36.52 ± 36.00	326.50 ± 58.00	2.368 ± 12.23	10.235 ± 13.25	1.668 ± 20.12	0.026 ± 0.35
Kidney weight (kg)	0.092 ± 2.54	1.054 ± 23.02	0.01 ± 0.35	0.05 ± 0.35	0.013 ± 0.23	0.00018 ± 0.12
Relative kidney weight (%)	0.252	0.322	0.422	0.489	0.779	0.692
Absolute cortex thickness (mm)	5.2 ± 0.3	5.7 ± 0.4	6.7 ± 0.3	8.4 ± 0.2	2.5 ± 0.6	1.0 ± 0.3
Absolute medulla thickness (mm)	7.0 ± 0.2	7.3 ± 0.4	8.8 ± 0.7	26.1 ± 0.5	8.3 ± 0.3	4.6 ± 0.2
Relative medulla thickness	0.57 ± 0.13	0.55 ± 0.05	0.68 ± 0.01	0.72 ± 0.08	0.74 ± 0.16	0.80 ± 0.12

3.2. Comparison of urinary ion and urea content in animals

The study demonstrated a strong correlation between sodium ion concentration in urine and diet, with higher sodium ion concentrations in food leading to increased sodium ion levels in urine. The results indicated that rodents had the highest urea nitrogen concentration, suggesting the strongest urine concentration capacity. Carnivorous animals, due to their long-term protein-rich diet, also exhibited higher overall BUN levels compared to rodents. Herbivores, on the other hand, maintained relatively low blood urea concentrations in their urine,

attributed to their lower protein intake over extended periods. The aforementioned studies indicate that due to long-term dietary habits and evolutionary characteristics, there are significant species-specific differences in the urine concentration capacity of kidneys among various species.

3.3. Comparison of serum ion content in animals

Through a comparative study of serum ion concentrations among various species, the results revealed the following: sodium (Na) ion concentrations ranged from 136 to 150 mmol/L, with no significant differences observed among species; potassium (K) ion concentrations ranged from 3.94 to 7.131 mmol/L, also showing no significant differences among species; and chloride (Cl) ion concentrations ranged from 102 to 130 mmol/L, with no significant differences among species as well.

3.4. Comparison of the effects of different protein intakes on urine concentration function

Research indicates that protein intake has a significant impact on the urine concentration function in rats, and the expression of aquaporin AQP2 and UT-A3 is also influenced by protein intake, confirming that urea generated from protein metabolism plays a significant role in regulating renal concentration capacity (refer **Figure 1**).

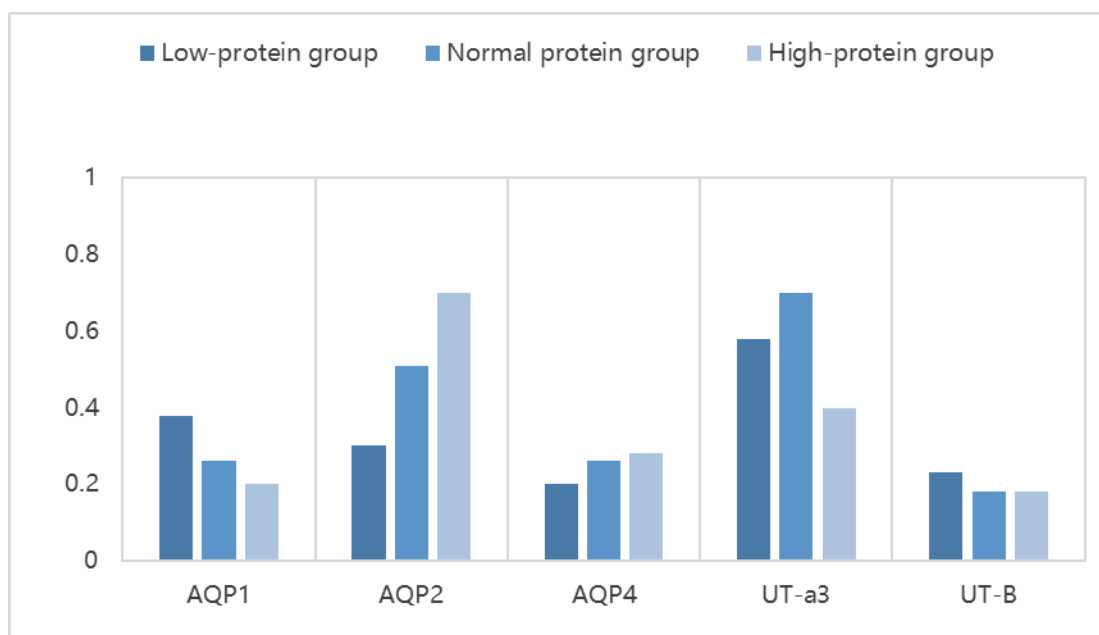


Figure 1. Quantitative analysis of urea transporter proteins and aquaporin proteins in rat kidneys with different protein intakes ($p < 0.05$).

3.5. Comparison of the permeability differences of water and urea in animal erythrocyte membranes

By comparing the differences in urea permeability of erythrocyte membranes among different species, this study discovered that there is species-specificity in the urea permeability of erythrocyte membranes, with the order being carnivores > rodents > herbivores; however, the water permeability of erythrocyte membranes is similar across different species.

4. Discussion

By comparing and observing the renal physiological structures of six species, measuring and calculating the absolute thickness of the renal cortex and medulla as well as their proportions in the kidneys of each species, this study confirmed that there are certain differences in renal tissues among different species both physiologically and anatomically. These differences provide a basis for further experimental research.

The experiment detected Na, K, Cl ions and urea N in the urine, serum, and various parts of the kidneys of six types of animals. It was concluded that there are no significant differences in serum sodium, potassium, and chloride ion contents among different species, but there are significant interspecies differences in blood urea nitrogen content. The variations in ion concentrations and urea concentrations in renal tissues are consistent with the differences in urine concentration abilities among different species^[7].

By employing methods such as fluorescent quantitative RT-PCR, Western-blot, and immunohistochemistry, we systematically studied the effects of different protein diets on renal function in rats and revealed their regulatory mechanisms^[8]. As the protein content in the feed increases, urine volume significantly increases. Different protein diets have no obvious effects on serum and urea nitrogen, but urea nitrogen in urine and urea clearance rate increase with the rise in protein concentration.

The stopped-flow light scattering method was employed to examine the permeability of erythrocyte membranes from six different animal species to urea, revealing significant interspecies differences^[9]. However, the permeability to water was found to be similar across species, with no notable differences observed.

5. Conclusion

In summary, this study demonstrates that hyperuricemia induced by a long-term high-protein diet can lead to adaptive changes in renal structure and function. The elevated urea concentration resulting from a high-protein diet significantly affects urine concentrating ability and the expression of channel proteins related to urine concentration.

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Disclosure statement

The authors declare no conflict of interest.

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Pathogenesis, Biomarkers, and Therapeutic Prospects of Sepsis-Associated Acute Kidney Injury

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Abstract: Sepsis-associated acute kidney injury (SA-AKI) is a common critical complication in the ICU, characterized by a complex pathogenesis involving the interplay of multiple factors such as inflammatory imbalance, vascular dysfunction, coagulation disorders, and cellular metabolic abnormalities. Traditional diagnostic indicators like serum creatinine and blood urea nitrogen exhibit lag time, making early identification challenging. In recent years, novel biomarkers have provided new directions for early diagnosis and risk stratification, including tubular injury markers (KIM-1, NGAL, L-FABP), renal function and glomerular injury markers (CysC, sCD35-uEV), cell cycle arrest markers ([TIMP-2] × [IGFBP7]), and inflammatory markers (IL-18, sTREM-1). Currently, supportive therapy remains the mainstay of treatment, encompassing early anti-infection measures, hemodynamic optimization, and timely renal replacement therapy. Novel therapeutic targets addressing the pathogenesis, such as regulating pyroptosis and improving mitochondrial dysfunction, are currently in preclinical and early clinical research stages, offering hope for future specific treatments.

Keywords: Sepsis-associated acute kidney injury; Biomarkers; Pathogenesis; Inflammatory response; Pyroptosis

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1. Introduction

Sepsis-associated acute kidney injury (SA-AKI) is the most prevalent critical complication in the intensive care unit (ICU), with an incidence rate reaching 40–50% ^[1]. Sepsis stands as the leading cause of AKI, and its renal injury mechanism is complex, involving the interplay of multiple pathophysiological processes such as cytokine storm, microcirculatory disturbances, coagulation disorders, and cell death ^[2].

Currently, the diagnosis of AKI primarily relies on the KDIGO criteria, which are based on elevated serum

creatinine levels and reduced urine output. However, changes in serum creatinine exhibit a lag time and are susceptible to interference from various non-renal factors ^[3]. Urine output indicators are also easily influenced by medications and fluid status, leading to delayed diagnosis and patients missing the optimal treatment window ^[4].

Therefore, the search for highly sensitive and specific biomarkers capable of providing early warning for kidney injury has become crucial for improving the clinical management of sepsis-associated acute kidney injury (SA-AKI) ^[5]. Meanwhile, a thorough elucidation of the multidimensional pathophysiological mechanism network of SA-AKI, particularly the interactions among core aspects such as inflammatory immune imbalance, microcirculatory disorders, coagulation abnormalities, and programmed cell death, is of paramount importance for developing specific therapeutic strategies that surpass traditional supportive therapies ^[6,7].

This article systematically reviews the latest research progress on SA-AKI: evaluating the diagnostic value and clinical significance of novel biomarkers; analyzing its complex pathogenesis, with a focus on key aspects such as inflammatory immunity, vascular dysfunction, coagulation disorders, and cellular injury and metabolic reprogramming; summarizing clinical management strategies; and looking ahead to novel therapeutic targets and intervention strategies targeting key pathological mechanisms, providing theoretical and practical guidance for the early identification, timely intervention, and improvement of prognosis for this disease.

2. Biomarkers for sepsis-associated acute kidney injury

Serum creatinine (Scr) and blood urea nitrogen (BUN) are widely used to assess renal function due to their ease of detection and low cost. However, they are influenced by various factors such as age, nutrition, and metabolism, and typically only increase after a significant decline in glomerular filtration rate, making it difficult to achieve early diagnosis and intervention for SA-AKI ^[1,2]. Therefore, the search for sensitive and specific early biomarkers is imperative. The following is a summary of various novel biomarkers for SA-AKI.

2.1. Renal tubular injury

2.1.1. Kidney injury molecule-1 (KIM-1)

A transmembrane glycoprotein that is highly expressed in the epithelial cells of the proximal renal tubules. After kidney injury, its levels rise faster than serum creatinine (Scr). Studies have shown that urinary KIM-1 begins to increase within 6 hours after patients with sepsis-associated acute kidney injury (SA-AKI) are admitted to the ICU, earlier than the 24-hour change in Scr. Its area under the curve (AUC) for diagnosing SA-AKI is 0.62, making it a superior biomarker to Scr ^[3,8].

2.1.2. Neutrophil gelatinase-associated lipocalin (NGAL)

A secreted protein with a molecular weight of approximately 25 kDa that is expressed at low levels under physiological conditions but significantly upregulated under pathological conditions such as inflammation and injury. Studies have confirmed the value of urinary, serum, and plasma NGAL in the early diagnosis of SA-AKI. Among them, urinary NGAL exhibits the best diagnostic performance (sensitivity 0.87, specificity 0.84, AUC 0.92) and is considered a novel biomarker for SA-AKI ^[4,5].

2.1.3. Liver-type fatty acid-binding protein (L-FABP)

A 14 kDa protein primarily synthesized in the liver. During renal tubular ischemia and hypoxia, its excretion in urine significantly increases. Studies have shown that urinary L-FABP has a sensitivity of 0.74 and a specificity of

0.78 for predicting acute kidney injury (AKI), making it a valuable early biomarker for AKI ^[6].

2.2. Renal function and glomerular injury

2.2.1. Cystatin C (CysC)

A protease inhibitor with a molecular weight of approximately 13 kDa, CysC is stably synthesized in all nucleated cells and is not affected by factors such as age, gender, or muscle mass. In the early diagnosis of sepsis-associated acute kidney injury (SA-AKI), CysC significantly outperforms serum creatinine (Scr), with a sensitivity of 0.84, specificity of 0.82, and an area under the curve (AUC) as high as 0.96 for predicting AKI. Studies have also found that combining CysC with tumor necrosis factor- α (TNF- α) can further enhance diagnostic performance (AUC 0.838) and predict mortality ^[7].

2.2.2. Single extracellular vesicle CD35 derived from glomerular podocytes (sCD35-uEV)

Professor Linli Lv's team has identified a novel biomarker, sCD35-uEV, which demonstrates excellent diagnostic performance (AUC 0.89) and enables early warning. During the subclinical phase when traditional indicators are abnormal, sCD35-uEV levels have already significantly decreased and are correlated with the severity of injury and prognosis. Research has revealed that podocyte injury is a key mechanism underlying SA-AKI ^[9].

2.3. Cell cycle arrest

2.3.1. Insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase-2 (TIMP-2)

IGFBP7 and TIMP-2 are biomarkers that mediate cell cycle arrest in renal tubular cells. In the early stages of renal injury, both are released by renal tubular cells. The product of their concentrations, $[\text{TIMP-2}] \times [\text{IGFBP7}]$, exhibits excellent predictive value for SA-AKI, with an AUC reaching 0.89 ^[10]. Combining this indicator with procalcitonin helps identify patients with SA-AKI and those at high risk of short-term adverse outcomes in the intensive care unit (ICU) ^[11].

2.4. Inflammatory response

2.4.1. Interleukin-18 (IL-18)

As a pro-inflammatory cytokine, IL-18 levels can be detected as elevated in urine within 4–6 hours after the onset of sepsis-associated acute kidney injury (SA-AKI). Studies have shown that urine IL-18 levels in SA-AKI patients in the ICU increase significantly at least 6 hours earlier than serum creatinine (Scr) levels. The diagnostic area under the curve (AUC) after 6 hours is 0.719, which is superior to the 0.677 of Scr, facilitating early prediction of SA-AKI ^[12,13].

2.4.2. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)

A protein of approximately 27 kDa, sTREM-1 is released into the bloodstream and can be excreted in urine during infection and renal injury. Research indicates that sTREM-1 demonstrates early predictive capability 24 hours before the clinical diagnosis of AKI, with AUC values of 0.746 in plasma and 0.778 in urine. Its diagnostic AUC for SA-AKI are 0.794 (plasma) and 0.707 (urine), respectively, and its concentration is positively correlated with the severity of sepsis ^[14].

3. Pathogenesis of sepsis-associated acute kidney injury

The pathogenesis of SA-AKI is a complex, multidimensional, and dynamically intertwined process involving imbalances in inflammatory and immune responses, vascular dysfunction, coagulation disorders, cellular damage, and metabolic disturbances. These mechanisms mutually reinforce each other, collectively driving the progression of renal injury^[15].

3.1. Imbalance between inflammatory and immune responses

During the onset and progression of sepsis-associated acute kidney injury (SA-AKI), the dynamic imbalance between pro-inflammatory and anti-inflammatory responses serves as the core mechanism driving the progression of renal injury. In the early stages of infection, the body simultaneously initiates pro-inflammatory and anti-inflammatory responses to maintain immune homeostasis. On one hand, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate immune cells and renal tubular epithelial cells via Toll-like receptors (TLRs), subsequently activating pathways such as nuclear factor kappa-B (NF- κ B) and mitogen-activated protein kinases (MAPKs). This leads to the release of a large number of pro-inflammatory cytokines, including interleukin-1 beta (IL-1 β), IL-6, tumor necrosis factor-alpha (TNF- α), and IL-18, forming an “inflammatory storm” that directly damages renal tissue and recruits immune cell infiltration^[16–19]. Concurrently, PAMPs/DAMPs can activate the NLRP3 inflammasome, which cleaves gasdermin D (GSDMD) through caspase-1 (classical pathway) or caspase-4/5/11 directly activated by intracellular lipopolysaccharide (LPS) (non-classical pathway), triggering pyroptosis and further amplifying the inflammatory response^[19, 20]. On the other hand, the body initiates anti-inflammatory regulation by expressing inhibitory molecules such as inhibitor of kappa B-alpha (I κ B- α) and activating mRNA degradation pathways^[21]. As sepsis progresses, this fine-tuned regulation becomes imbalanced, resulting in excessive production of pro-inflammatory cytokines and decreased renal clearance capacity. This directly damages renal tubules and microvessels by activating cell death pathways and causing tissue hypoxia^[18,22]. In the later stages of the disease, the body experiences “immune paralysis”, with comprehensive suppression of immune cell function, increasing the risk of secondary infections. This creates a vicious cycle of “uncontrolled inflammation—immunosuppression—re-infection”, continuously exacerbating renal injury^[18,22].

3.2. Vascular dysfunction

Vascular dysfunction represents a pivotal aspect in the pathogenesis of sepsis-associated acute kidney injury (SA-AKI), with its core lying in microcirculatory disturbances rather than the traditionally perceived renal ischemia. Studies have demonstrated that during the early stages of sepsis, total renal blood flow may remain normal or even increase; however, microcirculatory disorders and tissue hypoxia constitute the core mechanisms leading to renal injury^[23]. Macroscopic vascular dysfunction primarily manifests as abnormal renal blood flow distribution. Postglomerular arteriolar dilation and intrarenal shunting redirect blood from the renal medulla, which has a higher oxygen demand, to the cortex, thereby inducing medullary hypoxia^[24]. At the microvascular level, elevated pro-inflammatory cytokines and activated leukocytes during sepsis can trigger microthrombus formation, obstructing renal capillaries, reducing local blood flow, and limiting oxygen diffusion^[23]. Concurrently, they promote the generation of reactive oxygen species, further disrupting the epithelial barrier and exacerbating endothelial leakage^[23,25]. Dysfunction of renal microvascular endothelial cells plays a particularly crucial role in this process. Shedding of the endothelial glycocalyx is a common pathological alteration in sepsis, accompanied by an increase in soluble

glycocalyx components in plasma^[16]. The loss of the glycocalyx facilitates leukocyte leakage and platelet adhesion while reducing blood flow velocity, potentially leading to microthrombus formation and capillary obstruction^[16]. Molecular mechanisms such as the vascular endothelial growth factor/receptor 2 complex, the angiopoietin-Tie2 system, and the sphingosine-1-phosphate/its receptor 1 signaling pathway have all been confirmed to participate in regulating the increased renal microvascular permeability observed in sepsis^[26,27].

3.3. Coagulation dysfunction

In the state of sepsis, an imbalance occurs between the coagulation system and the anticoagulation system. Endothelial injury and inflammatory responses further amplify this imbalance, exacerbating renal injury^[28]. Sepsis rapidly induces an increased expression of procoagulant factors (such as thrombin and tissue factor) within the kidneys, leading to the deposition of fibrin in the glomeruli and microvasculature. Concurrently, microvascular endothelial cells upregulate the expression of protease-activated receptor 2, amplifying procoagulant signals^[29,30]. The weakened or ineffective function of the anticoagulation system further exacerbates the coagulation-anticoagulation imbalance. The quantity of endogenous anticoagulant substances decreases, and antithrombin undergoes accelerated degradation due to increased neutrophil elastase, significantly shortening its half-life; activated protein C (APC), which possesses both anticoagulant and anti-inflammatory properties, also experiences downregulated expression^[31,32]. Additionally, the formation of anticoagulant complexes is hindered. APC requires the synergistic action of endothelial protein C receptor (EPCR) and thrombomodulin (TM) to exert its anticoagulant effects. EPCR promotes the activation of protein C by the thrombin-TM complex, maintaining an anticoagulant state^[33]. During sepsis, the protein levels of EPCR and TM in the kidneys decrease by more than 50%, reducing the formation of anticoagulant complexes and inducing a procoagulant state; simultaneously, the levels of soluble EPCR and TM in the circulation increase, while plasma APC levels decrease, further weakening the body's anticoagulant capacity^[30,34].

3.4. Cellular injury and metabolic disorders

3.4.1. Pyroptosis

Pyroptosis is a form of programmed cell death distinct from apoptosis and necrosis, playing a significant role in the pathogenesis of sepsis-associated acute kidney injury (SA-AKI)^[35,36]. The essence of pyroptosis is triggered by the activation of inflammasomes, relies on Caspase-mediated processes, and ultimately leads to cell membrane perforation and rupture, releasing a large number of inflammatory factors^[37,38]. In SA-AKI, pyroptosis is mainly achieved through the core pathways of classical and non-classical routes: In the classical pathway, inflammasomes such as NLRP3 recognize pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and subsequently activate Caspase-1^[39,40], which then cleaves the GSDMD protein to form membrane pores and promotes the maturation and release of IL-1 β and IL-18^[41–43]. The non-classical pathway directly activates Caspase-4/5 or Caspase-11 through intracellular lipopolysaccharides (LPS), inducing GSDMD cleavage and triggering pyroptosis^[44,45]. Gene knockout studies have demonstrated that inhibiting Caspase-1/11 can significantly alleviate sepsis-induced kidney injury^[46,47].

In addition to the aforementioned core pathways, Z-DNA binding protein 1 (ZBP1) exacerbates pyroptosis-related cell death by recognizing damage signals, thereby intensifying inflammatory death in renal tubular epithelial cells^[48–50]. The activation of the NF- κ B pathway provides essential preparation for inflammasome assembly^[51,52]. Meanwhile, oxidative stress resulting from excessive production of mitochondrial reactive oxygen

species can directly activate NLRP3, forming a vicious cycle that exacerbates kidney injury^[53–55].

3.4.2. Apoptosis

As a form of programmed cell death, apoptosis serves as a crucial mechanism for maintaining intracellular homeostasis in sepsis-associated acute kidney injury (SA-AKI). During the early stages of SA-AKI, renal tubular epithelial cells undergo inflammation, oxidative stress, and ischemia-reperfusion injury, leading to excessive apoptosis in a large number of cells^[56]. Apoptosis occurs through the combined action of endogenous and exogenous pathways. The endogenous pathway involves the opening of mitochondrial permeability transition pores, the release of cytochrome c, the activation of caspase-9, and subsequently caspase-3, initiating the apoptotic cascade. The exogenous pathway is triggered by the binding of Fas to FasL, activating caspase-8, which ultimately also acts on caspase-3^[57,58]. Studies have shown that caspase-3 deficiency can reduce apoptosis in microvascular endothelial cells and renal tubular ischemia in mice with AKI, suggesting its central role in SA-AKI^[59]. Furthermore, pharmacological inhibition of caspase-3 expression significantly improves the survival rate of mice with SA-AKI^[60].

3.4.3. Mitochondrial dysfunction and energy crisis

The kidney, as a highly metabolic organ, is rich in mitochondria, and its functional status directly affects the survival of renal cells. In SA-AKI, mitochondrial dysfunction manifests as reduced ATP production and accumulation of reactive oxygen species, further inducing mitochondrial membrane potential collapse and cytochrome C release, promoting apoptosis and inflammation^[61]. Additionally, mitophagy is a crucial process for clearing damaged mitochondria, and its dysregulation can lead to the accumulation of reactive oxygen species (ROS) and cell death^[62]. PGC-1 α , a key regulator of mitochondrial biogenesis, exhibits decreased expression in sepsis-associated acute kidney injury (SA-AKI), with its levels inversely correlated with the severity of renal injury^[63]. Therefore, restoring mitochondrial function has emerged as a potential therapeutic target for SA-AKI.

3.4.4. Metabolic reprogramming and energy depletion

SA-AKI is accompanied by significant metabolic reprogramming. During the early stages of sepsis, the body initiates transcriptional and translational responses to combat infection, a process that is highly energy-consuming. As the disease progresses, cells enter a “shutdown phase”, characterized by global translational suppression, with eIF2 α phosphorylation serving as a key mechanism^[21]. While this translational shutdown aids in energy conservation, prolonged suppression becomes pathological, hindering repair^[64]. Studies have shown that the use of ISRIB or overexpression of GADD34 can reverse translational suppression and promote renal function recovery^[65]. Furthermore, polyamine metabolism plays a crucial role in renal injury repair, with A-to-I RNA editing of AZIN1 enhancing polyamine synthesis and promoting metabolic adaptation and tissue repair^[66].

4. Prospects for the treatment of sepsis-associated acute kidney injury

SA-AKI involves complex pathophysiological mechanisms, and currently, there are no specific therapeutic interventions available, with clinical management primarily relying on supportive care^[67]. Early identification and intervention are key to improving outcomes, including timely antimicrobial therapy, hemodynamic optimization, and avoidance of nephrotoxic drugs^[68].

Supportive therapy is based on controlling the source of infection and optimizing hemodynamics. According

to guidelines, broad-spectrum antibiotic therapy should be initiated within 1 hour ^[69]. For patients with tissue hypoperfusion or shock, it is recommended to start resuscitation with 30 ml/kg of crystalloid solution and adjust based on fluid responsiveness ^[70]. Although there is controversy regarding the type of crystalloid solution, existing evidence indicates that normal saline does not significantly increase the risk of acute kidney injury (AKI) when the total volume does not exceed 4 liters ^[71]. Norepinephrine is the preferred vasoactive drug, with the goal of maintaining a mean arterial pressure (MAP) > 65 mmHg. Patients with a history of hypertension may require a higher target (e.g., > 85 mmHg) to reduce the progression of AKI and the need for renal replacement therapy ^[72,73].

Novel biomarkers are helpful for early identification and risk stratification. Traditional indicators such as serum creatinine and urine output exhibit a lag in sepsis ^[74]. In contrast, urine [TIMP2] · [IGFBP7] demonstrates good performance in predicting severe AKI, while plasma neutrophil gelatinase-associated lipocalin (NGAL) can indicate tubular injury before creatinine levels rise ^[75,76]. Proenkephalin (penKid) levels are associated with mortality and aid in identifying subclinical AKI ^[77]. Renal resistive index (RRI) allows for bedside assessment of renal perfusion, but its value in predicting the persistence of AKI is limited ^[78].

Regarding renal replacement therapy (RRT), evidence does not support its early prophylactic use ^[79]. Initiation should be based on clear indications such as refractory fluid overload, severe electrolyte disturbances, or acidosis ^[80]. It is recommended that the dose of continuous RRT be set at 20–25 mL/kg/h, and the target for intermittent dialysis be a weekly Kt/V of 3.9 ^[81]. For patients with hemodynamic instability, continuous RRT may offer advantages, but the choice of modality should be individualized ^[82].

In research on novel therapeutic targets, angiotensin II has been shown to improve hemodynamics and reduce the need for RRT in patients with refractory shock ^[83]. Recombinant alkaline phosphatase demonstrates renal protective potential through the dephosphorylation of endotoxins ^[84]. Inhibitors targeting the pyroptosis pathway (such as NLRP3/caspase-1/GSDMD), including MCC950 and VX-765, have exhibited protective effects in preclinical studies ^[46,85]. Phytochemicals like curcumin have also demonstrated therapeutic value in experimental models through multiple mechanisms ^[19].

5. Summary

Sepsis-associated acute kidney injury (SA-AKI) remains a significant clinical challenge in critical care medicine. Despite increasing research into its pathophysiological mechanisms, specific targeted treatment options are still lacking in clinical practice. Reviewing relevant research progress, the main conclusions are as follows.

The key to early diagnosis and risk stratification lies in the application of novel biomarkers. Traditional indicators such as serum creatinine and urine output exhibit significant lag, whereas novel biomarkers (e.g., NGAL, CysC, [TIMP-2] × [IGFBP7], etc.) can provide early warnings of renal injury and offer crucial evidence for precise risk stratification, thereby compensating for the deficiencies of traditional indicators.

The pathogenesis of sepsis-associated acute kidney injury (SA-AKI) is characterized by multidimensional and dynamically intertwined processes, involving multiple aspects such as inflammatory and immune imbalance, vascular dysfunction, coagulation system disorders, cellular damage, and metabolic disturbances. Among these, pyroptosis mediated by the NLRP3 inflammasome/Caspase-1/GSDMD pathway serves as a core hub connecting infection signals to renal injury, playing a pivotal role in the onset and progression of the disease.

Currently, clinical treatment primarily relies on supportive care, emphasizing timely infection control and optimized hemodynamic management. The initiation of renal replacement therapy should be based on clear

clinical indications rather than early preventive application, and treatment plans need to be tailored individually.

The hope for future treatment lies in targeted therapies addressing key pathogenic mechanisms. Inhibitors targeting the pyroptosis pathway, as well as drugs such as angiotensin II and alkaline phosphatase, have demonstrated protective potential in research, while multi-target natural compounds like curcumin warrant further exploration.

Overall, the clinical management of sepsis-associated acute kidney injury (SA-AKI) is shifting from passive support to a precision medicine model based on early warning and targeted interventions. In the future, efforts should focus on promoting the clinical application of novel biomarkers, accelerating the clinical translation of targeted drugs, and exploring individualized treatment strategies to break through the current therapeutic status quo of SA-AKI and improve patient prognosis.

Disclosure statement

The authors declare no conflict of interest.

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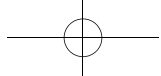
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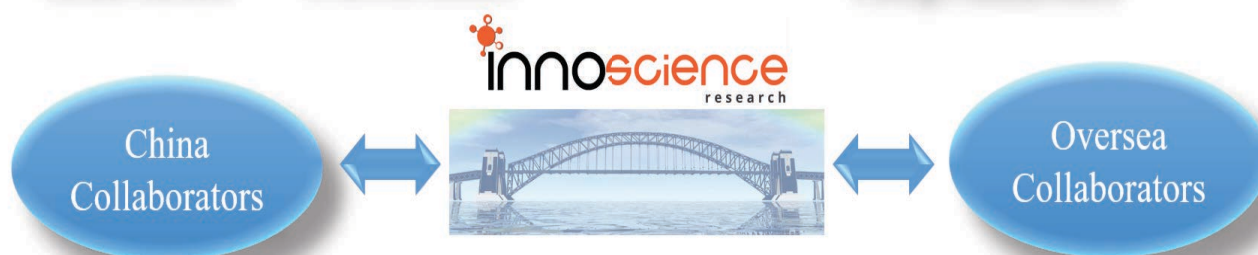
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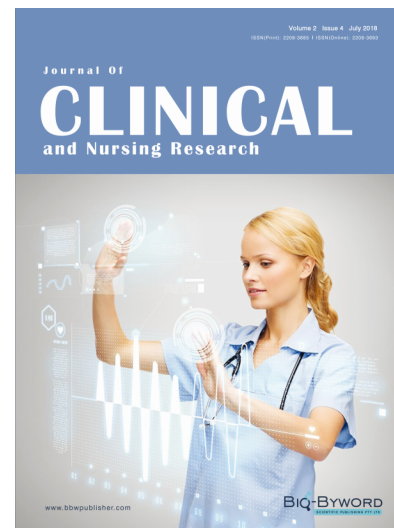
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