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Abnormal Uterine Bleeding in Female Kidney Transplant Recipients: A Cross-Sectional Study Using the FIGO PALM- COEIN Classification

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Abstract

Background

Menstrual disorders are common in chronic kidney disease (CKD), yet data on abnormal uterine bleeding (AUB) in kidney transplant recipients (KTRs) remain limited. We characterized AUB in female KTRs using the FIGO PALM-COEIN system.

Methods

This single-center cross-sectional study enrolled 258 reproductive-aged female KTRs (18–50 years) with stable graft function > 6 months post-transplant. AUB was assessed via a structured questionnaire and classified by PALM-COEIN. Reproductive hormones, transvaginal ultrasonography, and (when available) endometrial pathology were evaluated. Multivariable logistic regression identified factors associated with prevalent AUB.

Results

AUB was present in 94/258 patients (36.4%). Ovulatory dysfunction (36.2%), iatrogenic causes (24.5%), and endometrial causes (12.8%) were the predominant etiologies; heavy menstrual bleeding (37.2%) and irregular bleeding (26.6%) were the leading clinical patterns. Versus non-AUB, AUB patients had higher FSH/LH/prolactin and lower estradiol/progesterone/AMH/testosterone (all $P < 0.001$; testosterone $P = 0.007$). Adjusted ORs: cyclosporine vs. tacrolimus 3.41 (95% CI 1.52–7.66, $P = 0.003$); mTOR inhibitor 3.13 (1.41–6.96, $P = 0.005$); prednisone > 7.5 mg/day 2.05 (1.10–3.85, $P = 0.025$); dialysis vintage ≥ 3 years 1.97 (1.14–3.41, $P = 0.015$). Endometrial sampling in 38 high-risk AUB patients (40.4% of AUB) revealed hyperplasia in 28.9% and one endometrial carcinoma (0.4% of cohort).

Conclusions

AUB affects more than one-third of reproductive-aged female KTRs, driven by ovulatory dysfunction and iatrogenic causes. Cyclosporine, mTOR inhibitors, higher steroid dose, and longer dialysis vintage were independently associated with prevalent AUB. Routine gynecological assessment and individualized immunosuppressive optimization should be incorporated into long-term KTR care.

1. INTRODUCTION

Kidney transplantation is the optimal renal replacement therapy for patients with end-stage renal disease (ESRD), offering superior survival and quality of life compared with maintenance dialysis[1, 2]. Advances in surgical techniques and immunosuppressive regimens have substantially improved long-term graft

and patient survival, shifting the focus of post-transplant care toward chronic complication management and quality of life[3].

Among female kidney transplant recipients (KTRs), reproductive health issues, including menstrual irregularities, sexual dysfunction, and fertility concerns, are increasingly recognized as integral components of comprehensive post-transplant care[4, 5]. Chronic kidney disease (CKD) profoundly disrupts the hypothalamic-pituitary-ovarian (HPO) axis through uremic toxin accumulation, metabolic acidosis, hyperprolactinemia, and chronic inflammation, leading to a high prevalence of menstrual abnormalities ranging from amenorrhea to heavy menstrual bleeding[6–8]. A recent systematic review and meta-analysis demonstrated that menstrual abnormalities were present in 19%–47% of patients on hemodialysis and up to 75% of those on peritoneal dialysis, whereas kidney transplantation was associated with a 7%–30% reduction in the prevalence of these abnormalities[9, 10].

However, despite restoration of HPO axis function following successful kidney transplantation, a substantial proportion of female KTRs continue to experience menstrual disturbances[5, 8, 11]. The persistence of menstrual disorders in this population is multifactorial, encompassing residual endocrine dysfunction, immunosuppressive drug toxicity to the ovaries and endometrium, and comorbidities[4, 12]. The immunosuppressive agents that form the cornerstone of post-transplant management, including glucocorticoids, calcineurin inhibitors (CNIs), and mechanistic target of rapamycin (mTOR) inhibitors, exert multifaceted effects on the reproductive system[4, 13]. Sirolimus, in particular, has been associated with reversible gonadal dysfunction manifested by amenorrhea and ovarian cyst formation[14, 15].

Despite the clinical significance of this issue, the existing literature on menstrual disorders in KTRs is characterized by several limitations: small sample sizes (typically 20–60 patients), inconsistent definitions of menstrual abnormalities, the absence of standardized classification systems, and a paucity of data from Asian populations[9, 16]. The International Federation of Gynecology and Obstetrics (FIGO) PALM-COEIN classification system, introduced in 2011, provides a standardized framework that classifies the causes of AUB in non-pregnant reproductive-aged women as either structural (PALM: Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia) or non-structural (COEIN: Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, Not yet classified) [17]. To date, no study has systematically applied this classification to evaluate AUB in KTRs.

Therefore, we conducted this single-center cross-sectional study to: (1) determine the prevalence and spectrum of AUB in reproductive-aged female KTRs using the FIGO PALM-COEIN classification; (2) characterize the reproductive hormone profiles associated with AUB in this population; (3) identify factors independently associated with prevalent AUB, with particular attention to immunosuppressive regimens; and (4) describe endometrial histopathological findings in KTRs undergoing endometrial sampling.

2. METHODS

2.1 Study Design and Population

This single-center, cross-sectional study was conducted at The Second Affiliated Hospital of Guangzhou Medical University between January 2024 and December 2025. The study protocol was approved by the Institutional Review Board (Approval No. LYZX-2026-139; date of approval: March 1, 2024; the "2026" in the approval number reflects the institutional numbering convention rather than the year of approval) and complied with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Female KTRs were consecutively enrolled if they met the following inclusion criteria: (1) age 18–50 years at enrollment; (2) ≥ 6 months after kidney transplantation with stable graft function (defined as < 20% variation in serum creatinine over the preceding 3 months); (3) presence of a uterus and at least one ovary; and (4) ability to provide informed consent and complete the study questionnaire. Exclusion criteria were as follows: (1) current pregnancy or breastfeeding; (2) hysterectomy or bilateral oophorectomy prior to enrollment; (3) acute rejection episode within the preceding 3 months; (4) use of hormonal contraceptives therapy within the preceding 3 months; (5) known hypothalamic or pituitary disease unrelated to CKD; and (6) active malignancy other than non-melanoma skin cancer.

A total of 312 female KTRs were screened during the study period. Of these, 54 were excluded: 18 due to age > 50 years, 12 due to hysterectomy, 7 due to hormonal contraceptive therapy use, 8 due to acute rejection within the preceding 3 months, and 9 due to refusal to participate. No patients were excluded due to current pregnancy or breastfeeding.

2.2 Data Collection

Demographic, clinical, and transplant-related data were extracted from the institutional electronic medical record system and the transplant database. The following variables were collected: age, body mass index (BMI), etiology of ESRD, dialysis modality and vintage, donor type (living vs. deceased), date of transplantation, number of previous transplants, current immunosuppressive regimen (agents and dosages), trough levels of calcineurin inhibitors and mTOR inhibitors, serum creatinine, estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI 2021 equation), 24-hour urine protein, and comorbidities (hypertension, diabetes mellitus). Hemoglobin, ferritin, platelet count, and thyroid-stimulating hormone (TSH) were collected as part of the routine clinical laboratory panel and were available for analyses. Obstetric and gynecological history, including age at menarche, parity, and previous gynecological diagnoses or surgeries, was obtained through chart review and patient interview.

2.3 Assessment and Classification of Abnormal Uterine Bleeding

AUB was assessed using a structured questionnaire adapted from the FIGO AUB Symptom Questionnaire[18], which was translated into Chinese by two bilingual investigators and validated for internal consistency in a pilot sample of 30 patients (Cronbach's α = 0.86); face validity was assessed by

two gynecologists prior to the main study. An English-language version of the adapted questionnaire is provided as **Supplementary File 1**. The questionnaire captured detailed information on menstrual patterns over the preceding 6 months, including cycle length, duration of menses, regularity, flow volume (assessed by the Pictorial Blood Loss Assessment Chart, PBAC), and the presence of intermenstrual or postcoital bleeding.

AUB was defined according to FIGO criteria as any deviation from normal menstrual parameters: frequency (normal: 24–38 days), regularity (normal: cycle-to-cycle variation ≤ 7–9 days), duration (normal: ≤8 days), or volume (subjectively defined as heavy when it interferes with quality of life, or objectively when PBAC score > 100)[17, 18]. Patients meeting AUB criteria were further classified using the PALM-COEIN system based on clinical evaluation, laboratory testing, transvaginal ultrasonography (TVUS), and endometrial histopathology when available. Classification was independently performed by a gynecologist and a transplant nephrologist across all 94 AUB patients; the inter-rater agreement was substantial (Cohen's $\kappa = 0.82$). Discrepancies were resolved by consensus. All applicable PALM-COEIN categories were recorded for each patient, allowing for overlapping etiologies. For the primary analysis, a single dominant category was assigned; coexisting categories are reported in **Supplementary Table S1**. Ovulatory dysfunction (AUB-O) was diagnosed in patients with anovulatory bleeding patterns (cycle-to-cycle variation > 9 days, cycle length > 38 days, or amenorrhea ≥ 3 months) after clinical evaluation had excluded thyroid dysfunction (TSH), polycystic ovary syndrome (Rotterdam criteria), and premature ovarian insufficiency (FSH > 40 IU/L on two occasions); hyperprolactinemia was not used as an exclusion criterion but was considered a potential cause of ovulatory dysfunction, consistent with the FIGO PALM-COEIN framework in which hyperprolactinemia is a recognized cause of AUB-O. Single progesterone measurements were insufficient for diagnosis. Iatrogenic AUB (AUB-I) required documentation of a temporal relationship between immunosuppressive drug initiation or dose adjustment and AUB onset or exacerbation, with exclusion of alternative structural or endocrine causes.

2.4 Laboratory and Imaging Assessments

Fasting blood samples were collected during the early follicular phase (cycle days 2–5) in menstruating patients, or on any day in those with amenorrhea or oligomenorrhea. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone, prolactin, and testosterone were measured using electrochemiluminescence immunoassay (Roche Cobas e801, Mannheim, Germany). Anti-Müllerian hormone (AMH) was measured using the Elecsys AMH Plus assay (Roche Diagnostics). Trough levels of tacrolimus, cyclosporine, and everolimus were determined from whole blood samples. In practice, however, strict adherence to the cycle days 2–5 window was not achieved for all menstruating participants; post hoc review of the raw data indicated that a substantial proportion of samples were drawn outside the early follicular phase. Accordingly, all hormone comparisons should be interpreted with caution.

TVUS was performed in all enrolled patients by experienced sonographers using a Voluson E8 ultrasound system (GE Healthcare, Milwaukee, WI, USA) with a 5–9 MHz transvaginal probe. Parameters assessed included endometrial thickness, presence of polyps and submucosal fibroids, adenomyosis,

and ovarian morphology (volume and antral follicle count). To standardize measurements, TVUS was performed during the early follicular phase (cycle days 2–5) in menstruating patients or on a convenient day in those with amenorrhea or oligomenorrhea, and endometrial thickness was measured at its maximum in the sagittal plane by the same team of sonographers. Endometrial sampling (hysteroscopy-directed biopsy) was performed in patients with AUB who had an endometrial thickness > 10 mm on TVUS. This threshold, informed by the American College of Obstetricians and Gynecologists (ACOG) practice bulletin on AUB and consistent with local institutional protocol, was not applied as a stand-alone criterion; biopsy was also performed for clinical indications, including persistent irregular bleeding despite medical management and risk factors for endometrial pathology (obesity, diabetes, and prolonged unopposed estrogen exposure). Endometrial histopathology was classified according to the WHO Classification of Tumours of Female Reproductive Organs, 5th edition[19].

2.5 Statistical Analysis

Sample size was calculated based on an estimated AUB prevalence of 35% in KTRs, with a desired precision of ± 6% and a two-sided alpha of 0.05, yielding a minimum required sample of 243 patients. To account for approximately 6% incomplete data, a target enrollment of 258 was set.

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate based on distribution, and compared using the independent-samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were presented as frequencies (percentages) and compared using the chi-squared test or Fisher's exact test. Univariate logistic regression was performed to identify candidate variables associated with AUB ($P < 0.10$ threshold for inclusion in the multivariable model). Multivariable logistic regression with backward stepwise selection (chosen over forward selection to avoid suppressor effects) was used to identify factors independently associated with prevalent AUB, with results expressed as adjusted odds ratios (OR) and 95% confidence intervals (CI). Collinearity was assessed using variance inflation factors (VIF), with VIF > 5 considered indicative of significant multicollinearity. All VIF values were < 3, indicating no significant multicollinearity (range: 1.19 for CsA use to 2.38 for deceased donor status). Continuous variables were dichotomized using clinically relevant thresholds from the literature: age ≥ 40 years, dialysis vintage ≥ 3 years, time post-transplant ≥ 5 years, BMI ≥ 25 kg/m², and eGFR < 45 mL/min/1.73 m² (CKD stage 3b). Sensitivity analyses in which age, dialysis vintage, eGFR, and time post-transplant were retained as continuous covariates are presented in Supplementary Table S2. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test and the area under the receiver operating characteristic (ROC) curve (AUC).

Subgroup analyses were performed with stratification by immunosuppressive regimen (CNI type, mTOR inhibitor use) and age group (< 40 vs. ≥40 years). Results of the mTOR inhibitor subgroup comparison for AMH are reported in Section 3.5; other subgroup comparisons are presented in **Supplementary Table S3**. All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Given the exploratory nature of this study, no formal correction for multiple comparisons was applied; results should be interpreted accordingly. A two-sided P value < 0.05 was considered nominally significant.

3. RESULTS

3.1 Baseline Characteristics

The final study cohort comprised 258 patients. The baseline demographic and clinical characteristics, stratified by AUB status, are summarized in Table 1; ESRD etiologies are reported in the text and are not tabulated. The mean age was 36.7 ± 7.5 years (range 18–50) and the mean time post-transplant was 4.6 ± 2.8 years. The most common etiologies of ESRD were chronic glomerulonephritis (43.0%), hypertensive nephrosclerosis (16.3%), and diabetic nephropathy (11.6%). Living donor transplantation accounted for 25.6% of cases, and 6.2% of patients had undergone a previous transplant. The mean eGFR was 62.8 ± 19.6 mL/min/1.73 m². The most common immunosuppressive regimen was tacrolimus + mycophenolate mofetil + prednisone (61.6%), followed by cyclosporine + mycophenolate mofetil + prednisone (12.0%).

Table 1
Baseline Characteristics of Female Kidney Transplant Recipients Stratified by Abnormal Uterine Bleeding Status

Characteristic	Total (n = 258)	AUB (n = 94)	Non-AUB (n = 164)	P value
Age, years	36.7 ± 7.5	38.4 ± 7.2	35.7 ± 7.5	0.008
Age 18–30 years, n (%)	53 (20.5)	13 (13.8)	40 (24.4)	
Age 31–40 years, n (%)	113 (43.8)	42 (44.7)	71 (43.3)	0.096†
Age 41–50 years, n (%)	92 (35.7)	39 (41.5)	53 (32.3)	
BMI, kg/m²	23.7 ± 3.8	24.5 ± 4.3	23.3 ± 3.4	0.086
Time post-transplant, years	4.6 ± 2.8	4.7 ± 2.9	4.6 ± 2.8	0.795
Dialysis vintage, years	2.8 ± 1.9	3.2 ± 2.2	2.5 ± 1.7	0.022
Living donor, n (%)	66 (25.6)	24 (25.5)	42 (25.6)	0.989
Deceased donor, n (%)	192 (74.4)	70 (74.5)	122 (74.4)	
Previous transplant, n (%)	16 (6.2)	6 (6.4)	10 (6.1)	0.927
eGFR, mL/min/1.73m²	62.8 ± 19.6	59.1 ± 18.9	65.0 ± 19.8	0.054
eGFR < 45 mL/min/1.73m², n (%)	45 (17.4)	18 (19.1)	27 (16.5)	0.584
Serum creatinine, mg/dL	1.10 ± 0.42	1.13 ± 0.47	1.08 ± 0.39	0.243
Proteinuria ≥ 0.5 g/day, n (%)	55 (21.3)	28 (29.8)	27 (16.5)	0.012
Hypertension, n (%)	200 (77.5)	77 (81.9)	123 (75.0)	0.200
Diabetes mellitus, n (%)	30 (11.6)	17 (18.1)	13 (7.9)	0.014
Parity ≥ 1, n (%)	145 (56.2)	48 (51.1)	97 (59.1)	0.208
Menarche age, years	13.7 ± 1.5	13.7 ± 1.3	13.7 ± 1.6	0.915
Cycle length, days	33.7 ± 13.6	44.2 ± 17.6	27.6 ± 4.0	< 0.001
Duration of menses, days	5.7 ± 2.6	7.2 ± 3.6	4.9 ± 1.2	< 0.001

Data are presented as mean ± SD or n (%). AUB, abnormal uterine bleeding; BMI, body mass index; eGFR, estimated glomerular filtration rate, calculated using the CKD-EPI 2021 equation. †P value for the age strata (18–30, 31–40, and 41–50 years) refers to the overall comparison across the three age groups.

Compared with the non-AUB group, patients with AUB were significantly older (38.4 ± 7.2 vs. 35.7 ± 7.5 years, P = 0.008), had a longer dialysis vintage (3.2 ± 2.2 vs. 2.5 ± 1.7 years, P = 0.022). They also had a higher prevalence of diabetes mellitus (18.1% vs. 7.9%, P = 0.014) and proteinuria ≥ 0.5 g/day (29.8% vs. 16.5%, P = 0.012). By contrast, BMI (24.5 ± 4.3 vs. 23.3 ± 3.4 kg/m², P = 0.086), time post-transplant (4.7

± 2.9 vs. 4.6 ± 2.8 years, P = 0.795), and eGFR (59.1 ± 18.9 vs. 65.0 ± 19.8 mL/min/1.73 m², P = 0.054) did not differ significantly. Both cycle length (44.2 ± 17.6 vs. 27.6 ± 4.0 days) and duration of menses (7.2 ± 3.6 vs. 4.9 ± 1.2 days) were significantly longer in the AUB group (P < 0.001 for both).

3.2 Prevalence and Classification of AUB

AUB was diagnosed in 94 of 258 patients, yielding a prevalence of 36.4% (95% CI 30.5%–42.6%). Table 2 summarizes the distribution of AUB according to the FIGO PALM-COEIN classification. Among the 94 AUB patients, non-structural (COEIN) causes predominated, accounting for 74.5% (n = 70) of cases, whereas structural (PALM) causes accounted for 25.5% (n = 24). Ovulatory dysfunction (O; n = 34 of 94 AUB patients, 36.2%) was the single most common category, followed by iatrogenic causes (I, 24.5%) and endometrial disorders (E, 12.8%). Leiomyoma (L, 9.6%), polyps (P, 9.6%), adenomyosis (A, 4.3%), and malignancy/hyperplasia (M, 2.1%) accounted for the remaining structural causes. One patient (1.1%) had AUB attributed to coagulopathy (thrombocytopenia secondary to mycophenolate mofetil).

Table 2
Classification of Abnormal Uterine Bleeding According to the FIGO PALM-COEIN System (n = 94)

PALM-COEIN Category	**n**	**%**
PALM — Structural causes		
Polyp (P)	9	9.6
Adenomyosis (A)	4	4.3
Leiomyoma (L)	9	9.6
Malignancy & hyperplasia (M)	2	2.1
PALM subtotal	24	25.5
COEIN — Non-structural causes		
Coagulopathy (C)	1	1.1
Ovulatory dysfunction (O)	34	36.2
Endometrial (E)	12	12.8
Iatrogenic (I)	23	24.5
COEIN subtotal	70	74.5
Total	**94**	**100.0**

FIGO, International Federation of Gynecology and Obstetrics; PALM, structural causes (Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia); COEIN, non-structural causes (Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, Not yet classified). Some patients had overlapping etiologies; the primary contributing cause is reported. Percentages may not sum to the subtotals or to 100% because of rounding.

AUB-O was diagnosed in patients with anovulatory bleeding patterns after clinical exclusion of thyroid dysfunction, polycystic ovary syndrome, and premature ovarian insufficiency; hyperprolactinemia was considered a potential cause of ovulatory dysfunction rather than an exclusion criterion (see Methods Section 2.3*).*

Regarding clinical bleeding patterns (Table 3), heavy menstrual bleeding was the most common presentation (37.2%), followed by irregular menstrual bleeding (26.6%), oligomenorrhea (21.3%), secondary amenorrhea (7.4%), and intermenstrual bleeding (7.4%).

Table 3
Clinical Bleeding Patterns in Kidney Transplant Recipients with Abnormal Uterine Bleeding (n = 94)

Bleeding Pattern	n	%
Heavy menstrual bleeding	35	37.2
Irregular menstrual bleeding	25	26.6
Oligomenorrhea	20	21.3
Secondary amenorrhea	7	7.4
Intermenstrual bleeding	7	7.4
Total	**94**	**100.0**

AUB was defined according to FIGO criteria as any deviation from normal menstrual parameters in frequency, regularity, duration, or volume. Patients may have reported more than one bleeding pattern; the predominant pattern is reported.

3.3 Immunosuppressive Regimens and AUB Risk

The distribution of immunosuppressive regimens and their univariate associations with AUB are summarized in Table 4. Compared with the reference regimen of tacrolimus + mycophenolate mofetil + prednisone, the cyclosporine-based regimen was associated with the highest AUB risk (OR 3.45, 95% CI 1.56–7.65, P = 0.002), closely followed by the mTOR inhibitor–containing regimen (n = 31; tacrolimus + mycophenolate mofetil + prednisone + everolimus; OR 3.02, 95% CI 1.37–6.64, P = 0.006). Compared with low-dose prednisone (< 5 mg/day), AUB risk increased with higher prednisone doses in a dose-dependent manner (5–7.5 mg/day: OR 3.32, 95% CI 1.70–6.49, P < 0.001; >7.5 mg/day: OR 4.32, 95% CI 2.04–9.17, P < 0.001). Patients receiving tacrolimus + azathioprine + prednisone had the lowest AUB prevalence among treated patients (25.9%), although the difference relative to the reference regimen was not statistically significant (OR 0.76, 95% CI 0.30–1.92, P = 0.566). No AUB was observed among the 10 patients receiving other regimens.

Table 4
Immunosuppressive Regimens and Risk of Abnormal Uterine Bleeding in Female Kidney Transplant Recipients

Immunosuppressive Regimen	Total (n = 258)	AUB (n = 94)	Non-AUB (n = 164)	OR (95% CI)	P value
Tac + MMF + Pred	159 (61.6)	50 (53.2)	109 (66.5)	1.00 (Reference)	—
CsA + MMF + Pred	31 (12.0)	19 (20.2)	12 (7.3)	3.45 (1.56–7.65)	0.002
Tac + MMF + Pred + mTORi	31 (12.0)	18 (19.1)	13 (7.9)	3.02 (1.37–6.64)	0.006
Tac + Aza + Pred	27 (10.5)	7 (7.4)	20 (12.2)	0.76 (0.30–1.92)	0.566
Other regimens	10 (3.9)	0 (0.0)	10 (6.1)	Not estimable*	—
Prednisone dose					
< 5 mg/day	82 (31.8)	15 (16.0)	67 (40.9)	1.00 (Reference)	—
5–7.5 mg/day	115 (44.6)	49 (52.1)	66 (40.2)	3.32 (1.70–6.49)	< 0.001
> 7.5 mg/day	61 (23.6)	30 (31.9)	31 (18.9)	4.32 (2.04–9.17)	< 0.001

*Data are presented as n (%). OR, odds ratio; CI, confidence interval; Tac, tacrolimus; MMF, mycophenolate mofetil; Pred, prednisone; CsA, cyclosporine; mTORi, mechanistic target of rapamycin inhibitor (everolimus); Aza, azathioprine. ORs were calculated using univariate logistic regression, with Tac + MMF + Pred as the reference category for regimen comparisons and prednisone < 5 mg/day as the reference category for dose comparisons. *The odds ratio for other regimens could not be estimated because no AUB events occurred among the 10 patients in this subgroup.*

3.4 Factors Independently Associated with AUB

Multivariable logistic regression analysis identified four factors independently associated with prevalent AUB in female KTRs (Table 5). Cyclosporine use versus tacrolimus (reference) (adjusted OR 3.41, 95% CI 1.52–7.66, P = 0.003) and mTOR inhibitor use (adjusted OR 3.13, 95% CI 1.41–6.96, P = 0.005) were the factors most strongly associated with prevalent AUB, followed by prednisone dose > 7.5 mg/day (adjusted OR 2.05, 95% CI 1.10–3.85, P = 0.025) and dialysis vintage ≥ 3 years (adjusted OR 1.97, 95% CI 1.14–3.41, P = 0.015). Age ≥ 40 years, eGFR < 45 mL/min/1.73 m², BMI ≥ 25 kg/m², time post-transplant ≥ 5 years, and deceased donor status did not reach the P < 0.10 threshold for entry in univariate screening. The multivariable model demonstrated moderate discrimination (AUC 0.694, 95% CI 0.625–0.764) and suboptimal calibration (Hosmer-Lemeshow P < 0.001).

Table 5
Multivariable Logistic Regression Analysis: Independent Risk Factors for Abnormal Uterine Bleeding

Variable	Adjusted OR	95% CI	P value
CsA vs. Tac (reference)	3.41	1.52–7.66	0.003
mTOR inhibitor use (yes vs. no)	3.13	1.41–6.96	0.005
Prednisone dose > 7.5 mg/day	2.05	1.10–3.85	0.025
Dialysis vintage ≥ 3 years	1.97	1.14–3.41	0.015

Variables with P < 0.10 in univariate analysis were entered into the multivariable model. Backward stepwise selection was used. Age ≥ 40 years, eGFR < 45 mL/min/1.73 m², BMI ≥ 25 kg/m², time post-transplant ≥ 5 years, and deceased donor status did not reach the P < 0.10 threshold for entry in univariate screening and were not entered. The model demonstrated moderate discrimination (AUC 0.694, 95% CI 0.625–0.764) and suboptimal calibration (Hosmer-Lemeshow test, P < 0.001). OR, adjusted odds ratio; CI, confidence interval; mTOR, mechanistic target of rapamycin; CsA, cyclosporine; Tac, tacrolimus; eGFR, estimated glomerular filtration rate; BMI, body mass index.

3.5 Reproductive Hormone Profiles

Reproductive hormone levels stratified by AUB status are shown in Table 6. Patients with AUB exhibited a hormonal profile consistent with impaired ovarian function and HPO axis dysregulation. However, hormone measurements in amenorrheic/oligomenorrheic patients were obtained without cycle-phase control, limiting the interpretability of FSH, LH, estradiol, and progesterone in this subgroup. Hormone values stratified by menstrual status (menstruating, n = 67 vs. amenorrheic/oligomenorrheic, n = 27) are presented in **Supplementary Table S4**. Patients with AUB were characterized by significantly higher FSH (19.0 ± 11.5 vs. 10.7 ± 7.9 IU/L, P < 0.001), LH (13.9 ± 9.6 vs. 8.7 ± 5.7 IU/L, P < 0.001), and prolactin (29.2 ± 17.1 vs. 19.5 ± 11.0 ng/mL, P < 0.001), and significantly lower estradiol (51.5 ± 32.8 vs. 70.1 ± 34.7 pg/mL, P < 0.001), progesterone (median 3.1 [IQR 0.3–5.1] vs. 8.4 [IQR 3.5–12.6] ng/mL, P < 0.001), AMH (median 1.2 [IQR 0.3–2.0] vs. 2.9 [IQR 1.1–4.4] ng/mL, P < 0.001), and testosterone (0.40 ± 0.30 vs. 0.50 ± 0.30 ng/mL, P = 0.007). Hyperprolactinemia (prolactin > 25 ng/mL) was present in 107 of 258 patients (41.5%) overall and was significantly more frequent in AUB than non-AUB patients (54/94, 57.4% vs. 53/164, 32.3%; P < 0.001); among the 34 patients classified as AUB-O, 23 (67.6%) had prolactin levels > 25 ng/mL, indicating that prolactin elevation frequently coexists with anovulatory bleeding in this population. Of note, the median progesterone of 8.4 ng/mL (IQR 3.5–12.6) in the non-AUB group is not physiologically consistent with strict early follicular phase sampling; 64 of 164 (39.0%) non-AUB patients had progesterone levels > 10 ng/mL, confirming that a substantial proportion of samples were collected outside the early follicular phase, likely reflecting luteal-phase sampling despite protocol instructions. This reflects the real-world difficulty of precisely scheduling blood draws within narrow cycle windows in a busy transplant clinic. To further address this issue, we performed a sensitivity analysis restricted to participants with progesterone ≤ 1.5 ng/mL (indicative of true early follicular phase; n = 63: 33 AUB vs. 30 non-AUB), presented in **Supplementary Table S5**.

Table 6
Reproductive Hormone Profiles in Kidney Transplant Recipients with and without Abnormal Uterine Bleeding

Hormone	AUB (n = 94)	Non-AUB (n = 164)	P value
FSH, IU/L	19.0 ± 11.5	10.7 ± 7.9	< 0.001
LH, IU/L	13.9 ± 9.6	8.7 ± 5.7	< 0.001
Estradiol (E2), pg/mL	51.5 ± 32.8	70.1 ± 34.7	< 0.001
Progesterone, ng/mL	3.1 (0.3–5.1)	8.4 (3.5–12.6)	< 0.001
Prolactin, ng/mL	29.2 ± 17.1	19.5 ± 11.0	< 0.001
AMH, ng/mL	1.2 (0.3–2.0)	2.9 (1.1–4.4)	< 0.001
Testosterone, ng/mL	0.40 ± 0.30	0.50 ± 0.30	0.007

Data are presented as mean ± SD for normally distributed hormones and as median (IQR) for AMH and progesterone, which showed right-skewed distributions. Blood samples were collected during the early follicular phase (cycle days 2–5) in menstruating patients, or on any day in those with amenorrhea or oligomenorrhea. FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-Mullerian hormone. P values were calculated using the independent-samples t-test for normally distributed hormones and the Mann-Whitney U test for AMH and progesterone.

As shown in **Supplementary Table S4**, hormone profiles did not differ significantly between menstruating (n = 67) and amenorrheic/oligomenorrheic (n = 27) AUB patients (e.g., FSH 19.4 ± 11.2 vs. 18.1 ± 12.4 IU/L, P = 0.59; estradiol 51.3 ± 34.7 vs. 52.2 ± 28.2 pg/mL, P = 0.36; AMH median 1.2 [IQR 0.3–1.9] vs. 1.3 [IQR 0.3–2.4] ng/mL, P = 0.51; prolactin 31.1 ± 17.9 vs. 24.6 ± 14.5 ng/mL, P = 0.07). These data indicate that the ovarian dysfunction signal was shared across AUB phenotypes rather than confined to the non-cycling subgroup. However, the small size of the non-cycling subgroup (n = 27) limits the statistical power of these comparisons. AMH levels were also significantly lower in the mTOR inhibitor subgroup than in the non-mTOR inhibitor subgroup among AUB patients (median 0.9 [IQR 0.2–1.2] vs. 1.5 [IQR 0.3–2.1] ng/mL, P = 0.019), suggesting a more pronounced reduction in ovarian reserve associated with mTOR inhibitor exposure.

3.6 Endometrial Histopathology

Endometrial sampling was performed in 38 of the 94 AUB patients (40.4%). Indications for biopsy included: endometrial thickness > 10 mm on TVUS (n = 18), persistent irregular bleeding despite medical management (n = 12), and risk factors for endometrial pathology (n = 8). Histopathological findings are summarized in Table 7. These 38 patients thus represented a clinically selected high-risk subgroup. Proliferative endometrium was the most common finding (36.8%), followed by secretory endometrium (26.3%). Notably, endometrial hyperplasia was detected in 11 patients (28.9%), of whom 3 (7.9%) had atypical hyperplasia, a premalignant lesion. One patient (1/38 biopsies, 2.6%; 1/258 total cohort, 0.4%), a 46-year-old woman 8 years post-transplant receiving cyclosporine-based immunosuppression with obesity (BMI 32.5 kg/m²) and diabetes, was diagnosed with endometrioid endometrial carcinoma (FIGO

Grade 1, Stage IA). Of note, only 2 of the 94 AUB patients (2.1%) were assigned AUB-M as the primary PALM-COEIN category at clinical classification, despite histologically confirmed endometrial hyperplasia in 11 biopsied patients (and one case of carcinoma). Most hyperplastic lesions were not clinically suspected before biopsy and were identified only after histopathological examination, whereas AUB-M was reserved for patients in whom endometrial malignancy or hyperplasia was clinically suspected and subsequently confirmed. This discrepancy reflects the inherent limitation of clinical pre-biopsy classification.

Table 7
Endometrial Histopathological Findings in Kidney Transplant Recipients Undergoing Biopsy for Abnormal Uterine Bleeding (n = 38)

Histopathological Finding	**n**	**%**
Proliferative endometrium	14	36.8
Secretory endometrium	10	26.3
Endometrial hyperplasia without atypia	8	21.1
Endometrial hyperplasia with atypia	3	7.9
Atrophic endometrium	2	5.3
Endometrial carcinoma	1	2.6
Total	**38**	**100.0**
Endometrial sampling (pipelle biopsy or hysteroscopy-directed biopsy) was performed in patients with endometrial thickness > 10 mm on transvaginal ultrasonography, persistent irregular bleeding despite medical management, or additional risk factors for endometrial pathology. Histopathological classification followed the WHO classification of tumours of female reproductive organs.		
Among the 38 patients who underwent biopsy, endometrial hyperplasia was most frequent in the mTOR inhibitor group (5/9, 55.6%), followed by the tacrolimus + mycophenolate mofetil + prednisone group (4/13, 30.8%) and the cyclosporine-based group (2/9, 22.2%); no hyperplasia was observed among the 7 patients receiving tacrolimus + azathioprine + prednisone. The difference between cyclosporine- and tacrolimus-based regimens was not statistically significant (2/9 vs. 4/20, P = 1.000, Fisher's exact test), and the small subgroup sizes preclude definitive conclusions.		

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4. DISCUSSION

In this single-center cross-sectional study of 258 reproductive-aged female kidney transplant recipients, we present, to our knowledge, the first comprehensive characterization of AUB using the standardized FIGO PALM-COEIN classification. Our principal findings are as follows: (1) AUB affected more than one-third (36.4%) of female KTRs; (2) non-structural etiologies accounted for the majority of cases, predominantly ovulatory dysfunction (36.2%) and iatrogenic causes (24.5%); (3) cyclosporine use (adjusted OR 3.41) and mTOR inhibitor use (adjusted OR 3.13) were the factors most strongly associated with prevalent AUB; and (4) 28.9% of biopsied patients had endometrial hyperplasia, including 7.9% with atypical hyperplasia and one case of endometrial carcinoma.

The 36.4% prevalence of AUB observed in our cohort is consistent with the 19%–28% post-transplant range reported in the systematic review by Rytz et al. (2022)[9], albeit at the higher end of the spectrum. This may reflect the intentional recruitment of patients across a broad age range and the use of a structured, FIGO-based questionnaire that captures subtle menstrual abnormalities often missed in routine clinical encounters. As noted by Pellegrini et al. (2026), 20% of Italian transplant centers do not routinely inquire about gonadal function during follow-up visits[20], highlighting a systematic under-recognition of this issue. Our findings indicate that systematic screening for AUB is preferable to reliance on spontaneous patient reporting.

The predominance of non-structural causes of AUB, particularly ovulatory dysfunction and iatrogenic factors, points to disruption of the HPO axis and immunosuppressive drug effects as central mechanisms in the pathogenesis of post-transplant menstrual disorders. Our hormonal data corroborate this interpretation: AUB patients demonstrated a profile of elevated gonadotropins (FSH, LH) with low estradiol, consistent with impaired ovarian responsiveness. These hormonal differences were directionally consistent in the sensitivity analysis restricted to samples with progesterone ≤ 1.5 ng/mL (**Supplementary Table S5**); however, because a substantial proportion of hormone samples were not obtained under strict cycle-phase control, the present findings should be regarded as exploratory and do not permit definitive conclusions regarding the underlying ovarian phenotype. The significantly lower AMH levels in the AUB group (median 1.2 vs. 2.9 ng/mL) are consistent with impaired ovarian function, in line with the findings of Wiles et al. (2021), who demonstrated that AMH concentrations are altered across the spectrum of CKD severity and after kidney transplantation[10]. Because participants with AUB were significantly older than those without AUB (38.4 vs. 35.7 years), age is a potential confounder of the observed hormonal differences. However, within-age-stratum comparisons (< 40 vs. ≥40 years, **Supplementary Table S3**) showed that AUB remained associated with lower AMH and higher FSH/LH in both age groups, indicating that the hormonal differences are not fully attributable to age, although age-related ovarian changes likely contribute.

Hyperprolactinemia deserves particular attention in KTRs. Prolactin levels > 25 ng/mL were observed in 41.5% of the overall cohort and in 67.6% of patients classified as AUB-O, a prevalence markedly exceeding the low prevalence reported in the general reproductive-aged population. Elevated prolactin in KTRs is multifactorial, reflecting reduced renal clearance, altered hypothalamic dopaminergic tone in CKD[21], and drug-related effects (e.g., calcineurin inhibitors, glucocorticoids, and proton pump

inhibitors). Because a single measurement is insufficient to establish a diagnosis of hyperprolactinemia and confirmatory repeat testing was not routinely performed, patients with elevated prolactin were retained within the AUB-O category rather than excluded, in accordance with the FIGO framework in which hyperprolactinemia is a recognized cause of ovulatory dysfunction. Nonetheless, largely drug-related prolactin elevation may have contributed to ovulatory dysfunction in a substantial proportion of cases, and prospective studies incorporating confirmatory prolactin testing are needed to disentangle drug-related hyperprolactinemia from primary ovulatory dysfunction.

The strong association between mTOR inhibitor use and AUB (adjusted OR 3.13) is one of the most clinically relevant findings of this study. Whereas the gonadotoxic effects of sirolimus have been described in case series[15, 22], our study quantifies this association with multivariable adjustment, although the wide 95% confidence interval (1.41–6.96) reflects the limited number of mTOR inhibitor-treated patients (n = 31) and indicates imprecision in the point estimate. The biological plausibility is supported by animal studies demonstrating that mTOR inhibitors disrupt folliculogenesis and induce ovarian cyst formation through inhibition of the PI3K/Akt/mTOR signaling pathway, which is critical for primordial follicle activation and granulosa cell proliferation[23–25]. Clinically, reversible amenorrhea in female KTRs receiving sirolimus has been documented, with resumption of menses after drug discontinuation[15]. Our findings suggest that alternative immunosuppressive strategies should be considered for young female KTRs for whom reproductive health preservation is a priority, and that discontinuation of the mTOR inhibitor merits discussion when menstrual disturbances arise.

The differential association between CNI type and AUB risk, whereby cyclosporine conferred a higher risk than tacrolimus (adjusted OR 3.41), calls for further investigation. Previous studies have suggested that cyclosporine may be associated with a higher prevalence of abnormal endometrial pathology compared with tacrolimus[4]. Our endometrial biopsy data provide indirect support for this observation, as the prevalence of endometrial hyperplasia was higher in the cyclosporine subgroup. Potential mechanisms underlying this difference include differential effects on sex hormone metabolism, endometrial vascular remodeling, and local immune modulation[26]. However, given the observational nature of our data, residual confounding by indication cannot be excluded. Patients receiving different immunosuppressive regimens may differ systematically in graft function, rejection history, proteinuria, or malignancy risk, all factors that may influence both drug selection and menstrual outcomes. This limitation applies broadly to all regimen-based comparisons in this study.

The relationship between steroid dose and AUB risk (adjusted OR 2.05 for > 7.5 mg/day prednisone) extends the well-known effects of exogenous glucocorticoids on the HPO axis to the transplant population. Glucocorticoids suppress hypothalamic GnRH secretion, inhibit pituitary gonadotropin release, and directly impair ovarian steroidogenesis[4, 27]. Efforts to minimize steroid exposure through early withdrawal or avoidance protocols, which are already recommended for metabolic and cardiovascular benefits, may confer additional advantages for menstrual health in female KTRs.

In the clinically selected high-risk subgroup of 38 AUB patients who underwent biopsy, hyperplasia was detected in 11 patients (28.9%). While these descriptive findings raise important concerns regarding endometrial surveillance in KTRs, they cannot be generalized to all AUB patients or the broader KTR population given the targeted biopsy criteria. Although the single case of endometrial carcinoma represents 2.6% (1/38) of biopsied patients and 0.4% (1/258) of the total cohort, it should be interpreted cautiously given the small biopsy sample (n = 38) and the restriction of biopsy to symptomatic or high-risk patients. Nevertheless, chronic immunosuppression may alter the natural history of endometrial proliferative lesions[4]. Current guidelines do not recommend routine endometrial cancer screening in KTRs; however, our data support maintaining a low threshold for endometrial evaluation in KTRs presenting with AUB, particularly those with additional risk factors such as obesity, diabetes, prolonged unopposed estrogen exposure, and cyclosporine-based immunosuppression[4]. A diagnostic algorithm incorporating TVUS and selective endometrial sampling could be added to the transplant follow-up protocol.

The clinical implications of our findings extend beyond the immediate management of menstrual symptoms. AUB in KTRs may serve as a sentinel indicator of broader endocrine dysfunction, including premature ovarian insufficiency, which has implications for bone health (increased osteoporosis risk), cardiovascular risk (loss of premenopausal cardioprotection), and fertility planning[28, 29]. Moreover, menstrual disorders can significantly impair quality of life and contribute to sexual dysfunction, which is already highly prevalent in the CKD population[5, 30]. A multidisciplinary approach involving transplant nephrologists, gynecologists, and reproductive endocrinologists is therefore recommended for the comprehensive care of female KTRs.

4.1 Strengths and Limitations

This study has several strengths. First, it is the largest single-center study to date focusing specifically on AUB in KTRs (n = 258). Second, the application of the standardized FIGO PALM-COEIN classification represents a methodological advance over previous studies that employed heterogeneous and non-standardized definitions. Third, the comprehensive assessment of reproductive hormones, TVUS findings, and endometrial pathology provides a multi-dimensional characterization of AUB in this population. Fourth, the inclusion of patients across various immunosuppressive regimens enabled informative comparisons among different drug classes.

Several limitations must be acknowledged. The cross-sectional design precludes causal inference and does not capture the temporal evolution of menstrual patterns relative to the transplant event. The single-center nature of the study may limit the generalizability of our findings, although our patient demographics and immunosuppressive practices are broadly representative of transplant centers in China. The endometrial biopsy subset (n = 38) represents only 40% of AUB patients and is subject to selection bias, because patients with more severe symptoms or higher-risk profiles were preferentially selected for biopsy; the reported prevalence of endometrial pathology therefore likely overestimates the true rate in the broader KTR population. Information bias inherent in self-reported menstrual data cannot

be fully eliminated, although use of the structured FIGO questionnaire mitigates this concern. We note that Cronbach's α (0.86) assesses internal consistency; formal criterion validity against a clinical gold standard was not evaluated. Assignment of a single dominant PALM-COEIN category in patients with overlapping etiologies may underestimate the true complexity of AUB in this population, and coexisting categories should be considered when interpreting these results. In the multivariable model, the ratio of outcome events to predictor variables (approximately 23 events per variable) exceeded the commonly recommended minimum of 10; nevertheless, discrimination was only moderate (AUC 0.694) and calibration suboptimal (Hosmer-Lemeshow $P < 0.001$), indicating that the model explains only part of the variability in AUB status and requires external validation. As detailed in the Results, blood sampling was not consistently confined to the early follicular phase: 64 of 164 (39.0%) non-AUB samples had progesterone levels > 10 ng/mL, and hormone measurements in amenorrheic or oligomenorrheic patients were obtained without cycle-phase control. Because FSH, LH, estradiol, and progesterone are cycle-phase dependent, the hormone comparisons should be regarded as exploratory; directionally consistent results were nevertheless observed in the sensitivity analysis restricted to early follicular-phase samples (**Supplementary Table S5**). Backward stepwise selection also has recognized limitations in variable-selection stability; we therefore supplemented it with sensitivity analyses retaining continuous covariates (**Supplementary Table S2**). Dichotomizing continuous variables (age, dialysis vintage, time post-transplant, BMI, and eGFR) at clinically relevant thresholds may obscure non-linear dose-response relationships, which could be explored in larger datasets using restricted cubic splines. Coagulopathy status (including antiplatelet/anticoagulant use) and iron deficiency were not systematically evaluated, which may have contributed to residual confounding in the AUB-C classification. Future studies may consider regularization techniques such as LASSO for model validation. Finally, the restriction of the study population to Chinese KTRs limits generalizability to other ethnic groups, although it addresses a critical data gap given the growing transplant volume in Asia.

5. CONCLUSIONS

This study demonstrates that AUB affects over one-third of reproductive-aged female KTRs, with ovulatory dysfunction and iatrogenic factors constituting the predominant etiologies in the PALM-COEIN framework. Cyclosporine-based immunosuppression, mTOR inhibitor use, higher steroid dose, and longer dialysis vintage were factors independently associated with prevalent AUB. The high prevalence of endometrial hyperplasia (28.9%) and the identification of one endometrial carcinoma case, observed in a clinically selected high-risk subgroup undergoing biopsy, suggest that a low threshold for gynecological evaluation may be justified in this population, pending validation in larger cohorts. We recommend that menstrual health assessment be integrated as a standard component of post-transplant follow-up for all reproductive-aged female KTRs, with particular attention to those receiving mTOR inhibitors or higher-dose corticosteroids. Future prospective, multicenter studies with longitudinal follow-up should be undertaken to validate these findings and to establish evidence-based guidelines for the reproductive health management of female KTRs.

Abbreviations

ACOG
American College of Obstetricians and Gynecologists
Akt
protein kinase B
AMH
anti-Müllerian hormone
AUB
abnormal uterine bleeding
AUB-I
iatrogenic (category I of PALM-COEIN)
AUB-M
malignancy and hyperplasia (category M of PALM-COEIN)
AUB-O
ovulatory dysfunction (category O of PALM-COEIN)
AUC
area under the receiver operating characteristic curve
BMI
body mass index
CI
confidence interval
CKD
chronic kidney disease
CKD-EPI
Chronic Kidney Disease Epidemiology Collaboration
CNI
calcineurin inhibitor
CsA
cyclosporine
E2
estradiol
eGFR
estimated glomerular filtration rate
ESRD
end-stage renal disease
FIGO
International Federation of Gynecology and Obstetrics
FSH
follicle-stimulating hormone

GnRH
gonadotropin-releasing hormone
HPO
hypothalamic-pituitary-ovarian axis
IQR
interquartile range
KTR
kidney transplant recipient
LH
luteinizing hormone
mTOR
mechanistic target of rapamycin
OR
odds ratio
PALM-COEIN
polyp,adenomyosis,leiomyoma,malignancy and hyperplasia,coagulopathy,ovulatory dysfunction,endometrial,iatrogenic,not yet classified (FIGO classification of the causes of AUB)
PBAC
Pictorial Blood Loss Assessment Chart
PI3K
phosphatidylinositol 3-kinase
ROC
receiver operating characteristic
SD
standard deviation
TSH
thyroid-stimulating hormone
TVUS
transvaginal ultrasonography
VIF
variance inflation factor
WHO
World Health Organization.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of The Second Affiliated Hospital of Guangzhou Medical University (Approval No. LYZX-2026-139) and was conducted in accordance with the

Declaration of Helsinki. Written informed consent was obtained from all participants. All data were anonymized prior to analysis.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contribution Statement

The authors confirm contribution to the paper as follows: study conception and design: Z.C., H.Z.; data collection: Li Luo, R.C., J.W., Luhao Liu, G.L., J.F., Y.G.; analysis and interpretation of results: L.L., R.C., G.L., J.F., J.W.; draft manuscript preparation: Li Luo, R.C., Y.G., G.L., J.F., J.W., Luhao Liu, Z.C. All authors reviewed the results and approved the final version of the manuscript.

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Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: Z.C., H.Z.; data collection: Li Luo, R.C., J.W., Luhao Liu, G.L., J.F., Y.G.; analysis and interpretation of results: L.L., R.C., G.L., J.F., J.W.; draft manuscript preparation: Li Luo, R.C., Y.G., G.L., J.F., J.W., Luhao Liu, Z.C. All authors reviewed the results and approved the final version of the manuscript.

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Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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