

# Asia Pacific Journal of Clinical Medical Research

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## Asia Pacific Journal of Clinical Medical Research

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# Study on Mental Resilience Trajectory and Influencing Factors of Family Members of Young Suicide Attempters Who Took Poison

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**Abstract: Objective:** To explore the psychological resilience trajectories and influencing factors of family members of young people who attempted suicide by taking poison. **Method:** A convenience sampling method was used to select 158 family members of young people who attempted suicide by taking poison and were admitted to a hospital in Zhejiang Province from November 2023 to October 2024 as the research subjects. The general information questionnaire, general self-efficacy scale, social support rating scale, simple coping style questionnaire, and 10-item Connor-Davidson resilience scale were used to investigate them. A total of 158 questionnaires were distributed during hospitalization, and 158 valid questionnaires were recovered. 10 cases were lost to follow-up 1 month after discharge, 14 cases were lost to follow-up at 3 months, and 18 cases were lost at 6 months. Finally, a total of 118 patients completed the questionnaire. **Result:** Finally, three psychological elasticity category trajectories were obtained: decreasing psychological elasticity level, stable psychological elasticity level, and increasing psychological elasticity level. Multiple logistic regression analysis results showed that C1 VS. C3: social support OR value 0.535, coping style OR value 0.929; C2 VS. C3: social support OR value 0.766. P values are all <0.05. **Conclusion:** Families of young people who attempt suicide by poisoning may exhibit different types of psychological resilience trajectories. Social support and coping styles are factors that influence the psychological resilience trajectory of family members of young people who have attempted suicide by taking drugs. In clinical practice, personalized intervention should be provided based on the characteristics of different patients.

**Keywords:** Suicide; Psychological Resilience; Trajectory; Family Members; Longitudinal Study

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## 1. Introduction

Suicidal behavior is a serious public health issue<sup>[1]</sup>. Suicide attempted is a self-inflicted act with the intent of death that results in physical injury but not death. A survey by the Beijing Psychological Crisis Research and Intervention Center shows that suicide is the first leading cause of death for people aged 15-34<sup>[2-4]</sup>. As medical treatment of poisoning has improved, the success rate of poisonings has increased, and suicides attempted due to poisonings have risen<sup>[5, 6]</sup>. The “Healthy China Initiative 2019-2030” and the Outline of the “Healthy China 2023” plan place special emphasis on the popularization of mental health for the whole population and the early intervention of psychological problems in key populations. In addition, with the development of the modern nursing model, the object of nursing extends from patients to family members. Family

members are the patient's delegated authority, as well as key supporters and primary caregivers. Suicide attempts by patients are not only damaging to themselves but also have a significant impact on the physical and mental health of their families. Family members are prone to negative emotions such as guilt, anxiety, depression, psychological distress, helplessness, and sadness<sup>[7, 8]</sup>. Furthermore, the sense of shame and stigma caused by suicide will further increase the pressure and burden of family members and even produce suicidal ideation<sup>[9-11]</sup>. Therefore, it is particularly important to pay more attention to the mental health status of the families of suicide attempters<sup>[12]</sup>. However, existing research has focused primarily on the physical and mental health of patients who have attempted suicide, with insufficient attention paid to their families. Only a few qualitative studies have explored the caregiving capacity and mental health of family members. This study used a longitudinal approach to investigate the trajectories of psychological resilience among family members of youth who attempted suicide by self-poisoning and to explore the factors that predict psychological resilience in family members, thereby informing the development of effective prevention and intervention programs.

## 2. Method

### 2.1 Study Population and Design

This study is a prospective cohort study. The convenience sampling method was used to select family members of young people who attempted suicide by self-poisoning from November 2023 to October 2024 in a tertiary hospital in Zhejiang Province as study subjects.

Participants who met the following criteria were included: (1) Families of young people who attempted suicide by self-poisoning; (2) Assumption of primary caregiving responsibilities upon hospitalization and return home; (3) Age  $\geq 18$  years; (4) Use of mobile communication technology. Families of patients who died during the study period after a suicide attempt were excluded from the study.

According to the principles of sample size estimation in multifactor analysis, the sample size is required to be 5-10 times the observed variables. There were 13 variables in this study, and the sample size was 78-156 cases, taking into account the 20% loss rate. A total of 158 participants were included in this study, of which 118 participants completed the longitudinal survey.

### 2.2 Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (KY2023-116).

### 2.3 Measures

#### 2.3.1 Demographic Questionnaire

It was designed by the researcher after consultation with the experts of the research group based on the purpose of the study, including age, gender, marital status, residence, monthly income, education, occupation, relationship with patients, and number of patient suicides.

#### 2.3.2 General Self-Efficacy Scale (RS-SC)

The scale was developed by German psychologist Schwarzer<sup>[13]</sup> and was translated into a Chinese version by Jianxin Zhang. The scale has a single-dimensional structure with 10 items. It is a four-point Likert scale which ranges from 1 point (totally incorrect) to 4 points (totally correct), with higher scores indicating higher levels of general Self-efficacy. The Cronbach  $\alpha$  of RS-SC was 0.924 in the previous studies<sup>[14]</sup>.

#### 2.3.3 Social Support Rating Scale (SSRS)

The scale was developed by Shuiyuan Xiao with 10 items<sup>[15]</sup>. It has three dimensions including subjective support, objective support, and utilization of support. Scale scores of 12-22 points are classified as low level, 23-44 points as medium level, and 45-66 as high level, with higher scores indicating higher levels of social support. The Cronbach  $\alpha$  of SSRS was 0.819 in the previous studies<sup>[16]</sup>.

#### 2.3.4 Simplified Coping Style Questionnaire (SCSQ)

The scale was developed by Yaning Xie<sup>[17]</sup> in 1998 to assess the behavioral patterns of individuals coping with distress, which is divided into 2 dimensions: positive coping (12 entries) and negative coping (8 entries). It is a four-point Likert scale which

ranges from 0 points (not used) to 3 points (often used). The Cronbach  $\alpha$  of this scale is 0.90<sup>[18]</sup>.

### 2.3.5 10-item Connor-Davidson Resilience Scale (CD-RISC-10)

The scale was translated and revised by Wang<sup>[19]</sup>, which contains 10 entries, each rated on a 5-point Likert scale (0=almost never, 4=always) with a total score of 0-40. A higher total score on the scale represents a higher level of psychological resilience. The Cronbach's  $\alpha$  is 0.91<sup>[20]</sup>.

## 2.4 Data Collection

Data was collected by the researcher herself. Questionnaire survey and follow-up were conducted on the day of discharge (T1), 1 month after discharge (T2), 3 months after discharge (T3), and 6 months after discharge (T4). In the T1, a face-to-face survey was used to collect information from 158 participants including, demographic information, the General Self-Efficacy Scale, the Social Support Rating Scale, the Simple Coping Styles Questionnaire, and the Psychological Resilience Scale. In T2-4, 148, 134, and 118 participants provided complete 10-item Connor-Davidson resilience scale (SCSQ) data via WeChat, clinic visits, and phone calls. 40 cases did not complete follow-up due to poor adherence to follow-up, with an overall loss rate of 25.3%.

## 2.5 Statistical Analysis

Statistical analysis was performed using SPSS 26.0 and Mplus8.3. At first, we conducted a descriptive analysis of the demographic characteristics of the participants. Continuous variables were summarized as means and standard deviations with normal distribution patterns, or medians and interquartile ranges (IQRs) for non-normally distributed data, and categorical variables as rates or percentages. Second, we performed Latent Class Growth Analysis (LCGA) in Mplus version 8.3 to explore the trajectories of psychological resilience. Gradually increase the number of potential categories until optimal model fit is achieved. The lower the value of the Akaike information criterion (AIC), Bayesian information criterion (BIC), and sample size adjusted BIC (aBIC) of the model, the better the fit. The entropy represents the classification accuracy, which takes values from 0 to 1, and the larger value of it means the higher the accuracy. When entropy of 0.80 or greater, the accuracy of classification exceeds 90%. The significant p values for the LMR and BLRT indicate that a model with k classes is significantly better than a model with k-1 classes. Finally, We conducted  $\chi^2$  test, Independent Samples t-test, and multiple logistic regression analysis to explore predictors of the trajectories.  $P < 0.05$  indicating that the difference was statistically significant.

## 3. Result

### 3.1 Sociodemographic and Psychological Resilience of Participants

A total of 158 participants were enrolled in this study at baseline, and the relationships to the suicide attempters were 107 (67.7%) parents, 30 (19%) spouses, 8 (5.1%) children, 2 (1.3%) siblings, and 11 (7.0%) other relationships. A large proportion of participants 146 (92.4%) aged 18-60 years, and 136 (86.1%) were women. 121 (76.6%) participants were married, and 126 (79.7%) participants lived in the city. Many of the participants had a college or bachelor's degree in education ( $n=134, 84.8\%$ ). Occupation was mainly workers ( $n=62, 39.2\%$ ). Most participants reported a monthly family income of more than 5000 yuan ( $n=117, 74.1\%$ ). Most suicide attempters were first-time suicides ( $n=137, 86.7\%$ ), as shown in Table 2.

The psychological resilience scores of participants were  $17.43 \pm 5.635$ ,  $17.74 \pm 3.263$ ,  $17.56 \pm 2.236$ , and  $18.42 \pm 4.549$  in T1-4, respectively.

### 3.2 Latent Class Analysis

Participants who completed the four surveys were analyzed for potential categories of trajectories of change in psychological resilience, see Table 1. One to five latent psychological resilience classes were compared to identify the optimal model. AIC, BIC, and aBIC values decrease as the number of categories increases. when potential category is the 4-class, LMR values did not reach a significant level ( $P > 0.05$ ). when the potential category is the 5-class, LMR values did not reach a significant level ( $P > 0.05$ ), Entropy  $< 0.8$ , and the smallest group size is too small. This leads to low interpretability in clinical settings and a lack of credibility in replication. In summary, the results of the 3-class model were found to be superior to those of the other model.

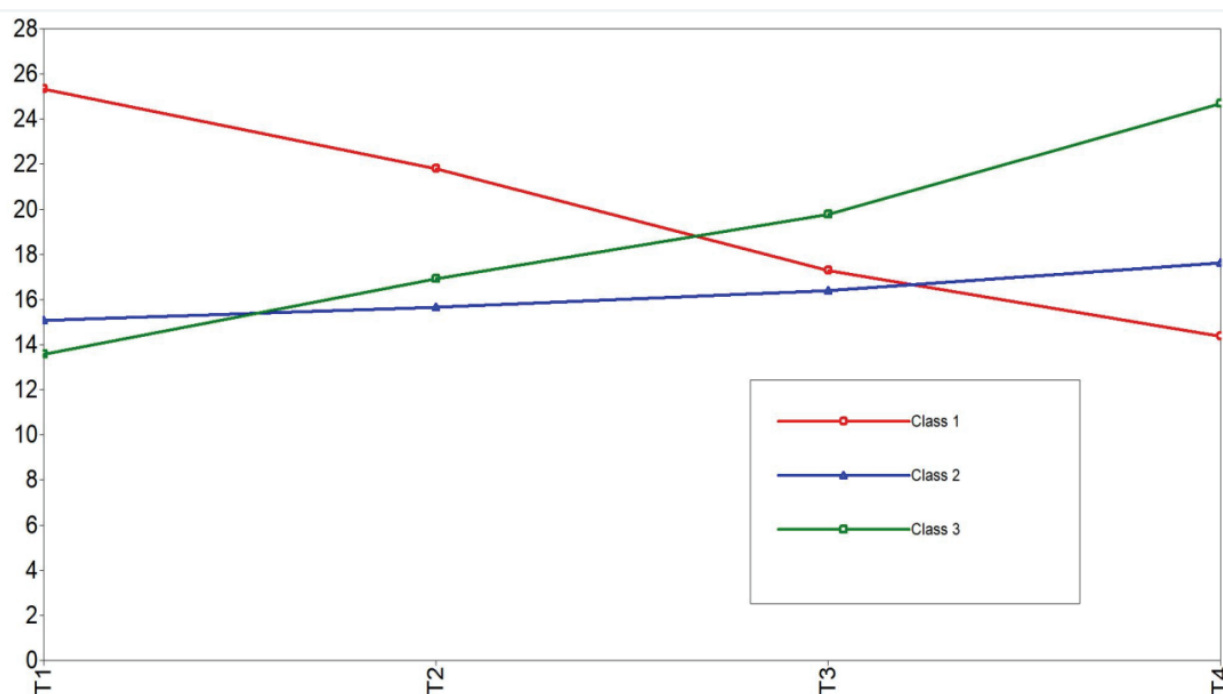
Table 1 Results of LCGA model fitting for participants' psychological resilience

Model	AIC	BIC	aBIC	Entropy	LMR(P)	BLRT(P)	Conditional Probability
1	3063.311	3081.687	3062.694	-	-	-	1
2	2861.890	2889.454	2860.964	0.943	0.0000	0.0000	0.73/0.27
3	2785.731	2822.482	2784.497	0.817	0.0014	0.0000	0.27/0.51/0.22
4	2775.782	2821.721	2774.238	0.813	0.0987	0.0000	0.08/0.20/0.25/0.47
5	2760.942	2816.069	2759.090	0.780	0.3770	0.0000	0.32/0.20/0.16/0.08/0.24

### 3.3 Latent Class Naming

Model 3 categorises participants' trajectories of psychological resilience into 3-class, see Figure 1. ① We named Class 1 (C1) the high-low psychological resilience group, which Psychological resilience levels were high at T1, and tended to decrease during follow-up. There were 42 (27%) participants in the group (Intercept 23.596, slope -1.690,  $P=0.000$ ). ② We named Class 2 (C2) the steady psychological resilience group. A total of 81 (51 %) participants were classified in this group. These participants had an average level of psychological resilience at T1, and the trend was not significant, remaining at a moderate level (Intercept 15.183, slope 0.408,  $p=0.000$ ). ③ We named Class 3 (C3) the low-high psychological resilience group. In this group, psychological resilience in 35(22%) participants was low at T1 but increased progressively during follow-up (Intercept 14.644, slope 1.704,  $p=0.000$ ).

Figure 1 Trajectory of development of a mixed model of growth of latent variable of psychological resilience of participants



Note: T1 is baseline (at discharge), T1, T2 and T3 are 1, 3 and 6 months after discharge, respectively.

### 3.4 Basic Characteristics of Trajectory Grouping

Basic characteristics and univariate analysis results of participants grouped according to different development tracks of psychological resilience. The results indicated that there were some differences between the participants in each subgroup in terms of the relationship with patient, first-time suicide, General self-efficacy, social support, coping style, all of which were statistically significant (Table 2).

Table2 Basic characteristics of trajectory grouping

Item	Total	C1(n=42)	C2(n=81)	C3(n=35)	$\chi^2$	P
Age					1.488	0.450
18-60	146(92.4)	39(92.9)	73(90.1)	34(97.1)		
>60	12(7.6)	3(7.1)	8(9.9)	1(2.9)		
Gander					0.563	0.755
male	22(13.9)	7(16.7)	10(12.3)	5(14.3)		
female	136(86.1)	35(83.3)	71(87.7)	30(85.7)		
Marital status					8.265	0.188
unmarried	20(12.7)	7(16.7)	10(12.3)	3(8.6)		
married	121(76.6)	33(78.6)	62(76.5)	26(74.3)		
divorced	9(5.7)	0(0)	7(8.6)	2(5.7)		
remarry	8(5.1)	2(4.8)	2(2.5)	4(11.4)		
Residence					3.636	0.162
city	126(79.7)	37(88.1)	60(74.1)	29(82.9)		
village	32(20.3)	5(11.9)	21(25.9)	6(17.1)		
Monthly household income					4.279	0.362
0-2999	18(11.4)	3(7.1)	10(12.3)	5(14.3)		
3000-5000	23(14.6)	6(14.3)	15(18.5)	2(5.7)		
>5000	117(74.1)	33(78.6)	56(69.1)	28(80)		
Education					1.341	0.889
Primary/Middle/High School	16(10.1)	3(7.1)	10(12.3)	3(8.6)		
College/Bachelor's degree	134(84.8)	37(88.1)	66(81.5)	31(88.6)		
postgraduates	8(5.1)	2(4.8)	5(6.2)	1(2.9)		
Occupation type					3.957	0.873
worker	62(39.2)	18(42.9)	32(39.5)	12(34.3)		
farmer	24(15.2)	4(9.5)	15(18.5)	5(14.3)		
Institutional personnel	17(10.8)	4(9.5)	9(11.1)	4(11.4)		
freelance work	30(19)	7(16.7)	15(18.5)	8(22.9)		
unemployed	25(15.8)	9(21.4)	10(12.3)	6(17.1)		
Relationship with patients					20.680	0.002
parent	107(67.7)	31(73.8)	50(61.7)	26(74.3)		
spouse	30(19)	3(7.1)	23(28.4)	4(11.4)		
children	8(5.1)	4(9.5)	0(0)	4(11.4)		
brothers and sisters	2(1.3)	0(0)	2(2.5)	0(0)		
others	11(7.0)	4(9.5)	6(7.4)	1(2.9)		
first-time suicide					7.717	0.022
yes	137(86.7)	33(78.6)	76(93.8)	28(80)		
no	21(13.3)	9(21.4)	5(6.2)	7(20)		
General self-efficacy	23.82±6.66	15.71±2.13	23.77±2.37	33.66±2.29	191.436	0.000
Social support	24.01±6.96	15.17±1.91	24.22±2.22	34.11±2.39	485.656	0.000
Coping style	39.96±11.44	22.95±4.89	43.35±2.00	52.54±4.29	95.3	0.000

### 3.5 Logistic Regression Analysis of Influencing Factors of Psychological Resilience

Variables that were statistically significant in the one-way analysis of variance (the relationship with patient, first-time suicide, General self-efficacy, social support, coping style) were used as independent variables, and the trajectory attribution category was included in the multiple logistic regression analysis as the dependent variables. Multiple logistic regression analysis was performed using the “low-high psychological resilience group” as a reference group. The results showed that the model could explain the effect of factors influencing the trajectory of psychological resilience in the families of young people attempting suicide by taking poison. The model is statistically significant ( $P < 0.05$ ). Social support and coping styles as influences on potential categories of participants’ psychological resilience trajectories ( $P < 0.05$ ), as show in Table 3.

*Table3 Logistic regression analysis of influencing factors of psychological resilience*

eDependent variable	Independent variable	$\beta$	SE	Wald $\chi^2$	P	OR	95%CI
C1 VS. C3	Constant	15.962	3.204	24.811	0.000		
	Social support	-.625	0.095	43.022	0.000	0.535	0.444-0.645
	Coping style	-.074	0.034	4.865	0.027	0.929	0.870-0.992
C2 VS. C3	Constant	7.904	2.476	10.188	0.001		
	Social support	-.267	0.057	22.175	0.000	0.766	0.685-0.856

## 4. Discussion

### 4.1 Trajectory Analysis of Psychological Resilience in the Families of Young People Attempting Suicide by Drug Use

The study identified three different trajectories of psychological resilience, named “low-high psychological resilience group”, “high-low psychological resilience group”, and “steady psychological resilience group”. It reflects the group heterogeneity of psychological resilience of the family members of young people who took poison to attempt suicide. About 27 % of the family members of young people who had attempted suicide by taking poison showed a decreasing level of psychological resilience. They may have experienced great psychological shock and stress when confronted with a loved one’s attempted suicide, leading to a reduction in their psychological resilience. The possible causes are as follows: Firstly, a loved one’s suicide attempt can be an extremely traumatic experience for families, which predisposes them to psychological trauma and affects their psychological resilience<sup>[21]</sup>. Secondly, young people are important pillars of a family and play a vital role in the family. Families may experience continued anxiety and worry, fearing the recurrence of similar incidents. In addition, Family members may blame themselves because they failed to prevent their loved one’s suicidal behavior and the patient’s condition is getting progressively worse. This sense of self-blame may lead to negative emotions and doubts about their abilities, which can affect psychological resilience<sup>[22]</sup>. Besides, they may develop a sense of uncertainty and fear about the future, which challenges psychological resilience. Worse still, the social stigma attached to suicide may make families feel socially excluded or suspicious, which may increase the risk of reduced psychological resilience<sup>[23]</sup>. Ultimately, the complexity of the patient’s condition may also require long-term hospitalization or outpatient follow-up, which can easily create a burden on family members who are under financial pressure and have difficulties accessing medical care<sup>[24]</sup>. This suggests that the initial level of psychological resilience in the families of young people attempting suicide does not represent the trend of psychological resilience after long-term treatment and that the characteristics of the dynamic development of psychological resilience and inter-individual differences must be taken into account. Healthcare professionals should assess early and take effective interventions to improve the psychological resilience of family members of suicide attempters.

Another approximately 51% of participants were in the group with a stable level of psychological resilience. Suicide attempters in this category are likely to be impulsive suicides, which are regretted afterward and regret, and the condition is mild with no impact on quality of life. Therefore, the level of psychological resilience of their dependents was affected to a limited extent. In addition, families may learn to cope with their own and their loved one’s emotions and gradually adjust to



the new reality.

The remaining 22% of participants showed an upward trend in their level of psychological resilience. Here are some possible reasons: (1) The Healing Power of Time: Over time, the initial shock and pain may lessen, giving families a chance to adapt and adjust. (2) Professional psychological support<sup>[25]</sup>: Families may have sought professional mental health support, such as the help of a psychologist. Psychologists may provide emotional comfort, problem-solving skills, and coping strategies to help families gradually recover and increase psychological resilience. (3) Patients in this category tend to be sicker, and the psychological resilience of family members is improved as they learn some life lessons in the course of caring for the patient and instead grow in the face of adversity. This suggests that healthcare professionals should pay more attention to family members with low levels of psychological resilience and guide them to face the difficulties they encounter with a positive mindset.

## **4.2 Factors Influencing the Trajectory of Psychological Resilience in Family Members of Youth Drug-related Suicide Attempts**

Multiple logistic regression analysis results indicated that social support has a significant predictive effect on the psychological resilience trajectory of the families of young people who attempted suicide by taking poison. That is, social support is a protective factor in the developmental trajectory of psychological resilience. This may be since social support helps to build and maintain social networks, increase social engagement, reduce feelings of isolation, and make them more able to cope with adversity more positively. Higher levels of social support not only provide greater understanding, concern, and encouragement for families but also have a therapeutic function by helping to reduce stress and create a buffering effect in times of difficulty<sup>[26]</sup>. These enable individuals to maintain relative emotional stability even in stressful scenarios. In addition, social support also includes practical help, such as assistance with daily chores, financial support, or assistance in caring for family members. This helps to reduce the burden on families and makes it easier for them to cope with stress, thus maintaining psychological resilience. This is similar to the findings of previous studies. A longitudinal follow-up survey shows that social relationships are better predictors of health than bioeconomic factors<sup>[27]</sup>. Another study suggests that patients who seek and receive support from close relationships are at a lower risk of developing PTSD. Whereas the level of psychological resilience declined in the absence of supporters. Moreover, coping styles were significant predictors of trajectories of psychological resilience in the families of youth suicide attempters. This suggests that proactive problem-solving and help-seeking coping styles may be able to help individuals enhance their psychological resilience<sup>[28]</sup>. This is also confirmed by Nan Zhang's study on caregivers for patients with chronic obstructive pulmonary disease<sup>[29]</sup>.

## **5. Conclusion**

Overall, our study revealed 3 types of developmental trajectories of psychological resilience in family members of youth who attempted suicide by taking poison. Social support and coping style may be two factors affecting the families' psychological resilience track. Clinicians can intervene based on the protective factors of the psychological resilience trajectory.

## **6. Limitation**

Our study has several limitations. First, we explored only preliminarily the variability across psychological resilience trajectories. Moreover, the study included a geographically homogenous study population, which resulted in a relatively underrepresented study. The follow-up study will be a multi-center, large-sample study to inform the development of interventions.

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## **Conflict of Interests**

The authors declare that there is no conflict of interest regarding the publication of this paper.

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# A Giant Uterine Hydropic Leiomyoma with Distinctive Radiological Patterns: A Challenging Case and Literature Review

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**Abstract:** Uterine hydropic leiomyoma is a rare condition. Only a few relevant cases have been reported until now. Distinguishing between uterine hydropic leiomyoma and other uterine malignancy tumors, such as leiomyosarcoma, using radiological-based methods is crucial. This can provide vital information on the inherent characteristics, facilitating clinical decision-making. We present a case report of a 42-year-old female patient diagnosed with a giant uterine hydropic leiomyoma with unique radiological characteristics. The patient recovered safely and remained in good condition after a successful surgical intervention.

**Keywords:** Hydropic Leiomyoma; Hydropic Degeneration; Radiological; Literature Review

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## 1. Introduction

Leiomyomas are the most prevalent benign mesenchymal neoplasms of the uterus, with an incidence rate of 2.5%. It occurs in approximately 70% of women of menopause age, with heavy menstrual bleeding in approximately one-third of these patients<sup>[1,2]</sup>. Leiomyoma of the uterus originates from the mesenchymal tissues and is considered to be a monoclonal tumor of smooth muscle cells (SMCs) in the uterus<sup>[3,4]</sup>. The degeneration of leiomyomas may present different histological characteristics. Leiomyomas can be classified into several subtypes based on their pathology<sup>[5]</sup>. Hydropic leiomyoma, with a prominent edematous stroma causing compartmentalization of the smooth muscles, is extremely rare<sup>[5]</sup>. Herein, we report a case of uterine hydropic leiomyoma.

## 2. Case presentation

A 42-year-old woman with regular menstruation visited a community hospital, complaining of progressive abdominal pain over the past 12 months. Clinical evaluation revealed postpartum perineum, slight leucorrhea, cervical hypertrophy, mild pain, and a bulky mass with poor mobility. Laboratory results revealed mild anemia with a hemoglobin level of 112 g/L (normal range: 115–150 g/L) and a hematocrit of 33.2% (normal range: 35–45%). Other laboratory tests and tumor markers were within normal limits.

Abdominal ultrasonography indicated a well-demarcated heterogeneous echogenic mass in the abdominopelvic region, measuring  $18.1 \times 12.6 \times 8.3$  cm, extending to the navel, with honeycomb-like septations inside and dotted blood flow signals around it (Figure 1). For subsequent evaluation, the patient was transferred to our hospital. Abdominopelvic non-contrast-enhanced computed tomography (CT) scan revealed a heterogeneous low-density cystic mass with thickened septations. To determine the tumor's origin, contrast-enhanced CT and routine magnetic resonance imaging (MRI) were performed successively. The contrast-enhanced CT showed intensified heterogeneous thickened septations with a degree of mild to moderate, while the mass's low-density zones showed no enhancement (Figure 2), MRI revealed a flat, elastic cystic component with a complex signal, including a heterogeneous low T1 signal, mixed high T2 signal, and atypical flow voids. DWI showed a hypointense signal (Figure 3).

Figure 1. A well-demarcated heterogeneous echogenicity mass in the abdominopelvic, honeycomb-like septations inside (A), and the dotted blood-flow signal around (B).

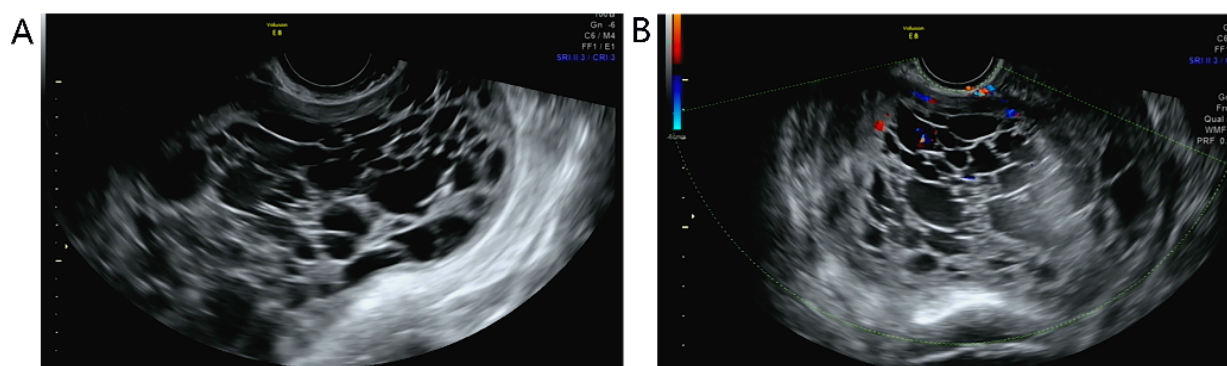


Figure 2. The heterogeneous thickened septations were intensified to a mild-to-moderate degree, while the low-density zone of the mass showed an absence of enhancement on contrast-enhanced CT (A, arterial phase B, venous phase C, equilibrium phase D, non-contrast-enhanced CT).

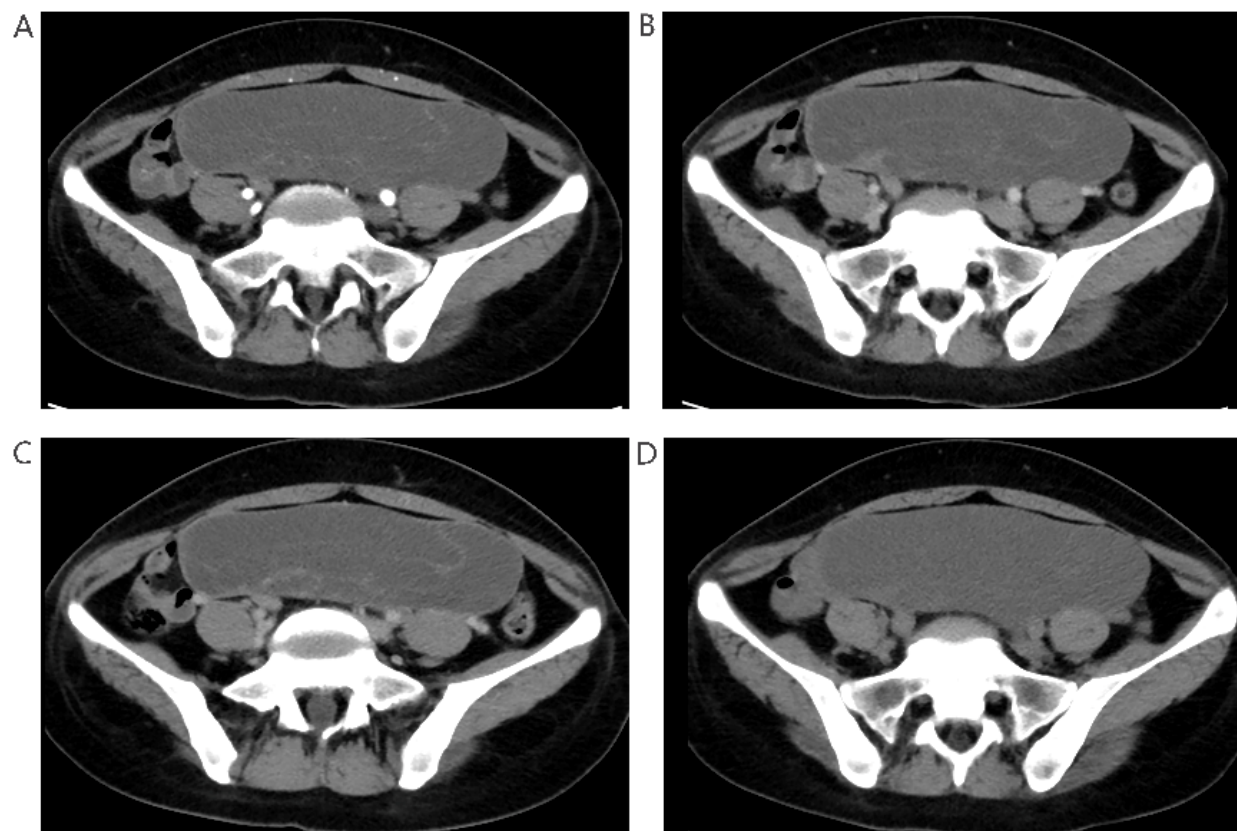
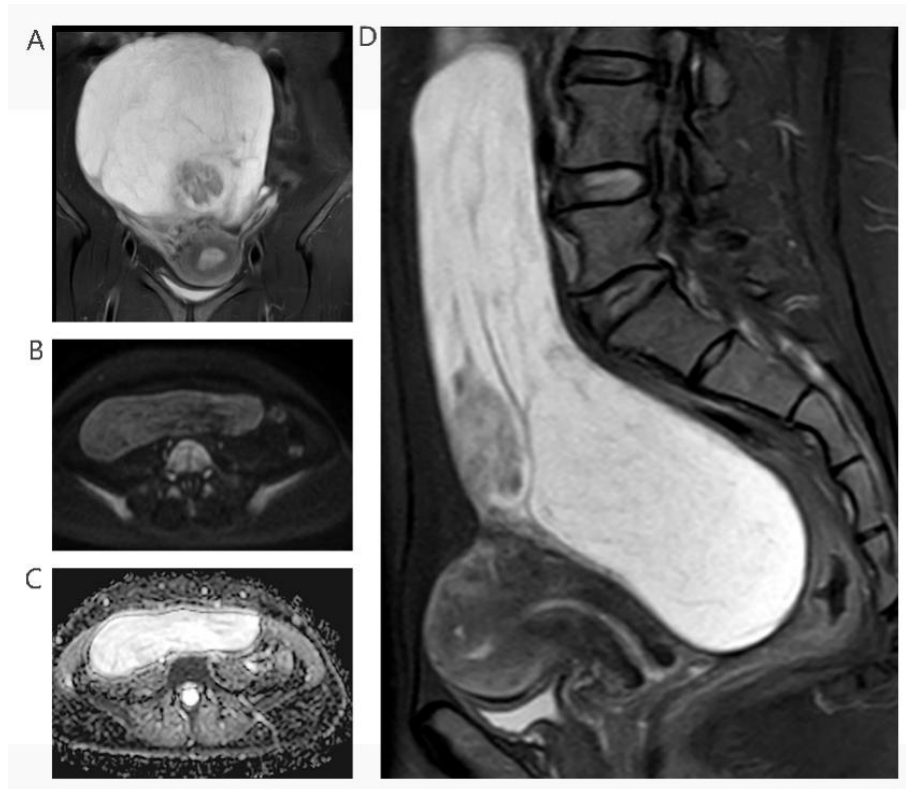


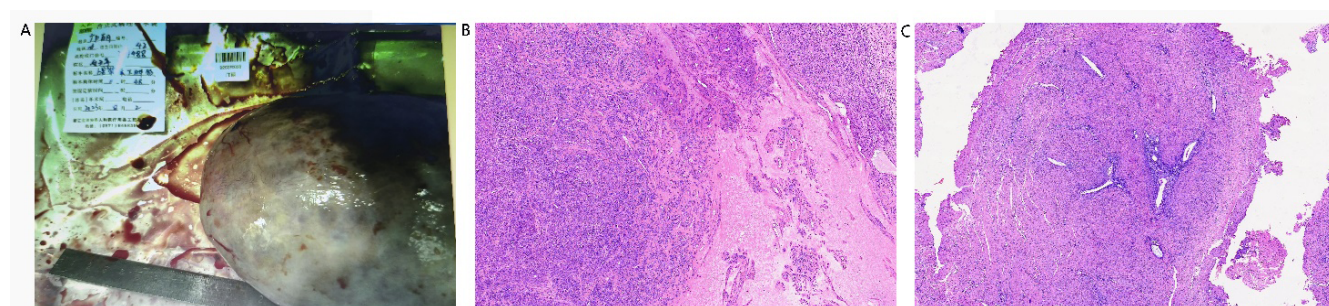


Figure 3. A&D, coronal, sagittal, T2 SPIR, a mixed high T2 signal combined with atypical flow voids. B&C, a hypointense DWI with a hyperintense ADC.



A benign neoplastic lesion was suspected, leading to surgical intervention. A subserosal tumor, measuring approximately  $18 \times 15 \times 10$  cm, was observed on the posterior wall of the uterus. It was cystic, soft, containing yellowish fluid, and attached by a thin stalk of 3 cm. Intraoperative pathology suggested a hydropic leiomyoma. Additionally, an interparietal myoma near the right uterine horn measuring  $1.5 \times 1.5$  cm, was found (Figure 4). The patient safely returned to the ward post-surgery and remained in good condition during the 6-month follow-up period.

Figure 4. Macropathology depicts a grayish-white mass, measuring  $18.1 \times 12.6 \times 8.3$  cm (A); the tumor cells are separated by excessive amounts of extracellular material (HE staining,  $\times 4$ ) and (B) an interparietal myoma was observed near the right uterine horn, measuring  $1.5 \times 1.5$  cm (D).



### 3. Discussion

Uterine leiomyoma, an important cause of morbidity among women of reproductive age, is marked by disordered smooth muscle proliferation, changed ECM deposition, and increased hormonal responsiveness, often leading to heavy menstrual bleeding and iron-deficiency anemia [6–8]. Based on the 5<sup>th</sup> edition of the female genital tumor classification by World Health Organization, the subtypes of leiomyoma include leiomyoma with bizarre nuclei, cellular leiomyoma, fumarate hydratase-deficient leiomyoma, mitotically active leiomyoma, hydropic leiomyoma, apoplectic leiomyoma, lipoleiomyoma, epithelioid leiomyoma, myxoid leiomyoma, dissecting leiomyoma, and diffuse leiomyomatosis [5].

Hydropic leiomyoma, an uncommon yet intriguing variant of uterine leiomyoma, is characterized by zonally segregated

edema, hypervascularity, and the arrangement of tumor cells in nodules or cords, along with distinctive features on medical imaging<sup>[9]</sup>. We searched PubMed for “hydropic leiomyoma” and “hydropic degeneration” and retrieved 22 records, which included 21 case reports and 1 research paper. Among these, 12 focused on imaging findings, 5 on pathology, and 1 on chromosome variation. Several older articles provided only descriptive reports without detailed imaging and pathology analysis. Typically, ultrasound imaging reveals a multilocular cystic area with hypoechogenicity, whereas color Doppler shows moderate vascularity near the uterine attachment and sparse vascularization peripherally<sup>[10–14, 18–19]</sup>. In the present study, the decreased blood flow and significant multilocular cystic areas within the lesion suggest a more complete process of degeneration and a less aggressive nature. We identified a cystic-dominated mass with heterogeneous thickened septations on CT and MRI imaging, exhibiting a more typical radiological pattern compared to previous literature<sup>[14–18, 28–30]</sup>. Imaging characteristics revealed both macro- and microscopic tumor characteristics, with abundant watery edema exhibiting T2 hyperintensity, whereas the tumor’s thick-walled vessels appear as cord-like structures with T2 hypointensity<sup>[15, 16]</sup>. Microscopically, the accumulation of watery edema fluid is usually associated with hyalinized blood vessels and collagen deposition<sup>[17]</sup>. Griffin B. B. et al. reported that hydropic leiomyoma, distinguished by a large tumor size with edematous tumor cells exhibiting round-oval nuclei arranged in cords or perinodular patterns around vessels and increased thick-walled vessels, varies from usual leiomyoma. Immunohistochemistry showed high mobility group AT-hook 2 (HMGA2) overexpression and rearrangement<sup>[9]</sup>. Along with hydropic leiomyoma, similar imaging findings can be observed in uterine fibroids with cystic and myxoid degeneration. In uterine fibroids with cystic degeneration, considerable edematous changes can lead to the complete replacement of neoplastic cells. MRI imaging typically shows T2 hyperintensity signals without enhancement on post-contrast sequences. In the case of uterine fibroids with myxoid degeneration, MRI typically reveals T1 hypo- or hyperintensity, T2 hyperintensity, and DWI hyperintensity signals. This is due to the accumulation of mucopolysaccharides and proteins, with smooth muscle cells separated by hyaluronic acid-rich mucoid substances, giving the tissue a soft texture, transparency, and well-defined solidity<sup>[19, 20]</sup>. Nevertheless, the imaging findings of uterine leiomyoma with myxoid degeneration can resemble those of myxoid leiomyosarcoma, a sarcoma with poor outcomes characterized by large spindle cells of smooth muscles, which may complicate clinical diagnosis<sup>[21–23]</sup>. Furthermore, smooth muscle tumors of uncertain malignant potential, endometrial stromal sarcomas, adenosarcoma, and uterine carcinosarcoma can mimic the cystic degeneration of uterine leiomyoma and exhibit similar radiological patterns due to changing degrees of cystic degeneration and necrosis, which can contribute to the same radiological patterns<sup>[24]</sup>. Radiological methods can be challenging in distinguishing these diseases; however, there are still diagnostic clues to follow. Usually, uterine malignant tumors are more aggressive, characterized by rich blood supply, rapid growth, rapid early enhancement, central necrosis, and ill-defined, irregular margins. However, benign tumors are more indolent, with poor blood supply, slow growth, mild or delayed enhancement, and well-defined margins<sup>[25–27]</sup>. Studies have reported that lobulated borders, T2 dark areas, necrosis, hyperintensity of the tumor compared with the myometrium post-contrast administration, “split fiber” sign with limited or poor enhancement post-contrast, and a high signal on b1000 DWI can differentiate between atypical leiomyomas and leiomyosarcomas<sup>[14, 31]</sup>.

## 4. Conclusion

To summarize, we report a giant uterine hydropic leiomyoma with unique radiological patterns. Our findings can improve the understanding of its clinical, imaging, and pathological characteristics, providing valuable practical experience for clinicians and radiologists.

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No

## Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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# Research Progress on the Neural Mechanisms and Brain Network Plasticity of Repetitive Transcranial Magnetic Stimulation in the Treatment of Chronic Insomnia

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**Abstract:** Chronic insomnia is a common sleep disorder characterized by difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening. Accumulating evidence suggests that chronic insomnia is not merely a consequence of sleep loss or psychological stress, but a neuropsychiatric disorder involving abnormal cortical excitability, neurotransmitter imbalance, hypothalamic–pituitary–adrenal axis hyperactivation, and disrupted large scale brain network connectivity. In recent years, repetitive transcranial magnetic stimulation, as a safe and noninvasive neuromodulation technique, has shown promising therapeutic potential in the treatment of chronic insomnia. By modulating cortical excitability, synaptic plasticity, neurotransmitter release, and functional connectivity among sleep related brain networks, repetitive transcranial magnetic stimulation may improve sleep initiation, sleep maintenance, and associated emotional symptoms. This review summarizes the neurophysiological basis of chronic insomnia, the mechanisms and stimulation parameters of repetitive transcranial magnetic stimulation, and recent advances in brain network plasticity research related to its therapeutic effects. Current evidence indicates that repetitive transcranial magnetic stimulation can suppress hyperactivity of the default mode network, enhance executive control network function, regulate salience network activity, and restore the integration of thalamocortical and limbic circuits. These network level changes provide objective neuroimaging support for the clinical benefits of repetitive transcranial magnetic stimulation in chronic insomnia. Future studies should combine individualized neuronavigated stimulation with multimodal neuroimaging and longitudinal follow up to clarify the spatiotemporal dynamics of brain network plasticity and optimize precision nonpharmacological interventions for chronic insomnia.

**Keywords:** Chronic Insomnia; Repetitive Transcranial Magnetic Stimulation; Neural Mechanisms; Brain Network Plasticity; Functional Connectivity; Neuromodulation

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## 1. Introduction

Chronic insomnia is one of the most common sleep disorders and is primarily characterized by difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening <sup>[1]</sup>. Epidemiological studies indicate that nearly one third of adults experience insomnia symptoms, and approximately 10% to 15% suffer from chronic insomnia, with a higher prevalence among older adults, women, and individuals exposed to high levels of stress <sup>[2]</sup>. Long term insomnia not only impairs quality of life and social functioning, but may also lead to cognitive decline, emotional disturbances, immune dysregulation, and



an increased risk of cardiovascular disease<sup>[3]</sup>. Current guidelines emphasize that chronic insomnia is not simply a result of insufficient sleep duration or psychological stress, but rather a neuropsychiatric disorder involving dysfunction across multiple brain regions, neurotransmitter systems, and neural networks. Its core pathological mechanisms are thought to be closely related to dysregulated cortical excitability, impaired emotion regulation circuits, and overactivation of the hypothalamic–pituitary–adrenal axis<sup>[4]</sup>.

At present, treatment strategies for chronic insomnia include both pharmacological and nonpharmacological approaches. In clinical practice, pharmacotherapy remains the dominant option; however, it may cause adverse effects such as drug dependence, rebound insomnia, anxiety, depression, and even cognitive impairment after long term use<sup>[3]</sup>. Consequently, nonpharmacological interventions for chronic insomnia have become a major focus in sleep medicine research. In recent years, with the rapid development of neuromodulation technologies, repetitive transcranial magnetic stimulation, abbreviated as rTMS, has attracted increasing attention as a safe and noninvasive brain stimulation technique for neuropsychiatric disorders. Based on the principle of electromagnetic induction, rTMS applies pulsed magnetic fields to specific regions of the central nervous system, induces electric currents by altering neuronal membrane potentials, and thereby modulates neuronal metabolism, synaptic connectivity, synaptic plasticity, and neural network organization. As an externally applied electric field across the cell membrane, rTMS can alter transmembrane potential differences, induce depolarization, and activate excitable tissues. Its regulatory effects on neural excitability depend strongly on stimulation parameters, especially frequency. Different frequencies, intensities, and stimulation patterns may produce excitatory or inhibitory effects, thereby promoting the remodeling of dysfunctional brain networks<sup>[5]</sup>.

A growing number of studies have shown that rTMS has significant therapeutic effects in chronic insomnia, including shortening sleep latency, improving sleep efficiency, and alleviating accompanying symptoms such as anxiety and depression<sup>[6]</sup>. Neuroimaging evidence further suggests that rTMS may promote the reorganization of functional connectivity in the prefrontal cortex, thalamus, hippocampus, and other sleep related regions, while enhancing the dynamic balance between the default mode network and the executive control network, thus reflecting substantial brain network plasticity<sup>[7]</sup>. In addition, rTMS may regulate the gamma aminobutyric acid and glutamate balance<sup>[8]</sup>, restore hypothalamic–pituitary–adrenal axis function, and reduce central hyperarousal<sup>[9]</sup>, thereby providing a neurophysiological basis for its therapeutic effects. Therefore, this review systematically summarizes the neural mechanisms and brain network plasticity associated with rTMS in the treatment of chronic insomnia, with the aim of clarifying its multilevel mechanisms of action and network modulation patterns, and providing a theoretical basis and future directions for precision nonpharmacological interventions in chronic insomnia.

## 2. Neurophysiological Basis of Chronic Insomnia

The development and persistence of chronic insomnia involve a complex, multilevel interaction among central nervous system dysfunction, abnormal neurotransmitter regulation, and disrupted brain connectivity patterns. With the advancement of neuroimaging and electrophysiological techniques, the conceptual framework of chronic insomnia has gradually shifted from a traditional model of psychological and behavioral dysregulation to one of neural network abnormalities, providing new evidence for understanding its underlying neurobiology.

### 2.1 Functional Imbalance Between Cortical and Subcortical Structures

Studies using functional magnetic resonance imaging and functional near infrared spectroscopy have shown significant alterations in functional connectivity within the frontal lobe, parietal lobe, and limbic system in patients with chronic insomnia<sup>[10]</sup>. In particular, decreased activity in the dorsolateral prefrontal cortex, abbreviated as DLPFC, may weaken executive control and emotional inhibition, whereas hyperactivation of the amygdala and insula is closely associated with heightened emotional arousal and anxiety<sup>[11]</sup>. Dysfunction within the prefrontal–amygdala circuit is considered one of the key pathological features of chronic insomnia. In addition, the thalamus serves as a gating structure in the sleep wake transition<sup>[12]</sup>. Excessive thalamic excitability may disrupt the sleep wake cycle and impair both sleep initiation and sleep maintenance.

### 2.2 Abnormal Regulation of Neurotransmitter Systems

Neurotransmitters provide the essential chemical basis for maintaining the balance between sleep and wakefulness. Animal

studies have shown that mice with insomnia exhibit significantly reduced gamma aminobutyric acid, abbreviated as GABA, levels and elevated glutamate, abbreviated as Glu, levels, indicating an imbalance between cortical excitation and inhibition<sup>[13]</sup>. Magnetic resonance spectroscopy studies have further demonstrated that decreased GABA concentrations in the prefrontal cortex and thalamus are positively associated with prolonged sleep latency and increased nocturnal awakenings<sup>[14]</sup>. In addition, monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine also participate in sleep regulation. Reduced serotonin levels may decrease the proportion of slow wave sleep, whereas excessive norepinephrine release may promote wakefulness. Recent evidence suggests that rTMS may help restore neurochemical homeostasis in insomnia by modulating the GABA to glutamate balance and monoamine neurotransmitter release<sup>[14]</sup>.

### 2.3 Hyperactivation of the Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal axis, abbreviated as the HPA axis, is not only a central component of the stress response but also plays an important role in the regulation of the neuroendocrine immune network. Studies have shown that HPA axis activity is closely related to the sleep wake cycle and serves as a reliable indicator of hyperarousal in patients with insomnia<sup>[15]</sup>. Elevated adrenocorticotrophic hormone levels may increase sympathetic tone and substantially affect the alternation of the sleep wake cycle<sup>[16]</sup>. Long term HPA axis hyperactivity may suppress melatonin secretion through feedback mechanisms, disrupt circadian rhythms, and establish a vicious cycle of hyperarousal, insomnia, and stress<sup>[17]</sup>. Electrophysiological studies indicate that rTMS may improve sleep architecture and stress responses by suppressing excessive cortical excitability and reducing cortisol levels<sup>[18]</sup>, thereby providing a physiological basis for further neuromodulation research.

### 2.4 Disrupted Brain Network Connectivity Patterns

Recent brain network studies have demonstrated that chronic insomnia is characterized by widespread functional connectivity imbalance<sup>[19]</sup>. Functional connectivity analyses suggest that patients with insomnia exhibit hyperactivity in the default mode network, abbreviated as DMN, together with reduced activity in the executive control network, abbreviated as ECN, and the salience network, abbreviated as SN, resulting in persistently elevated arousal. In particular, reduced connectivity between the prefrontal cortex and the hippocampus and thalamus may impair sleep related information integration and memory consolidation<sup>[20]</sup>. This network imbalance not only reflects the neurophysiological nature of insomnia, but also provides a rationale for targeting brain networks through neuromodulation techniques.

## 3. Mechanisms and Parameter Characteristics of Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation is a noninvasive neuromodulation technique based on the principle of electromagnetic induction. By placing a stimulation coil over the scalp and delivering rapidly changing magnetic fields, rTMS induces electric currents in the cortex and modulates neuronal membrane potentials and synaptic transmission. rTMS can produce sustained neuroplastic changes in both local and remote brain regions and has been widely investigated in the treatment of depression, anxiety, chronic pain, and sleep disorders<sup>[21]</sup>. Its core therapeutic value lies in the bidirectional regulation of cortical excitability and network activity through specific parameter settings.

### 3.1 Basic Principles of rTMS

rTMS applies pulsed magnetic fields to specific areas of the central nervous system, induces electric currents by altering cortical neuronal membrane potentials, and thereby influences neuronal metabolism, synaptic connectivity, synaptic plasticity, and neural network optimization. As an externally superimposed electric field across the cell membrane, rTMS can change transmembrane potential differences, induce membrane depolarization, and activate excitable tissues. Repeated magnetic stimulation may produce long term potentiation like or long term depression like effects at the synaptic level, thereby enabling plastic regulation of neural circuits<sup>[22]</sup>.

The therapeutic effects of rTMS are closely associated with stimulation frequency, intensity, number of pulses, target site, and treatment duration. Different combinations of frequency and intensity can induce specific physiological responses in different brain regions and generate either facilitatory or inhibitory effects on cortical activity. High frequency stimulation, defined as 5 Hz or higher, is generally considered excitatory and may enhance neural excitability, whereas low frequency stimulation,

defined as 1 Hz or lower, is usually inhibitory and may reduce cortical activity. Theta burst stimulation, abbreviated as TBS, delivers short bursts of high frequency pulses nested within a low frequency rhythm and can induce long term potentiation like or long term depression like synaptic plasticity <sup>[23]</sup>.

In clinical practice, stimulation intensity is usually expressed as a percentage of the individual motor threshold, abbreviated as MT, typically ranging from 80% to 120% of MT. Intensities that are too low may fail to induce significant effects, whereas intensities that are too high may increase the risk of adverse events. With regard to stimulation targets, the left DLPFC is one of the most frequently used sites in insomnia treatment because of its close involvement in emotion regulation, attentional control, and sleep initiation. Some studies have also applied stimulation over the right DLPFC to improve sleep quality and anxiety symptoms. Recent expert consensus suggests that bilateral DLPFC stimulation may be more effective than unilateral stimulation for insomnia <sup>[24]</sup>. Regarding treatment duration, most clinical studies adopt a protocol of one session per day for two to four weeks, and cumulative stimulation dose appears to be positively associated with therapeutic efficacy.

### 3.2 Neural Regulatory Mechanisms of rTMS

The mechanisms by which transcranial magnetic stimulation improves chronic insomnia are related to reduced cortical excitability, shortened sleep latency, and increased slow wave sleep <sup>[5]</sup>. The therapeutic effects of rTMS on insomnia severity may involve neurotransmitter release, synaptic plasticity, and neural network optimization. Through cumulative stimulation effects, rTMS excites neurons in multiple directions and at multiple levels, thereby facilitating not only regional reconstruction of cortical function but also long lasting biological effects through long term potentiation like mechanisms, ultimately enhancing synaptic plasticity.

Studies have shown that patients with chronic insomnia exhibit abnormal cortical activity, including disturbances in sleep wake rhythm regulation and neurotransmitter control <sup>[18]</sup>. By acting on the cerebral cortex, rTMS may improve sleep quality through normalization of these abnormal cortical activities. rTMS can modulate postsynaptic receptor density and neurotransmitter release and induce long term potentiation like and long term depression like plasticity, thereby providing a basis for brain plasticity <sup>[25]</sup>. The dorsolateral prefrontal cortex has direct fiber projections to the hypothalamus and direct or indirect connections with the basal forebrain. By strengthening communication between the prefrontal cortex, hypothalamus, and basal forebrain, rTMS may optimize neural network organization and trigger chain like changes in interregional functional connectivity, thereby restoring the dynamic balance of sleep wake related networks in patients with chronic insomnia.

### 3.3 Parameter Applications in Chronic Insomnia

In studies on chronic insomnia, most protocols have used low frequency 1 Hz rTMS over the left DLPFC to inhibit excessive cortical excitability, reduce arousal, and improve sleep architecture. Some studies have applied high frequency stimulation over the right DLPFC to enhance prefrontal regulation of the limbic system and thereby alleviate anxiety and emotional hyperarousal <sup>[26]</sup>. More recent research has combined functional neuroimaging with neuronavigated rTMS to individualize target localization according to each patient's functional connectivity profile, thereby improving treatment precision and reproducibility <sup>[26]</sup>.

## 4. Research Progress on Brain Network Plasticity Induced by rTMS in Chronic Insomnia

With the rapid development of neuroimaging techniques, research on sleep disorders has shifted from focusing on dysfunction within isolated brain regions to examining abnormal coordination across distributed brain networks. Chronic insomnia is increasingly regarded as a typical disorder of large scale brain network dysconnectivity, characterized by an imbalance between persistently hyperactive arousal networks and suppressed sleep initiation networks. By modulating specific cortical targets and their remote connectivity pathways, rTMS can induce plastic reorganization of brain networks and thereby improve the neural circuitry underlying insomnia. Recent studies using functional magnetic resonance imaging, functional near infrared spectroscopy, and electroencephalography imaging fusion techniques have highlighted the important role of rTMS in promoting network level integration and remodeling.

#### 4.1 Remodeling of the Default Mode Network

The default mode network mainly includes the medial prefrontal cortex, posterior cingulate cortex, precuneus, and hippocampus, and is closely associated with self referential thinking and resting state arousal. Patients with chronic insomnia often exhibit excessive activation of the DMN, especially increased functional connectivity between the medial prefrontal cortex and posterior cingulate cortex, which may contribute to heightened presleep arousal and excessive cognitive activity. By suppressing frontal hyperactivity, rTMS may reduce overall DMN coupling strength<sup>[27]</sup>. Studies have shown that after low frequency rTMS over the left DLPFC, functional connectivity between the medial prefrontal cortex and posterior cingulate cortex is significantly reduced in patients with insomnia, DMN resting state activity tends to normalize, and subjective sleep latency and nocturnal awakenings are significantly decreased<sup>[28]</sup>. Functional near infrared spectroscopy studies have also found that rTMS can reduce fluctuations in oxygenated hemoglobin concentration in the frontal cortex, indicating a suppressive effect on cortical metabolic activity<sup>[29]</sup>, which supports restoration of the DMN from an energy metabolism perspective.

#### 4.2 Enhancement of the Executive Control Network

The executive control network mainly includes the dorsolateral prefrontal cortex and posterior parietal regions and is responsible for higher order functions such as attentional control, emotional regulation, and cognitive inhibition. Patients with chronic insomnia often show impaired ECN function and are less able to suppress internal thoughts and negative emotions effectively<sup>[30]</sup>. By targeting the left DLPFC, rTMS may restore functional connectivity within the ECN and enhance its integration efficiency<sup>[31]</sup>. rTMS intervention has been reported to increase prefrontal activation and task related response speed, suggesting long term plastic improvements in cognitive control and sustained attention. Functional magnetic resonance imaging studies have shown that after rTMS treatment, functional connectivity between the DLPFC and parietal regions is significantly increased, while negative coupling between the DLPFC and the amygdala and hippocampus is enhanced, suggesting that rTMS may strengthen the top down inhibitory influence of the executive control network over emotional and arousal systems<sup>[32]</sup>.

#### 4.3 Regulation of the Salience Network

The salience network, composed primarily of the anterior cingulate cortex and insula, is responsible for switching attention between internal and external stimuli and regulating emotional arousal. Chronic insomnia is often associated with excessive SN activity, especially increased insular activation, which may lead to sustained activation of the arousal system<sup>[33]</sup>. After stimulation of the DLPFC, rTMS may reduce the hypersensitivity of the salience network through cross network regulation, thereby restoring normal response thresholds to internal and external stimuli. Studies have shown that the functional connectivity between the anterior cingulate cortex and insula decreases after rTMS treatment and is significantly negatively correlated with subjective anxiety scores and arousal levels<sup>[34]</sup>. These findings suggest that rTMS may help restore the dynamic balance between arousal and sleep initiation by downregulating salience network activity.

#### 4.4 Integration of Thalamocortical Circuits and Limbic System Networks

The thalamus is a key relay structure in sleep wake regulation. Thalamocortical circuits involving the cortex, hippocampus, and limbic system play essential roles in sleep regulation. Functional connectivity of the thalamus is generally increased in patients with chronic insomnia, suggesting impairment of its gating function. rTMS may restore synchronous rhythms within cortical thalamic circuits by modulating remote connectivity between the DLPFC and thalamus. Studies have reported that following rTMS, functional connectivity between the thalamus and frontal and parietal cortices is significantly reduced, alpha power increases, and the number of sleep spindles rises, suggesting facilitation of slow wave sleep generation and suppression of wakefulness. At the same time, rTMS may improve connectivity within limbic circuits involving the hippocampus, amygdala, and prefrontal cortex, thereby enhancing the stability of emotional and memory processing and providing a neural basis for sleep consolidation<sup>[35]</sup>.

### 5. Conclusion

The neurophysiological basis of chronic insomnia is mainly characterized by increased cortical excitability, reduced

inhibitory neurotransmission, and impaired integration of large scale brain networks. These abnormal mechanisms interact with one another and jointly maintain the pathological state of insomnia. A deeper understanding of these neural mechanisms not only helps clarify the biological nature of insomnia but also provides a theoretical foundation for neuromodulation techniques such as rTMS.

By applying an external magnetic field to cortical neurons, rTMS can regulate neuroplasticity at the cortical and subcortical circuit level, restore brain network balance, and promote reconstruction of sleep related function in patients with chronic insomnia. The brain network plasticity induced by rTMS is mainly reflected in suppression of default mode network hyperactivity, reduction of resting state hyperarousal, enhancement of executive control network function, improvement of emotional and attentional regulation, modulation of salience network activity, restoration of the balance between arousal and sleep initiation, and reconstruction of thalamocortical and limbic circuits, thereby synchronously optimizing sleep rhythms and cognitive function. These network level changes provide objective neuroimaging evidence for the therapeutic effects of rTMS in chronic insomnia and offer new directions for future precision brain modulation interventions. Future studies should combine individualized neuronavigated rTMS with multimodal imaging techniques to further clarify the spatiotemporal evolution of brain network plasticity from the perspective of dynamic connectivity and directional causal interactions.

## 6. Future Perspectives

Current research on the mechanisms by which rTMS improves insomnia remains largely focused on the regulation of cortical excitability and neurotransmitter balance, whereas its effects on multiregional circuits and dynamic interactions across brain networks have not yet been fully elucidated. Future studies should integrate multimodal neuroimaging and molecular biomarker monitoring to establish multiscale mechanistic models spanning molecular, cellular, circuit, and systems levels. High temporal resolution electroencephalography combined with high spatial resolution functional imaging may help reveal the dynamic evolution of rTMS induced neuroplasticity across different time windows and provide spatiotemporal evidence for its long term regulatory effects.

The efficacy of rTMS is highly dependent on precise parameter settings and appropriate target selection. At present, most studies still rely on empirical stimulation protocols and lack precision targeting strategies based on individual brain functional characteristics. Future research should develop individualized target localization methods based on neuroimaging navigation systems combined with resting state functional connectivity maps, cortical thickness, and metabolic indicators. Machine learning models may also be used to identify optimal combinations of stimulation frequency, intensity, pulse number, and treatment duration, thereby improving personalization and reproducibility. In addition, the development of closed loop neuromodulation systems that monitor brain activity in real time and adaptively adjust stimulation parameters may substantially improve therapeutic efficiency and the induction of neuroplasticity.

Although rTMS alone can improve sleep quality and emotional status, its effects may be limited in magnitude and duration. Future studies should explore multimodal intervention strategies that combine rTMS with cognitive behavioral therapy, exercise interventions, mindfulness based approaches, and pharmacotherapy to promote coordinated recovery of sleep and emotional systems from multiple dimensions. Investigation of the synergistic mechanisms underlying these combined treatments may provide new theoretical foundations and clinical pathways for comprehensive insomnia management.

Most existing studies have focused on short term therapeutic effects and lack follow up data or long term plasticity indicators. Future longitudinal studies should include follow up assessments at six to twelve months after treatment to evaluate the durability and reversibility of neural network remodeling. In addition, structural plasticity changes induced by rTMS, such as alterations in gray matter volume, white matter integrity, and synaptic density, should be examined. By integrating diffusion tensor imaging and morphometric analysis, researchers may better elucidate the structural mechanisms by which rTMS promotes neural network reconstruction and thereby provide empirical support for its long term efficacy.

Clinical translation of rTMS in insomnia treatment still faces several challenges, including insufficient standardization, large interindividual variability, and a lack of objective evaluation systems. Future work should establish multidimensional evaluation frameworks based on neuroimaging and physiological signals by integrating subjective sleep questionnaires, objective polysomnography, and brain network functional indices to generate quantitative efficacy criteria. At the same time,



multicenter randomized controlled trials are needed to develop unified parameter protocols and safety assessment systems, thereby strengthening the evidence base for the clinical application of rTMS in chronic insomnia. Ethical and safety issues should also be given close attention, and risk warning and patient suitability screening mechanisms should be established to ensure the scientific rigor and controllability of rTMS interventions.

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## Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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# Analysis on the Key Role of Head Nurses' Leadership in Nursing Team Management and Its Realization Paths

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**Abstract:** As the core leader of the nursing team, head nurses play a vital role in improving the professional competence of the team, enhancing team cohesion, upgrading nursing quality, ensuring nursing safety, and promoting nursing innovation. This study takes 15 head nurses from different levels and departments as research subjects, and collects data through semi-structured interviews and observation methods. Combined with transformational leadership theory, social learning theory and organizational commitment theory, an “Input-Process-Output (IPO)” analytical framework is constructed. Through thematic induction and cross-case analysis, this paper systematically explores the mechanism and realization paths of head nurses' leadership in nursing team management. The results show that through exemplary leadership, scientific management and effective communication, head nurses not only improve the professional literacy and teamwork ability of nursing staff, but also promote the continuous optimization of nursing quality and safety management. This study further puts forward strategies to strengthen the capacity building of head nurses themselves, improve the management system and focus on personnel training, to provide theoretical support and empirical reference for nursing management practice and policy formulation.

**Keywords:** Head Nurse; Nursing Team Management; Transformational Leadership; Team Cohesion; Nursing Quality Management

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## 1. Introduction

Nursing is an important component of the medical service system, and its quality and efficiency are directly related to patients' rehabilitation outcomes and the overall level of medical care <sup>[1]</sup>. As the main implementers of nursing services, the professional quality, collaborative competence and job performance of the nursing team not only determine the quality of nursing services, but also affect patient satisfaction and the operational efficiency of medical institutions <sup>[2]</sup>. Within this system, head nurses, as the backbone and core managers of the nursing team, undertake multiple responsibilities including organizational coordination, quality monitoring, personnel training and innovation leadership <sup>[3,4]</sup>.

In recent years, academic and industry practices have paid increasing attention to nursing leadership. Especially under theoretical frameworks such as Transformational Leadership, Servant Leadership and Authentic Leadership, studies have found that head nurses' leadership styles and management strategies exert significant effects on nursing quality, patient safety and team stability <sup>[5,6]</sup>. Transformational leadership theory emphasizes that leaders can effectively boost team morale and

work performance through visionary motivation, intellectual stimulation and individualized consideration<sup>[7]</sup>. Social Learning Theory provides a theoretical basis for explaining the exemplary role of head nurses, in that team members form professional norms and value identity by observing and imitating leaders' behaviors<sup>[8]</sup>. In addition, Organizational Commitment Theory reveals the positive effects of leadership behaviors on employees' affective commitment, retention intention and work engagement<sup>[9]</sup>.

Although existing studies have provided important references for understanding the role of head nurses in nursing team management, two limitations remain. First, some studies focus on descriptive analysis and lack a systematic framework integrating multiple theories. Second, insufficient exploration has been conducted on the internal mechanisms of head nurses' leading roles across different functional dimensions (e.g., quality assurance, safety management, innovation promotion, etc.), making it difficult to provide an operable management model for practice. Based on the above deficiencies, this study proposes three core questions: (1) How do head nurses exert leadership in different contexts? (2) Through what process mechanisms are the effects of their leadership realized? (3) What strategies can optimize the leadership effectiveness of head nurses? To address these issues, this study constructs an Input–Process–Output (IPO) framework based on transformational leadership theory, social learning theory and organizational commitment theory, and collects evidence through semi-structured interviews and observational methods to explore the realization paths and functional mechanisms of head nurses' leadership in nursing team management.

## 2. Literature Review

### 2.1 Role Orientation of Head Nurses in Nursing Team Management

The nursing team constitutes an important part of the medical service system, and its work quality is directly related to patients' treatment outcomes and medical safety<sup>[1]</sup>. As core managers, head nurses are mainly responsible for formulating nursing work plans, arranging staff schedules reasonably, coordinating job connections, and ensuring efficient and orderly nursing services through scientific management<sup>[4]</sup>. In surgical wards of large general hospitals, nursing tasks cover multiple stages including preoperative, intraoperative and postoperative care. Head nurses need to allocate tasks scientifically and coordinate cross-departmental processes by comprehensively considering factors such as patients' conditions, surgical arrangements, professional skills of nursing staff and workload, to guarantee nursing quality and patient safety.

In foreign research, a cross-sectional survey of 12 countries by Aiken et al. showed that the level of nursing leadership is significantly positively correlated with patient safety, nursing quality and nurse satisfaction<sup>[6]</sup>. Domestic studies have mostly focused on post competency of head nurses<sup>[10]</sup>, leadership styles<sup>[11]</sup>, and the relationship between leadership and nursing quality<sup>[12]</sup>.

### 2.2 Manager and Supervisor of Nursing Quality

As the primary person responsible for nursing quality, head nurses are required to establish and improve nursing quality standards, standardize operational procedures, and ensure quality through regular inspections and performance evaluations<sup>[12, 6]</sup>. In practice, head nurses regularly organize nursing quality ward rounds to conduct systematic inspections of key links such as basic nursing, specialized nursing and nursing documents, and formulate improvement measures through Root Cause Analysis. This process not only improves nursing quality but also fosters a culture of continuous quality improvement with full participation<sup>[13]</sup>. For identified problems, head nurses organize nursing staff to analyze and discuss them, identify root causes, and develop corresponding improvement measures through continuous quality monitoring.

In recent years, leadership theories have been widely applied in the field of nursing management<sup>[14]</sup>. Among them, Transformational Leadership emphasizes enhancing team morale and performance through visionary inspiration, intellectual stimulation and individualized consideration<sup>[7]</sup>. A systematic review by Gebreheat et al. showed that transformational leadership can significantly improve nurses' job satisfaction and organizational commitment and reduce staff turnover<sup>[5]</sup>. Servant Leadership focuses more on subordinate development and well-being, and studies have shown that it can enhance nurses' professional well-being and team cohesion<sup>[15]</sup>. Authentic Leadership emphasizes leaders' self-awareness and transparent communication, which can strengthen trust and psychological safety within nursing teams<sup>[16]</sup>. In practice, it can effectively control risks, improve service content, and continuously upgrade the quality of nursing services.

## 2.3 Trainer and Mentor of Nursing Staff

Head nurses play a key role in the career development of nursing staff and need to design personalized training and guidance programs according to the needs of nurses at different career stages<sup>[17, 16]</sup>. Studies have shown that systematic post competency training can not only improve clinical skills but also enhance team members' professional confidence and retention intention<sup>[13]</sup>. For example, with the help of preceptorship, newly recruited nurses can master nursing procedures and standards more quickly and reduce errors caused by insufficient experience. Nurses in practice also undertake the important responsibility of cultivating and improving the professional quality of nursing staff. Scholars such as Ma Li et al. argued that personalized training plans should be formulated according to the actual situation and development needs of nursing staff, professional learning and skill training activities should be organized, and nursing staff should be guided to solve difficult problems encountered in work<sup>[17]</sup>.

At the initial stage of new nurses' employment, head nurses assign experienced preceptors to provide one-on-one guidance, helping new nurses become familiar with the working environment as soon as possible and master basic nursing skills and work procedures. At the same time, head nurses also need to regularly organize nursing lectures, case discussions, nursing skill competitions and other activities to encourage nursing staff to continuously learn new knowledge and skills and improve their professional competence.

In the long-term research on head nurse leadership and management, several theories have been summarized to support the interpretation of head nurses' exemplary role, as shown in Table 1:

- (1) Transformational Leadership Theory: Explains how head nurses promote team initiative and innovation through strategic vision, exemplary role and incentive mechanisms<sup>[7]</sup>.
- (2) Social Learning Theory: Points out that head nurses' behaviors provide observable and imitable learning models for team members, thereby influencing professional behaviors and values<sup>[18]</sup>.
- (3) Organizational Commitment Theory: Emphasizes that leadership behaviors can strengthen team members' affective commitment and sense of belonging, thereby improving job performance and retention intention<sup>[9]</sup>.

*Table 1: Support of Relevant Theories for the Exemplary Role of Head Nurses*

Theory Name	Core Ideas	Interpretation & Application to Head Nurses' Exemplary Role
Transformational Leadership Theory	Visionary inspiration, intellectual stimulation, individualized consideration	Motivates team initiative and improves performance
Social Learning Theory	Formation of behavioral and value identity through observation and imitation	Exemplary behaviors shape team professional norms
Organizational Commitment Theory	Enhances affective commitment and sense of belonging	Improves employees' work engagement and retention intention

As shown in Table 1, transformational leadership theory, social learning theory and organizational commitment theory are generally summarized to provide theoretical support for the exemplary role of head nurses, explaining how leaders influence the management effectiveness of nursing teams through motivation, demonstration and affective commitment. These three theories fully explain the positive exemplary role of head nurses in the team.

Combined with the results of semi-structured interviews, head nurses from medical institutions at different levels show differentiated practices in nursing staff training, all centered on the core of "matching personalized needs". The head nurse of the ICU in a tertiary hospital (Interviewee 3) stated that a mode of "high-fidelity simulation training plus practical combat review" was adopted for critical care skills training. For instance, by simulating scenarios of "rescue of patients with multiple organ failure", nurses mastered core techniques such as CRRT operation and ventilator parameter adjustment through hands-on practice. After the training, the team rescue success rate increased from 88% to 95%. The head nurse of general practice in a community hospital (Interviewee 9), in response to the needs of elderly chronic disease management, designed "dialect versions of health education manuals plus practical guidance for home visits". After new nurses completed more than 30

home visits with senior nurses under the “preceptorship system”, the implementation rate of standardized chronic disease care rose from 78% to 92%.

The practice of the head nurse of pediatrics in a secondary hospital (Interviewee 15) further verified the effectiveness of training. Through “cartoon teaching tools plus staged assessment” — newly recruited nurses focused on basic puncture and communication skills, while nurses with 3–5 years of experience focused on specialized neonatal care — the success rate of intravenous puncture increased from 85% to 96%, and parents’ satisfaction with nursing services improved from 82% to 94%. The above interview results are consistent with the viewpoint of “personalized training plans” proposed by Ma Li et al. and supplement the implementation paths in different medical scenarios, providing practical evidence for the improvement of the nursing staff training system <sup>[17]</sup>.

## 2.4 Promoter and Maintainer of Team Building

Head nurses should emphasize the construction of nursing teams, create a positive, united and collaborative working atmosphere, and enhance team cohesion and self-efficacy <sup>[19,20]</sup>. By organizing team activities and caring for the personal lives and career development of nursing staff, head nurses can stimulate nurses’ enthusiasm and initiative and improve overall team effectiveness. Effective team building includes not only worklevel collaboration but also the establishment of emotional support and interpersonal trust <sup>[21]</sup>. Through team-building activities and career development guidance, head nurses can cultivate mutual trust and cooperation among members, thereby improving team resilience and overall performance.

In long-term practice, head nurses can regularly organize outdoor team-building activities for nursing teams to strengthen communication and trust among members. They can also pay attention to nurses’ career development needs, provide promotion opportunities and career planning guidance for potential nurses, and make nursing staff feel cared for and supported by the team. In this way, nurses will be more willing to contribute to the development of the team.

## 2.5 Deficiencies in Current Research

Although existing studies have provided important references for understanding the role of head nurses in nursing team management, several deficiencies remain:

First, most studies focus on descriptive discussions and lack a systematic analytical framework integrating multiple theories, resulting in a disconnect between theory and practice.

Second, research on the exemplary role of head nurses mostly concentrates on its positive impacts on nursing quality and team performance, while in-depth analysis of its differences across different contexts (such as hospital levels, department types, and cultural backgrounds) is insufficient.

Third, some studies ignore the potential negative effects of exemplary leadership, such as reduced team autonomy caused by excessive reliance on individual leadership, and conflicts between management and clinical roles.

Therefore, it is necessary to integrate multiple leadership theories and combine the contextual characteristics of nursing management to construct an analytical framework with stronger explanatory power and practical guidance, so as to systematically explore the multidimensional impacts and optimization paths of head nurses’ exemplary role.

Based on the above research gaps and theoretical analysis, under the comprehensive guidance of transformational leadership theory, social learning theory and organizational commitment theory, this study focuses on five core dimensions — “improving professional competence, enhancing team cohesion, upgrading nursing quality, ensuring nursing safety, and promoting nursing innovation” — to deeply elaborate the importance of head nurses’ exemplary role in nursing team management and its realization mechanism.

## 3. Research Methods and Data Collection

This study adopts a mixed method combining semi-structured interviews and on-site observations, with head nurses as the core research subjects, and the sample size is set at 15. Interviewees are head nurses from different hospital levels (tertiary hospitals, secondary hospitals, and community health institutions), different departments (surgery, internal medicine, ICU, pediatrics, etc.) and with different years of working experience, to ensure sample diversity. The research focuses on exploring the decision-making logic of leadership implementation, difficulties encountered, and optimization experience.

(1) Data collection: Interviews were conducted in March 2024, each lasting approximately 60 minutes. With the consent of

the interviewees, the whole process was recorded and transcribed (see Table 3). Observations were mainly carried out during nursing ward rounds and regular quality management meetings, and observation notes were formed accordingly.

(2) Data analysis: Data analysis was performed through the three-step process of open coding, axial coding, and selective coding based on grounded theory, and main categories were extracted using thematic induction. To ensure the credibility of the results, the research team conducted triangulation verification and, when necessary, followed up with interviewees for member checking. Data saturation was reached at the 13th interviewee, and no new themes emerged from the subsequent two interviewees.

(3) Reliability assurance: The transparency and credibility of the research were ensured through cross-validation among researchers, recording of the analysis process in research diaries, and discussions within the research team.

*Table 2: Interview Outline (Partial)*

Core Module	Questions for Head Nurses
Perception of Leadership Role	1. What do you believe is your most effective exemplary behavior when improving the professional competence of your team? Please provide one specific case. 2. How do you judge whether team cohesion has improved? What data or phenomena can support this?
Implementation Details of Paths	1. When establishing a nursing quality management system, how do you encourage nurses to participate voluntarily rather than implement passively? 2. Faced with the training needs of different nurses, how do you balance “unified requirements” and “personalized design”?
Contextual Differences and Challenges	1. Compared with other departments (or hospitals of different levels), what are the special characteristics of leadership implementation in your department? 2. What is your greatest difficulty in balancing clinical work and management responsibilities?

*Table 3: Summary of Basic Information of Interviewees*

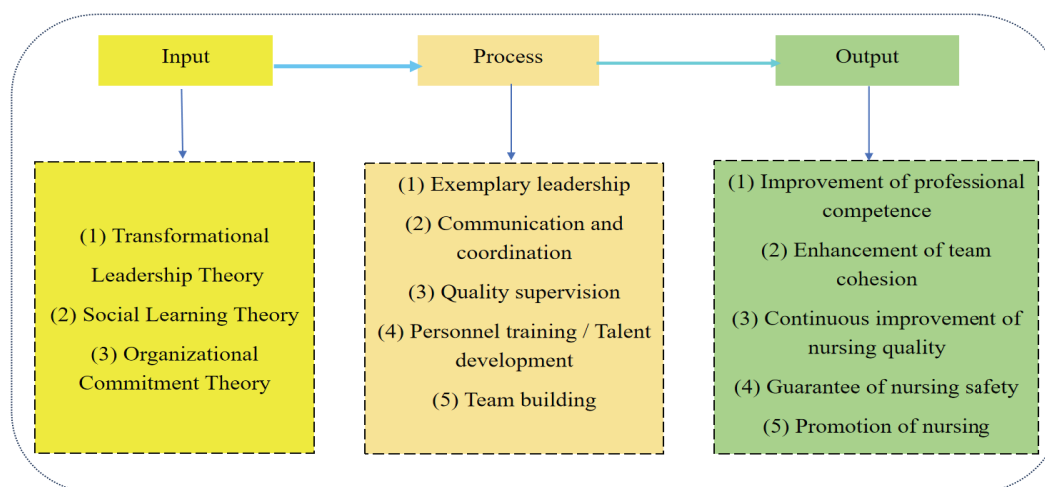
No.	Interviewee	Hospital Level	Department	Years of Employment	Interview Location
1	Head Nurse Zhang	Tertiary Hospital	Surgery	8 years	Head Nurse Office, Surgery Department
2	Head Nurse Li	Tertiary Hospital	Internal Medicine	6 years	Conference Room, Internal Medicine Department
3	Head Nurse Wang	Tertiary Hospital	ICU	5 years	Medical Office, ICU
4	Head Nurse Zhao	Tertiary Hospital	Pediatrics	7 years	Head Nurse Office, Pediatrics Department
5	Head Nurse Sun	Secondary Hospital	Surgery	4 years	Conference Room, Surgery Department
6	Head Nurse Zhou	Secondary Hospital	Internal Medicine	3 years	Head Nurse Office, Internal Medicine Department
7	Head Nurse Wu	Secondary Hospital	Obstetrics and Gynecology	6 years	Conference Room, Obstetrics and Gynecology Department
8	Head Nurse Zheng	Secondary Hospital	Emergency Department	5 years	Medical Office, Emergency Department
9	Head Nurse Qian	Community Hospital	General Practice	10 years	Conference Room, Community Hospital
10	Head Nurse Feng	Community Hospital	Geriatrics	8 years	Head Nurse Office, Geriatrics Department
11	Head Nurse Chen	Tertiary Hospital	Obstetrics and Gynecology	9 years	Head Nurse Office, Obstetrics and Gynecology Department
12	Head Nurse Chu	Secondary Hospital	ICU	4 years	Conference Room, ICU
13	Head Nurse Wei	Community Hospital	General Practice	7 years	Medical Office, Community Hospital
14	Head Nurse Jiang	Tertiary Hospital	Emergency Department	6 years	Head Nurse Office, Emergency Department
15	Head Nurse Shen	Secondary Hospital	Pediatrics	5 years	Conference Room, Pediatrics Department



#### 4. The Importance of Head Nurses' Exemplary Role in Nursing Team Management

To systematically demonstrate the realization mechanism of head nurses' exemplary role, this study constructs an Input–Process–Output (IPO) analytical framework based on transformational leadership theory, social learning theory and organizational commitment theory (see Figure 1). The framework clearly shows how the theoretical foundation (input) is transformed into specific management behaviors of head nurses (process), and ultimately promotes the improvement of nursing team professionalism, team cohesion, nursing quality and other aspects (output).

Figure 1: Schematic Diagram of the IPO Theoretical Framework



##### 4.1 Improving the Professional Level of the Nursing Team

With solid professional knowledge and rich clinical experience, head nurses play an important exemplary and leading role for nursing staff<sup>[22]</sup>. In daily management and clinical work, head nurses provide direct learning opportunities for team members by personally participating in nursing practice and handling complex nursing problems. For example, in the care of critically ill patients, head nurses can quickly assess changes in the patient's condition and formulate scientific nursing plans<sup>[23]</sup>. Through collaborative work, nursing staff can receive on-the-job training in clinical decision-making and operational skills, thereby improving their professional competence.

At the same time, head nurses actively participate in academic research and continuing education activities, introduce the latest nursing concepts and technologies into the department, and organize group study and discussions to promote the clinical application of new knowledge and techniques. This continuous knowledge updating mechanism helps improve the professional literacy of nursing staff and enhances the overall clinical competence and adaptability of the team. As shown in Table 4, the core responsibilities and corresponding management measures of head nurses in nursing team management reflect how head nurses effectively improve the professionalism and overall effectiveness of nursing services through scientific organization, quality control, personnel training and team building.

Table 4: Responsibilities of Head Nurses and Corresponding Management Measures

Head Nurse Responsibilities	Specific Management Measures	Expected Outcomes
Nursing planning	Reasonable scheduling, coordination of handovers	Efficient and orderly nursing services
Nursing quality management	Establish quality standards, regular ward rounds, root cause analysis	Steady improvement of nursing quality
Training and guidance for nursing staff	Organize professional training, preceptorship, one-on-one guidance	Improved skills and confidence of nursing staff
Team building and communication	Organize team activities, support career development of nurses	Enhanced team cohesion and solidarity
Safety management and risk prevention	Safety education, standardized operation procedures, risk screening	Reduced nursing errors and ensured patient safety

Semi-structured interviews further verified the actual effects of the management measures listed in Table 4. All 15 head nurses mentioned that “exemplary leadership plus systematic training” constitutes the core approach to improving the professional level of nursing teams, with differing practice priorities across hospital levels:

The head nurse of obstetrics and gynecology in a tertiary hospital (Interviewee 11) adopted “demonstration of emergency care for high-risk pregnant women plus multidisciplinary collaborative drills.” As a result, the team’s emergency response time for massive hemorrhage caused by pernicious placenta previa was shortened from 20 minutes to 10 minutes, with a rescue success rate of 98%.

The head nurse of the emergency department in a secondary hospital (Interviewee 8) organized targeted training on “one-minute rapid assessment” for nurses to improve trauma triage efficiency. With the help of “mnemonics plus flowcharts,” triage accuracy increased from 88% to 96%.

The head nurse of geriatrics in a community hospital (Interviewee 10) provided “hands-on demonstration of pressure injury care for disabled elderly patients plus family collaborative guidance.” The standardized implementation rate of pressure injury prevention in the team rose from 82% to 95%, and the incidence of pressure injuries among elderly patients decreased from 12% to 3%.

## 4.2 Enhancing Cohesion and Solidarity of the Nursing Team

The leadership style and management approach of head nurses directly affect the cohesion and organizational solidarity of nursing teams<sup>[20]</sup>. Leaders with strong communication skills, attention to staff care, and leading by example can often gain the trust and respect of team members and create a positive and harmonious working atmosphere. When facing clinical and management challenges, the sense of responsibility and execution of head nurses can invisibly strengthen team members’ work engagement and willingness to cooperate.

In the process of team building, head nurses establish a supportive management mechanism by focusing on the career development and personal needs of nursing staff. They provide timely guidance and resource support for setbacks encountered at work, and offer appropriate care and assistance for personal difficulties. Such measures can improve nurses’ sense of organizational belonging and identity, thereby enhancing team cohesion and collaborative stability.

Interview results show that empathic management and risk sharing are key mechanisms for enhancing team cohesion. Most head nurses emphasized that leaders’ personal participation in high-pressure situations can effectively improve the team’s willingness to cooperate. For example, the head nurse of the emergency department in a tertiary hospital (Interviewee 14) coordinated the division of labor and participated in rescue operations at the first-time during mass casualty treatment, resulting in a 100% voluntary overtime rate among nurses. The head nurse of the ICU in a secondary hospital (Interviewee 12) continuously took night shifts during periods of sudden patient surge, leading to a significant reduction in the team’s job burnout.

Cross-case comparison reveals differences in pathways to enhance cohesion across hospital levels: tertiary hospitals focus more on high-intensity emergency collaboration, secondary hospitals emphasize daily work pressure sharing, and community hospitals prioritize humanistic care and flexible scheduling. This difference indicates that head nurses’ leadership presents diverse pathways in different organizational contexts and needs to be optimized according to local conditions.

In addition, in response to the potential problem of “excessive team reliance on individual decision-making”, some head nurses (such as Interviewees 3 and 7) have begun to establish a hierarchical decision-making mechanism: routine issues are discussed under the leadership of charge nurses, and complex issues are determined through multidisciplinary meetings, gradually cultivating team autonomy. This practice also provides a direction for further optimizing management pathways.

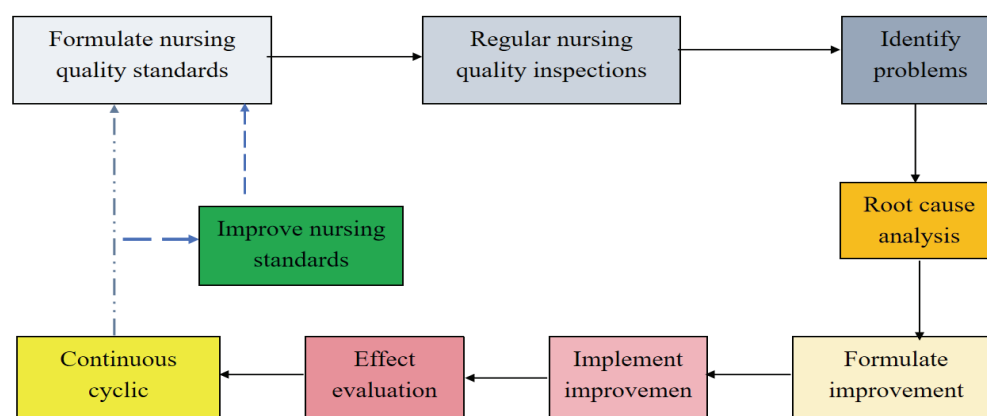
## 4.3 Promoting Continuous Improvement of Nursing Quality

As the main manager and supervisor of nursing quality, the management intensity and implementation level of head nurses directly determine the stability and improvement potential of nursing quality<sup>[6]</sup>. By establishing a systematic nursing quality management system and formulating clear quality standards and assessment systems, head nurses can monitor and evaluate nursing work in the whole process and in all aspects to ensure that all links meet the established standards.

In practice, regular quality inspections and performance appraisals help identify potential problems and formulate targeted

improvement measures. At the same time, guiding nursing staff to participate in quality improvement activities and forming a culture of continuous improvement with full participation can optimize nursing processes, reduce error risks, and overall improve patient care experience and safety.

Figure 2: Flow Chart of Nursing Quality Management



Combined with the interview results, the core of head nurses' promotion of quality improvement lies in problem tracing plus full participation, and the improvement priorities of different departments are highly consistent with the "nursing quality management" measures in Table 2. The head nurse of obstetrics and gynecology in a tertiary hospital (Interviewee 7) addressed abdominal distension after cesarean section by implementing "shortened fasting time plus early mobilization guidance," reducing the incidence of abdominal distension from 25% to 10%. During this process, nurses' suggestions on "adjusting analgesic dosage" were incorporated into the improvement plan. The head nurse of internal medicine in a secondary hospital (Interviewee 6) implemented "timesegmented medicine boxes plus family reminders" to tackle missed oral medications among elderly patients, lowering the misseddose rate from 15% to 5%. Nurses' enthusiasm for participation in improvement was further stimulated through "point rewards." The head nurse of geriatrics in a community hospital (Interviewee 10) carried out "home safety hazard inspection plus antislip equipment recommendation," reducing the incidence of falls in elderly patients from 20% to 8%. The formulation of improvement measures fully absorbed opinions from nurses and family members.

Nursing quality management is a dynamic circular process (see Figure 2), covering the complete workflow from formulating nursing quality standards to continuous improvement. Through strict inspection, root cause analysis, and continuous improvement, head nurses ensure the safety and high quality of nursing services, thereby improving patient satisfaction and treatment outcomes.

#### 4.4 Ensuring Nursing Safety and Reducing Nursing Errors

Nursing safety is one of the core objectives of nursing management, directly related to patients' life, health and overall medical safety <sup>[24]</sup>. Head nurses undertake key responsibilities in safeguarding nursing safety. Their main measures include strengthening safety education, standardizing operational procedures, and establishing a sound risk prevention and control system to reduce the incidence of nursing errors. Regular safety training can improve nursing staff's safety awareness and risk prevention capabilities; strict compliance with regulations helps reduce nonstandard operations. In addition, regular inspection and maintenance of the working environment and equipment can eliminate potential hazards in a timely manner and ensure that facilities and instruments are in good condition. For example, timely handling of highrisk factors such as wet floors and setting warning signs, as well as periodic maintenance of nursing equipment, can effectively reduce the probability of safety incidents.

All 15 head nurses interviewed emphasized the importance of "strengthening safety awareness and rigidifying procedures," and their practical measures were consistent with the core requirements of "nursing safety management." The head nurse of the ICU in a tertiary hospital (Interviewee 3) established a "safety early warning mechanism" with red labeling for highrisk patients and key inspections by nurses every shift, reducing the incidence of catheterrelated infections from 5%



to 2%. The head nurse of pediatrics in a secondary hospital (Interviewee 15) implemented “electronic medical orders plus doublechecking by reading aloud” to address medication errors, eliminating medication errors completely from 8%. The head nurse of general practice in a community hospital (Interviewee 9) launched a “quick photo of home safety hazards” campaign, shortening the response time for nurses to identify and rectify problems such as wet floors and equipment abnormalities from 30 minutes to 10 minutes.

Meanwhile, head nurses generally followed a nonpunitive principle in handling safety incidents. For instance, Interviewee 8 (emergency department, secondary hospital), after an infusion error, prioritized analyzing “process loopholes” rather than blaming individuals. By revising the “regulations on medication administration periods,” no similar incidents occurred in the following six months, which also enhanced nurses’ willingness to participate in safety management.

#### **4.5 Promoting Nursing Innovation and Advancing Nursing Discipline**

With continuous advances in medical technology and diversified patient needs, nursing innovation has become an important driving force for the development of nursing discipline<sup>[25]</sup>. As team leaders, head nurses need keen industry insight and innovative awareness to identify new trends and demands in clinical nursing and guide the team in relevant exploration and practice. In promoting innovation, head nurses support research projects, introduce new technologies and new service models, and foster autonomy and creativity in solving clinical problems. For example, targeting the high incidence of pressure injuries in longterm bedridden patients, the team is organized to conduct research on the effectiveness of interventions, develop scientific and effective pressure injury prevention protocols, and promote their application in the department. Such innovative practices not only improve nursing quality but also provide theoretical and methodological references for nursing discipline.

Interview results show that head nurses focus innovation on solving clinical pain points plus resource integration, with different innovation pathways across hospital levels. The head nurse of the emergency department in a tertiary hospital (Interviewee 14) cooperated with the information department to develop a “rescue module layout system,” shortening the time for nurses to retrieve instruments from 5 minutes to 2 minutes, with relevant achievements winning a provincial nursing innovation award. The head nurse of the ICU in a secondary hospital (Interviewee 12) designed a “simplified ICU vital signs record form,” reducing recording time by 50% and improving data accuracy from 90% to 98%. The head nurse of geriatrics in a community hospital (Interviewee 10) created a “simple turning aid belt,” shortening the time for nurses to assist disabled elderly patients in turning over from 10 minutes to 3 minutes and reducing physical exertion.

In addition, head nurses also act as “experience disseminators” in discipline development. For example, Interviewee 11 (obstetrics and gynecology, tertiary hospital) organized the “ERAS nursing pathway for highrisk pregnant women” into standardized materials and promoted them among regional hospitals, promoting homogeneous nursing quality. This verifies the bridging role of head nurses in nursing discipline construction.

### **5. Strategies and Methods to Give Play to the Exemplary Role of Head Nurses**

#### **5.1 Strengthen SelfConstruction and Improve Comprehensive Quality**

Head nurses should continuously update their professional knowledge and follow the latest developments in nursing discipline to maintain a high professional level<sup>[26]</sup>. Meanwhile, they should systematically study management and leadership knowledge to continuously improve organizational coordination and leadership capabilities. Participating in professional training, academic exchanges, and reading authoritative literature in the field can expand knowledge and vision, laying a foundation for fulfilling dual responsibilities of management and clinical practice.

In terms of professional ethics, head nurses should adhere to integrity and lead by example. With a stable, rational working attitude and proactive responsibility, they establish a professional role model to enhance trust and recognition among team members.

#### **5.2 Establish a Scientific and Reasonable Management Mechanism**

Head nurses should, based on departmental realities, construct scientific and operable nursing management systems and workflows, clarify job responsibilities and work standards, to institutionalize and standardize management. An assessment and incentive mechanism based on objective indicators should be established to ensure a fair and transparent evaluation process, with corresponding rewards and punishments according to assessment results, thereby improving nursing staff’s

work motivation and sense of responsibility.

During system formulation, opinions and suggestions from nursing staff should be solicited to enhance their participation and ownership. Meanwhile, systems and procedures should be regularly revised and optimized according to actual operational effects to ensure continuous adaptation to clinical needs and management goals.

### 5.3 Focus on Talent Training and Build a HighQuality Nursing Team

Head nurses should attach great importance to the career development of nursing staff and formulate targeted training programs and development paths based on individual characteristics and career plans<sup>[13]</sup>. Through professional training, skill competitions, academic exchanges and other forms, diverse learning opportunities should be provided to continuously improve nursing staff's professional ability and comprehensive quality.

In the training process, emphasis should be placed on developing teamwork and communication skills, promoting knowledge sharing and mutual support among members. Meanwhile, promotion opportunities and career guidance should be provided to potential staff to fully leverage talent advantages and elevate the overall level of the team.

*Table 5: Talent Training System for Nursing Teams*

Training Stage	Main Contents	Objectives and Effects
Training for New Nurses	Preceptorship, one-to-one guidance, basic skill training	Quickly adapt to the post and master basic operations
On-the-Job Skill Improvement	Professional training, skill competitions, academic lectures	Improve professional competence and enhance teamwork
Training for Potential Talents	Career planning guidance, promotion opportunities, leadership training	Promote talent echelon construction and enhance core competitiveness of the team

As shown in Table 5, the main stages of talent training in the nursing team and their corresponding objectives are systematically summarized. Through multi-level and multi-form training, head nurses effectively promote the professional growth of nursing staff and the improvement of the team's comprehensive quality, which can enhance the team's capacity for sustainable development.

Semi-structured interviews further enriched the practical details in Table 5, and training measures for different career stages have been implemented and verified in hospitals at all levels:

- (1) Training for newly recruited nurses: The head nurse of pediatrics in a secondary hospital (Interviewee 15) adopted a "one-on-one preceptorship plus 30 practical assessments", which shortened the time for new nurses to independently complete venipuncture from 2 weeks to 1 week, meeting the objective of "quickly adapting to the post" in Table 3;
- (2) On-the-job skill improvement: The head nurse of the ICU in a tertiary hospital (Interviewee 3) organized "difficult case review meetings plus special skill competitions", raising nurses' mastery rate of core skills from 90% to 100%, in line with the requirement of "improving professional competence";
- (3) Training of potential talents: The head nurse of general practice in a community hospital (Interviewee 13) provided key nurses with "district-level training plus the leading role in health education", enabling two nurses to become community nursing instructors, thus achieving the goal of "talent echelon construction" in Table 5.

### 5.4 Strengthen Communication and Collaboration to Create a Favorable Working Atmosphere

Head nurses should improve the communication mechanism with nursing staff, understand their work and living conditions, listen to their opinions and suggestions, and provide timely support when problems or difficulties arise<sup>[16]</sup>. At the same time, they should actively promote collaboration with other members of the medical team, establish stable doctor-nurse, nurse-patient and cross-departmental cooperative relationships to jointly improve the quality of patient care.

In communication practice, appropriate communication skills should be used, maintaining a sincere, equal and respectful attitude, focusing on listening and providing timely feedback<sup>[27]</sup>. A sound environment for communication and collaboration helps build a harmonious working atmosphere and improve team operation efficiency and service quality<sup>[28]</sup>.

## 6. Conclusion

Within the qualitative sample of this study, head nurses demonstrate significant leadership and exemplary roles in nursing team management, particularly in professional guidance, team building, quality management, safety assurance, and innovation promotion. This finding supports the importance of head nurses' leadership in nursing management practice, yet its mechanism and scope of influence still require further verification with larger samples and in multiple contexts<sup>[29]</sup>. These roles are not only related to the quality of nursing services and patient safety, but also directly affect the sustainable development of the nursing discipline. Medical institutions should attach great importance to the development of the head nurse team, and give full play to their exemplary role through institutional guarantees and capacity-building measures. Meanwhile, head nurses themselves need to continuously update their professional and management knowledge, and improve their leadership and execution ability to perform their duties effectively in the ever-changing medical environment. Through joint efforts, it is possible to better meet the needs of medical services in the new era and provide patients with high-quality, efficient and safe nursing care.

Based on semi-structured interviews and observations of 15 head nurses, this study verifies the applicability of the Input-Process-Output (IPO) framework in nursing team management, and reveals the important role of head nurses' leadership in professional guidance, team building, quality management, safety assurance and innovation promotion. However, this study still has limitations: the sample size is limited, so the qualitative results are not generalizable; there is a lack of longitudinal tracking data; and some findings need further validation through large-scale quantitative research. Future studies may adopt questionnaires or mixed methods to explore the differences and long-term effects of head nurses' leadership across hospital levels. Interviews also revealed that head nurses still face challenges in practice such as "limited innovation resources" and "insufficient decision-making ability of young nurses", which also points out directions for follow-up research: it is necessary to further explore leadership adaptation models in different medical scenarios and how to provide more innovation support for head nurses through institutional design. Overall, the interview findings and the theoretical framework mutually confirm each other, providing more operable references for nursing management practice and reinforcing the conclusion that "head nurses' leadership is a core element in constructing a high-quality nursing system".

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No

## Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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# Prognostic Model for Colon Cancer (COAD) Based on Migrasome-Related LncRNAs

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**Abstract: Objective:** Colon adenocarcinoma (COAD) is a leading cause of cancer-related mortality worldwide. In recent years, migrasomes—a newly identified class of extracellular vesicles—have attracted increasing attention for their potential role in intercellular communication. This study aimed to investigate the role of migrasome-associated long non-coding RNAs (CMiSLncRNAs) in COAD progression using bioinformatics approaches and to evaluate their potential as diagnostic biomarkers or therapeutic targets. **Method:** Migrasome-associated genes were identified through a comprehensive literature review and intersected with LncRNAs expressed in COAD. A total of 41 co-expressed CMiSLncRNAs were identified. Univariate Cox regression analysis revealed 13 CMiSLncRNAs with significant prognostic value. A prognostic model was constructed using LASSO regression combined with multivariate Cox proportional hazards analysis, and patients were stratified into high- and low-risk groups based on the median risk score. Kaplan–Meier analysis, principal component analysis (PCA), and functional enrichment analysis were performed to compare the two risk groups. Finally, the influence of CMiSLncRNAs on tumor immune infiltration, immune function, and drug sensitivity was investigated. **Results:** Thirteen CMiSLncRNAs with prognostic significance were identified. The prognostic model demonstrated strong discriminatory ability, with low-risk patients showing significantly better overall survival than high-risk patients across training, testing, and full cohorts. Multivariate Cox analysis confirmed that the risk score was an independent prognostic factor. Functional enrichment analysis indicated that CMiSLncRNAs are involved in pathways such as Hippo, mTOR, and Wnt signaling. Immune analysis revealed a more active immune microenvironment in the low-risk group, characterized by higher immune function scores and increased infiltration of activated NK cells and mast cells. Drug sensitivity analysis revealed distinct drug response profiles between the two risk groups. **Conclusion:** The CMiSLncRNA-based prognostic model offers novel insights for risk stratification and personalized treatment in COAD. These findings highlight the significant roles of CMiSLncRNAs in tumor progression, immune regulation, and drug sensitivity.

**Keywords:** Colon Cancer; Migrasome; LncRNA; Immunotherapy; Tumor Microenvironment

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## 1. Introduction

COAD is a multifactorial disease driven by complex interactions between genetic and environmental factors. The lack of



distinct early symptoms results in a substantial proportion of patients being diagnosed at advanced stages, thereby greatly diminishing treatment efficacy<sup>[1]</sup>. Despite continuous progress in therapeutic approaches, tumor metastasis and chemotherapy resistance remain pivotal determinants of patient prognosis.

Migrasomes, a newly characterized class of extracellular structures, were first described by Liang Ma and colleagues in 2014. These structures originate from retraction fibers left behind by migrating cells<sup>[2, 3]</sup>. With diameters ranging from approximately 50 to 100 nm, migrasomes are extracellular vesicles that contain specific proteins, RNAs, and organelles<sup>[3, 4]</sup>, and play a critical role in material exchange and signal transduction between tumor cells<sup>[2]</sup>. In addition, their involvement in the regulation of vascular homeostasis, as well as in tumor invasion and metastasis, has been reported<sup>[5, 6]</sup>. Migrasomes have been identified in various tumor cell types, including human breast cancer MDA-MB-231 cells and human colon cancer HCT116 cells<sup>[5]</sup>.

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs exceeding 200 nucleotides in length and are known to exert diverse regulatory functions within cells<sup>[7, 8]</sup>. Accumulating evidence indicates that lncRNAs can promote tumor proliferation and metastasis, positioning them as promising biomarkers and therapeutic targets in cancer<sup>[8-10]</sup>. For instance, H19 and HEIH are upregulated in gastric cancer and contribute to enhanced proliferation<sup>[11, 12]</sup>, while MNX1-AS1 facilitates colorectal tumor progression<sup>[8]</sup>.

Both migrasomes and lncRNAs have been implicated in tumor progression; however, the functional role of migrasome-associated lncRNAs (CMiSlncRNAs) in tumors remains poorly understood. In this study, we employed bioinformatics approaches to systematically investigate the role of CMiSlncRNAs in the progression of colon adenocarcinoma (COAD) and to evaluate their potential as diagnostic biomarkers or therapeutic targets, aiming to provide novel strategies for the clinical diagnosis and treatment of colon cancer.

## 2. Methods

### 2.1 Data Processing and Analysis

COAD were obtained from The Cancer Genome Atlas (TCGA) database (<https://portal.gdc.cancer.gov>). The dataset included 524 clinical files, comprising 483 tumor samples and 41 non-tumor samples. Transcriptome data were processed using Perl (strawberry-perl-5.30.1) to generate separate mRNA and lncRNA expression matrices, as well as to process the corresponding clinical and survival data. Drug sensitivity was predicted using the Tumor Immune Dysfunction and Exclusion (TIDE) database, and data processing and visualization were performed with the “ggpubr” and “limma” R packages.

### 2.2 Screening and Analysis of Migrasome-Related lncRNAs

Migrasome-associated genes were integrated with mRNA data obtained from TCGA using the “limma” R package to construct a migrasome gene expression matrix. Subsequently, co-expression analysis was performed with predefined thresholds ( $\text{corFilter} > 0.4$ ,  $P < 0.001$ ), leading to the identification of 4,948 CMiSlncRNA. The results of the co-expression analysis were visualized as a Sankey diagram using the “ggalluvial” R package.

### 2.3 Construction and Validation of the Prognostic Model

The “limma” R package was used to integrate the CMiSlncRNA expression data of COAD patients with clinical data to generate an expression profile dataset. Subsequently, the dataset was randomly divided into training and testing sets at a 1:1 ratio using the “caret” R package. Univariate and multivariate Cox regression analyses were performed, and the least absolute shrinkage and selection operator (LASSO) algorithm combined with ten-fold cross-validation was applied to determine the penalty parameter corresponding to the point with the minimum cross-validation error. A prognostic model was then constructed based on the training set. The model building process was carried out using the “glmnet”, “survminer”, “timeROC”, and “survival” R packages, and the predictive accuracy of the model was evaluated using the testing set.

### 2.4 Prognostic Analysis and Nomogram Development Independently

To assess the independence of clinical features (age, sex, grade) and the model-derived risk score as prognostic factors, univariate and multivariate Cox regression analyses were performed. A nomogram integrating these clinical factors with the risk score was developed to predict 1-, 3-, and 5-year overall survival, and its performance was validated using calibration plots.



## 2.5 Examination of Principal Components and Functional Enrichment

The “scatterplot3d” R package was used for principal component analysis (PCA) to classify CMiSLncRNA expression and visualize the spatial distribution of low- and high-risk groups. KEGG and GO enrichment analyses were performed with the “org.Hs.eg.db” and “enrichplot” R packages, while gene set variation analysis (GSVA) was conducted using the “GSVA” R package.

## 2.6 Tumor Immunity Assessment

To investigate the association between immune cell infiltration and risk stratification, the CIBERSORT algorithm was employed to predict the correlation between risk scores and immune cell abundance. Single-sample gene set enrichment analysis (ssGSEA) was conducted using the “GSVA” R package, with resulting scores subsequently normalized. Box plots were then generated to illustrate the scores of immune-related functions across distinct risk groups.

## 2.7 Identification of Potential Therapeutic Drugs for Colorectal Cancer

To forecast potential therapeutic agents for colon cancer, drug sensitivity analysis was performed for both high-risk and low-risk groups. The “oncoPredict” R package was utilized to estimate drug response sensitivity in colorectal cancer patients stratified by risk group.

## 2.8 Statistical Analysis

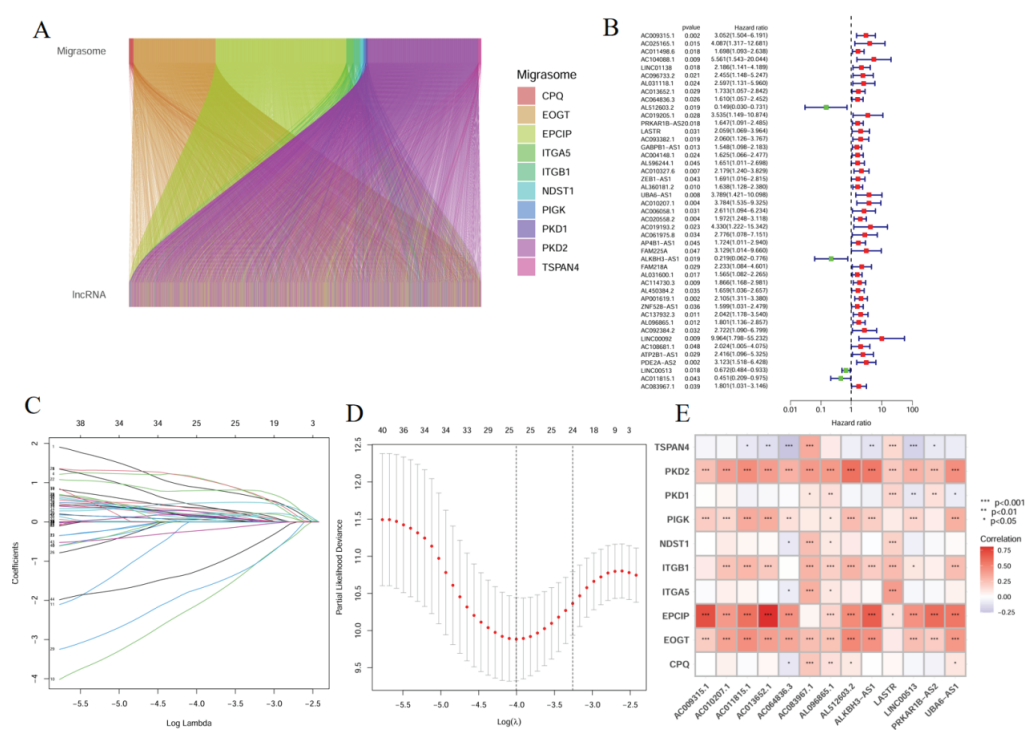
All statistical analyses were performed using R software (version 4.4.0) and Perl (strawberry-perl-5.30.1). Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were analyzed using the chi-square test.  $P < 0.05$  was considered statistically significant.

## 3. Results

### 3.1 LncRNA Identification of 13 Prognostically Significant Migrasome-Related LncRNAs

Expression data for 16,876 LncRNAs associated with COAD were retrieved from the TCGA database, and ten migrasome-related genes were collected from the literature. PCA was conducted to evaluate co-expression relationships between these LncRNAs and the migrasome-associated genes, resulting in the identification of 4,948 LncRNAs. A Sankey diagram was used to visualize the co-expression network between migrasome-related genes and their associated LncRNAs. (Figure 1A).

Figure 1: A The relationship between 10 migrasome-associated genes and LncRNAs. B Univariate Cox analysis shows that 41 LncRNAs are associated with OS prognosis. C, D Lasso analysis. E Co-expression analysis heatmap of 10 migration-associated genes and 13 LncRNAs; “\*”:  $P < 0.05$ , “\*\*”:  $P < 0.01$ , “\*\*\*”:  $P < 0.001$ .

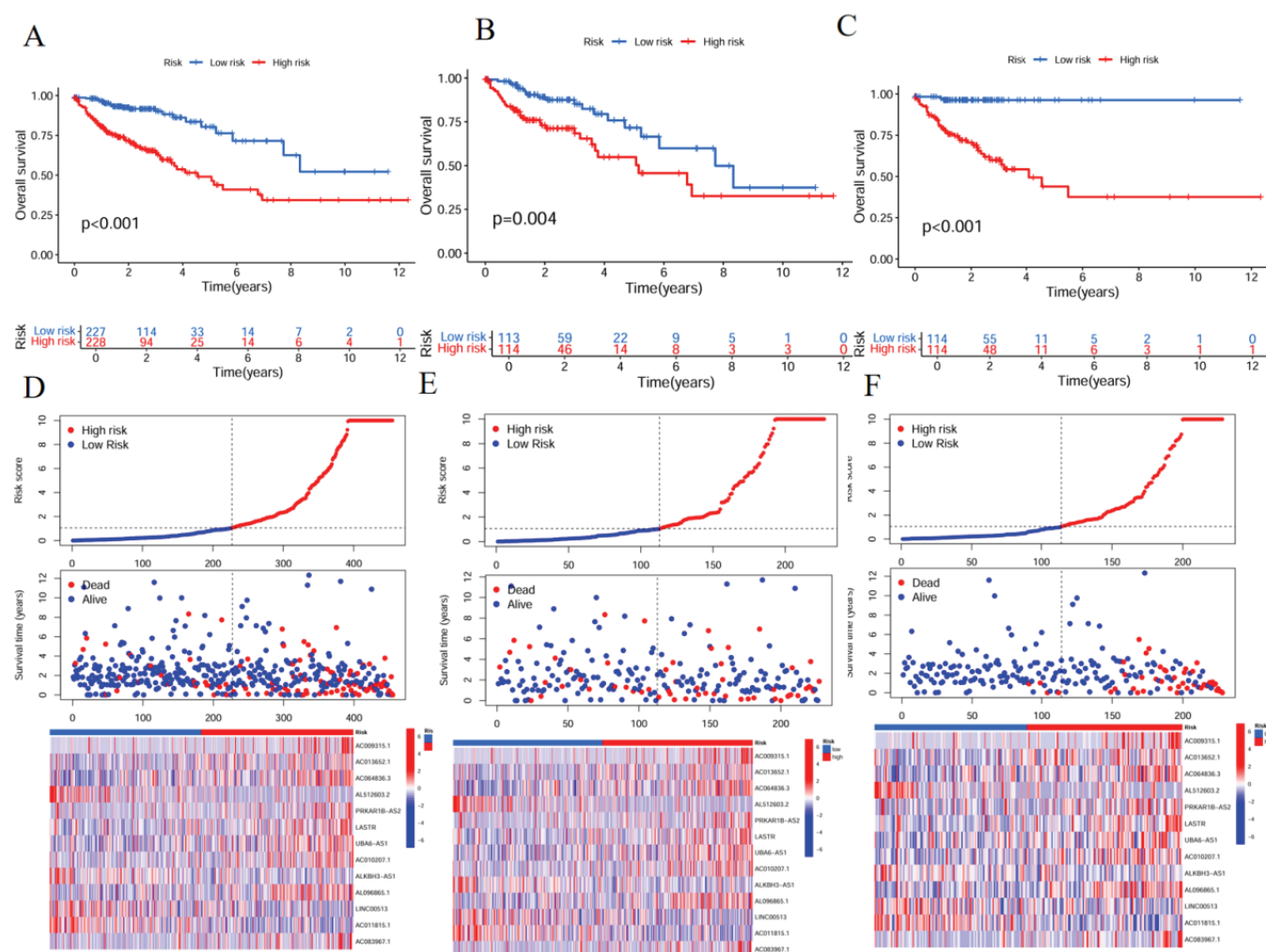


Univariate Cox regression analysis was conducted on the training set, identifying 41 LncRNAs as risk factors ( $HR > 1$ ) and 4 LncRNAs as protective factors ( $HR < 1$ ), as shown in the forest plot (Figure 1B). LASSO regression analysis was subsequently performed, resulting in the selection of 25 LncRNAs (Figure 1C, D). Multivariate Cox analysis further revealed 13 CMiSLncRNA with significant prognostic value in COAD. A heatmap was generated to display the co-expression patterns of these 13 LncRNAs and the 10 CMiSLncRNA (Figure 1E).

### 3.2 Evaluation of a Colorectal Cancer Prediction Model Based on CMiSLncRNA

The dataset was randomly divided into training and testing sets with balanced sample distribution. Patients were subsequently classified into low-risk and high-risk groups based on their risk scores. Kaplan–Meier survival curves demonstrated that, in the training, testing, and full cohorts, patients in the low-risk group had significantly better overall survival (OS) than those in the high-risk group (Figure 2A–C). Heatmaps depicting the expression patterns of the 13 CMiSLncRNAs in low- and high-risk groups revealed consistent expression profiles across the training set, testing set, and the entire cohort (Figure 2D–F).

Figure 2: A Evaluation of the risk model in all samples. B Risk model in the test group. C Risk model in the validation group. D Prediction of the risk model in all samples. E Prediction of the risk model in the test group. F Prediction of the risk model in the validation group.



### 3.3 The CMiSLncRNAs-Based Model Independently Predicts Outcomes for Colon Cancer Patients.

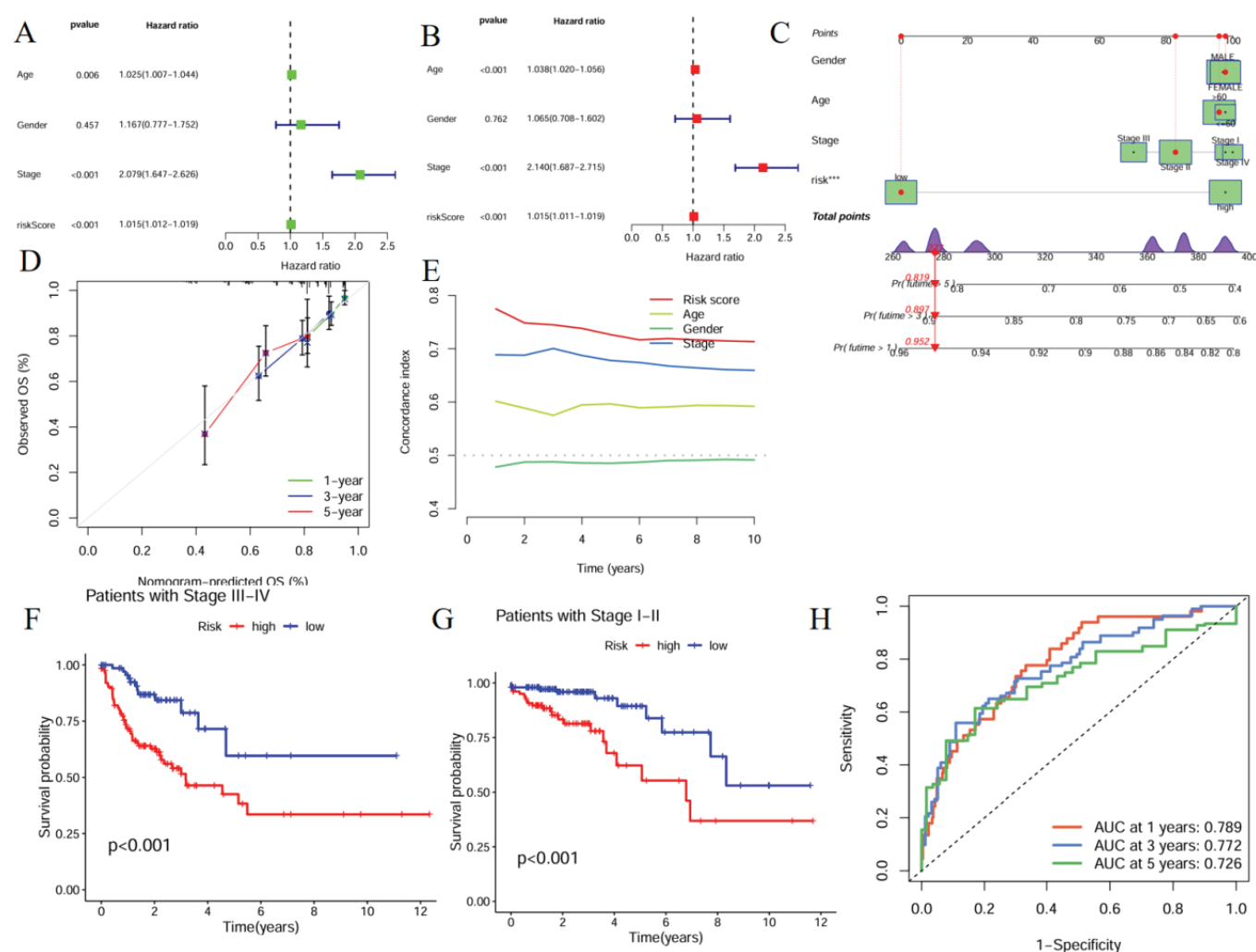
Univariate and multivariate Cox regression analyses were performed to evaluate whether the CMiSLncRNA-based prognostic model served as an independent prognostic factor for COAD (Figure 3A, B). Multivariate Cox regression analysis revealed that age ( $HR = 1.038$ , 95% CI: 1.020–1.056,  $P < 0.001$ ), tumor stage ( $HR = 2.140$ , 95% CI: 1.687–2.715,  $P < 0.001$ ), and risk score ( $HR = 1.015$ , 95% CI: 1.011–1.019,  $P < 0.001$ ) were independent prognostic factors (Figure 3B).

A prognostic nomogram was subsequently constructed incorporating sex, age, stage, and the risk model to predict 1-, 3-, and 5-year survival rates of COAD patients (Figure 3C). Calibration curves demonstrated good predictive accuracy of

the nomogram for 1- and 3-year survival rates (Figure 3D). The concordance index (C-index) was calculated to assess the predictive performance of the model, with results indicating that the risk score derived from the model exhibited the highest predictive accuracy (Figure 3E).

To evaluate the prognostic value of the CMiSLncRNA-based model across different disease stages, separate survival analyses were conducted for COAD patients stratified by stage I–II and stage III–IV (Figure 3F, G). Survival analysis revealed that low-risk patients had significantly better clinical outcomes compared to high-risk patients in both stage I–II ( $P < 0.001$ ) and stage III–IV ( $P < 0.001$ ) subgroups (Figure 3F, G). Furthermore, based on the entire cohort, the area under the curve (AUC) values for 1-, 3-, and 5-year survival were 0.789, 0.772, and 0.726, respectively (Figure 3H), suggesting that the CMiSLncRNA signature exhibits moderate prognostic predictive capability.

*Figure 3: A-B Uni-Cox and multi-Cox analyses of clinical pathological factors and risk scores with overall survival. C Nomogram for predicting overall survival. D Calibration curves for 1-year, 3-year, and 5-year overall survival. E CIR-score and other clinical indicators were evaluated using c-index curves. F-G Kaplan-Meier (KM) curves for clinical prognosis based on staging. H AUC curves for 1-year, 3-year, and 5-year survival.*



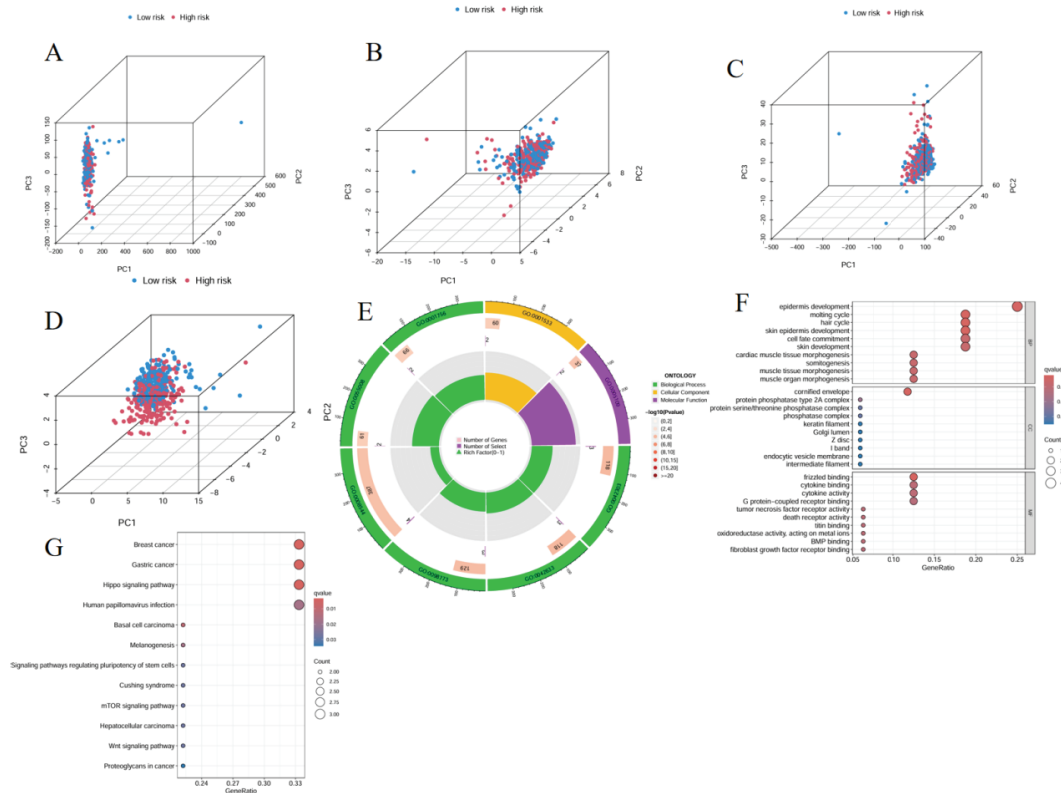
### 3.4 Principal Component Analysis and Functional Enrichment Analysis

To evaluate whether the LncRNAs incorporated into the prognostic model could effectively distinguish between high-risk and low-risk samples, principal component analysis (PCA) was performed based on the CMiSLncRNA dataset. When PCA was applied to the risk model, the CMiSLncRNAs, migrasome-related genes, and all genes, the results demonstrated that the model effectively differentiated high-risk samples from low-risk samples (Figure 4A–D).

Differential pathway analysis between high-risk and low-risk groups was conducted using the TCGA cohort. GO analysis revealed that CMiSLncRNAs were associated with biological processes including epidermis development, the molting cycle,

and the hair cycle (Figure 4E, F). KEGG analysis showed significant enrichment in pathways such as breast cancer, gastric cancer, the Hippo signaling pathway, pathways regulating pluripotency of stem cells, and the mTOR signaling pathway (Figure 4G). These findings suggest that CMiSLncRNAs may influence the invasion and metastasis of COAD by modulating cell differentiation and tissue remodeling.

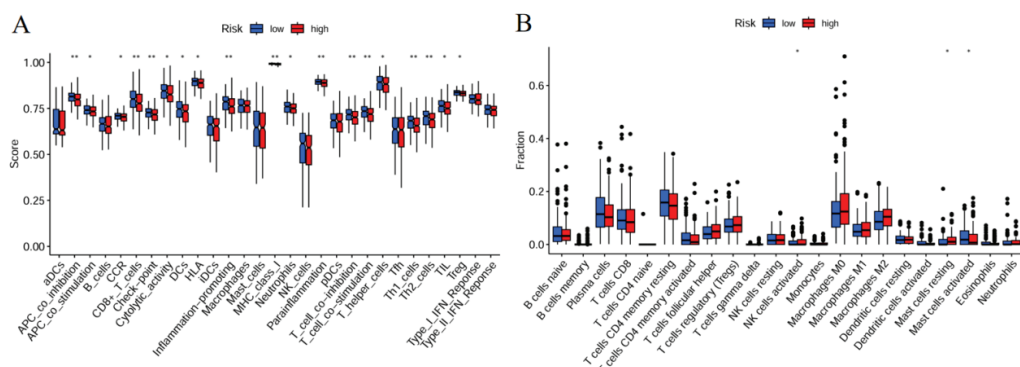
Figure 4: A-D PCA analysis of all genes, migration-associated genes, migration-related LncRNAs, and the risk model we constructed. E-F GO analysis. G KEGG analysis.



### 3.5 Differences in Tumor Immune Microenvironment (TIME) Between High-Risk and Low-Risk Groups

Immune function scores, assessed via CIBERSORT, were significantly higher in the low-risk group than in the high-risk group, indicating an immunosuppressive state in the latter (Figure 5A). Analysis of 22 immune cell subtypes showed that activated NK cells and activated mast cells were more abundant in the low-risk group, while resting mast cells predominated in the high-risk group (Figure 5B). These findings suggest that the low-risk group maintains a more active immune microenvironment conducive to tumor suppression, whereas the high-risk group exhibits a relatively suppressed immune state that may promote tumor progression.

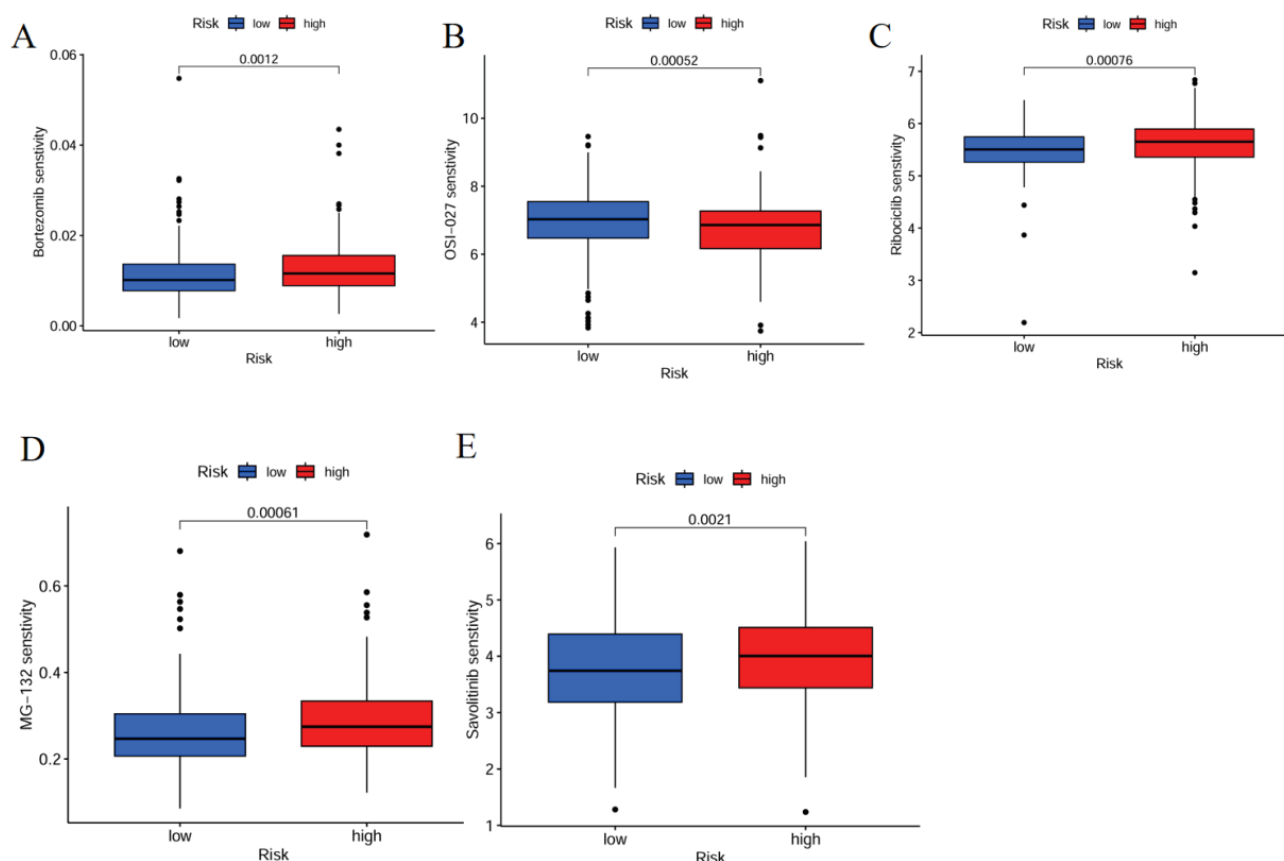
Figure 5: A Differential analysis of immune-related activities between high and low-risk groups(“\*”:  $P<0.05$ , “\*\*\*”:  $P<0.01$ ). B Immune cell infiltration analysis in the tumor microenvironment between high and low-risk groups. (“\*”:  $P<0.05$ , “\*\*\*”:  $P<0.01$ ).



### 3.6 Assessment of Drug Responsiveness Based on a Prognostic Risk Model

Sensitivity to 30 of 198 drugs differed significantly between risk groups. Five key drugs (Figure 6A–E) were identified: bortezomib, ribociclib, MG-132, and savolitinib were more sensitive in the low-risk group, whereas OSI-027 showed greater efficacy in the high-risk group. The above findings indicate that patients in different risk groups exhibit distinct drug sensitivity profiles, suggesting that the prognostic risk model holds potential value for guiding personalized therapeutic strategies.

Figure 6: Drug Sensitivity Analysis of High and Low-Risk Groups. A Bortezomib. B OSI-027. C Ribociclib. D MG-132. E Savolitinib.



## 4. Discussion

CRC ranks among the most prevalent malignancies worldwide<sup>[13]</sup>. In 2020, approximately 147,950 new cases of CRC were reported globally, with an estimated 36% of diagnosed patients succumbing to the disease. The annual incidence of colon and rectal tumors is increasing at a rate of 1.8% and is progressively affecting younger populations<sup>[14, 15]</sup>. Consequently, there is an urgent need for the development of novel therapeutic strategies for colon tumors.

LncRNAs have been identified as promoters of invasion and metastasis in various tumor types, including breast cancer<sup>[16]</sup>, non-small cell lung cancer<sup>[17]</sup>, and CRC<sup>[18]</sup>. Research has also demonstrated that lncRNAs play critical roles in conferring resistance to cisplatin in head and neck squamous cell carcinoma<sup>[19]</sup> and to oxaliplatin in colorectal cancer<sup>[20]</sup>. As a result, targeting lncRNAs has emerged as a growing focus in cancer research. For instance, Qu et al. reported that locked nucleic acid antisense oligonucleotides (LNA ASOs) can effectively overcome resistance in advanced renal cell carcinoma<sup>[21]</sup>.

Migrasomes, which are extracellular vesicles resembling exosomes, have been observed to form during cell migration<sup>[22, 23]</sup>. Given the highly migratory nature of tumor cells, migrasomes may play a significant role in tumor metastasis<sup>[23]</sup>. Studies have shown that exosomes secreted by metastatic cancer cells can induce epithelial–mesenchymal transition (EMT) in adjacent cells, thereby facilitating cancer dissemination<sup>[24]</sup>. Furthermore, migrasomes possess the capacity to transport exosomes, which may also contribute to enhanced tumor cell infiltration and metastasis<sup>[24]</sup>.

In this study, we comprehensively utilized CMiSLncRNAs to construct a prognostic risk model for colorectal cancer



patients based on data from TCGA database. Our analysis revealed the potential roles of these LncRNAs in tumor migration, prognostic prediction, and regulation of the tumor immune microenvironment. We further validated their value across different clinical stages and in relation to drug sensitivity. By analyzing co-expression relationships between migrasome-related genes and LncRNAs, we identified LncRNAs associated with colorectal cancer migration. Using LASSO regression and multivariate Cox regression models, we selected 13 CMiSLncRNAs with prognostic significance: AC009315.1, AC010207.1, AC011815.1, AC013652.1, AC064836.3, AC083967.1, AL096865.1, AL512603.2, ALKBH3-AS1, LASTR, LINC00513, PRKAR1B-AS2, and UBA6-AS1.

The roles of these LncRNAs in promoting tumor progression have been documented in the literature. For example, the LncRNA LASTR regulates SART3 activity to promote cancer cell adaptation<sup>[25]</sup>. Manhui Xia et al. demonstrated that LASTR promotes lung cancer progression through the miR-137/TGFA/PI3K/AKT axis<sup>[26]</sup>. ALKBH3-AS1 enhances the growth and metastasis of hepatocellular carcinoma cells<sup>[27]</sup>. PRKAR1B-AS2 promotes tumorigenesis, survival, and chemoresistance via the PI3K/AKT/mTOR pathway<sup>[28]</sup>. UBA6-AS1 enhances proliferation in glioblastoma and triple-negative breast cancer<sup>[29, 30]</sup>. LINC00513 accelerates the malignant progression of colorectal cancer by stabilizing connective tissue growth factor (CTGF) mRNA<sup>[31]</sup>.

In this model, the risk score derived from these LncRNAs demonstrated strong discriminatory ability across the training set, testing set, and the entire cohort, with low-risk patients exhibiting significantly higher survival rates than those classified as high-risk. Multivariate Cox analysis further confirmed that the CMiSLncRNA-derived risk score serves as an independent prognostic factor, irrespective of age and tumor stage. Calibration curves for the nomogram predicting 1-, 3-, and 5-year survival rates demonstrated moderate prognostic predictive capability. This may be attributed to the fact that migrasome formation is dependent on cell migration status, potentially playing a critical role during specific stages of tumor progression—such as invasion or hematogenous metastasis—while exerting limited effects at other stages. Consequently, a migrasome activity-based signature may show stronger predictive value in certain subgroups, such as patients with established metastases, while appearing moderate in the overall population. PCA further revealed that the CMiSLncRNA-based risk model distinguished high-risk from low-risk patients more clearly than models based on migrasome-related genes, all genes, or other gene sets. Pathway enrichment analysis of differentially expressed genes between the high- and low-risk groups indicated that CMiSLncRNAs are predominantly enriched in pathways such as the Hippo signaling pathway (involved in regulating stem cell pluripotency), the mTOR signaling pathway, and the Wnt signaling pathway. These findings suggest that CMiSLncRNAs may contribute to tumor initiation and progression by influencing cancer cell differentiation, proliferation, and key signaling pathways.

LncRNAs play important roles in the metabolic reprogramming of both tumor and immune cells, thereby influencing antitumor immunity, reshaping the tumor immune microenvironment (TIME), and promoting oncogenesis<sup>[32-35]</sup>. In our examination of the immune microenvironment, we observed that the low-risk group exhibited significantly higher immune function scores compared to the high-risk group, indicating a more robust immune response. The increased infiltration of natural killer (NK) cells and activated mast cells in the low-risk group may contribute to tumor control<sup>[36]</sup>. In contrast, the immune system of the high-risk group appeared to be in a suppressed state, characterized by significant infiltration of resting mast cells, which may facilitate immune evasion and tumor progression<sup>[37]</sup>. Through CIBERSORT analysis and assessment of immune cell proportions, we further validated the marked differences in immune regulation between the high-risk and low-risk groups.

Drug sensitivity analysis demonstrated distinct drug response profiles between risk groups: patients in the low-risk group showed higher sensitivity to bortezomib and ribociclib, while those in the high-risk group exhibited stronger responsiveness to OSI-027. These findings provide a theoretical basis for drug selection in personalized treatment strategies and underscore the critical role of CMiSLncRNAs in guiding therapeutic decisions.

However, several limitations of this study should be considered. The data were obtained from the TCGA database, necessitating further validation of the model's stability and clinical applicability using independent multicenter cohorts. Moreover, additional in vitro and in vivo studies are required to elucidate the molecular mechanisms through which CMiSLncRNAs influence colorectal cancer development and progression, thereby facilitating the identification of potential therapeutic



targets. Collectively, the CMiSncRNA-based prognostic model developed in this study provides novel perspectives for risk stratification and personalized treatment in colorectal cancer patients.

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## Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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# Urinary Arsenic, Lead, and Their Joint Effects on Hypotension in Children and Adolescents Aged 8–17 Years: A Cross-Sectional Analysis of NHANES 2007–2018

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**Abstract:** Background: Evidence on the joint effects of arsenic and lead exposure on pediatric hypotension is limited. The modifying roles of age, sex, and body weight in this association remain unclear. Methods: Using NHANES 2007–2018 data (2,043 adolescents aged 8–17y), we employed survey-weighted logistic regression (hypotension risk), weighted linear regression (blood pressure percentiles), and Weighted Quantile Sum regression (joint effects). Results: In weighted logistic regression, Model 1 (adjusted for age, sex, race) showed arsenic fourth quartile increased hypotension risk (OR=1.73, 95%CI:1.13–2.64, P=0.01). After full adjustment (Model 2: Model 1+ BMI, income, sodium, calories, household size), this risk remained significant (OR=1.63, 95%CI:1.03–2.5, P=0.04) with a significant trend (P-trend=0.04). For lead, Model I fourth quartile risk (OR=1.66, 95%CI:1.05–2.64, P=0.03) shifted to third quartile significance in Model 2 (OR=1.54, 95%CI:1.04–2.28, P=0.03). Linear regression revealed arsenic third quartile significantly reduced diastolic blood pressure percentile in both Model 1 ( $\beta$ =6.20, 95%CI:-10.92–1.47, P=0.01) and Model 2 ( $\beta$ =5.75, 95%CI:-10.41–1.09, P=0.02). The Weighted Quantile Sum (WQS) index showed consistent risk in the main model (OR=1.21, 95%CI:1.03–1.42, P=0.02). Stratified analyses (Model 2 based) showed males had higher lead sensitivity Q2 (OR = 2.01, P = 0.005), normal weight individuals had strongest associations lead Q4 (OR = 2.14, P = 0.02): arsenic Q4 (OR = 2.04, P = 0.02) and early puberty (11–13 years) exhibited peak lead risk Q3 (OR = 2.45, P = 0.005). Conclusion: Arsenic and lead additively increase pediatric hypotension risk, with effects modified by sex, BMI, and pubertal stage. Normal-weight males in early puberty are the most vulnerable subgroup.

**Keywords:** NHANES; Hypotension; Heavy Metals; Lead; Arsenic

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## 1. Introduction

Abnormal blood pressure (including hypertension and hypotension) during childhood and adolescence is closely associated with the risk of cardiovascular diseases in adulthood, making it a critical focus in public health <sup>[1,2]</sup>. While research on

hypertension is relatively advanced, systematic exploration of the etiologies and environmental influencing factors of hypotension remains insufficient. In recent years, the potential hazards of environmental heavy metal exposure to the cardiovascular system have gained increasing attention. Among these, arsenic (As) and lead (Pb) have become research hotspots due to their widespread presence in air, water, and food, as well as their neurotoxic and cardiovascular toxic properties<sup>[3,4]</sup>.

Arsenic and lead can enter the body through various exposure routes. Children and adolescents may ingest them via diet (e.g., contaminated water and food), air, and hand-to-mouth contact<sup>[5]</sup>. Existing studies have shown that arsenic exposure can affect vascular tone through oxidative stress and endothelial dysfunction<sup>[6]</sup>, while lead exposure may interfere with the sympathetic nervous system and the renin-angiotensin system, leading to abnormal blood pressure regulation<sup>[7]</sup>. However, most current studies focus on the association between heavy metals and hypertension<sup>[8,9]</sup>, and there is no consensus on their relationship with hypotension. For example, Yao et. found no significant association between low-level lead exposure and blood pressure in children, but studies on adults suggest that mixed heavy metal exposure may affect blood pressure distribution<sup>[10,11]</sup>.

Furthermore, children and adolescents are in a critical period of growth and development, with immature blood pressure regulation mechanisms, which may increase their sensitivity to environmental pollutants<sup>[5]</sup>. Factors such as hormonal changes during puberty and body weight status may further modify the association between heavy metals and blood pressure<sup>[12]</sup>. Meanwhile, environmental pollutants usually exist in the form of “mixed exposure,” and analyzing single pollutants may underestimate their combined effects. Statistical methods such as Weighted Quantile Sum (WQS) regression provide effective tools for interpreting the health effects of mixed exposures<sup>[13,14]</sup>.

Based on this, this study uses large-scale NHANES data to systematically explore the association between urinary arsenic and lead exposure and hypotension in children and adolescents, analyze the dose-response relationship and the combined effects of mixed exposures, and investigate the modifying roles of age, gender, and BMI in these associations. It aims to provide a scientific basis for the prevention of hypotension in children and adolescents and environmental risk management.

## 2. Methods

### 2.1 Study population

This study utilized cross-sectional data from six consecutive cycles (2007-2008 to 2017-2018) of the NHANES(<https://www.cdc.gov/nchs/nhanes>). Employing a stratified multistage probability sampling design, NHANES represents non-institutionalized U.S. children and adolescents aged 8-17 years. The study protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, with written informed consent obtained from all participants/parents/guardians. Through integration of multi-cycle data using NHANES' official weight-combining methodology, the initial screened cohort comprised 9,847 eligible individuals. After excluding 7,804 participants with incomplete data, the final weighted analytical sample represented 2,043 participants.

### 2.2 Blood pressure (BP)

All blood pressure measurements were conducted at the Mobile Examination Center (MEC). Participants were seated with feet flat on the floor and rested for 5 minutes before measurements. Trained examiners performed three consecutive right-arm blood pressure measurements using a mercury sphygmomanometer with an appropriately sized cuff. The average of  $\geq 2$  valid readings was recorded as the final systolic blood pressure (SBP) and diastolic blood pressure (DBP) values. The diagnostic criteria for hypotension strictly adhered to the 2017 American Academy of Pediatrics (AAP) clinical guidelines. Age-, sex-, and height-specific Z-score formulas recommended by the guidelines were employed to calculate blood pressure percentiles, with hypotension defined as either systolic or diastolic blood pressure below the 5th percentile. Specifically: (1) simplified age-based formulas were used to compute Z-scores for children aged 8–12 years, while (2) composite formulas incorporating both age and sex parameters were applied for adolescents aged 13–17 years, with final blood pressure percentiles derived through standard normal distribution conversion for clinical determination<sup>[15]</sup>.

### 2.3 Urinary arsenic (UAs) and lead (UPb) concentrations

All metal detection data in this study was based on urine samples. During participant appointments at the NHANES Mobile Examination Center (MEC), spot urine samples were collected and analyzed for total arsenic concentrations using dynamic

reaction cell inductively coupled plasma mass spectrometry (DRC-ICP-MS) and for lead concentrations using inductively coupled plasma mass spectrometry (ICP-MS). Comprehensive instructions for laboratory methods utilized to measure the urinary metal concentrations can be found on the NHANES website. The limits of detection (LOD) ranged from 0.26 to 0.74  $\mu\text{g/L}$  for arsenic and 0.05 to 0.28  $\mu\text{g/L}$  for lead (cycle-specific values available in NHANES Laboratory Manuals). Values below LOD were imputed as  $\text{LOD}/\sqrt{2}$ . Following creatinine correction ( $\mu\text{g/g}$  creatinine) to account for urine dilution effects, creatinine-adjusted values underwent natural logarithmic transformation rounded to two decimal places (yielding variables  $\ln\_UAs$  and  $\ln\_UPb$ ), with these transformed values directly utilized in subsequent regression analyses.

## 2.4 Covariates

Based on previous literature, several covariates were included in this study as potential confounding factors. The selected covariates included age, sex, race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other races), household size, family poverty income ratio (PIR), and urinary creatinine (measured by enzymatic method using Roche Cobas 6000 analyzer). Urinary creatinine was used to adjust heavy metal concentrations ( $\mu\text{g/g}$  creatinine) to eliminate the effect of urine dilution. Considering that fluctuations in sex hormones may lead to changes in vascular tone, age was grouped according to key stages of sexual development: 8–10 years (pre-puberty), 11–13 years (early puberty), and 14–17 years (mid-puberty) <sup>[16]</sup>. The family poverty income ratio (PIR) was categorized into a categorical variable based on clinical economic thresholds:  $<1$  (poverty), 1–1.99 (low income), and  $\geq 2$  (middle-high income). Additionally, total energy intake (kcal/d) and sodium intake (mg/d) assessed via the first 24-hour dietary recall were also included as covariates in the model. Body mass index (BMI) was calculated using the formula weight (in kilograms) divided by the square of height (in meters). Underweight was an age-and gender-specific BMI below the 5th percentile on the 2000 Centers for Disease Control and Prevention (CDC) age-and gender-specific growth charts, normal weight was a BMI below the 85th percentile but at or above the 5th percentile, overweight was a BMI falling between the 85th and 95th percentiles, and obesity was a BMI at or above the 95th percentile <sup>[17]</sup>.

## 2.5 Statistical analysis

Data from six NHANES cycles (2007–2018) were merged under a stratified, multi-stage probability design. Sample weights (WTMEC2YR), strata (SDMVSTRA) and primary sampling units (SDMVPSU) were incorporated; original 2-year weights were retained without rescaling. After restricting the sample to participants aged 8–17 years, complete-case analyses were performed.

Descriptive statistics Continuous variables are presented as mean  $\pm$  standard deviation and categorical variables as  $n$  (%). Group differences were assessed with Student's  $t$ -tests for continuous measures and  $\chi^2$  tests for categorical variables.  $UAs$  and  $Pb$  concentrations, creatinine-adjusted, were log-transformed and then were categorized based on quartiles (quartile 1,  $<25$ th percentile; quartile 2,  $\geq 25$ th to 50th percentile; quartile 3,  $\geq 50$ th to 75th percentile; quartile 4,  $\geq 75$ th percentile). Survey-weighted logistic regression models estimated odds ratios (OR) and 95% confidence intervals (CI) for the association between metal quartiles and hypotension, with Q1 serving as the reference. Model 1 adjusted for age (continuous) and sex. Model 2 additionally adjusted for race/ethnicity, BMI, family income-to-poverty ratio ( $<1$ , 1–1.99,  $\geq 2$ ), household size, total daily energy intake and dietary sodium intake. To determine whether the associations between urinary arsenic/lead and hypotension vary by age, sex, or BMI, we applied survey-weighted logistic regression models—mirroring the Model 2—within each stratum (age: 8–10, 11–13, 14–17 years; sex: male/female; BMI: underweight, normal, overweight, obese) and tested for heterogeneity by including interaction terms between metal quartiles and the stratification variables.

The Weighted Quantile Sum (WQS) method has been widely used to investigate the cumulative effects of environmental mixtures on health outcomes and assess the contribution of individual metals <sup>[14]</sup>. In this study, the WQS regression model was employed to evaluate the cumulative effect of mixed exposure to  $UAs$  and  $Pb$  on hypotension in adolescents, as well as their respective independent contributions. This data-driven approach assigns weight coefficients to each component in the mixture, with weights ranging from 0 to 1 and summing to 1, where the weight value reflects the relative importance of each component in explaining the variation in health outcomes <sup>[18]</sup>. The specific steps are as follows: (1) The handling of exposure variables strictly followed the description in Section 2.3. The concentrations of  $\ln\_UAs$  and  $\ln\_UPb$ , after creatinine



adjustment and natural logarithm transformation, were divided into four quartiles (Q1-Q4) respectively, with the lowest quartile group (Q1) serving as the reference.(2) Regarding the inclusion of covariates, unlike “Model 2” in Section 3.1, in the WQS model, BMI was used as a categorical variable to assess the effect modification of different weight categories on the association between mixed UAs and Pb exposure and hypotension. Meanwhile, we also conducted WQS analyses in age subgroups. A bootstrap sampling method (with 1000 repetitions) was adopted, randomly selecting 60% of the samples as the training set and 40% as the validation set. In the training set, the weight coefficients of each metal were estimated through iterative optimization, and a WQS index was constructed, which represents the cumulative effect of all urinary toxicants on blood pressure. A metal was identified as a major contributing factor in the mixture when its average weight exceeded 0.5 (i.e., 1 divided by the total number of variables)<sup>13</sup>.(3) We evaluated the predictive performance of the WQS index for hypotension in the validation set and calculated odds ratios (ORs) and 95% confidence intervals (CIs) using weighted logistic regression to quantify the strength of the association between mixed exposure and hypotension. Additionally, we performed subgroup WQS analyses stratified by age to examine the effect modification on the mixed exposure-hypotension association.

In our sensitivity analysis, we initially considered the potential non-linear and non-additive relationships among urine metals. All statistical analyses were performed with R statistical software(V.4.5.1),<sup>3</sup> and a two-sided p value <0.05 was considered statistically significant. The R packages gWQS and nhanesR were applied to construct the WQS model and weighted logistic regression.

### 3. Results

#### 3.1 Baseline characteristics of the participants

This study included a total of 2,043 participants, comprising 1,484 (72.6%) without hypotension and 559 (27.4%) with hypotension. The baseline characteristics of both groups are presented in Table 1. Regarding demographic characteristics, no statistically significant differences were observed in gender distribution ( $P=0.20$ ), racial composition ( $P=0.47$ ), or income-to-poverty ratio ( $P=0.72$ ). However, significant differences existed in age distribution ( $P<0.001$ ): the hypotension group had a significantly lower proportion of pre-puberty children (8-10 years) compared to the non-hypotension group (23.26% vs 39.96%), while demonstrating a higher proportion of mid-puberty adolescents (14-18 years) (41.14% vs 29.78%). In anthropometric measures, BMI categories showed significant between-group differences ( $P=0.02$ ), with the hypotension group exhibiting a lower prevalence of obesity (7.87% vs 12.06%). For clinical indicators, the hypotension group demonstrated significantly lower systolic blood pressure ( $102.7\pm9.8$  vs  $107.3\pm9.3$  mmHg,  $P<0.001$ ) and diastolic blood pressure ( $44.4\pm16.1$  vs  $60.6\pm8.5$  mmHg,  $P<0.001$ ), consistent with the group definitions. Laboratory analyses revealed no significant differences in urinary creatinine ( $P=0.32$ ), urinary arsenic ( $P=0.22$ ), or urinary lead ( $P=0.82$ ) levels between groups. Dietary intake measures, including sodium intake ( $P=0.45$ ) and total calorie consumption ( $P=0.49$ ), also showed no statistically significant differences.

Table 1. Descriptive characteristics of children and adolescents aged 8–17 years with and without hypotension in the 2007–2018 National Health and Nutrition Examination Study (NHANES)

	No hypotension (n=1484)	Hypotension (n=559)	P. value
Gender n (%)			0.20
Male	729 (49.12%)	293 (52.42%)	
Female	755 (50.88%)	266 (47.58%)	
Race n (%)			0.47
Non-Hispanic White	443 (29.85%)	171 (30.59%)	
Mexican American	337 (22.71%)	129 (23.08%)	
Other Hispanic	147 (9.91%)	65 (11.63%)	
Non-Hispanic Black	366 (24.66%)	118 (21.11%)	
Other Race n (%)	191 (12.87%)	76 (13.6%)	



	No hypotension (n=1484)	Hypotension (n=559)	P. value
Age Group			<0.001
Pre-Puberty (8–10 years)	593 (39.96%)	130 (23.26%)	
Early-Puberty (11–13 years)	449 (30.26%)	199 (35.6%)	
Mid-Puberty (14–17 years)	442 (29.78%)	230 (41.14%)	
Income-to-Poverty Ratio n (%)			0.72
<1.0	448 (30.19%)	179 (32.02%)	
1.0-1.99	411 (27.7%)	152 (27.19%)	
≥2.0	625 (42.12%)	228 (40.79%)	
BMI Category n (%)			0.02
Under weight	417 (28.10%)	153 (27.37%)	
Normal weight	697 (46.97%)	274 (49.02%)	
Over weight	191 (12.87%)	88 (15.74%)	
Obesity	179 (12.06%)	44 (7.87%)	
Household size	4.7 ± 1.4	4.8 ± 1.4	0.30
Systolic blood pressure (mmHg)	107.3 ± 9.3	102.7 ± 9.8	<0.001
Diastolic blood pressure (mmHg)	60.6 ± 8.5	44.4 ± 16.1	<0.001
Urinary creatinine (mg/dL)	124.2 ± 64.3	127.4 ± 65.4	0.32
Urinary As (µg/g creatinine)	9.5 ± 21.0	10.9 ± 22.9	0.22
Urinary Pb (µg/g creatinine)	0.4 ± 0.5	0.4 ± 0.4	0.82
Sodium intake (mg)	3278.5 ± 1714.3	3341.0 ± 1645.7	0.450
Total calorie intake (kcal)	2038.9 ± 944.8	2069.7 ± 891.3	0.493

### 3.2 Association of single metal exposure with hypotension

Comprehensive analysis reveals significant associations between arsenic/lead exposure and blood pressure dysregulation in children and adolescents. As shown in Table 2, the highest arsenic quartile (Q4) increased hypotension risk by 63% (OR=1.63, 95%CI:1.03-2.58) with significant dose-response trend (p-trend=0.04), while lead exposure Q3 increased risk by 54% (OR=1.54, P=0.03). These findings align with the blood pressure percentile analysis in Table 3: arsenic exposure significantly reduced diastolic pressure (-5.75 percentiles in Q3, P=0.02) with marked linear trend (P-trend=0.049); lead exposure Q4 reduced diastolic pressure by 3.40 percentiles and systolic pressure by 1.82 percentiles, showing borderline significant systolic trend (P-trend=0.05). Crucially, the highest exposure groups (Q4) consistently demonstrated the most pronounced effects across both analyses, with directional consistency between diastolic pressure reduction and increased hypotension risk, suggesting metal exposure may increase hypotension susceptibility by altering blood pressure distribution patterns, particularly diastolic regulation.

Table 2. Associations Between Arsenic and Lead Exposure and Hypotension Risk in Children and Adolescents Aged 8–17 Years

Metal	Model	Exposure Category	Odds Ratio (95% CI)	P-value	P-trend
Log Urinary As (µg/g creatinine)	Model 1	Q2 vs Q1	1.44 (0.93–2.24)	0.11	0.01*
		Q3 vs Q1	1.44 (0.91–2.29)	0.12	
		Q4 vs Q1	1.73 (1.13–2.64)	0.01*	
	Model 2	Q2 vs Q1	1.44 (0.92–2.25)	0.12	0.04*
		Q3 vs Q1	1.42 (0.88–2.29)	0.16	
		Q4 vs Q1	1.63 (1.03–2.58)	0.04*	

Metal	Model	Exposure Category	Odds Ratio (95% CI)	P-value	P-trend
Log Urinary Pb (µg/g creatinine)	Model 1	Q2 vs Q1	1.41 (0.98–2.03)	0.07	
		Q3 vs Q1	1.66 (1.13–2.45)	0.01*	0.02*
		Q4 vs Q1	1.66 (1.05–2.64)	0.03*	
	Model 2	Q2 vs Q1	1.38 (0.96–1.98)	0.09	
		Q3 vs Q1	1.54 (1.04–2.28)	0.03*	0.06
		Q4 vs Q1	1.48 (0.93–2.34)	0.10	

Reference group: Q1 (lowest quartile); \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ ; Units: µg/g – Micrograms per gram; Model 1: Adjusted for age, sex and race. Model 2: Model 1 + BMI, income-to-poverty ratio, sodium intake, total calorie intake and household size

*Table 3. Analysis of the Impact of Urinary Arsenic (As) and Lead (Pb) Exposure on Systolic and Diastolic Blood Pressure Percentiles in Children and Adolescents Based on Weighted Multivariable Linear Regression*

Metal	Exposure Category	Model 1		Model 2	
		β (95% CI)	P. value	β (95% CI)	P. value
Systolic blood pressure percentile (mm Hg)					
Log Urinary As (μg/g creatinine)	Q2 vs Q1	0.68 (-3.81-5.18)	0.76	0.79 (-3.43-5.01)	0.71
	Q3 vs Q1	-0.21 (-4.58-4.17)	0.93	0.30 (-3.89-4.48)	0.89
	Q4 vs Q1	-1.38 (-5.50-2.74)	0.51	0.38 (-3.52-4.28)	0.85
P-trend		0.66		0.90	
Log Urinary Pb (μg/g creatinine)	Q2 vs Q1	-1.98 (-5.80-1.85)	0.31	-1.09 (-4.61-2.44)	0.55
	Q3 vs Q1	-3.92 (-8.11-0.26)	0.07	-2.66 (-6.76-1.44)	0.21
	Q4 vs Q1	-3.82 (-8.22-0.58)	0.09	-1.82 (-5.72-2.09)	0.36
P-trend		0.05*		0.24	
Diastolic blood pressure percentile (mm Hg)					
Log Urinary As (μg/g creatinine)	Q2 vs Q1	-2.31 (-7.44-2.82)	0.37	-2.02 (-7.16-3.11)	0.43
	Q3 vs Q1	-6.20 (-10.92--1.47)	0.01*	-5.75 (-10.41--1.09)	0.02*
	Q4 vs Q1	-4.31 (-9.32-0.70)	0.09	-3.87 (-8.89-1.16)	0.13
P-trend		0.03*		0.05*	
Log Urinary Pb (μg/g creatinine)	Q2 vs Q1	0.50 (-3.77-4.78)	0.82	0.74 (-3.33-4.81)	0.72
	Q3 vs Q1	0.33 (-3.62-4.27)	0.87	0.93 (-3.01-4.87)	0.65
	Q4 vs Q1	-4.01 (-8.41-0.39)	0.08	-3.40 (-7.69-0.90)	0.13
P-trend		0.13		0.22	

Reference group: Q1 (lowest quartile); \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ ; Units: µg/g – Micrograms per gram; mmHg: Millimeters of mercury; Model 1: Adjusted for age, sex and race.; Model 2: Model 1 + BMI, income-to-poverty ratio, sodium intake, total calorie intake and household size.

### 3.3 Effect modification analysis of urinary metal exposure and hypotension association

Effect modification analyses (Table 7) confirmed that pubertal stage significantly modified lead exposure effects, with a significant interaction in mid-puberty ( $p$ -interaction = 0.03). This complements subgroup findings showing peak lead effects in mid-puberty (Q3: OR = 2.45,  $P$  = 0.005; Table 4), suggesting developmentally specific susceptibility windows. Although arsenic exposure demonstrated strong mid-pubertal associations (Q4: OR = 2.62,  $P$  = 0.001), no significant age interaction was

detected (p-interaction for mid-puberty = 0.48; Table 7). Gender-stratified analyses (Table 5) indicated male-predominant lead risk (Q2: OR = 2.01, P = 0.005) and female-specific arsenic vulnerability (Q4: OR = 1.82, P = 0.04), but gender interactions were non-significant (P-interaction = 0.89). BMI stratification (Table 6) revealed heightened sensitivity in normal-weight individuals to both metals (lead Q4: OR = 2.14, P = 0.02; arsenic Q4: OR = 2.04, P = 0.02), with borderline arsenic risk in obese individuals (Q4: OR = 2.99, P = 0.07), yet BMI interactions were non-significant (P-interaction > 0.24).

Table 4. Age Subgroup Analysis of Metal Exposure and Hypotension Risk

Metal	Age Group	Exposure	Odds Ratio (95% CI)	P-value
Log Urinary Pb (µg/g creatinine)	Pre-puberty (8–10y)	Q2 vs Q1	0.66 (0.25-1.72)	0.40
		Q3 vs Q1	0.53 (0.20-1.40)	0.21
		Q4 vs Q1	0.53 (0.22-1.32)	0.18
	Early-puberty (11–13y)	Q2 vs Q1	1.74 (0.95-3.19)	0.08
		Q3 vs Q1	2.45 (1.35-4.46)	0.005**
		Q4 vs Q1	2.02 (1.01-4.02)	0.05
	Mid-puberty (14–17y)	Q2 vs Q1	1.24 (0.72-2.15)	0.44
		Q3 vs Q1	1.29 (0.73-2.31)	0.39
		Q4 vs Q1	1.75 (0.81-3.81)	0.16
Log Urinary As (µg/g creatinine)	Pre-puberty (8–10y)	Q2 vs Q1	0.78 (0.28-2.13)	0.62
		Q3 vs Q1	0.99 (0.38-2.57)	0.98
		Q4 vs Q1	1.34 (0.45-4.00)	0.60
	Early-puberty (11–13y)	Q2 vs Q1	2.01 (1.08-3.74)	0.03*
		Q3 vs Q1	1.18 (0.60-2.31)	0.64
		Q4 vs Q1	1.08 (0.59-1.98)	0.81
	Mid-puberty (14–17y)	Q2 vs Q1	1.61 (0.93-2.78)	0.10
		Q3 vs Q1	2.07 (1.03-4.15)	0.04*
		Q4 vs Q1	2.62 (1.47-4.67)	0.001**

Reference group: Q1 (lowest exposure quartile); \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001; Units: µg/g – Micrograms per gram.

Table 5. Gender Subgroup Analysis of Metal Exposure and Hypotension Risk

Metal	Gender	Exposure	Odds Ratio (95% CI)	P-value
Log Urinary Pb (µg/g creatinine)	Male	Q2 vs Q1	2.01 (1.26-3.21)	0.005**
		Q3 vs Q1	1.84 (1.04-3.26)	0.04*
		Q4 vs Q1	1.27 (0.71-2.29)	0.43
	Female	Q2 vs Q1	0.80 (0.46-1.39)	0.43
		Q3 vs Q1	1.22 (0.71-2.08)	0.48
		Q4 vs Q1	1.51 (0.82-2.80)	0.19
Log Urinary As (µg/g creatinine)	Male	Q2 vs Q1	1.28 (0.71-2.30)	0.41
		Q3 vs Q1	1.28 (0.70-2.34)	0.42
		Q4 vs Q1	1.51 (0.86-2.64)	0.16
	Female	Q2 vs Q1	1.68 (0.93-3.05)	0.09
		Q3 vs Q1	1.59 (0.92-2.73)	0.10
		Q4 vs Q1	1.82 (1.04-3.20)	0.04*

Reference group: Q1 (lowest exposure quartile); \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001; Units: µg/g – Micrograms per gram.

Table 6. BMI Subgroup Analysis of Metal Exposure and Hypotension Risk

Metal	BMI Category	Exposure	Odds Ratio (95% CI)	P-value
Log Urinary Pb (µg/g creatinine)	Normal	Q2 vs Q1	1.30 (0.78-2.16)	0.31
		Q3 vs Q1	1.76 (0.98-3.16)	0.06
		Q4 vs Q1	2.14 (1.15-3.97)	0.02*
	Underweight	Q2 vs Q1	2.06 (0.94-4.49)	0.07
		Q3 vs Q1	1.51 (0.62-3.68)	0.37
		Q4 vs Q1	1.37 (0.56-3.35)	0.49
	Overweight	Q2 vs Q1	1.10 (0.46-2.63)	0.83
		Q3 vs Q1	0.78 (0.36-1.66)	0.52
		Q4 vs Q1	0.67 (0.27-1.69)	0.41
	Obese	Q2 vs Q1	0.75 (0.26-2.22)	0.62
		Q3 vs Q1	1.93 (0.70-5.31)	0.21
		Q4 vs Q1	0.62 (0.19-2.03)	0.44
Log Urinary As (µg/g creatinine)	Normal	Q2 vs Q1	1.65 (0.96-2.84)	0.07
		Q3 vs Q1	1.87 (1.04-3.37)	0.04*
		Q4 vs Q1	2.04 (1.14-3.67)	0.02*
	Underweight	Q2 vs Q1	1.20 (0.44-3.23)	0.73
		Q3 vs Q1	0.90 (0.38-2.17)	0.82
		Q4 vs Q1	1.10 (0.45-2.65)	0.84
	Overweight	Q2 vs Q1	1.28 (0.49-3.34)	0.62
		Q3 vs Q1	1.03 (0.38-2.79)	0.96
		Q4 vs Q1	1.17 (0.44-3.07)	0.76
	Obese	Q2 vs Q1	0.71 (0.28-1.79)	0.48
		Q3 vs Q1	1.67 (0.64-4.33)	0.30
		Q4 vs Q1	2.99 (0.94-9.49)	0.07

Reference group: Q1 (lowest exposure quartile); \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ ; Units: µg/g – Micrograms per gram;

Table 7. Interaction Analysis for Effect Modification

Metal	Effect Modifier	Interaction P-value
Log Urinary Pb (µg/g creatinine)	Age (Early-puberty)	0.06
	Age (Mid-puberty)	0.03*
	Gender	0.91
	BMI	0.94
Log Urinary As (µg/g creatinine)	Age (Early-puberty)	0.16
	Age (Mid-puberty)	0.48
	Gender	0.89
	BMI	0.24

P-interaction for age groups (vs. pre-puberty reference); \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ ; Units: µg/g – Micrograms per gram

### 3.4 Association of urinary metal co-exposure with hypotension

The WQS regression model was used to study the effect of mixed metals on hypotension. After adjusting for all selected confounders, the WQS index of mixed metal exposure was significantly associated with the risk of hypotension (master model OR = 1.21, 95% CI: 1.03-1.42,  $P=0.02$ ), with UAs and Pb weights of 50.03% and 49.97%, respectively, as shown in (Figure 1). Stratified analysis showed that the association was strongest among normal weight adolescents (OR=1.45, 95%CI: 1.16-1.81,  $P=0.001$ ), and the obese group had the largest effect value but no statistically significant (OR=1.67, 95%CI: 0.92-3.16,  $P=0.10$ ). The most obvious risk trend was shown in early adolescence (OR=1.27, 95%CI: 0.97-1.69,  $P=0.09$ ).

Figure 1: Association of metal mixture exposure with hypotension risk in adolescents using weighted quantile sum regression

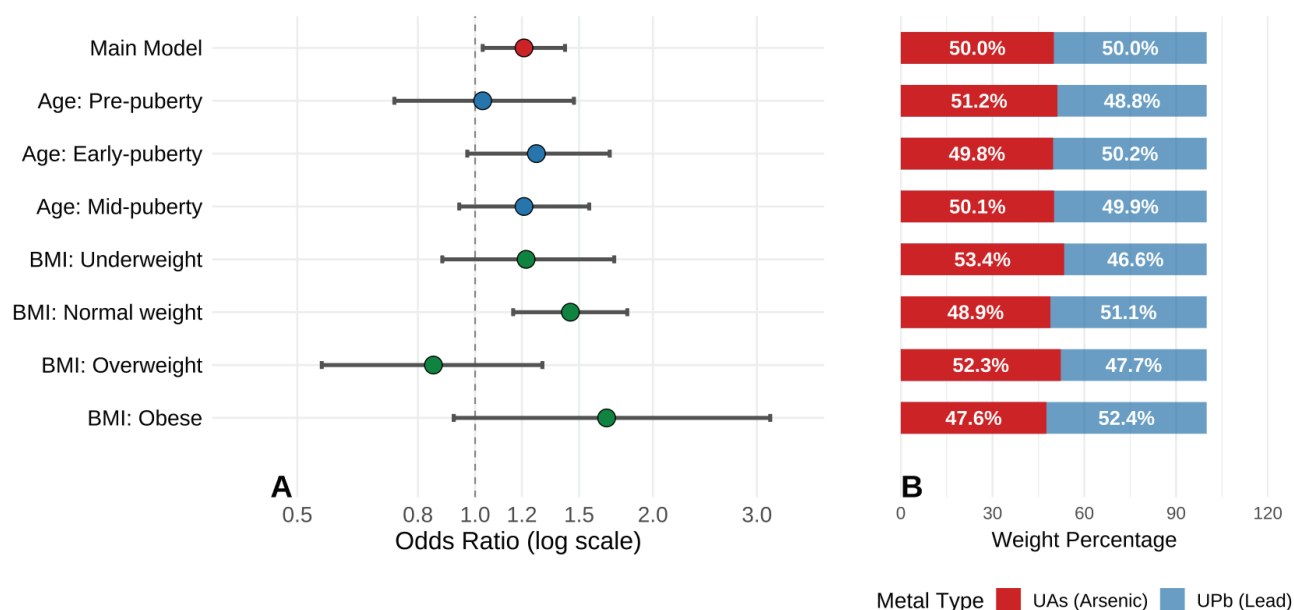


FIGURE 1:

(A) Forest plot showing odds ratios (OR) and 95% confidence intervals for the association between the metal mixture index and hypotension risk.

(B) Bar plot showing weight distribution of arsenic and lead in the weighted quantile sum (WQS) index.

The main model ( $n=2043$ ) was adjusted for age, sex, race/ethnicity, BMI category, household income, family size, energy intake and sodium intake.

### 3.5 Sensitivity Analysis

To verify the robustness of the model, sensitivity analyses were performed to assess potential non-linear and non-additive relationships between UAs, UPb, and hypotension. For non-linear relationships, natural spline models ( $df=3$ ) were compared with linear models using Rao-Scott likelihood ratio tests (LRT). Results showed no significant non-linear trends:  $LRT=3.36$  ( $P=0.190$ ) for  $\ln\_UAs$  and  $LRT=1.40$  ( $P=0.489$ ) for  $\ln\_UPb$ , supporting the use of linear models in primary analyses. For non-additive relationships, an interaction term ( $\ln\_UAs: \ln\_UPb$ ) was included in the Weighted Quantile Sum (WQS) model. The interaction term (coefficient=-0.06,  $SE=0.04$ ,  $z=-1.60$ ,  $P=0.11$ ) was not statistically significant, indicating no evidence of synergistic or antagonistic effects between the two metals. In summary, the sensitivity analysis confirmed the robustness of the model, with linear associations and no significant non-additive effects.

## 4. Discussion

This study investigated the associations of UAs and Pb exposure—both individually and in mixture—with hypotension among 2,043 children and adolescents, while exploring effect modification by pubertal stage, gender, and BMI. Our key findings reveal that both single and co-exposure to arsenic and lead are associated with an increased risk of hypotension, with distinct susceptibility patterns across developmental stages and anthropometric subgroups.

Our primary results highlight three critical observations: (1) individual arsenic and lead exposure are independently associated

with elevated hypotension risk, with more pronounced effects on diastolic blood pressure; (2) arsenic and lead co-exposure demonstrated additive effects on hypotension risk, with nearly equal contributions from each metal; (3) these associations are modified by pubertal stage and BMI, with normal-weight and pubescent adolescents appearing most vulnerable. First, the positive associations between arsenic (Q4: OR=1.63) and lead (Q3: OR=1.54) exposure and hypotension risk, coupled with their dose-dependent reductions in diastolic blood pressure percentiles, align with emerging evidence that environmental metals may disrupt blood pressure regulation beyond hypertension. While most prior studies focus on metal-induced hypertension in adults<sup>[19,20]</sup>, our findings in children and adolescents suggest a contrasting or context-dependent effect—potentially driven by the unique physiological dynamics of pediatric blood pressure regulation, which is still maturing during puberty<sup>[21]</sup>. The stronger impact on diastolic pressure (e.g., arsenic Q3 reducing diastolic percentiles by -5.75) is noteworthy, as diastolic pressure in youth is more closely linked to vascular resistance and autonomic nervous system (ANS) function<sup>[22]</sup>, hinting at metal-induced disruption of these pathways. Second, the WQS model revealed that co-exposure to arsenic and lead jointly increases hypotension risk (master model OR=1.21), with nearly equal weights (50.03% vs. 49.97%). This finding echoes the combined toxicity mechanism of cadmium-lead mixtures on renal function in a cohort of Mexican children, suggesting that heavy metal mixtures may affect cardiovascular homeostasis through multiple pathway superposition or toxicity amplification effects<sup>[23]</sup>; our results suggest that arsenic and lead may exert additive effects on hypotension, consistent with their overlapping mechanisms of vascular and neural toxicity. The comparable weights imply neither metal dominates the association, underscoring the need to consider co-exposure in pediatric populations, where cumulative toxicant burdens may disproportionately affect developing systems.

Our effect modification analyses identified key subgroups with heightened vulnerability. Lead's association with hypotension was strongest in early puberty (Q3: OR=2.45), while arsenic showed pronounced effects in mid-puberty (Q4: OR=2.62). Puberty is a critical period for cardiovascular maturation, and early puberty specifically represents a key window for vascular development and sympathetic nervous system maturation. During this stage, the vascular smooth muscle and autonomic regulatory pathways are still plastic, making them highly susceptible to environmental toxicants. Lead, which disrupts calcium signaling, could exacerbate vascular smooth muscle dysfunction during this critical growth phase—potentially amplifying hypotensive effects by impairing vasoconstrictive responses that maintain normal blood pressure. This developmental vulnerability may explain why lead's risk peaks in early puberty, while arsenic—known to alter endothelial nitric oxide (NO) production—might exacerbate diastolic dysfunction as blood pressure stabilizes in mid-puberty<sup>[24,25]</sup>. Normal-weight adolescents exhibited the strongest association between mixed metal exposure and hypotension (OR=1.45), while obese individuals showed a large but imprecise effect (OR=1.67, 95% CI:0.92–3.16). This contrasts with adult studies linking obesity to hypertension but aligns with the baseline finding that hypotension is less common in obese youth. Normal-weight individuals may lack the adipokine-mediated or volume-expanded buffering mechanisms present in obesity, making their blood pressure regulation more susceptible to metal-induced disruption<sup>[26,27]</sup>. The wide CI in obese groups likely reflects smaller sample size (hypotension group obesity=7.87%), limiting statistical power. Male-predominant lead risk and female-specific arsenic vulnerability, though non-significant in interaction tests, mirror reports of gender-dependent metal toxicity. Testosterone may enhance lead's vascular effects, while estrogen's modulation of endothelial function could amplify arsenic's impact on diastolic pressure in females—warranting further investigation<sup>[28,29]</sup>.

The observed associations may stem from shared and distinct mechanisms of arsenic and lead toxicity. Arsenic inhibits endothelial NO synthase, reducing NO-mediated vasodilation and lowering diastolic pressure<sup>[30]</sup>. Lead disrupts calcium homeostasis in vascular smooth muscle, impairing vasoconstriction—critical for maintaining systolic pressure<sup>[31]</sup>. Together, these effects could shift blood pressure distribution toward hypotension, particularly in developing vasculature. Both metals target the ANS; lead alters sympathetic tone via central nervous system toxicity, while arsenic impairs parasympathetic modulation. In adolescents, where ANS balance is still maturing, such disruption could exaggerate hypotensive tendencies. Though urinary creatinine (a proxy for renal function) showed no group differences, metals may subtly impair renal sodium handling, affecting blood volume and pressure—consistent with our finding that dietary sodium (a key regulator) did not confound associations<sup>[32]</sup>.



Limitations should be noted: (1) Cross-sectional design precludes causal inference; longitudinal studies are needed to establish temporality. (2) Urinary metals reflect recent (not cumulative) exposure; hair or bone biomarkers could better capture long-term burden. (3) Unmeasured confounders (e.g., genetic polymorphisms in metal transporters, physical activity) may influence results. (4) The obese subgroup's wide CI limits interpretation of its large effect size.

## 5. Conclusion

This study confirmed that environmental arsenic and lead exposure were independent risk factors for hypotension in children and adolescents, and there was a significant additive effect. Normal-weight, early adolescent males are at high risk, and their blood pressure regulation mechanisms may be more susceptible to metal toxicity during the critical period of development.

## Funding

No

## Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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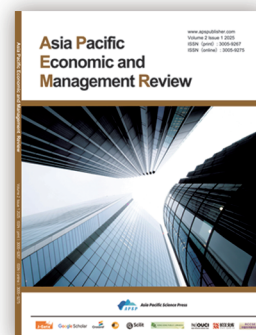
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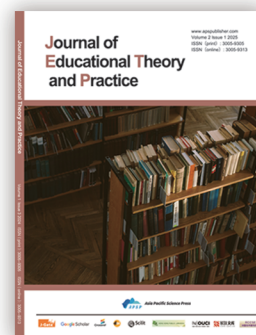
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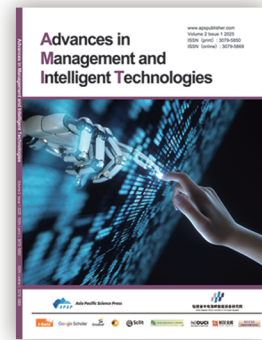


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