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Original Research

Risk Factors and Severity Indicators of Female Pelvic Organ Prolapse: Insights from a Comprehensive Retrospective Study with a Large Sample Size

Qiao Li[1,2], Xiaoyu Niu[1,2], Yueyue Chen[1,2], Can Luo[1,2], Yueting Zhang[1,2], Jian Meng[1,2], Dongmei Wei[1,2,*]

[1]Department of Gynecology and Obstetrics, West China Second Hospital, Sichuan University, 610041 Chengdu, Sichuan, China
[2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, 610041 Chengdu, Sichuan, China
*Correspondence: weidongmei@scu.edu.cn (Dongmei Wei)
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Abstract

Background: Pelvic organ prolapse (POP) is a common condition worldwide, predominantly affecting middle-aged and elderly postmenopausal women. However, its pathogenesis, etiology, and associated risk factors remain unclear. This study aimed to analyze the distribution of POP severity stages, identify associated risk factors, and explore its underlying pathogenesis to develop strategies for early prevention and intervention. **Methods**: This retrospective study included all patients diagnosed with POP using the pelvic organ prolapse quantification (POP-Q) system at the outpatient clinic of West China Second Hospital, Sichuan University, between January 2015 and January 2019. A univariate Chi-square test and multivariate logistic regression analysis were performed to evaluate the relationships between the identified factors. **Results**: Among 9569 patients with anterior vaginal wall prolapse, the severity was distributed as follows: grade I (38.52%), grade II (60.70%), grade III (0.77%), and grade IV (0.01%). Among the 9495 patients with posterior vaginal wall prolapse, the severity was distributed as follows: grade I (90.37%), grade II (9.47%), and grade III (0.16%). Among the 932 patients with uterine prolapse, the severity was distributed as follows: grade I (85.84%), grade II (5.36%), grade III (7.62%), and grade IV (1.18%). Multivariate logistic regression analysis identified several significant risk factors associated with the progression of anterior vaginal wall prolapse, including advanced maternal age (AMA) ($\geq$35 years), body mass index (BMI) ($\geq$25 kg/m^2), parity ($\geq$2), and vaginal delivery ($p < 0.05$). For posterior vaginal wall prolapse, significant risk factors included AMA ($\geq$35 years), BMI ($\geq$25 kg/m^2), manual labor, and vaginal delivery ($p < 0.001$). Additionally, AMA ($\geq$35 years) was identified as a significant risk factor for the progression of uterine prolapse ($p < 0.05$). **Conclusions**: Grade II prolapse was most commonly observed in the anterior vaginal wall, whereas grade I prolapse predominantly occurred in the posterior vaginal wall. Key risk factors for POP include childbearing age, parity, BMI, and mode of delivery, with AMA identified as independent risk factors. Vaginal delivery specifically increases the likelihood of vaginal prolapse, while occupations involving prolonged physical labor correlate with a higher incidence of posterior vaginal wall prolapse. Based on the identified risk factors, targeted prevention and intervention measures are recommended to facilitate early identification and reduce the incidence of POP.

Keywords: pelvic organ prolapse; risk factor; advanced maternal age; manual labor

1. Introduction

Pelvic organ prolapse (POP) is increasingly prevalent due to an aging population, affecting up to 50% of parous women, the majority of whom are over the age of 60 years [1,2]. Epidemiological data indicate that the incidence of POP in women over 60 years of age in China reaches 73.9% [3]. Clinical manifestations of POP include pelvic pain and descent of the vaginal wall or apex, often accompanied by urinary, sexual, and anorectal dysfunction [4]. Although POP is not life-threatening, its prevalence increases markedly with advancing age [5,6].

Currently, the pathogenesis of POP remains unclear, with its etiology and associated risk factors still under debate [7]. It is generally believed that POP results from chronic damage to the pelvic floor support structures, influenced by risk factors such as pregnancy, childbirth, prolonged elevated intra-abdominal pressure, and estrogen deficiency [8]. POP significantly impacts the quality of life for middle-aged and older women, making the identification of key risk factors essential for raising awareness and enabling early prevention. However, large-scale studies on the prevalence and risk factors for POP in Chinese women are scarce. One study involving 2668 women identified aging, menopause, number of pregnancies, childbirth, body mass index (BMI), and mode of delivery as associated factors of POP and urinary incontinence [9]. However, its smaller sample size may have underestimated the true prevalence and severity of the condition.

The present study aimed to analyze the distribution of POP across various severity stages, identify its risk factors, and explore its underlying pathogenesis in a large cohort of Chinese women. The findings are expected to promote self-examination and early prevention among women, while also assisting clinicians in improving preoperative assessments and advancing individualized, precision-based treatment strategies.

2. Methods

2.1 Study Participants

This retrospective study enrolled all patients diagnosed with POP through pelvic floor functional detection at the postpartum gynecological clinic of West China Second Hospital, Sichuan University, between January 2015 and January 2019.

Diagnosis was performed by the same physician using the pelvic organ prolapse quantification (POP-Q) system [10]. Patients presenting with anterior vaginal wall prolapse, uterine prolapse, posterior vaginal wall prolapse, or vaginal vault prolapse were diagnosed with POP. Prolapse severity was staged according to the criteria jointly recommended by the International Urogynecological Association and the International Continence Society [10]:

Stage 0: No prolapse detected;

Stage 1: The most distal portion of the prolapse is more than 1 cm above the level of the hymen;

Stage 2: The most distal portion of the prolapse is located between 1 cm above the hymen and 1 cm below the hymen;

Stage 3: The most distal portion of the prolapse extends more than 1 cm beyond the plane of the hymen but is everted at least 2 cm less than the total vaginal length;

Stage 4: Complete eversion or eversion within 2 cm of the total length of the lower genital tract.

Inclusion criteria included: (1) women who underwent pelvic floor screening (with the most recent results selected from repeated screenings); (2) women who were fully informed, voluntarily participated; and (3) women who were able to undergo long-term follow-ups. Exclusion criteria included: (1) age $<$20 years; (2) abnormal vaginal bleeding; (3) acute urinary infection (e.g., frequent urination, urgent urination, and hematuria); (4) urinary leakage during pregnancy, including transient urinary leakage; (5) pregnancy or menstruation; and (6) absence of sexual history.

Ethical approval was granted by the Ethics Committee of West China Second Hospital of Sichuan University (No. 2023179) on September 21, 2023. Informed consent was obtained from all participants. All procedures were performed in accordance with the relevant guidelines.

2.2 Statistical Analysis

Based on previous research and clinical practice, we screened and collected clinical information and medical histories pertaining to POP in women. The key variables included childbearing age, BMI, parity, delivery mode, family history of POP, occupation type (manual *vs*. mental labor), diabetes, hypertension, chronic cough, smoking, constipation, and POP index. These variables were analyzed using univariate Chi-square (χ^2) tests. Based on the results of the univariate analysis, a multivariate logistic regression model was constructed to account for potential confounding factors. The factors included in the model were selected for their clinical relevance and associations reported in prior studies. Categorical parameters were presented as frequencies and percentages. All statistical analyses were performed via SPSS 26.0 software (IBM Corp., Armonk, NY, USA), with significance set at $p < 0.05$.

3. Results

3.1 Analysis of the Staging and Distribution of POP in Different Anatomical Regions

According to the findings from clinical assessments, a total of 9569 patients were diagnosed with anterior vaginal wall prolapse, 9495 with posterior vaginal wall prolapse, and 932 with uterine prolapse. Among these patients, 9474 (98.62%) were diagnosed with both anterior and posterior vaginal wall prolapse concurrently. The ages of the patients ranged from 20 to 76 years, with a mean age of 44.02 $\pm$ 9.80 years.

We initially evaluated the site and severity of POP in all patients. As shown in Table 1, the severity of anterior vaginal wall prolapse was classified as follows: grade I (38.52%), grade II (60.70%), grade III (0.77%), and grade IV (0.01%). For posterior vaginal wall prolapse, the distribution was as follows: grade I (90.37%), grade II (9.47%), and grade III (0.16%). Among the 932 patients with uterine prolapse, the severity was classified as grade I (85.84%), grade II (5.36%), grade III (7.62%), and grade IV (1.18%). In general, grade II prolapse is most commonly observed in the anterior vaginal wall, whereas grade I prolapse is most prevalent in the posterior vaginal wall.

Table 1. Analysis of prolapse grading and the distribution of POP across different anatomical regions.

Prolapse type	Grade I	Grade II	Grade III	Grade IV
Anterior vaginal wall prolapse	38.52% (3686)	60.70% (5808)	0.77% (74)	0.01% (1)
Posterior vaginal wall prolapse	90.37% (8581)	9.47% (899)	0.16% (15)	0.00% (0)
Uterine prolapse	85.84% (800)	5.36% (50)	7.62% (71)	1.18% (11)

POP, pelvic organ prolapse.

3.2 Results of the Univariate Analysis of Risk Factors Associated with Varying Degrees of Anterior Vaginal Wall Prolapse

To investigate the risk factors associated with different degrees of anterior vaginal wall prolapse, we conducted comparative analyses of various variables between grade I prolapse and the other severity levels. As depicted in Table 2, univariate analysis revealed that BMI (≥25 kg/m^2), family history of POP, parity (≥2), vaginal delivery, and manual labor were significant risk factors for the progression of anterior vaginal wall prolapse ($p < 0.05$). However, no significant associations were found with constipation, hypertension, diabetes, or smoking ($p > 0.05$).

Table 2. Univariate analysis of risk factors associated with varying degrees of anterior vaginal wall prolapse.

Variables	I	II/III/IV	χ^2 value	*p*-value
Age (years)			1.5065	0.2197
<35	2076	3238		
≥35	1610	2645		
BMI (kg/m^2)			8.5966	**0.0034**
<25	3027	4688		
≥25	659	1195		
Occupation type			19.5505	<**0.0001**
Mental labor	1212	2706		
Manual labor	101	377		
Parity			33.8572	<**0.0001**
1	1415	2369		
≥2	855	1948		
Delivery mode			437.6261	<**0.0001**
Cesarean section	1054	1487		
Vaginal delivery	335	1994		
Diabetes			0.339	0.5604
Negative	3377	5285		
Positive	136	227		
Hypertension			0.812	0.3675
Negative	1439	3309		
Positive	25	71		
Family history of POP			9.527	**0.002**
Negative	2773	4623		
Positive	108	258		
Smoking			0.089	0.7654
Negative	3440	5432		
Positive	21	36		
Cough			0.3046	0.581
Negative	3455	5406		
Positive	51	88		
Constipation			0.0179	0.8936
Negative	2658	4159		
Positive	857	1350		

The bold values represent $p < 0.05$. χ^2, Chi-square; BMI, body mass index; POP, pelvic organ prolapse.

3.3 Multivariate Analysis for Risk Factors Associated with Varying Degrees of Anterior Vaginal Wall Prolapse

Multivariate logistic regression analysis (Table 3) identified significant risk factors for the progression of anterior vaginal wall prolapse: childbearing age (≥35 years) (odds ratio (OR): 1.278; 95% confidence interval (CI): 1.077–1.517), BMI (≥25 kg/m^2) (OR: 1.372; 95% CI: 1.131–1.665), parity (≥2) (OR: 1.335; 95% CI: 1.127–1.581), and vaginal delivery (OR: 4.791; 95% CI: 4.045–5.675) ($p < 0.05$). Specifically, individuals aged 35 years or older are 1.27 times more likely to develop grade II or higher prolapse compared to those younger than 35 years. Similarly, a BMI of 25 kg/m^2 or greater increases the likelihood of developing grade II or higher prolapse by 1.37 times compared to individuals with a lower BMI. Women with two or more deliveries have a 1.33 times higher probability of developing grade II or higher anterior vaginal wall prolapse compared to those with only one delivery. Additionally, a history of vaginal delivery increases the risk by 4.79 times compared to cesarean delivery.

3.4 Results of the Univariate Analysis of Risk Factors Associated with Varying Degrees of Posterior Vaginal Wall Prolapse

As illustrated in Table 4, the univariate analysis showed that childbearing age (≥35 years), BMI (≥25 kg/m^2), family history of POP, parity (≥2), vaginal delivery, diabetes, hypertension, and chronic cough were identified as risk factors for the exacerbation of posterior vaginal wall prolapse ($p < 0.05$).

3.5 Multivariate Analysis of Risk Factors Associated with Varying Degrees of Posterior Vaginal Wall Prolapse

The multivariate logistic regression analysis (Table 5) identified several significant risk factors for the exacerbation of posterior vaginal wall prolapse, including age (≥35 years) (OR: 2.028; 95% CI: 1.532–2.684), BMI (≥25 kg/m^2) (OR: 1.624; 95% CI: 1.218–2.165), manual labor (OR: 1.997; 95% CI: 1.510–2.642), and vaginal delivery (OR: 3.852; 95% CI: 2.901–5.116) ($p < 0.001$). Individuals aged 35 or older are twice as likely to develop grade II or higher posterior vaginal wall prolapse compared to those younger than 35. A BMI of 25 or greater increases this likelihood by 1.62 times. Additionally, individuals with a history of vaginal delivery are 3.85 times more likely to experience grade II or higher posterior vaginal wall prolapse compared to those who delivered via cesarean section. Individuals engaged in manual labor are also twice as likely to experience grade II or higher posterior vaginal wall prolapse compared to those in mental occupations.

3.6 Univariate Analysis of Risk Factors Associated with Varying Degrees of Uterine Prolapse

Univariate analysis (Table 6) revealed that childbearing age (≥35 years), BMI (≥25 kg/m^2), manual labor, diabetes, and chronic cough were identified as risk factors for

Table 3. Multivariate analysis of risk factors for different degrees of anterior vaginal wall prolapses.

Variables	OR	95% CI	*p*-value
Age (years) (≥35 *vs.* <35)	1.278	1.077–1.517	**0.0049**
BMI (kg/m^2) (≥25 *vs.* <25)	1.372	1.131–1.665	**0.0013**
Parity (≥2 *vs.* 1)	1.335	1.127–1.581	**0.0008**
Vaginal delivery *vs.* Cesarean section	4.791	4.045–5.675	<**0.0001**

The bold values represent $p < 0.05$. OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table 4. Univariate analysis of risk factors associated with varying degrees of posterior vaginal wall prolapse.

Variables	I	II/III/IV	χ^2 value	*p*-value
Age (years)			125.4828	<**0.0001**
<35	4920	347		
≥35	3661	567		
BMI (kg/m^2)			34.0921	<**0.0001**
<25	6980	670		
≥25	1601	244		
Occupation type			57.3406	<**0.0001**
Mental labor	3595	286		
Manual labor	393	84		
Parity			130.291	<**0.0001**
1	3525	220		
≥2	2388	396		
Delivery mode			132.6288	<**0.0001**
Cesarean section	2390	120		
Vaginal delivery	1978	335		
Diabetes			5.4818	0.0192
Negative	7778	819		
Positive	338	21		
Hypertension			31.271	<**0.0001**
Negative	4295	408		
Positive	71	24		
Family history of POP			1.9066	0.1673
Negative	6667	671		
Positive	322	41		
Smoking			1.101	0.294
Negative	7972	834		
Positive	53	3		
Cough			10.6206	**0.0011**
Negative	7974	819		
Positive	113	24		
Constipation			0.1293	0.7192
Negative	6127	639		
Positive	1987	201		

The bold values represent $p < 0.05$. χ^2, Chi-square; BMI, body mass index; POP, pelvic organ prolapse.

the exacerbation of uterine prolapse ($p < 0.05$). No significant associations were found with delivery mode, parity, constipation, family history, hypertension, or smoking.

3.7 Multivariate Analysis of Risk Factors Associated with Varying Degrees of Uterine Prolapse

Multivariate logistic regression (Table 7) revealed that childbearing age (≥35 years) (OR: 2.171; 95% CI: 1.078–4.371) is a significant risk factor for exacerbated uterine prolapse ($p < 0.05$). Individuals aged 35 years or older are 2.17 times more likely to develop grade II or higher uterine prolapse compared to those younger than 35 years. In contrast, long-term engagement in manual labor and having given birth two or more times (≥2) were protective factors against uterine prolapse. The risk was 0.48 times that of individuals engaged in mental work and 0.437 times that of women who have given birth once, respectively.

4. Discussion

POP is a chronic condition that predominantly affects middle-aged and elderly postmenopausal women, primarily due to the weakening of pelvic floor tissues [11]. With the aging global population and an increasing emphasis on quality of life, resulting in a growing number of patients seeking diagnosis and treatment. Our study shows that grade II prolapse is most commonly observed in the anterior vaginal wall, whereas grade I prolapse is more prevalent in the posterior vaginal wall. Factors such as childbearing age, parity, BMI, and mode of delivery are associated with POP, with advanced maternal age (AMA) identified as independent risk factors. Vaginal delivery significantly increases the risk of vaginal prolapse, while occupations involving prolonged physical labor are associated with an increased risk of posterior vaginal wall prolapse.

The International Federation of Gynecology and Obstetrics and the American College of Obstetricians and Gynecologists defined AMA as 35 years or older at the estimated date of delivery [12,13]. Our findings indicate a correlation between AMA and an elevated risk of POP, with vaginal deliveries being associated with a 3.85-fold higher likelihood of prolapse compared to cesarean sections. Supporting this, Wang *et al.* [14] reported a 6% increase in prolapse rates for each year of delay in first childbirth, with rates more than tripling when comparing first-time births at ages 20 and 40. This increase is attributed to a higher risk of severe pelvic floor injuries, including levator ani avulsion and severe perineal lacerations, which are more commonly associated with older maternal age [15,16]. Consequently, women of AMA may be more susceptible to POP,

Table 5. Multivariate analysis of risk factors associated with varying degrees of posterior vaginal wall prolapse.

Variables	OR	95% CI	*p*-value
Age (years) (≥35 *vs.* <35)	2.028	1.532–2.684	**<0.0001**
BMI (kg/m^2) (≥25 *vs.* <25)	1.624	1.218–2.165	**0.001**
Mental labor *vs.* Manual labor	1.997	1.510–2.642	**0.0004**
Parity (≥2 *vs.* 1)	0.550	1.218–2.165	**<0.0001**
Vaginal delivery *vs.* Cesarean section	3.852	2.901–5.116	**<0.0001**

The bold values represent $p < 0.05$. OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table 6. Univariate analysis of risk factors associated with varying degrees of uterine prolapse.

Variables	I	II/III/IV	χ^2 value	*p*-value
Age (years)			14.5508	**0.0001**
<35	347	34		
≥35	453	98		
BMI (kg/m^2)			4.1006	**0.0429**
<25	622	92		
≥25	178	40		
Occupation type			5.7999	**0.016**
Mental labor	275	40		
Manual labor	50	16		
Parity			0.0006	0.9811
1	248	44		
≥2	272	48		
Delivery mode			2.6471	0.1037
Cesarean section	137	21		
Vaginal delivery	242	58		
Diabetes			4.4256	**0.03**
Negative	712	117		
Positive	21	9		
Hypertension			3.426	0.064
Negative	357	70		
Positive	13	7		
Family history of POP			0.038	0.846
Negative	577	109		
Positive	24	5		
Smoking				1.000
Negative	723	125		
Positive	3	0		
Cough			4.790	**0.029**
Negative	713	118		
Positive	17	8		
Constipation			0.709	0.400
Negative	545	98		
Positive	189	28		

The bold values represent $p < 0.05$. χ^2, Chi-square; BMI, body mass index; POP, pelvic organ prolapse.

aligning with National Institute for Health and Care Excellence (NICE) guidelines, which identify maternal age over 30 years at childbirth as a risk factor for pelvic floor dysfunction [17].

Table 7. Multivariate analysis of risk factors associated with varying degrees of uterine prolapse.

Variables	OR	95% CI	*p*-value
Age (years) (≥35 *vs.* <35)	2.171	1.078–4.371	**0.0299**
Mental labor *vs.* Manual labor	0.480	0.239–0.964	**0.0004**
Parity (≥2 *vs.* 1)	0.437	0.194–0.984	**<0.0001**

The bold values represent $p < 0.05$. OR, odds ratio; CI, confidence interval; BMI, body mass index.

Our study further identified prolonged physical labor as a significant risk factor for posterior vaginal wall prolapse. From an abdominal-pelvic biomechanics perspective, maintaining a stable balance of dynamic forces within the abdominopelvic cavity is crucial for maintaining normal function. Prolonged physical labor elevates intra-abdominal pressure, disrupting this balance [18] and stressing pelvic floor structures. This stress leads to muscle and connective tissue fatigue and relaxation, thereby heightening the risk of prolapse. This may help explain the higher prevalence of POP among women in low-income environments. A study from rural areas indicates that insufficient postpartum rest and heavy lifting during daily chores are major contributors to prolapse [19]. Lifting heavy objects for five or more hours daily is associated with anatomical prolapse [20]. Frequent activities like lifting, bending, and carrying increase biomechanical loads on the pelvic region, further contributes to the risk of prolapse.

Research shows that changes in body position can also impact intra-abdominal pressure and uterine movement [21]. Various body positions exert different stresses on the uterus and its supporting ligaments, thereby influencing physiological alignment. Prolonged heavy lifting often involves repetitive postures, such as standing, excessive forward bending, and backward leaning. Such postures can lead to abnormal tilting of the uterus (forming a 90° angle with the cervix pointing downward) and cervical descent [22]. This reduces the angle between the uterus and vagina, thereby contributing to significant downward prolapse. As the anterior and middle-posterior vaginal walls tilt towards the pubic bone, the posterior wall may adopt a “kneeling” posture, compressing the uterus and rectum against the vaginal wall, potentially leading to uterine and

posterior vaginal wall prolapse [18,22]. However, our study did not identify physical labor as a risk factor for uterine prolapse. Instead, it appeared to have a protective effect, possibly due to the small number of uterine prolapse cases in our sample, particularly the limited number of stage IV cases. Future research should aim to increase sample sizes and conduct stratified analyses to gain a more comprehensive understanding of this issue.

This study has several limitations. Firstly, the recruitment of subjects from our hospital's postpartum gynecology clinic resulted in a sample predominantly consisting of young women with mild to moderate prolapse, potentially introducing selection bias. Secondly, our study did not analyze the descent or socioeconomic status of the included population, limiting our ability to assess whether the risk of POP is higher among individuals from underdeveloped regions or those facing adverse childbirth conditions. Lastly, the study incorporated a limited number of variables and lacked detailed categorization, which may have restricted the depth of our analysis. Future research should expand the range of variables, conduct long-term follow-ups, and implement prospective cohort studies with larger sample sizes to more comprehensively identify risk factors for POP.

Despite these limitations, our large-scale study is clinically significant in identifying risk factors for POP and implementing early prevention strategies. Our findings indicate that specific groups of women—particularly older mothers, those with two or more vaginal deliveries, those who are obese, and manual laborers—are at higher risk for POP. For these high-risk groups, we propose the following prevention and intervention measures to facilitate early identification and reduce the incidence of POP:

(1) Enhanced screening for high-risk groups: Regular POP screening should be conducted for high-risk groups, including mothers aged $\geq$35 years, those with multiple vaginal deliveries, obese individuals, and manual laborers. These screenings should be integrated into routine gynecological check-ups, especially during the postpartum and perimenopausal periods.

(2) Personalized prevention: Tailored strategies should be developed based on identified risk factors. Postpartum pelvic floor strengthening exercises (e.g., Kegel exercises) should be recommended for older mothers and women with multiple vaginal deliveries. Additionally, education on minimizing abdominal pressure (e.g., adopting proper work posture and using support tools) should be emphasized for manual laborers.

(3) Health education: Raise awareness about POP among high-risk women through healthcare facilities and online platforms. Key educational topics should include the importance of pelvic floor exercises, precautions during manual labor, and postpartum recovery strategies.

(4) Clinical tools development: We plan to develop a POP risk assessment tool based on factors such as age, childbirth history, and occupation, providing personalized risk reports to aid clinical decision-making and follow-up plans for high-risk women.

5. Conclusions

This study demonstrated that, in patients with POP, grade II prolapse is most prevalent in the anterior vaginal wall, whereas grade I prolapse predominates in the posterior vaginal wall. The incidence of POP is associated with childbearing age, parity, BMI, and mode of delivery, with AMA identified as an independent risk factors. Vaginal delivery specifically increases the risk of vaginal prolapse, while occupations involving prolonged physical labor are associated with an increased risk of posterior vaginal wall prolapse. Addressing these high-risk factors is crucial for the effective prevention of POP. Efforts should focus on disease prevention, enhancing awareness about POP, promoting early detection, and ensuring timely treatment to improve women's health and quality of life.

Availability of Data and Materials

All data generated or analyzed during this study are accessible.

Author Contributions

DW, QL, YZ and XN: Project development, data collection, manuscript writing. DW, YC, JM and CL: Data collection and analysis. All authors: Manuscript writing and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of West China Second Hospital of Sichuan University (No. 2023179) on September 21, 2023. Informed consent was obtained from all participants. All procedures were performed in accordance with relevant guidelines.

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Conflict of Interest

The authors declare no conflict of interest.

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