

Featured Article

Nomogram for predicting cognitive impairment in postpartum depression patients after pharmacotherapy: Development and validation

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Abstract: Objective: To develop and validate a clinical feature-based nomogram for predicting the risk of significant cognitive impairment in postpartum depression (PPD) patients treated with selective serotonin reuptake inhibitors (SSRIs). **Methods:** A retrospective study was conducted on 350 PPD patients treated with SSRI monotherapy at our institution between January 2020 and December 2024. Cognitive function was assessed at week 8 using the Montreal Cognitive Assessment (MoCA), with MoCA < 26 defined as significant cognitive impairment. Predictors were screened using LASSO regression, and a multivariate logistic regression model was built to construct the nomogram. Internal validation was performed via bootstrapping (1000 repetitions). Model discrimination, calibration, and clinical utility were evaluated using the C-statistic, calibration curve, and decision curve analysis (DCA). **Results:** Six predictors were identified: age, baseline depression severity (HAMD-17 score), years of education, SSRI type (paroxetine vs. others), baseline sleep quality (PSQI score), and postpartum duration. The model exhibited a C-statistic of 0.82 (95% CI: 0.78–0.86). The calibration curve demonstrated good agreement between predicted and actual risks. DCA indicated significant clinical net benefit across a wide threshold probability range (0.1–0.6). **Conclusion:** This nomogram effectively predicts individualized risk of significant cognitive impairment in SSRI-treated PPD patients, demonstrating good discrimination, calibration, and clinical utility. It serves as a valuable tool to aid clinical decision-making.

Keywords: postpartum depression; antidepressive agents; cognitive dysfunction; selective serotonin reuptake inhibitors; nomograms; risk prediction

1. Introduction

Postpartum depression (PPD) is a common and serious mental disorder affecting 10%–15% of women globally, significantly impairing maternal-infant health and bonding [1]. Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacotherapy for PPD, demonstrating established efficacy [2]. However, concerns regarding their potential cognitive side effects are growing. Studies indicate that some PPD patients may experience impairments in attention, memory, and executive function following SSRI treatment [3,4]. Such pharmacotherapy-associated cognitive impairment not only adversely affects quality of life, social functioning, and treatment adherence but may also impede full symptomatic remission [5].

Currently, clinicians primarily rely on experience to assess individual risk of cognitive impairment, lacking validated individualized prediction tools. The nomogram, an intuitive visual statistical prediction tool, integrates multiple predictors to quantify the probability of specific clinical outcomes [6,7]. While widely used in

oncology and cardiology, its application in psychiatry, particularly for predicting cognitive side effects of PPD pharmacotherapy, remains limited.

Therefore, this study aims to develop and validate a nomogram based on readily available clinical baseline characteristics to predict the risk of significant cognitive impairment in PPD patients receiving SSRI treatment. This tool aims to facilitate early risk identification and support individualized treatment decisions.

2. Subjects and methods

2.1. Study subjects

PPD patients meeting the following criteria were retrospectively enrolled from the psychiatric or obstetric-gynecologic outpatient clinics of a tertiary hospital between 1 January 2020, and 31 December 2024:

- 1) Met DSM-5 diagnostic criteria for PPD.
- 2) Age ≥ 18 years.
- 3) Postpartum duration ≤ 12 months.
- 4) Received monotherapy with one SSRI (fluoxetine, paroxetine, sertraline, citalopram, or escitalopram) at an adequate dose (minimum recommended therapeutic dose) for at least 8 weeks.
- 5) Completed comprehensive cognitive assessments (MoCA) before treatment and at week 8.
- 6) Had complete baseline clinical data (demographics, medical history, scale scores).
- 7) *Exclusion Criteria:*
- 8) Comorbid bipolar disorder, schizophrenia, or other psychotic disorders.
- 9) Severe neurological (e.g., dementia, epilepsy, stroke history) or major somatic diseases.
- 10) Use of other psychotropic medications significantly affecting cognition during pregnancy or lactation.
- 11) History of substance abuse.
- 12) Baseline MoCA < 26 , indicating pre-existing significant cognitive impairment.
- 13) Incomplete data.
- 14) A total of 350 patients were included.

2.2. Research methods

- **Cognitive Function Assessment:** The primary outcome was cognitive function at week 8, assessed using the Chinese version of the Montreal Cognitive Assessment (MoCA). MoCA < 26 was defined as significant cognitive impairment (Nasreddine et al., 2005).
- **Baseline Data Collection:**
 - Demographics: Age, years of education, parity, mode of delivery (vaginal/cesarean), postpartum duration (weeks).
 - Clinical Features: Time of PPD diagnosis (postpartum weeks), history of prior depressive episodes, family history of PPD.
 - Treatment Information: Specific SSRI used, starting dose, target dose.

- Baseline Scale Assessments:
 - Depression Severity: 17-item Hamilton Depression Rating Scale (HAMD-17).
 - Anxiety Severity: Hamilton Anxiety Rating Scale (HAMA).
 - Sleep Quality: Pittsburgh Sleep Quality Index (PSQI).
 - Social Support: Perceived Social Support Scale (PSSS).

2.3. Prediction model development and validation

- 1) **Predictor Screening:** All potential predictors (age, education years, parity, delivery mode, postpartum duration, prior depression history, PPD family history, SSRI type, baseline HAMD-17, baseline HAMA, baseline PSQI, baseline PSSS) were included in Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis. LASSO regression, by applying an L1 penalty, effectively handles multicollinearity and selects the most predictive variables (Tibshirani, 1996). The optimal lambda value (minimizing cross-validation error) was selected using 10-fold cross-validation.
- 2) **Multivariate Logistic Regression Modeling:** Variables selected by LASSO were entered into a multivariate logistic regression model, with MoCA < 26 at week 8 as the dependent variable (Yes = 1, No = 0). Backward stepwise regression (elimination criterion $P > 0.10$) identified the final independent predictors and their regression coefficients (β). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each predictor.
- 3) **Nomogram Construction:** Based on the final multivariate logistic regression model, a nomogram was constructed using the rms package in R. The nomogram assigns points (Points axis) for each predictor value. The total points from all predictors (Total Points) are then mapped to the risk axis (Risk of Cognitive Impairment), providing the predicted probability.
- 4) **Model Performance Evaluation:**
 - **Discrimination:** The area under the receiver operating characteristic curve (AUC) or C-statistic assessed the model's ability to distinguish between patients with and without cognitive impairment. A C-statistic > 0.7 indicates good discrimination; >0.8 indicates excellent discrimination.
 - **Calibration:** Calibration curves assessed the agreement between predicted and observed risks. A plot of predicted risk (X -axis) against actual risk (Y -axis) was generated, fitted with a smooth curve (e.g., Loess). Proximity to the ideal diagonal line (slope = 1) indicates good calibration. The Hosmer-Lemeshow goodness-of-fit test ($P > 0.05$ indicates no significant difference between predicted and observed values) was also used.
 - **Clinical Utility:** Decision curve analysis (DCA) evaluated the net benefit of using the model for clinical decisions across various threshold probabilities. The DCA curve plots net benefit against threshold probability, comparing it to the "treat all" (assuming all patients develop impairment) and "treat none" (assuming no patients develop impairment) strategies. A model curve above both reference lines within a threshold range indicates clinical utility (Vickers and Elkin, 2006).

- 5) Internal Validation:** Bootstrap resampling (1000 repetitions) was used for internal validation to estimate model optimism and correct the C-statistic and calibration curve, providing performance estimates closer to what might be expected in future independent samples (Steyerberg et al., 2001).

2.4. Statistical analysis

Statistical analyses were performed using R software (version 4.3.0). Normally distributed continuous variables are reported as mean $\pm$ standard deviation (SD) and compared using independent samples t-tests. Non-normally distributed continuous variables are reported as median (interquartile range, IQR) and compared using Mann-Whitney U tests. Categorical variables are reported as number (percentage) and compared using Chi-square or Fisher's exact tests. LASSO regression used the glmnet package. Logistic regression, nomogram construction, ROC analysis, calibration curves, DCA, and bootstrap validation used the rms package. The Hosmer-Lemeshow test used the ResourceSelection package. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient baseline characteristics

350 PPD patients were included. Based on MoCA scores at week 8, patients were divided into a cognitive impairment group (MoCA < 26 , $n = 87$) and a cognitively normal group (MoCA ≥ 26 , $n = 263$). Significant differences (all $P < 0.05$) were observed between groups for age, years of education, baseline HAMD-17 score, SSRI type (higher proportion using paroxetine), baseline PSQI score, and postpartum duration. Details are in **Table 1**.

Table 1. Comparison of baseline characteristics of postpartum depression patients [Data: Mean $\pm$ SD/Median(IQR)/N(%)].

Variable	Overall ($n = 350$)	Cognitive Impairment ($n = 87$)	Cognitively Normal ($n = 263$)	P-value
Demographics				
Age (years)	30.4 $\pm$ 4.8	32.1 $\pm$ 5.2	29.8 $\pm$ 4.5	<0.001
Education (years)	14.0 (12.0, 16.0)	12.0 (10.0, 14.0)	15.0 (13.0, 16.0)	<0.001
Parity (Primiparous/Multiparous)	248 (70.9%)/102 (29.1%)	58 (66.7%)/29 (33.3%)	190 (72.2%)/73 (27.8%)	0.322
Mode of delivery (Vaginal/Cesarean)	198 (56.6%)/152 (43.4%)	45 (51.7%)/42 (48.3%)	153 (58.2%)/110 (41.8%)	0.299
Clinical Features				
Postpartum duration (weeks)	12.5 $\pm$ 6.3	14.8 $\pm$ 7.1	11.7 $\pm$ 5.8	<0.001
Time to PPD diagnosis (weeks postpartum)	8.0 (6.0, 10.0)	8.0 (6.0, 10.0)	8.0 (5.0, 10.0)	0.421
History of prior depression (Yes)	89 (25.4%)	25 (28.7%)	64 (24.3%)	0.410
Family history of PPD (Yes)	42 (12.0%)	13 (14.9%)	29 (11.0%)	0.322

Table 1. (Continued).

Variable	Overall (<i>n</i> = 350)	Cognitive Impairment (<i>n</i> = 87)	Cognitively Normal (<i>n</i> = 263)	<i>P</i> -value
Treatment Information				
SSRI type (Paroxetine/Other*)	110 (31.4%)/240 (68.6%)	42 (48.3%)/45 (51.7%)	68 (25.9%)/195 (74.1%)	<0.001
Baseline Scale Scores				
HAMD-17	24.6 ± 4.1	26.8 ± 3.8	23.8 ± 3.9	<0.001
HAMA	19.3 ± 5.2	20.1 ± 5.5	19.0 ± 5.1	0.087
PSQI	12.0 (9.0, 15.0)	14.0 (12.0, 16.0)	11.0 (8.0, 14.0)	<0.001
PSSS	56.0 ± 11.8	53.9 ± 12.5	56.7 ± 11.5	0.057

*Note: Other SSRIs include fluoxetine, sertraline, citalopram, escitalopram.

3.2. Predictor screening via LASSO regression

The LASSO regression cross-validation curve identified 6 variables with non-zero coefficients at the optimal lambda (lambda.min): Age, Education years, Baseline HAMD-17 score, SSRI type (Paroxetine = 1, Other = 0), Baseline PSQI score, Postpartum duration (Figure 1: LASSO coefficient path plot; Figure 2: Cross-validation error plot). These variables were included in the subsequent multivariate logistic regression.

3.3. Multivariate logistic regression and nomogram construction

Multivariate logistic regression (backward stepwise) confirmed all 6 LASSO-selected variables as independent predictors of significant cognitive impairment in SSRI-treated PPD patients (all *P* < 0.05). Results are in **Table 2**.

Table 2. Multivariate logistic regression analysis for significant cognitive impairment in SSRI-treated PPD patients.

Predictor	β -coefficient	Std. Error	Wald χ^2	<i>P</i> -value	OR (95% CI)
Age (per 1-year increase)	0.112	0.032	12.25	<0.001	1.12 (1.05–1.19)
Education (per 1-year increase)	−0.215	0.050	18.49	<0.001	0.81 (0.73–0.89)
Baseline HAMD-17 (per 1-point increase)	0.150	0.043	12.16	<0.001	1.16 (1.07–1.27)
SSRI type (Paroxetine vs. Other)	1.105	0.285	15.05	<0.001	3.02 (1.73–5.29)
Baseline PSQI (per 1-point increase)	0.098	0.035	7.84	0.005	1.10 (1.03–1.18)
Postpartum duration (per 1-week increase)	0.065	0.025	6.76	0.009	1.07 (1.02–1.12)
Constant	−7.893	1.612	23.97	<0.001	-

The nomogram was constructed based on this model (Figure 3). It visually displays each predictor's contribution to the total points and the corresponding risk probability. Example: A 32-year-old patient (≈45 points), 12 years education (≈30 points), baseline HAMD-17 = 27 (≈50 points), taking Paroxetine (70 points), baseline PSQI = 14 (≈40 points), postpartum duration = 15 weeks (≈30 points) has a total score of 265 points, corresponding to a predicted cognitive impairment risk probability of approximately 0.75 (75%).

3.4. Model performance evaluation

The apparent (original) model C-statistic (AUC) was 0.82 (95% CI: 0.78–0.86) (Figure 4: ROC curve). After 1000 bootstrap internal validations, the calculated optimism was 0.015, yielding a bias-corrected C-statistic of 0.805, indicating good discrimination. The apparent model calibration curve (Figure 5) showed good alignment between predicted and observed risks along the ideal diagonal line, indicating good calibration. The Hosmer-Lemeshow test ($\chi^2 = 8.73$, $P = 0.366$) confirmed good model fit ($P > 0.05$). The bootstrap-corrected calibration curve closely resembled the apparent curve, demonstrating model robustness. Decision curve analysis (DCA) (Figure 6) demonstrated that across a threshold probability range of 0.1 to 0.6, using the nomogram to guide clinical decisions (e.g., enhanced cognitive monitoring, medication switch, or adjunctive cognitive interventions for high-risk patients) provided higher net benefit compared to both the “treat all” and “treat none” strategies. This confirms the model’s potential clinical value.

4. Discussion

This study successfully developed and validated a nomogram based on routine clinical indicators to predict the risk of significant cognitive impairment in PPD patients treated with SSRIs. The model integrates six independent predictors: age, years of education, baseline depression severity (HAMD-17) [8,9], SSRI type (higher risk with paroxetine), baseline sleep quality (PSQI), and postpartum duration. It demonstrates good predictive performance (bias-corrected C-statistic 0.805), calibration, and clinical utility [10,11].

Advancing age is a well-established risk factor for cognitive decline; each additional year increased risk by 12% in our model. Lower education (<12 years) significantly increased risk (OR = 0.81), suggesting individuals with lower cognitive reserve are more susceptible to the neurotoxic effects of medication [12], consistent with findings on antidepressant cognitive side effects [13]. Each 1-point increase in baseline HAMD-17 increased risk by 16%. Severe depression itself impairs neuroplasticity and cognitive function [14]. SSRI treatment may not fully reverse this impairment and could potentially add drug-related side effects in some patients, highlighting the importance of baseline assessment. Paroxetine use conferred significantly higher risk than other SSRIs (OR = 3.02). Paroxetine possesses notable anticholinergic activity [10], a key mechanism implicated in memory impairment and other cognitive side effects. This supports the strategy of choosing SSRIs with minimal anticholinergic activity (e.g., sertraline, escitalopram) to potentially mitigate cognitive risk in PPD. Sleep disturbance is a core symptom of PPD and an independent predictor of cognition. Each 1-point increase in PSQI increased risk by 10%. Sleep deprivation impairs hippocampal neurogenesis and synaptic plasticity, potentially amplifying SSRI-induced interference within cognitive networks. Improving sleep should be integral to PPD management. Longer postpartum duration (>12 weeks) was associated with higher risk (OR = 1.07). Delayed intervention and chronicity of depression may involve neurobiological changes that exacerbate cognitive vulnerability, suggesting heightened vigilance for cognitive side effects in patients presenting later postpartum.

Model Value and Clinical Implications:

The core value of this nomogram lies in its ability to provide individualized risk prediction:

- **Early Identification of High-Risk Patients:** Utilizing routine baseline data (e.g., older age, low education, severe depression, poor sleep, longer postpartum duration, planned paroxetine use), high-risk individuals can be identified before initiating SSRIs.
- **Guiding Individualized Treatment:**
 - *High-Risk:* Prioritize SSRIs with low anticholinergic burden (sertraline, escitalopram); initiate lower doses and titrate slower; conduct baseline and serial cognitive monitoring (e.g., MoCA at 4 & 8 weeks); consider early adjunctive non-pharmacological interventions (CBT, light therapy); intensify sleep interventions.
 - *Low-Risk:* Proceed with standard SSRI therapy and periodic cognitive assessment.
- **Enhancing Patient-Clinician Communication:** The visual nomogram facilitates explaining individualized risk to patients, fostering shared decision-making and improving adherence.
- **Optimizing Research Design:** Provides a tool for selecting high-risk populations for future interventional studies (e.g., combining neuroprotective agents).

Strengths and Limitations:

Strengths:

- 1) Focuses on SSRI cognitive side effects specifically in PPD, addressing a gap in prediction models.
- 2) Based on readily available clinical indicators, ensuring ease of application without costly tests.
- 3) Adheres rigorously to prediction model research standards (TRIPOD guidelines): LASSO screening, multivariate modeling, bootstrap internal validation, comprehensive evaluation (discrimination, calibration, DCA).
- 4) Develops a practical, visual nomogram tool for clinical use.

Limitations:

- 1) **Single-Center Retrospective Design:** Vulnerable to selection and information bias. Requires validation in multi-center prospective studies.
- 2) **Sample Size Constraint:** While the number of cognitive impairment events ($n = 87$) meets the basic requirement for prediction modeling ($EPV > 10$), a larger sample would enhance model stability and external validity.
- 3) **Cognitive Assessment Tool:** MoCA is a screening tool and does not cover all cognitive domains (e.g., social cognition). Future studies should incorporate comprehensive neuropsychological batteries.
- 4) **Unmeasured Confounders:** Factors like breastfeeding status, infant health, and social stressors may influence cognition but were not captured due to data limitations.
- 5) **Lack of External Validation:** Model performance needs further validation in independent, heterogeneous cohorts.
- 6) **Focus on SSRIs Only:** Does not address other antidepressant classes (e.g.,

SNRIs).

5. Conclusion

This study successfully developed and internally validated a nomogram incorporating six predictors: age, years of education, baseline depression severity, SSRI type, baseline sleep quality, and postpartum duration. The model effectively predicts the individualized risk of significant cognitive impairment in SSRI-treated PPD patients, demonstrating good discrimination, calibration, and clinical utility. This tool serves as an aid for clinicians in making individualized PPD pharmacotherapy decisions, enabling the identification of high-risk patients, optimization of drug selection, enhanced monitoring, and timely treatment adjustments. By doing so, it aims to minimize drug-related cognitive side effects while ensuring antidepressant efficacy, ultimately improving long-term functional outcomes. Future multi-center, prospective, large-scale studies are needed for external validation, and exploration of incorporating biological markers could further enhance predictive power.

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Data availability: The data associated with this study are available from the corresponding author upon reasonable request (Email: 13465868216@163.com).

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Third hospital of Shijiazhuang (No. THS-2023-3216).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Conflict of interest: The authors declare no conflict of interest.

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