

Severity Stratification of Postpartum Depression Using Combined Clinical and Radiological Markers: A Preliminary Exploratory Study

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Abstract

Purpose: Objective, measurable biomarkers for grading postpartum depression (PPD) severity are lacking. We mapped regional oxygen extraction fraction (OEF) alterations across deep brain nuclei in women with PPD and built a clinical-radiological model to distinguish moderate-to-severe (sPPD) from mild PPD (mPPD).

Methods: We enrolled 38 PPD patients, 38 healthy parturients (PHCs), and 38 non-postpartum healthy females (NPHCs), all of whom completed clinical evaluation, blood tests, and 1.5T MRI. OEF in 16 deep brain nuclei was quantified using the QSM+qBOLD (QQ) algorithm, with FDR-corrected group comparisons. An exploratory multivariate logistic regression model incorporating right globus pallidus OEF (GPrh-OEF), platelet distribution width (PDW), age, and education was used to discriminate sPPD from mPPD, with performance assessed by ROC analysis, 1,000-resample bootstrap validation, and decision curve analysis (DCA).

Results: Relative to PHCs, PPD patients showed significantly elevated OEF in the bilateral hippocampus, amygdala, and right globus pallidus (all $P < 0.05$), which positively correlated with EPDS scores. sPPD patients had higher OEF in these regions and elevated PDW compared with mPPD. The combined model reached an apparent AUC of 0.884 (95% CI 0.771–0.997; optimism-corrected AUC 0.827), with 86.7% specificity and 82.6% sensitivity at the optimal cutoff, and showed higher net benefit than single markers on decision curve analysis.

Conclusions: PPD is associated with elevated OEF in limbic and pallidal regions that tracks symptom severity. GPrh-OEF and PDW are preliminary predictive markers for sPPD, and their combination shows promising discriminative performance; larger, multi-center studies are needed before clinical application.

1. Introduction

Postpartum depression (PPD) is a mood disorder developing after delivery, with core symptoms including sadness, depressed mood, irritability, sleep disturbances and compulsive behaviors [1]. Driven by rising psychosocial stress, approximately 10% to 20% of postpartum women are diagnosed with PPD, emerging as a major public health concern that profoundly impacts mothers, infants, and their families [2, 3]. At present, the clinical diagnosis of PPD mainly relies on clinical symptoms and psychological assessment scales, such as the commonly used Edinburgh Postnatal Depression Scale (EPDS) [4]. However, these assessment methods are inherently highly subjective, and there has been a lack of mature and verifiable objective biomarkers for a long time, making it difficult to accurately determine the severity of the condition [5, 6]. In addition, PPD shows significant clinical heterogeneity. The pathological mechanisms and treatment needs of mild and moderate patients differ, which further increases the difficulty of clinical diagnosis [7, 8]. Therefore, early and accurate identification of severe postpartum depression is of crucial significance for formulating individualized treatment plans, avoiding maternal suicidal tendencies, and preventing adverse outcomes such as infant developmental delays [9]. Moreover, the existing PPD risk prediction models mostly only combine social and psychological

indicators and lack neurobiological objective evidence, so their reliability in stratifying the severity of the condition is very limited [10].

Abnormal cerebral oxygen metabolism is an important pathological feature of depression [11]. The levels of oxygen utilization, blood perfusion and energy metabolism in brain tissue can be reflected through physiological indicators such as fraction of oxygen uptake (OEF), cerebral blood flow (CBF) and cerebral oxygen metabolism rate (CMRO₂). In the healthy brain, there is a tight coupling relationship between CBF and CMRO₂, and blood flow supply matches metabolic demand; however, this coupling is disrupted in patients with depression, and even if cerebral blood flow is normal, it cannot meet the demand of cerebral oxygen metabolism [12]. Affected by unique physiological changes during the perinatal period, PPD is also linked to a mismatch between cerebral oxygenation and neural activity [13], so it is crucial to analyze the pattern of cerebral oxygen metabolic disturbance in the development of PPD. Neuroimaging serves as a valuable tool for objectively assessing such physiological changes. Traditionally, OEF, CBF and CMRO₂ are measured by positron emission tomography (PET), which is widely recognized as the gold standard for quantitative imaging of OEF and CMRO₂ [14]. However, PET has limitations in the non-invasive diagnosis of PPD and its clinical application.

Advances in MRI now allow a variety of quantitative methods—such as dual-calibrated fMRI, quantitative susceptibility mapping (QSM), and quantitative blood oxygen level-dependent imaging (qBOLD)—to evaluate OEF through the amplitude and phase information of MR signals [15, 16]. Recently, an integrated method named the QSM+qBOLD (QQ) model has been introduced [17], which integrates information from the phase and amplitude signals in the multi-echo gradient echo (mGRE) sequence. OEF mapping based on the QQ model serves as a reliable and efficient tool for evaluating cerebral oxygen metabolism [18]. Our team has previously applied QSM- and OEF-related quantitative MRI techniques to pregnancy-related brain disorders and identified abnormal susceptibility and cerebral oxygen-metabolism changes, providing methodological and pathophysiological support for further exploring OEF in PPD [19]. Similarly, OEF has also demonstrated promising potential as a neuroimaging biomarker in other neurological disorders, such as evaluating whole-brain oxygen metabolic characteristics in Alzheimer's disease [20]. Yet few studies have quantified subcortical OEF changes specifically in postpartum women, and whether such metabolic shifts track depressive symptom severity remains largely unexplored [21]. To address this gap, we designed the present study around three linked questions: whether subcortical OEF differs between PPD patients and demographically matched healthy parturients; whether OEF within these same regions differs between mild and moderate-to-severe PPD; and whether combining these imaging markers with routine hematological indices into a single clinical-radiological model can support more objective severity stratification.

2. Methods

This study consecutively enrolled PPD patients admitted to the Affiliated Jinan Maternity and Child Care Hospital of Shandong First Medical University from February 2022 to December 2024, and non-postpartum age-matched healthy women who underwent physical examination in the same hospital

during the same period were included as controls. All subjects completed clinical data collection, routine blood tests, 1.5 T brain MRI scanning and depression scale assessment. This study was approved by the Ethics Committee of Jinan Maternity and Child Care Hospital Affiliated to Shandong First Medical University (Approval Number: KY R-25-052), and all subjects signed written informed consent forms. The study protocol was in accordance with the relevant requirements of the Declaration of Helsinki.

2.1 Study Subjects

The recruited subjects were finally divided into three groups: the postpartum depression (PPD) group (n = 38), the healthy parturient group (PHCs, n = 38), and the non-postpartum healthy women group (NPHCs, n = 38). The NPHC group was included solely as a physiological reference to disentangle PPD-specific OEF alterations from normative postpartum changes. They were not included in the primary clinical severity analyses. Eligibility criteria were as follows. Inclusion criteria for the PPD group: women of childbearing age who were within 6 months postpartum and met the DSM-5 diagnostic criteria for PPD, had an EPDS score ≥ 10 , and were able to complete MRI scanning, clinical assessment, and blood sampling with complete clinical data. Inclusion criteria for the control groups: PHCs (healthy women within 6 months postpartum) and NPHCs (healthy non-postpartum women) were required to have an EPDS score < 10 . Participants were excluded if they had a personal or family history of psychiatric disorders; neurological disorders; contraindications to MRI; pregnancy- or delivery-related complications that may affect cerebral or systemic oxygenation, such as preeclampsia, eclampsia, gestational hypertension, gestational diabetes, or major postpartum hemorrhage; incomplete clinical, imaging, or laboratory data; use of medications affecting cerebral metabolism, mood, or hemodynamics within 4 weeks pre-enrollment (antidepressants, antipsychotics, sedatives, hormones, steroids, antihypertensives included). Enrollment, clinical diagnosis, and grouping were independently performed by two trained clinical psychologists, and discrepancies were resolved by consensus (Fig. 1). Trained psychiatrists assessed PPD severity using the EPDS, remaining strictly blinded to both imaging data and group allocations. Participants were stratified by EPDS scores into mild (mPPD: 10–12) and moderate-to-severe (sPPD: ≥ 13) subgroups [22].

2.2 Collection of Clinical Data and Hematological Indices

A standardized questionnaire was used to collect the demographic and anthropometric variables of all subjects, including age, years of education, height and body weight. The body mass index (BMI) was calculated according to the formula: $BMI = \text{body weight (kg)} / \text{height}^2 (\text{m}^2)$. Fasting elbow venous blood samples (5 mL) were obtained in the early morning using EDTA anticoagulant tubes. Routine blood indices included white blood cell count, lymphocyte ratio, monocyte ratio, neutrophil ratio, eosinophil ratio, basophil ratio, red blood cell count, hemoglobin, hematocrit, platelet count and platelet distribution width.

2.3 Brain MRI Acquisition and Oxygen Extraction Fraction (OEF) Processing

2.3.1 MRI acquisition.

Brain imaging was performed on a 1.5 T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) equipped with an 8-channel SENSE head coil. For quantitative susceptibility mapping (QSM), data were collected using a three-dimensional multi-echo spoiled gradient-echo sequence with parameters as follows: repetition time (TR) = 50 ms; five equally spaced echoes with a first echo time (TE₁) = 5.0 ms and echo spacing (Δ TE) = 9.0 ms (TEs = 5.0, 14.0, 23.0, 32.0, and 41.0 ms); flip angle = 20°; field of view (FOV) = 200 × 200 mm; and acquisition matrix = 200 × 200 (reconstructed to 400 × 400). Slices (n = 85) were acquired at 3.0 mm thickness and reconstructed to 1.5 mm slice spacing, yielding a voxel size of 0.5 × 0.5 × 1.5 mm³. The receiver bandwidth was 172 Hz/pixel and the SENSE acceleration factor was 1.4, resulting in a total scan time of approximately 5 min. Both magnitude and phase images across all five echoes were preserved for QSM reconstruction. High-resolution anatomical references were acquired using a 3D T1-weighted spoiled gradient-echo sequence (TR = 25 ms, TE = 6.1 ms, flip angle = 30°, FOV = 230 × 183 mm, acquisition matrix = 400 × 400 reconstructed to 512 × 512, 160 slices, slice thickness/spacing = 1.6/0.8 mm, reconstructed voxel size = 0.45 × 0.45 × 0.8 mm³, SENSE factor = 1.6, scan time ≈ 6.7 min).

2.3.2 QSM reconstruction and OEF estimation

Quantitative susceptibility maps were reconstructed from the multi-echo gradient-echo magnitude and phase data using the MEDI toolbox [23] (Cornell MRI Research Lab; <https://pre.weill.cornell.edu/mri/pages/qsm.html>). Voxel-wise oxygen extraction fraction (OEF) was computed by jointly fitting the quantitative BOLD (qBOLD) signal model [24] to the multi-echo magnitude data together with the reconstructed susceptibility map, using the QSM + qBOLD (QQ) "challenge-free"/cluster (QQ-CCTV) framework [17, 25]. The model jointly estimated OEF, deoxygenated (venous) blood volume, non-blood tissue susceptibility, R2, and the initial signal S0; tissue partial-volume (GM/WM/CSF) segmentation from the registered T1w image (FSL FAST) [26] constrained the fit, and R2*-outlier voxels were removed prior to fitting.

2.3.3 ROI quantification.

Susceptibility and OEF maps were co-registered to native T1-weighted space and normalized to the MNI152 (2009c, 1 mm) template utilizing transformation matrices generated by fMRIPrep [27]. Regional mean OEF values were extracted from 16 bilateral subcortical regions defined by Scale I of the Melbourne Subcortical Atlas [28], including the hippocampus (HIP), amygdala (AMY), posterior thalamus (pTHA), anterior thalamus (aTHA), nucleus accumbens (NAc), globus pallidus (GP), putamen (PUT), and caudate (CAU).

2.4 Statistical Analysis

The statistical analysis was conducted using SPSS 26.0 and R 4.5.2 software. All tests were performed in a two-tailed manner, with $P < 0.05$ serving as the criterion for significance. When the continuous variables did not meet the normal distribution, the results were presented as the median (interquartile

range IQR) and non-parametric tests were used. The overall differences among the three groups of samples were determined by the Kruskal-Wallis H test, and pairwise comparisons between groups were further achieved through Dunn's post-hoc test. Multiple comparisons were corrected across all variables and post-hoc links using the Benjamini-Hochberg False Discovery Rate (FDR) procedure. However, to isolate disease-specific pathological effects, the primary analytical focus was placed on the comparison between the PPD and PHC groups. Consequently, only brain regions exhibiting significant differences between the PPD and PHC groups were retained for subsequent correlational and predictive analyses. Between-group comparisons were performed using the independent-samples t test, Mann-Whitney U test, or χ^2 test, as appropriate. Spearman rank correlation was used to assess associations between EPDS scores and neuroimaging/hematological indices. Univariate logistic regression analyses were conducted to identify independent factors associated with disease severity. Missing data were handled using multiple imputation by chained equations (MICE; $m = 5$ imputed datasets); results from each imputed dataset were pooled using Rubin's rules. As an exploratory analysis, we fitted a multivariate logistic regression model on the pooled multiply imputed datasets to examine whether the candidate markers could jointly discriminate sPPD from mPPD. The model included GPrh-OEF, PDW, age, and education. Discrimination was assessed by ROC analysis, with 95% CIs for the AUC obtained by the DeLong method; 1,000 bootstrap resamples were used to obtain the optimism-corrected AUC and calibration slope. Nomogram construction and decision curve analysis (DCA) were performed for visual and clinical utility evaluation.

3. Results

3.1 Characteristics of All Participants

A total of 114 participants were enrolled and categorized into three groups ($n = 38$ each): non-postpartum healthy controls (NPHCs), healthy pregnant controls (PHCs), and patients with postpartum depression (PPD). Baseline characteristics and baseline demographic data are summarized in Table 1. No significant inter-group differences were observed in age ($P > 0.05$), whereas educational attainment varied significantly ($P < 0.05$). For peripheral hematological parameters, significant overall variations were detected among the three cohorts ($P < 0.05$, Table 1). Subsequent FDR-corrected pairwise comparisons between the PPD and PHC groups revealed that the PPD cohort exhibited significant alterations in BMI, white blood cell count, erythrocyte count, hemoglobin, hematocrit, and specific leukocyte differential ratios (neutrophils, lymphocytes, eosinophils, and basophils) relative to healthy parturients ($P < 0.05$).

Table 1
Clinical characteristics of the participants.

Characteristics	NPHCs (n = 38)	PHCs (n = 38)	PPDs (n = 38)	P	PPDs vs PHCs
Age (years)	29.76 ± 3.66	30.05 ± 4.94	29.26 ± 3.76	0.705	0.762
Education (years)	16.00 (16.00, 16.00)	15.00 (15.00, 16.00)	16.00 (15.00, 16.00)	< 0.001	0.071
BMI (kg/m ²)	21.63 (19.89, 23.30)	27.26 (24.54, 30.77)	24.22 (22.04, 25.51)	< 0.001	0.002
WhiteBloodCell (×10 ⁹ /L)	6.67 (5.35, 8.34)	9.28 (7.81, 11.55)	5.48 (5.29, 6.11)	< 0.001	< 0.001
LymphocyteRatio (%)	32.70 (27.10, 37.60)	17.55 (15.18, 23.50)	33.25 (27.35, 39.05)	< 0.001	< 0.001
MonocyteRatio (%)	5.95 ± 1.22	5.29 ± 1.34	5.37 ± 0.86	0.043	0.780
NeutrophilRatio (%)	58.98 ± 8.93	73.69 ± 7.26	59.42 ± 7.96	< 0.001	< 0.001
EosinophilRatio (%)	2.00 (1.30, 3.00)	0.70 (0.43, 1.08)	1.55 (0.93, 3.30)	< 0.001	< 0.001
BasophilRatio (%)	0.20 (0.10, 0.30)	0.20 (0.12, 0.30)	0.50 (0.40, 0.60)	< 0.001	< 0.001
RedBloodCell (×10 ¹² /L)	4.45 (4.25, 4.70)	3.76 (3.55, 4.03)	4.38 (4.15, 4.50)	< 0.001	< 0.001
Hemoglobin (g/L)	136.00 (128.00, 140.00)	117.00 (113.25, 126.00)	130.50 (120.00, 137.00)	< 0.001	0.001
Hematocrit (%)	40.80 (38.50, 41.80)	35.35 (34.20, 38.40)	40.65 (37.92, 42.00)	< 0.001	< 0.001
Platelet (×10 ⁹ /L)	238.00 (210.00, 285.00)	201.00 (181.25, 242.75)	235.00 (177.25, 276.50)	0.032	0.222
PlateletDistributionWidth (fl)	16.10 (15.60, 16.40)	15.60 (15.40, 15.83)	15.80 (15.53, 16.30)	0.005	0.119
Data are displayed as mean ± standard deviation, number of patients (%), or median (interquartile range). NPHCs: non-pregnant healthy controls; PHCs: pregnant healthy controls; PPD: Postpartum depression; BMI: Body Mass Index;					

3.2 OEF Values in Deep Brain Nuclei

Cross-group comparisons of OEF values across 16 deep brain nuclei revealed widespread variations, with most regions reaching statistical significance ($P < 0.05$, Table 2). An example of a 25-year-old

typical postpartum depression (PPD) patient's OEF brain map was overlaid with relevant anatomical regions of interest (ROIs) (Fig. 2). In order to distinguish the specific abnormal signals caused by depression from the physiological changes during postpartum, this study only conducted post hoc paired comparisons after FDR correction between the PPD group and the PHC group. Compared to the PHC group, the right hippocampus (HIPrh), right amygdala (AMYrh), right globus pallidus (GPrh), left hippocampus (HIPlh), and left amygdala (AMYlh) of PPD patients showed significantly increased OEF levels, and all brain regions met $P < 0.05$ (Fig. 3). These five brain regions were thus determined as the research target areas for subsequent downstream analysis.

Table 2
ROI-based difference analysis of OEF values among NPHCs, PHCs and PPD.

Gray Matter Nuclei	OEF value ($\times 10^{-2}$)			<i>p</i>	<i>q</i>	<i>P</i> (post-hoc)		
	NPHCs	PHCs	PPD			NPHCs vs. PHCs	NPHCs vs. PPDs	PHCs vs. PPDs
Hippocampus-rh	29.88 $\pm$ 4.28	33.12 $\pm$ 2.07	37.32 $\pm$ 9.18	< 0.001	< 0.001	0.002	< 0.001	0.032
Amygdala-rh	29.09 $\pm$ 3.95	31.93 $\pm$ 2.74	35.96 $\pm$ 9.99	< 0.001	< 0.001	0.014	< 0.001	0.015
Globus Pallidus-rh	31.49 $\pm$ 3.62	35.41 $\pm$ 2.66	38.6 $\pm$ 6.93	< 0.001	< 0.001	0.005	< 0.001	0.037
Caudate Nucleus-rh	31.36 $\pm$ 4.68	34.85 $\pm$ 4.03	40.07 $\pm$ 10.04	< 0.001	< 0.001	< 0.001	< 0.001	0.155
Anterior Thalamus-rh	30.63 $\pm$ 4.64	34.44 $\pm$ 3.18	39.28 $\pm$ 9.64	< 0.001	< 0.001	< 0.001	< 0.001	0.143
Nucleus Accumbens-rh	30.99 $\pm$ 4.36	34.73 $\pm$ 3.03	38.42 $\pm$ 10.41	< 0.001	< 0.001	< 0.001	< 0.001	0.128
Putamen-rh	31.63 $\pm$ 4.52	36.04 $\pm$ 3.74	39.9 $\pm$ 9.86	< 0.001	< 0.001	< 0.001	< 0.001	0.579
Posterior Thalamus-rh	30.49 $\pm$ 4.5	34.97 $\pm$ 3.56	38.3 $\pm$ 9.11	< 0.001	< 0.001	< 0.001	< 0.001	0.855
Hippocampus-lh	29.5 $\pm$ 4.1	32.37 $\pm$ 2.27	36.63 $\pm$ 9.05	< 0.001	< 0.001	0.018	< 0.001	0.003
Amygdala-lh	29.08 $\pm$ 4.01	32.45 $\pm$ 3.05	36.18 $\pm$ 9.76	0.002	0.002	0.002	< 0.001	0.023
Globus Pallidus-lh	31.52 $\pm$ 3.52	35.43 $\pm$ 2.77	38.05 $\pm$ 7.2	< 0.001	< 0.001	< 0.001	< 0.001	0.69
Caudate Nucleus-lh	30.62 $\pm$ 4.45	33.84 $\pm$ 2.95	39.14 $\pm$ 9.38	< 0.001	< 0.001	0.001	< 0.001	0.077
Anterior Thalamus-lh	30.2 $\pm$ 4.59	33.92 $\pm$ 2.77	38.38 $\pm$ 9.06	0.001	0.001	< 0.001	0.001	0.205
OEF: oxygen extraction fraction; NPHCs: non-pregnant healthy controls; PHCs: pregnant healthy controls; PPD: postpartum depression; ROI: region of interest; rh: right; lh: left. All post-hoc P-values from Dunn's test (following the Kruskal-Wallis H test) were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) procedure.								

Gray Matter Nuclei	OEF value ($\times 10^{-2}$)			<i>p</i>	<i>q</i>	<i>P</i> (post-hoc)		
	NPHCs	PHCs	PPD			NPHCs vs. PHCs	NPHCs vs. PPDs	PHCs vs. PPDs
Nucleus Accumbens-lh	30.76 $\pm$ 4.34	34.42 $\pm$ 3.03	37.87 $\pm$ 11.45	< 0.001	< 0.001	< 0.001	< 0.001	0.215
Putamen-lh	31.61 $\pm$ 4.61	36.06 $\pm$ 3.77	39.99 $\pm$ 10.26	< 0.001	< 0.001	< 0.001	< 0.001	0.832
Posterior Thalamus-lh	30.3 $\pm$ 4.51	34.75 $\pm$ 3.47	38.59 $\pm$ 9.1	< 0.001	< 0.001	< 0.001	< 0.001	0.317
OEF: oxygen extraction fraction; NPHCs: non-pregnant healthy controls; PHCs: pregnant healthy controls; PPD: postpartum depression; ROI: region of interest; rh: right; lh: left. All post-hoc P-values from Dunn's test (following the Kruskal-Wallis H test) were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) procedure.								

3.3 Differences in OEF Between Mild and Moderate-to-Severe PPD

Based on the established cut-off value of 13 points on the EPDS scale, we divided the PPD cohort into the mPPD subgroup ($n = 15$; scores 10–12) and the sPPD subgroup ($n = 23$; scores ≥ 13) (Table 3). After comparing all peripheral blood indicators, we found that only PDW showed a significantly higher level in the sPPD subgroup compared to the mPPD subgroup ($P < 0.01$). We further conducted regional-specific analysis on the core brain regions of the limbic system, namely GPrh, HIPrh, HIPlh, AMYrh, and AMYLh. The results showed that the OEF values in these brain regions of the sPPD subgroup were significantly higher than those of the mPPD subgroup, and all brain regions achieved a statistical difference of $P < 0.05$ (Table 3).

Table 3
Baseline characteristics between mPPD and sPPD groups.

Characteristics	mPPD group (n = 15)	sPPD group (n = 23)	P value
Age (years)	31.00 (28.50, 33.00)	28.00 (27.00, 30.50)	0.119
Education (years)	16.00 (15.00, 16.00)	16.00 (15.00, 16.00)	0.753
Height (cm)	160.00 (159.00, 164.00)	163.00 (160.00, 165.00)	0.282
BMI (kg/m ²)	25.02 ± 3.89	24.01 ± 3.64	0.432
WhiteBloodCell (×10 ⁹ /L)	7.09 (5.75, 8.29)	6.27 (5.20, 8.31)	0.267
LymphocyteRatio (%)	31.17 ± 10.08	33.76 ± 6.17	0.392
MonocyteRatio (%)	6.70 (6.10, 7.30)	5.30 (4.90, 6.25)	0.022
NeutrophilRatio (%)	60.19 ± 11.39	58.09 ± 6.79	0.548
EosinophilRatio (%)	2.50 (1.12, 3.10)	1.70 (1.35, 2.45)	0.636
BasophilRatio (%)	0.15 (0.10, 0.30)	0.20 (0.15, 0.30)	0.264
RedBloodCell (×10 ¹² /L)	4.41 ± 0.33	4.51 ± 0.31	0.373
Hemoglobin (g/L)	131.43 ± 6.81	136.00 ± 7.39	0.076
Hematocrit (%)	39.77 ± 2.09	40.88 ± 2.02	0.136
Platelet (×10 ⁹ /L)	270.00 (235.00, 312.00)	213.00 (199.50, 249.50)	0.007
PlateletDistributionWidth (fl)	15.82 ± 0.41	16.25 ± 0.45	0.005
HIPrh-OEF	0.33 (0.31, 0.36)	0.38 (0.35, 0.42)	0.009
AMYrh-OEF	0.33 (0.30, 0.35)	0.37 (0.32, 0.42)	0.018
GPrh-OEF	0.34 (0.32, 0.37)	0.41 (0.37, 0.44)	0.003
HIPlh-OEF	0.33 (0.31, 0.36)	0.38 (0.35, 0.42)	0.005
AMYlh-OEF	0.33 (0.31, 0.35)	0.38 (0.34, 0.42)	0.009
Data are displayed as mean ± standard deviation, number of patients (%), or median (interquartile range). mPPD: mild postpartum depression; sPPD: moderate-to-severe postpartum depression; BMI: Body Mass Index; OEF: oxygen extraction fraction; HIP: hippocampus; GP: globus pallidus; AMY: amygdala; rh: right; lh: left.			

3.4 Correlation Between OEF Values and Clinical Variables

We employed Spearman rank correlation analysis to conduct a correlation assessment on the clinical symptoms, hematological indicators of all PPD patients, and the five OEF parameters selected through the previous screening (Table 4, Fig. 4). The results showed that the EPDS score was positively

correlated with the OEF values of these brain regions (HIPrh, AMYrh, GPrh, HIPlh, AMYlh), and the P values for all brain regions were less than 0.05. In addition, we also observed a positive correlation between the PDW index and the EPDS score ($P < 0.05$).

Table 4
Spearman correlation analysis between baseline-differentiated features and EPDS scores.

Variables	Spearman's Rho	P value	FDR q value
PlateletDistributionWidth	0.441	0.006	0.023
GPrh-OEF	0.420	0.009	0.023
HIPlh-OEF	0.419	0.009	0.023
AMYlh-OEF	0.404	0.012	0.024
HIPrh-OEF	0.391	0.015	0.024
AMYrh-OEF	0.333	0.041	0.055
Platelet	-0.235	0.156	0.156
MonocyteRatio	-0.256	0.121	0.138
EPDS: Edinburgh Postnatal Depression Scale; FDR: false discovery rate; OEF: oxygen extraction fraction; HIP: hippocampus; GP: globus pallidus; AMY: amygdala; rh: right; lh: left.			

3.5 Analysis of Predictors Related to the Severity of PPD

We further conducted a univariate logistic regression analysis to identify the central nervous system and peripheral blood-related variables that were associated with the severity of postpartum depression (Table 5). At the hematological parameter level, an increase in the proportion of monocytes, elevated platelet count, and increased PDW values were all significantly associated with an increased risk of moderate to severe PPD. All these indicators met the criterion of $P < 0.05$. In the neuroimaging indicators, the OEF values of several brain regions such as GPrh, HIPlh, HIPrh, and AMYLh were also significantly correlated with sPPD ($P < 0.05$). Subsequently, we included these batch of central and peripheral indicators as candidate predictors for the construction of the multivariate model.

Table 5
Univariate logistic regression of baseline-differentiated features for sPPD.

Variables	OR (95% CI)	P value
MonocyteRatio	0.454 (0.199–0.914)	0.026
Platelet	0.488 (0.227–0.951)	0.034
PlateletDistributionWidth	2.628 (1.242–6.554)	0.010
HIPrh-OEF	2.182 (1.033–6.850)	0.040
AMYrh-OEF	2.071 (0.993–6.955)	0.053
GPrh-OEF	2.982 (1.245–9.364)	0.011
HIPlh-OEF	2.785 (1.183–10.879)	0.014
AMYlh-OEF	2.639 (1.121–10.875)	0.021
ORs represent the change per 1-SD increase in each standardized variable. sPPD: moderate-to-severe postpartum depression; OEF: oxygen extraction fraction; HIP: hippocampus; GP: globus pallidus; AMY: amygdala; rh: right; lh: left.		

3.6 Construction and Evaluation of the Clinical-Radiological Combined Model

This study involved only 23 sPPD cases. To avoid model overfitting, we constructed an exploratory multivariate logistic regression model. The model included two core candidate markers, GPrh-OEF and PDW, and adjusted for two baseline confounding factors, age and education level. The apparent AUC of this clinical-imaging combined model reached 0.884, with a 95% confidence interval of 0.771–0.997 (Fig. 5A). We then completed internal validation through 1000 Bootstrap resampling, and after optimistic correction, the AUC was 0.827, with a 95% confidence interval of 0.765–1.000. The optimal Youden index corresponding to the cutoff threshold resulted in a specificity of 0.867, a sensitivity of 0.826, and an optimistic corrected calibration slope of 0.620 (Fig. 5B). Additionally, we also drew a clinical nomogram for individualized risk assessment (Fig. 5C). From the results of the decision curve DCA, it can be seen that compared to relying solely on GPrh-OEF or PDW, this combined model can achieve higher net benefits in all probability threshold intervals (Fig. 5D).

4. Discussion

This study employed the QQ algorithm to analyze the changes in the local OEF of deep brain nuclei in patients with PPD. After correcting for the physiological variations after the PHC cohort was used as the main control group, the results showed that the OEF levels in multiple brain regions such as the bilateral hippocampus, bilateral amygdala, and the right globus pallidus of PPD patients were significantly increased. The increase in OEF in these brain regions was associated with the aggravation of depressive symptoms, and it could effectively distinguish mild from moderate to severe PPD cases. OEF, as a

physiological indicator representing brain oxygen metabolism, is closely related to local brain function. Therefore, the detected increase in OEF suggests that the oxygen utilization pattern of this subcortical specific network changes in the PPD state, resulting in a local imbalance between oxygen supply and demand.

The metabolic changes observed in this cohort mainly concentrated in the limbic system and subcortical structures related to functional integration. Current neuroimaging studies have shown that the pathological physiology of PPD can involve the default mode network, salience network, and cortical-mesolimbic system network. The amygdala is the core abnormal brain region [29]. The exacerbation of perinatal depressive symptoms is associated with longitudinal changes in the right amygdala, and prenatal stress can affect the bilateral hippocampus. The hippocampus-amygdala complex thus becomes a key site for the interaction between perinatal emotional susceptibility and neural plasticity [30]. The postpartum hippocampal morphology is not only related to the mother's nurturing behavior and treatment prognosis [31], but also has an evolutionary pattern different from major depression [32]. Resting-state fMRI has also reported functional abnormalities in the medial / dorsomedial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex, as well as impaired functional connectivity of the posterior cingulate cortex - right amygdala [33, 13]. These network abnormalities can interfere with psychological processes such as self-reference processing, emotion recognition, and assessment of maternal cues. Therefore, the increased OEF of bilateral hippocampus and amygdala found in this study represents an increase in local metabolic demand for neural circuits involved in negative emotion processing, stress memory integration, and maternal cue regulation.

The core clinical finding of this study is that the OEF value of the right globus pallidus is significantly positively correlated with the EPDS score, and it can serve as an independent predictive factor for moderate to severe postpartum depression. The globus pallidus, in addition to participating in the regulation of basal ganglia movement, is also a core structure of the fronto-limbic-striatal-globus pallidus-thalamic reward circuit, mainly involved in the information processing of pleasure stimuli [34]. Existing studies have shown that PPD patients often have abnormal reward circuits centered on the ventral striatum, manifested as weakened circuit connections, declined reward responses, and insufficient striatal responses, etc. [29]. Research on the maternal reward mechanism has also confirmed that the mesolimbic dopamine pathway responsible for regulating emotions, behavioral motivation, and maternal behavior is functionally impaired in PPD patients [35]. It is worth noting that although this study included the nucleus accumbens and dorsal striatum in the region of interest analysis, no significant OEF abnormalities were detected in these two brain regions. Based on this, it can be speculated that the increased OEF of the globus pallidus observed in this study is an embodiment of the overall local metabolic upregulation of the cortico-striatal-globus pallidus circuit, which is also consistent with the recent research results using the functional characteristics of the globus pallidus to identify PPD [36]. Since OEF is an indirect indicator for evaluating cerebral oxygen metabolism and cannot directly reflect neuronal discharge activity, this metabolic abnormality may result from compensatory metabolic upregulation of brain tissue, microvascular oxygen supply-demand imbalance, or disrupted inhibitory signal transmission. This study only completed the quantitative detection of OEF

and did not simultaneously map cerebral blood flow and CMRO₂. Therefore, in the future, it is necessary to combine multimodal perfusion and metabolic imaging techniques to further clarify its specific pathological mechanism.

This study combines radiological features with peripheral biomarkers for analysis, enabling simultaneous capture of the pathological and physiological changes in the central nervous system and the systemic physiological responses of patients with postpartum depression. Previous studies have confirmed that patients with severe depression often show an upward trend in the ratios of neutrophils to lymphocytes, platelets to lymphocytes, and monocytes to lymphocytes [37]. However, no prospective study specifically targeting the postpartum depression cohort has yet demonstrated a direct correlation between these inflammatory ratios and the EPDS depression score [38]. Although classic inflammatory markers such as IL-6, IL-8, CRP, and TNF- α have been proven to be related to perinatal depression symptoms, this correlation shows significant dynamic changes and individual heterogeneity across different postpartum stages and sampling time windows [39]. Unlike conventional inflammatory indicators, platelets, in addition to mediating the body's hemostasis function, are also important peripheral mediators connecting the inflammatory cascade, thrombosis, and emotional regulation. Therefore, parameters related to platelets, such as PDW, can serve as potential peripheral assessment indicators for postpartum depression and its comorbidities [40].

Growing bodies of research have highlighted the synergistic value of integrating neuroimaging signatures with peripheral biomarkers to enhance predictive accuracy and patient-stratification performance [41–43]. Existing PPD risk prediction models can achieve good prediction performance, but such models are mainly based on psychosocial parameters such as sleep disorders, family status, and prenatal stress [44–46], and still lack objective neurobiological markers [10]. To compensate for this deficiency, a hierarchical model of PPD severity was established in this study, including the OEF value and PDW value of the right globulus pallidus. The former reflects the metabolic state of the central reward circuit, and the latter characterizes the activation and inflammation of peripheral platelet. Compared with single indicator, the combined model has better discrimination power, suggesting that central metabolic evaluation and peripheral blood tests can provide complementary diagnostic information, which needs to be further verified in independent cohorts.

There are several limitations of this study, which may affect the extrapolation of the results in terms of sample source, study design, analysis strategy, and evaluation method. Firstly, the sample came from a single maternal and child specialist hospital, which limited the sample size and statistical power. Although the Bootstrap internal validation was used to alleviate overfitting, external validation in a multicenter cohort is still needed. Second, the calibration slope of 0.620 after optimism correction suggested significant overfitting, which was related to an insufficient number of outcome events to match the complexity of the predictor variables. Moreover, the cross-sectional design of this study cannot establish causality, and it is not possible to determine whether the increase in OEF is a predisposing trait, a direct pathological change of PPD, or a downstream compensatory response. At the same time, the region of interest only analyzes the deep brain nuclei and does not include multiple key

cortical brain regions, which lacks a global assessment of the whole brain metabolic topology. In addition, healthy parturients and non-postpartum women were included in the study, but the healthy postpartum group was not further stratified, so it is difficult to accurately distinguish postpartum physiological changes and mood-related metabolic abnormalities. Finally, the severity of the disease was based on the EPDS threshold, no structured clinical diagnosis was used, the subgroup samples of mild, moderate and severe PPD were too small, and the relevant results were only preliminary findings. In conclusion, this study suggests that PPD is a multidimensional disorder with simultaneous abnormalities of cerebral oxygen metabolism and changes in peripheral physiological markers. The results of this study provide quantitative neurobiological evidence, which is expected to provide reference for the objective identification and risk stratification of moderate and severe postpartum depression.

Abbreviations

PPD

Postpartum depression

PHCs

Healthy parturient controls

NPHCs

Non-postpartum healthy women controls

mPPD

Mild postpartum depression

sPPD

Moderate-to-severe postpartum depression

OEF

Oxygen extraction fraction

QSM

Quantitative susceptibility mapping

qBOLD

Quantitative blood oxygen level-dependent

EPDS

Edinburgh Postnatal Depression Scale

ROIs

Regions of interest

MRI

Magnetic resonance imaging

ROC

Receiver operating characteristic

DCA

Decision curve analysis

AUC
Area under the curve
PDW
Platelet distribution width
HIP
Hippocampus
AMY
Amygdala
GP
Globus pallidus

Declarations

CRedit authorship contribution statement

Qingqing Wang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation.
Linfeng Yang: Data curation. Shimin Yang: Data curation. Hao Qi: Formal analysis. Changhu Liang: Data curation. Chaofan Sui: Writing – Data curation. Tao Chen: Formal analysis. Wenying Nie: Writing – review & editing. Lingfei Guo: Project administration. Meng Li: Project administration.

Ethical approval

This study was approved by the Ethics Committee of Jinan Maternity and Child Care Hospital Affiliated to Shandong First Medical University (Approval Number: KY R-25-052). The study was conducted in accordance with the Declaration of Helsinki.

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Declaration of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data that support the findings of this study are available on request from the corresponding author, Meng Li. The data are not publicly available due to privacy or ethical restrictions.

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Figures

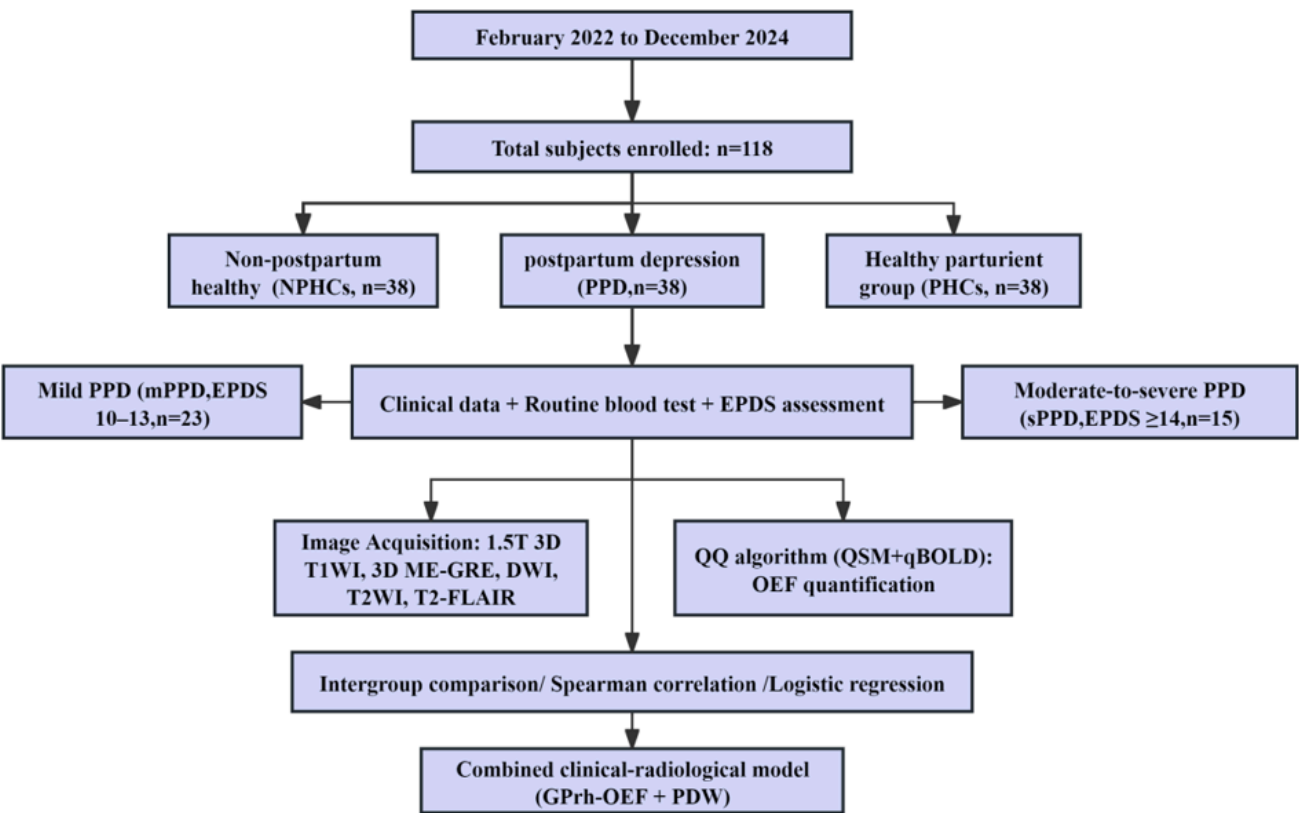


Figure 1

Flow diagram of the study

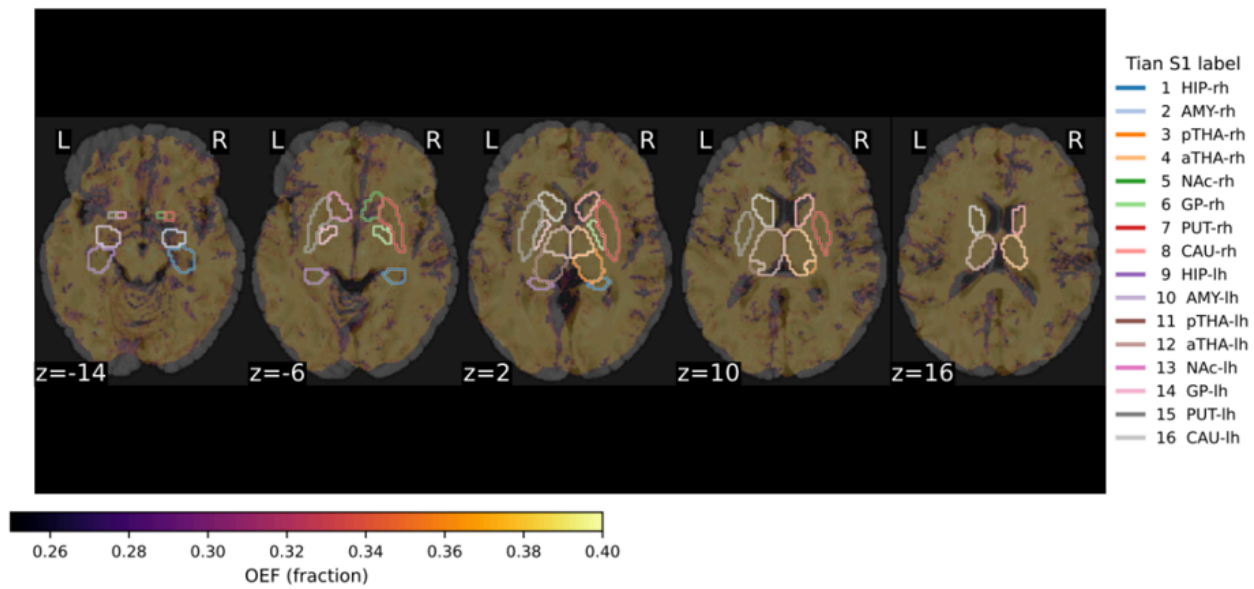


Figure 2

Automatic segmentation atlas of subcortical gray matter based on the Melbourne Subcortical Atlas.

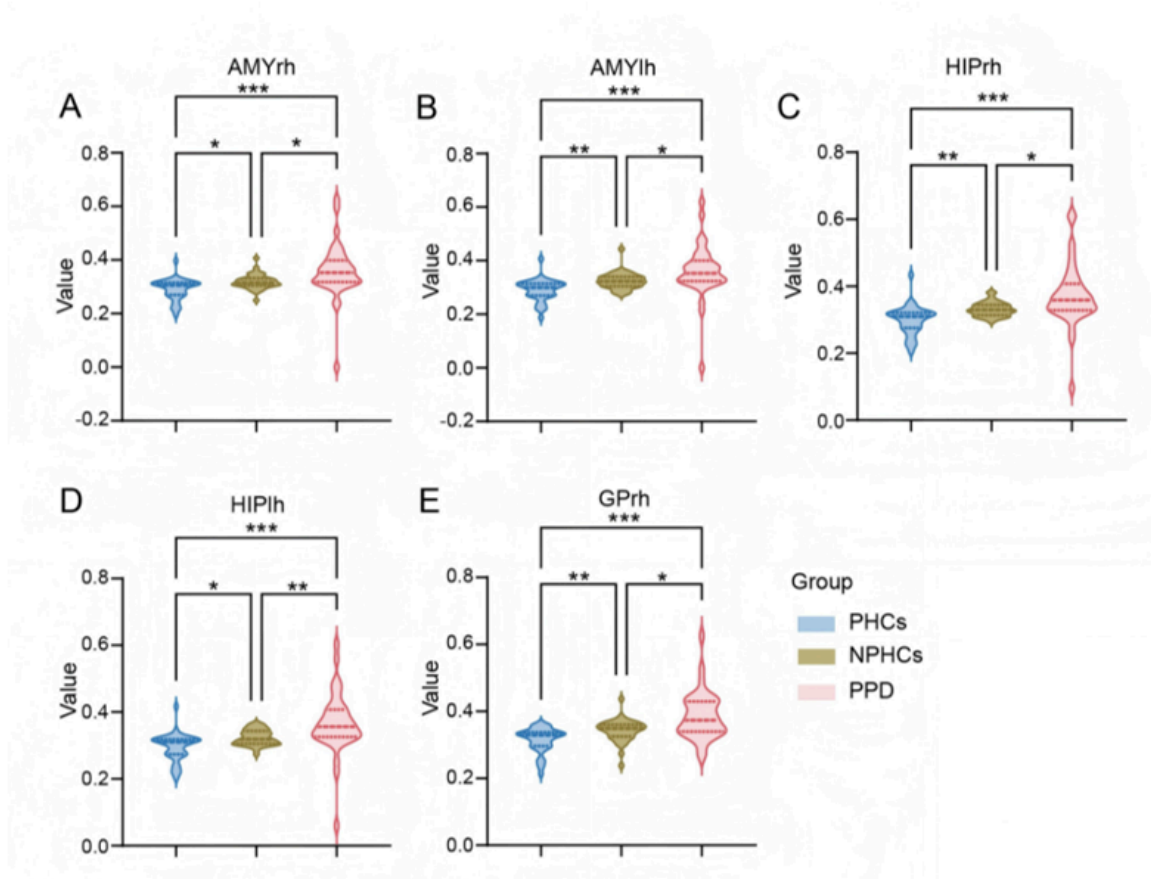


Figure 3

OEF values in subcortical nuclei of three groups. Raincloud plots show OEF values in the right and left amygdala (A, B), right and left hippocampus (C, D), and right globus pallidus (E) among the PPD, PHCs, and NPHCs groups. * $P < 0.05$, ** $P < 0.01$. Abbreviations: OEF, oxygen extraction fraction; PPD, postpartum depression; PHCs, healthy parturient group; NPHCs, non-postpartum healthy women group.

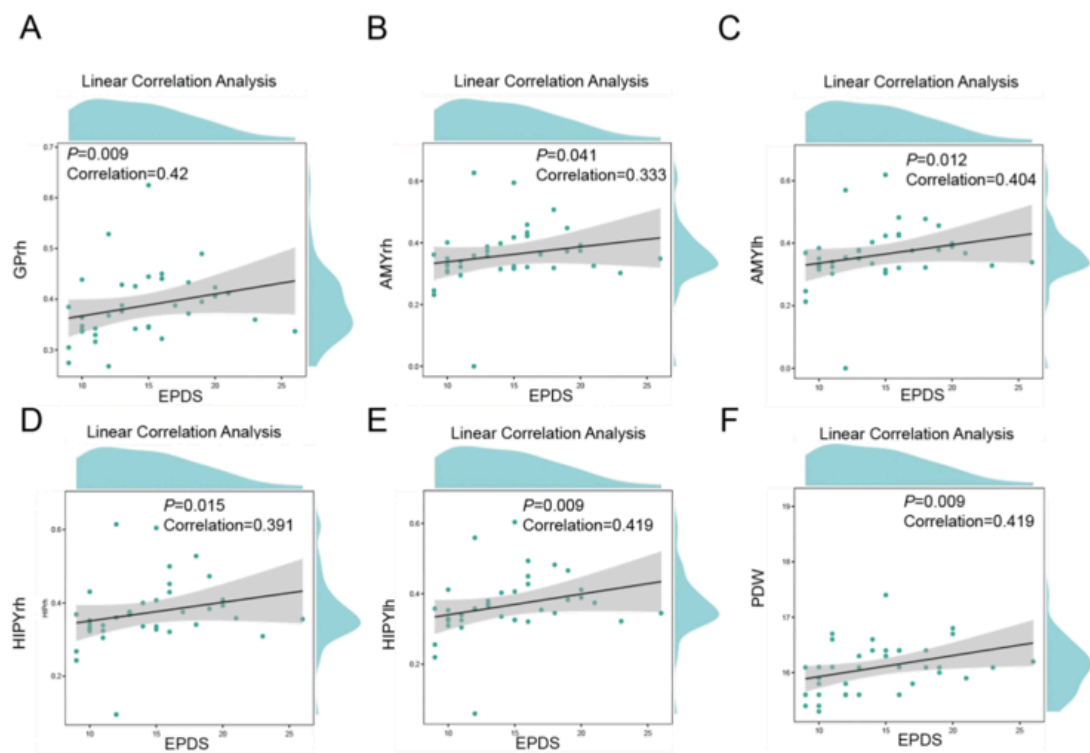


Figure 4

Linear correlations between EPDS scores and OEF/PDW levels. Scatter plots show positive linear correlations between EPDS scores and OEF values in subcortical nuclei (A–E) and PDW levels (F). Correlation coefficients and P-values are indicated in each panel.

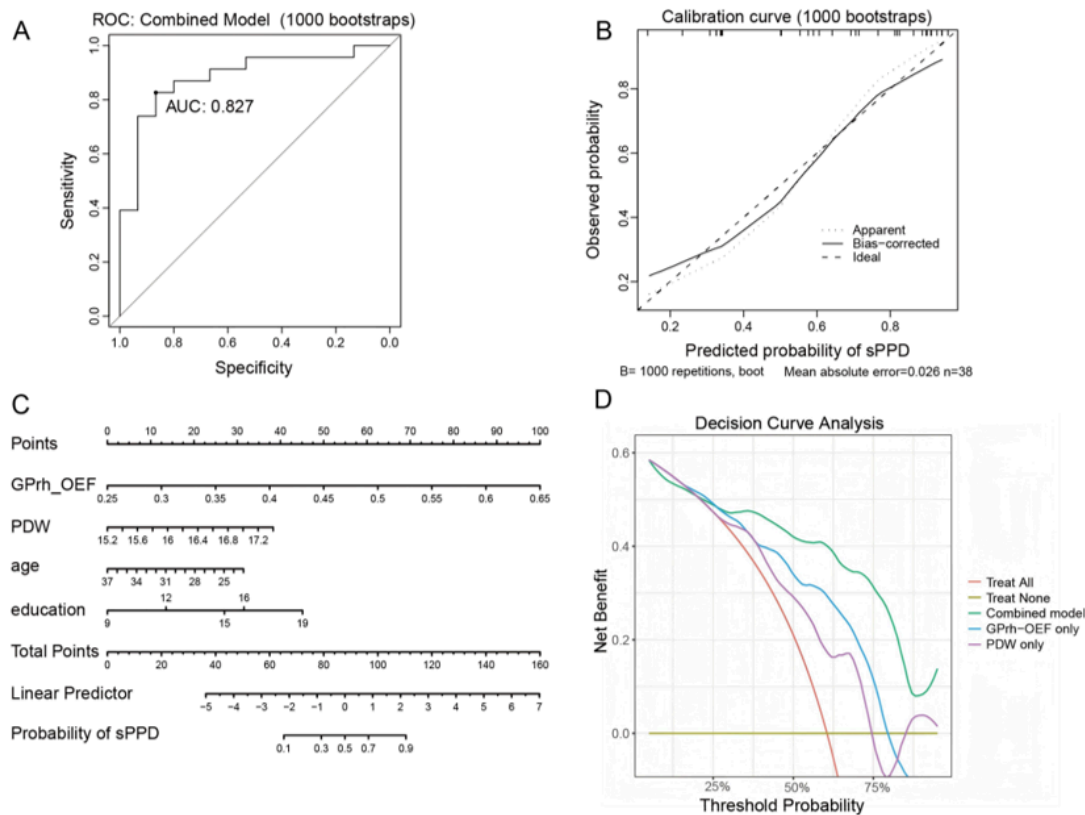


Figure 5

Diagnostic performance, clinical utility, and validation of the sPPD prediction model. (A) Receiver operating characteristic (ROC) curve analysis of the combined multivariate model for discriminating sPPD. The model exhibited an apparent AUC of 0.884 (95% CI: 0.771–0.997 by the DeLong method; optimism-corrected AUC = 0.827, bootstrap 95% CI: 0.765–1.000). At the optimal cutoff determined by the maximum Youden index, the model achieved a specificity of 0.867 and a sensitivity of 0.826. (B) Calibration plot with the optimism-corrected calibration slope (0.620) derived from 1,000 bootstrap resamples, indicating the degree of model overfitting. (C) Nomogram for individualized sPPD risk discrimination using age, education, PDW, and GPrh-OEF. (D) Decision Curve Analysis (DCA) demonstrating the net clinical benefit of the combined model versus GPrh-OEF or PDW alone across a range of threshold probabilities.