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Development and validation of a nomogram for failure to collect oocytes in POSEIDON Groups 3 and 4 undergoing IVF/ICSI treatment

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This study aimed to develop and validate a predictive model for failure to collect oocytes in the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) Groups 3 and 4 during their first in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycle. A retrospective analysis was conducted on patients in POSEIDON Groups 3 and 4 who underwent their first IVF/ICSI cycle at our center from January 2016 to December 2023. A total of 2,373 patients were randomly assigned to the training or validation cohort at a ratio of 6:4. Univariate analysis, the least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression analysis were used to identify the risk factors. It revealed that the anti-Müllerian hormone (AMH) concentration, controlled ovarian stimulation (COS) protocols, the number of follicles ≥ 14 mm on the day of trigger, and the change in estradiol level between the day before trigger and the trigger day (ΔE2) were the independent predictors. A nomogram was constructed accordingly. The areas under the receiver operating characteristic curves (ROC) of the training and the validation cohorts were 0.868 (95% CI: 0.835–0.902) and 0.860 (95% CI: 0.823–0.897), respectively. The calibration curve showed that the predicted risk of the model was in good agreement with the actual results. Decision curve analysis (DCA) demonstrated the clinical value of this nomogram. Our nomogram provides a practical and user-friendly tool for clinical decision-making.

Keywords Failure to collect oocytes, Expected poor ovarian responder, POSEIDON criteria, Nomogram, Prediction model, In vitro fertilization

It has been reported that one in six couples will encounter personal fertility difficulties in their lifetime, and with the increasing popularity and success of fertility treatment, an increasing number of couples are seeking the help of assisted reproductive technology (ART) to produce offspring[1]. It is estimated that more than 9 million babies are born through ART treatment worldwide[2]. The management of patients with poor ovarian response (POR) has always been a challenge for ART therapy. The definitions of POR have varied among studies over the past decades. In 2016, the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) group proposed a novel and comprehensive classification system[3]. According to the POSEIDON criteria, patients were divided into two groups: unexpected poor responders (Groups 1 and 2) and expected poor responders (Groups 3 and 4). Compared with unexpected poor responders and non-POSEIDON patients, expected poor responders (POSEIDON Groups 3 and 4) had fewer oocytes retrieved and worse pregnancy outcomes[4,5]. Patients in POSEIDON Groups 3 and 4 were more likely to have adverse outcomes, such as a lower ovarian response, a higher cycle cancellation rate, a lower live birth rate and a lower cumulative live birth rate[6–8].

Failure to collect oocytes after successful ovarian stimulation is rare[9]. The overall incidence of failure to collect oocytes (including a minimum controlled ovarian stimulation protocol with clomiphene citrate) was

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0.045%-7%[10]. However, the likelihood of failure to collect oocytes even after an adequate pre-retrieval human chorionic gonadotropin (HCG) or agonist trigger is still heightened in patients with POR. A previous study showed that oocyte retrieval failed in 8.6% of patients with only a single follicle[11]. At present, research on patients in POSEIDON Groups 3 and 4 has focused mostly on the refinement of the controlled ovarian stimulation (COS) protocol or medication[12–14]. However, for such patients, all COS protocols and medications are limited by an insufficient number of retrieved oocytes, difficulty in collecting oocytes, and failure to collect oocytes.

Clinical prediction models have been widely used in many disciplines[15,16]. In the field of ART, it has been reported that prediction models can be used to predict the risks of a thin endometrium[17], ovarian hyperstimulation syndrome (OHSS)[18], live birth[8] and fertilization failure[19]. However, less emphasis has been placed on the failure to collect oocytes in POSEIDON Groups 3 and 4. There is still a lack of comprehensive, intuitive and individualized prediction models for the failure to collect oocytes from such patients. Although rare, adverse outcomes may be devastating to the individual, both economically and psychologically. To our knowledge, our study is the first to construct a nomogram model for the failure to collect oocytes in POSEIDON Groups 3 and 4 based on logistic regression analysis. Our model can help clinicians provide better clinical consultation and decisions together with patients. In this manner, the patient's economic burden and psychological pressure caused by failure to collect oocytes will be minimized, and the patient's interests will be maximized.

Results

Demographics and general characteristics

The baseline demographics and general characteristics are summarized in Table 1. Our study included a total of 2,373 patients according to the inclusion and exclusion criteria. Among them, 137 patients were in the no-oocyte-acquired (NOA) group. The overall incidence of NOA was 5.77%. Based on the need to establish and evaluate the prediction model, all patients were randomly divided into a training cohort (n = 1,424) and a validation cohort (n = 949) at a ratio of 6:4. There was no significant difference in the baseline demographics between the two cohorts ($P > 0.05$). The incidence of NOA was 5.69% and 5.90% in the training and validation cohorts, respectively.

Univariate analysis of failure to collect oocytes in POSEIDON Groups 3 and 4

In the training cohort, there were 81 patients in the NOA group and 1,343 patients in the oocyte acquisition (OA) group. There were significant differences in basal follicle-stimulating hormone (bFSH), basal luteinizing hormone (bLH), anti-Müllerian hormone (AMH), antral follicle count (AFC), COS protocol, total dose of gonadotropin (Gn), duaration of stimulation, number of follicles ≥ 14 mm on the day of trigger, change in estradiol (E2) level between the day before trigger and the trigger day (ΔE2), change in LH level between the day before trigger and the trigger day (ΔLH) and change in progesterone (P) level between the day before trigger and the trigger day (ΔP) between the two groups ($P < 0.05$; Table 2). The progestin-primed ovarian stimulation (PPOS) protocol accounted for 29.63% and 6.92% of the patients in the NOA and OA groups, respectively. The proportions of mild stimulation/natural cycle in the NOA and OA groups were 14.81% and 2.53%, respectively (Table 2). In the NOA group, the percentages of patients with 0 pg/ml ≤ E2 < 150 pg/ml and E2 < 0 pg/ml were 64.20% and 16.05%, respectively (Table 2).

Preliminary screening of predictors for failure to collect oocytes in POSEIDON Groups 3 and 4

The least absolute shrinkage and selection operator (LASSO) regression was applied to analyze the 11 factors mentioned above further to minimize potential collinearity and overfitting of variables. The coefficient track diagram is shown in Fig. 1A. Figure 1B shows the cross-validation error curve of the LASSO regression model. By controlling the optimal parameter λ, the cross-validation error of the model is minimized (logλ min). The variables with nonzero coefficients were screened by LASSO regression. The best matching predictors were as follows: bFSH, AMH, AFC, COS protocol (including PPOS, and mild stimulation/natural cycle), duaration of stimulation, ΔE2 (including 0 pg/ml ≤ ΔE2 < 150 pg/ml and ΔE2 < 0 pg/ml) and number of follicles ≥ 14 mm on the day of trigger. The receiver operating characteristic curve (ROC) analysis of the above variables revealed that all the area under the curve (AUC) values were greater than 0.5 (Supplementary Fig. 1).

Multivariate logistic regression analysis of failure to collect oocytes in POSEIDON Groups 3 and 4

The above variables were further substituted into multivariate logistic regression analysis. AMH (OR = 0.28, 95% CI: 0.08–0.99, $P = 0.048$), PPOS protocol (OR = 2.68, 95% CI: 1.15–6.27, $P = 0.023$), mild stimulation/natural cycle (OR = 2.99, 95% CI: 1.02–8.81, $P = 0.047$), ΔE2 < 0 pg/ml (OR = 2.99, 95% CI: 1.28–7.02, $P = 0.012$) and number of follicles ≥ 14 mm on the day of trigger (OR = 0.40, 95% CI: 0.28–0.57, $P < 0.001$) were identified as independent risk factors for failure to collect oocytes in POSEIDON Groups 3 and 4 (Fig. 2). Among these factors, AMH and the number of follicles ≥ 14 mm on the day of trigger were determined to be independent protective factors. Compared with the agonist protocol, the PPOS and mild stimulation/natural cycle were determined to be independent risk factors. A decrease in the serum E2 concentration on the trigger day compared with the previous day was a risk factor.

Construction and validation of a nomogram model for predicting failure to collect oocytes in POSEIDON Groups 3 and 4

According to the multivariate logistic regression findings, the logistic regression equation was as follows: log(Y) = -1.261–1.403 × AMH + 0.980 × (COS protocol = PPOS)/1.040 × (COS protocol = mild stimulation/natural cycle) + 1.039 × (ΔE2 < 0 pg/ml)—0.889 × number of follicles ≥ 14 mm on the day of trigger. A nomogram that integrates all significant independent factors for the failure to collect oocytes in POSEIDON Groups 3 and

Characteristics	Training Cohort ($n = 1,424$)	Validation Cohort ($n = 949$)	*P*
Age (year)	38.00 (33.00, 42.00)	37.00 (33.00, 42.00)	0.344
Infertility type, *n* (%)			0.172
Primary infertility	448 (31.46)	324 (34.14)	
Secondary infertility	976 (68.54)	625 (65.86)	
Infertility duration (year)	3.00 (1.00, 5.00)	3.00 (1.00, 6.00)	0.169
Gravidity	1.00 (0.00, 3.00)	1.00 (0.00, 2.00)	0.092
Parity	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.214
BMI (kg/m^2), *n* (%)			0.341
< 25	1022 (71.77)	698 (73.55)	
≥ 25	402 (28.23)	251 (26.45)	
Basal FSH (mIU/ml)	9.73 (7.24, 13.12)	9.70 (7.32, 13.24)	0.616
Basal LH (mIU/ml)	4.58 (3.37, 6.33)	4.60 (3.39, 6.39)	0.981
Basal E2 (pg/ml)	38.53 (25.29, 54.99)	38.56 (24.84, 54.97)	0.766
Basal P (ng/ml)	0.31 (0.20, 0.47)	0.31 (0.18, 0.48)	0.950
AMH (ng/ml)	0.49 (0.27, 0.74)	0.48 (0.27, 0.77)	0.620
TSH (μIU/ml)	2.20 (1.51, 3.10)	2.21 (1.55, 3.08)	0.410
AFC	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.883
Infertility diagnosis, *n* (%)			0.122
Tubal factor	642 (45.08)	380 (40.04)	
Anovulatory	5 (0.35)	2 (0.21)	
Endometriosis	101 (7.09)	65 (6.85)	
Male factor	95 (6.67)	74 (7.80)	
Unexplained	581 (40.80)	428 (45.10)	
COS protocol, *n* (%)			0.501
Agonist	820 (57.58)	526 (55.43)	
Antagonist	441 (30.97)	322 (33.93)	
PPOS	117 (8.22)	72 (7.59)	
Mild stimulation/natural cycle	46 (3.23)	29 (3.06)	
Total dose of Gn	3600.00 (2700.00, 4200.00)	3350.00 (2700.00, 4200.00)	0.399
Duaration of stimulation	12.00 (9.00, 14.00)	12.00 (9.00, 14.00)	0.229
Fertilization method, *n* (%)			0.305
IVF	1160 (81.46)	757 (79.77)	
ICSI	264 (18.54)	192 (20.23)	
No. of follicles ≥ 14 mm on trigger	3.00 (1.00, 4.00)	3.00 (1.00, 4.00)	0.263
ΔE2 (pg/ml), *n* (%)			0.806
≥ 150	834 (58.57)	566 (59.64)	
< 150 and ≥ 0	495 (34.76)	325 (34.25)	
< 0	95 (6.67)	58 (6.11)	
ΔLH (mIU/ml)	0.02 (-0.38, 0.59)	0.06 (-0.30, 0.79)	0.067
ΔP (ng/ml)	0.09 (0.00, 0.21)	0.09 (0.00, 0.21)	0.828
Group, *n* (%)			
OA	1343 (94.31)	893 (94.10)	
NOA	81 (5.69)	56 (5.90)	

Table 1. Characteristics of the training and validation cohorts. Variables were presented as median (interquartile range), or *n* (%). BMI = body mass index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; E2 = estradiol; P = progesterone; AMH = anti-Müllerian hormone; TSH = thyroid stimulating hormone; AFC = antral follicle count; COS = controlled ovarian stimulation; PPOS = progestin-primed ovarian stimulation; Gn = gonadotropin; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; ΔE2 = change in E2 level between the day before trigger and the trigger day; ΔLH = change in LH level between the day before trigger and the trigger day; ΔP = change in P level between the day before trigger and the trigger day; OA = oocytes acquired; NOA = no oocytes acquired.

Characteristics	OA ($n=1,343$)	NOA ($n=81$)	*P*
Age (year)	38.00 (33.00, 42.00)	39.00 (33.00, 43.00)	0.457
Infertility type, *n* (%)			0.386
Primary infertility	419 (31.20)	29 (35.80)	
Secondary infertility	924 (68.80)	52 (64.20)	
Infertility duration (year)	3.00 (1.00, 5.00)	3.00 (1.00, 5.00)	0.920
Gravidity	1.00 (0.00, 3.00)	1.00 (0.00, 3.00)	0.886
Parity	0.00 (0.00, 1.00)	1.00 (0.00, 1.00)	0.682
BMI (kg/m^2), *n* (%)			0.973
<25	964 (71.78)	58 (71.60)	
≥ 25	379 (28.22)	23 (28.40)	
Basal FSH (mIU/ml)	9.57 (7.09, 12.91)	12.03 (9.91, 19.60)	<0.001
Basal LH (mIU/ml)	4.56 (3.31, 6.27)	5.51 (4.15, 7.83)	<0.001
Basal E2 (pg/ml)	38.83 (25.70, 54.92)	35.14 (20.58, 56.91)	0.425
Basal P (ng/ml)	0.31 (0.20, 0.48)	0.31 (0.19, 0.41)	0.446
AMH (ng/ml)	0.50 (0.29, 0.76)	0.23 (0.10, 0.37)	<0.001
TSH (μIU/ml)	2.20 (1.52, 3.09)	2.14 (1.45, 3.21)	0.982
AFC	3.00 (2.00, 4.00)	2.00 (1.00, 3.00)	0.001
Infertility diagnosis, *n* (%)			0.328
Tubal factor	608 (45.27)	34 (41.98)	
Anovulatory	5 (0.37)	0 (0.00)	
Endometriosis	91 (6.78)	10 (12.35)	
Male factor	88 (6.55)	7 (8.64)	
Unexplained	551 (41.03)	30 (37.04)	
COS protocol, *n* (%)			<0.001
Agonist	805 (59.94)	15 (18.52)	
Antagonist	411 (30.60)	30 (37.04)	
PPOS	93 (6.92)	24 (29.63)	
Mild stimulation/natural cycle	34 (2.53)	12 (14.81)	
Total dose of Gn	3600.00 (2700.00, 4200.00)	2700.00 (1800.00, 3600.00)	<0.001
Duaration of stimulation	12.00 (10.00, 14.00)	10.00 (7.00, 12.00)	<0.001
Fertilization method, *n* (%)			0.996
IVF	1094 (81.46)	66 (81.48)	
ICSI	249 (18.54)	15 (18.52)	
No. of follicles ≥ 14 mm on trigger	3.00 (2.00, 5.00)	1.00 (1.00, 1.00)	<0.001
ΔE2 (pg/ml), *n* (%)			<0.001
≥ 150	818 (60.91)	16 (19.75)	
<150 and ≥ 0	443 (32.99)	52 (64.20)	
<0	82 (6.11)	13 (16.05)	
ΔLH (mIU/ml)	0.01 (-0.39, 0.55)	0.34 (-0.21, 2.40)	0.004
ΔP (ng/ml)	0.09 (0.00, 0.22)	0.04 (-0.04, 0.15)	0.003

Table 2. Univariate analysis of influencing factors of failure to collect oocytes in training cohort. Variables were presented as median (interquartile range), or *n*(%). BMI = body mass index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; E2 = estradiol; P = progesterone; AMH = anti-Müllerian hormone; TSH = thyroid stimulating hormone; AFC = antral follicle count; COS = controlled ovarian stimulation; PPOS = progestin-primed ovarian stimulation; Gn = gonadotropin; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; ΔE2 = change in E2 level between the day before trigger and the trigger day; ΔLH = change in LH level between the day before trigger and the trigger day; ΔP = change in P level between the day before trigger and the trigger day; OA = oocytes acquired; NOA = no oocytes acquired.

4 is shown in Fig. 3. Moreover, the longer the length of the line is, the greater the effect of these factors on the risk of developing failed oocyte retrieval. According to the nomogram, the number of follicles ≥ 14 mm on the day of trigger had the greatest effect on the occurrence of failed oocyte retrieval. The top line of the nomogram corresponded to the score for each factor. Scores for each parameter were pooled, with higher scores indicating a greater risk of developing failed oocyte retrieval.

In the training cohort, the AUC was 0.868 (95% CI: 0.835–0.902), indicating good performance with 75.1% sensitivity and 84.0% specificity. The validation cohort had similar results, with an AUC of 0.860 (95% CI: 0.823–

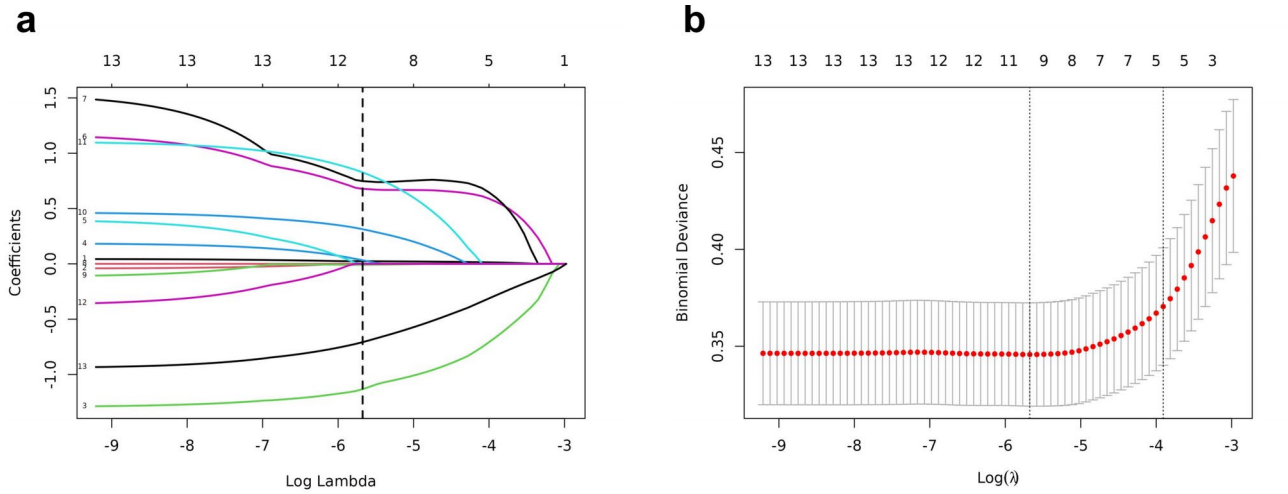

Fig. 1. Best match factor screening by LASSO regression model. (**a**) is the LASSO regression path diagram. Each continuous variable is shown as a coloured line; the classification variables are split to dummy variables, and each dummy variable is shown as a coloured line. The vertical dotted line represents the optimal λ, with which eight variables with non-zero coefficients were screened out. (**b**) is the plot of the best matching factors screened by the tenfold cross validation method, and the best matching factors were selected using lambda.min as the criterion.

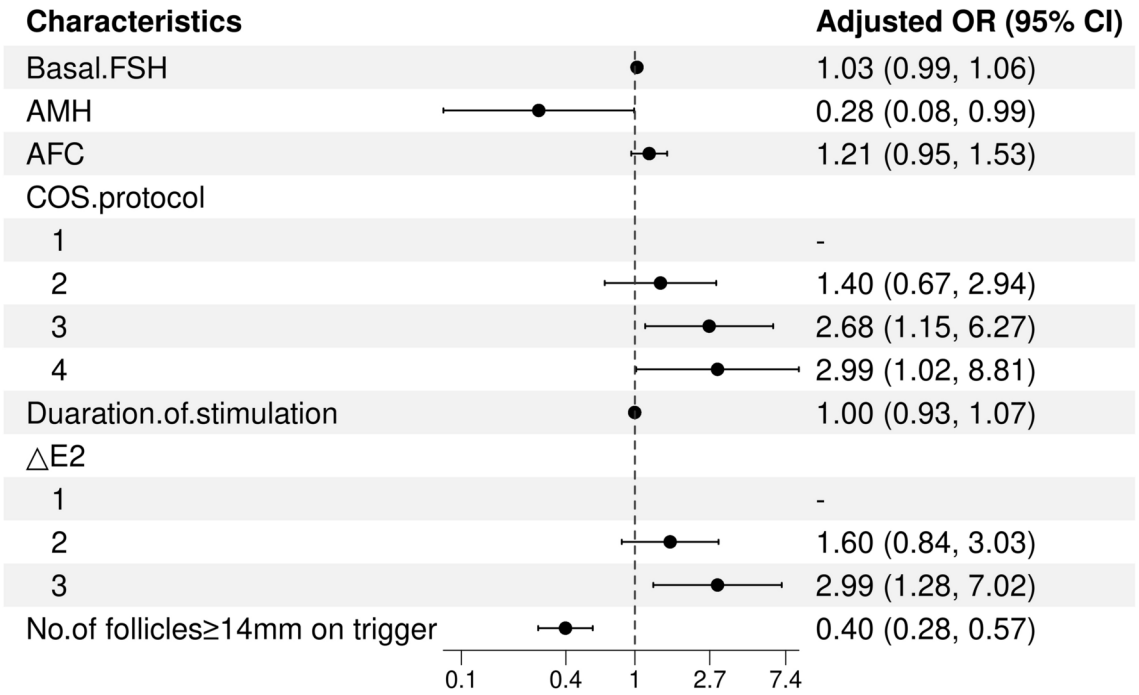

Fig. 2. Forest plots of independent influencing factors for failure to collect oocytes by multivariate analysis. bFSH = basal follicle-stimulating hormone; AMH = anti-Müllerian hormone; COS = controlled ovarian stimulation; ΔE2 = change in E2 level between the day before trigger and the trigger day; COS protocol (1: Agonist; 2: Antagonist; 3: PPOS; 4: Mild stimulation/natural cycle); ΔE2 (1: ≥ 150 pg/ml; 2: < 150 pg/ml and ≥ 0 pg/ml; 3: < 0 pg/ml); OR = odds ratio; CI = confidence interval.

0.897), 72.7% sensitivity, and 89.3% specificity (Fig. 4). The calibration curves in the training and validation cohorts demonstrated good agreement between the predicted and ideal lines. The Hosmer–Lemeshow test revealed no statistically significant difference between the predicted and observed probabilities in either the training cohort ($\chi^2 = 8.886$, $P = 0.352 > 0.05$) or the validation cohort ($\chi^2 = 11.551$, $P = 0.172 > 0.05$), suggesting that the model accurately predicted the probability of failure to collect oocytes in POSEIDON Groups 3 and 4

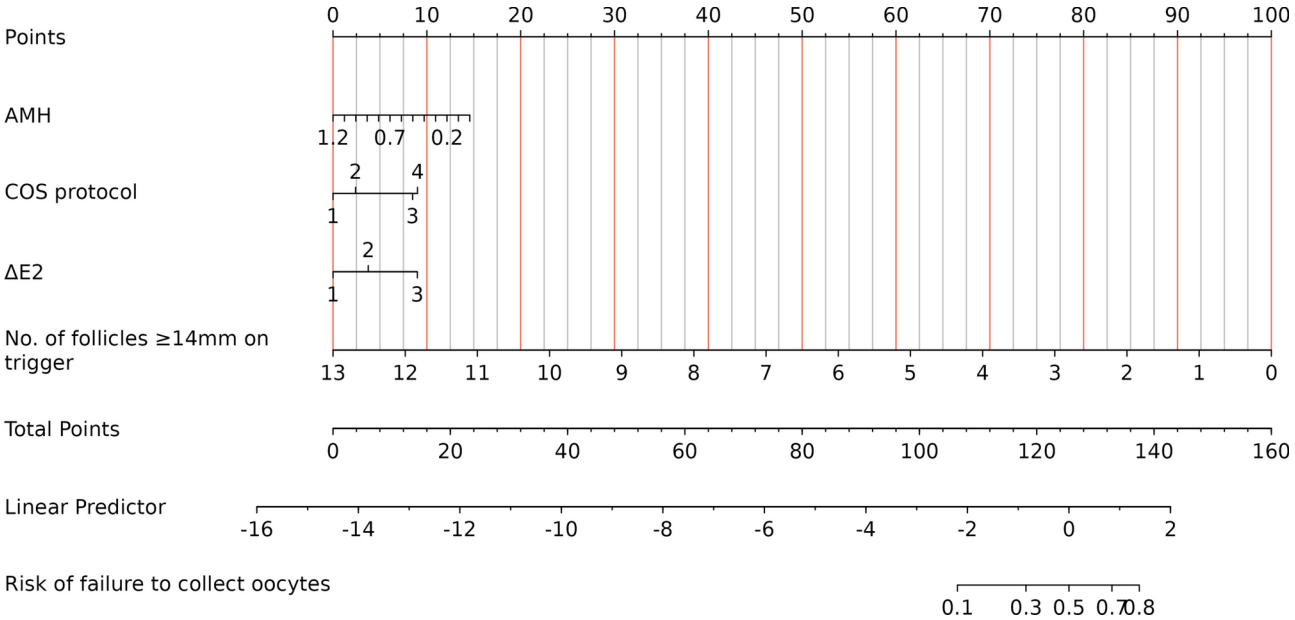

Fig. 3. Nomogram of the prediction model for failure to collect oocytes in POSEIDON Groups 3 and 4. AMH = anti-Müllerian hormone; COS = controlled ovarian stimulation; ΔE2 = change in E2 level between the day before trigger and the trigger day; COS protocol (1: Agonist; 2: Antagonist; 3: PPOS; 4: Mild stimulation/ natural cycle); ΔE2 (1: ≥ 150 pg/ml; 2: < 150 pg/ml and ≥ 0 pg/ml; 3: < 0 pg/ml).

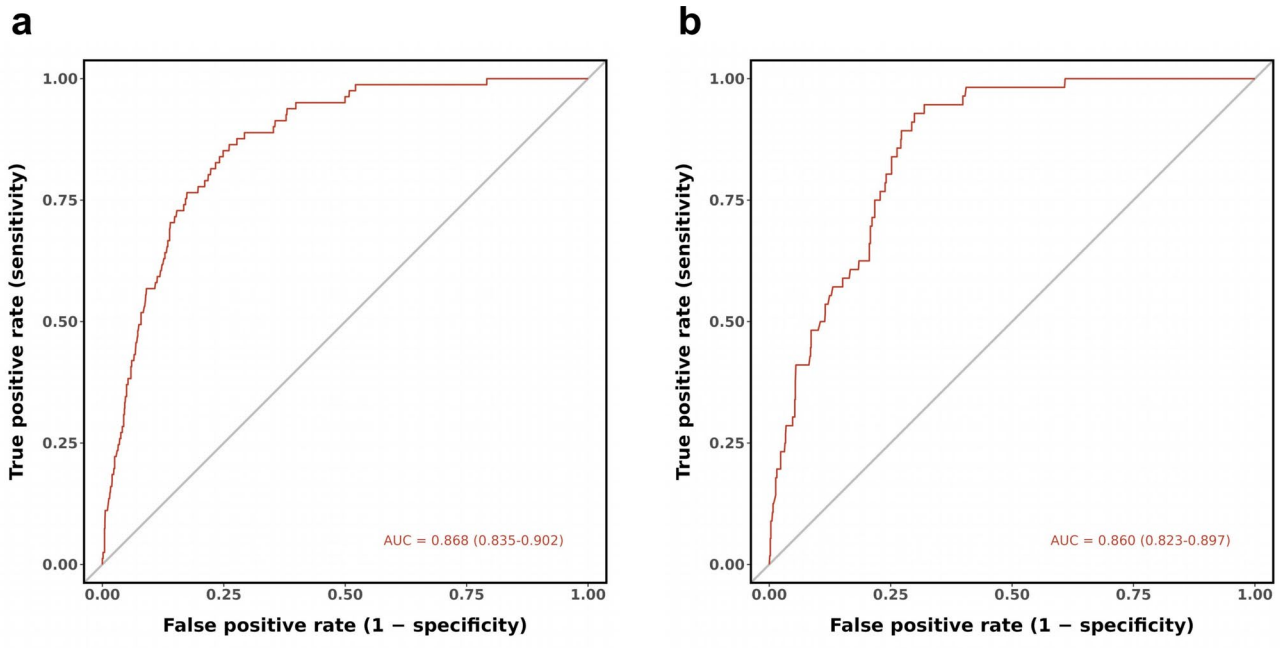

Fig. 4. Discriminative power of the nomogram for failure to collect oocytes in POSEIDON Groups 3 and 4. **(a)** shows the receiver operating curve of the training cohort. The area under the curve was 0.868 (95% CI 0.835–0.902). **(b)** shows the receiver operating curve of the validation cohort. The area under the curve was 0.860 (95% CI 0.823–0.897).

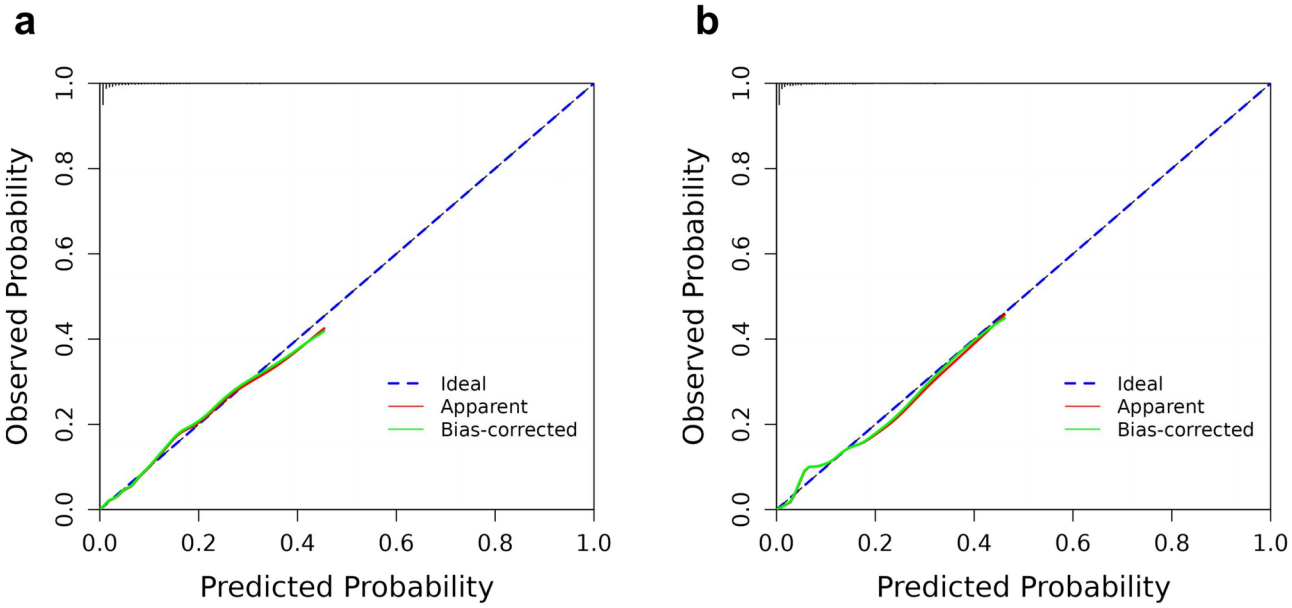

Fig. 5. Calibration curve of the nomogram for failure to collect oocytes in POSEIDON Groups 3 and 4. (**a**) and (**b**) are calibration curves of the training cohort and the validation cohort, respectively.

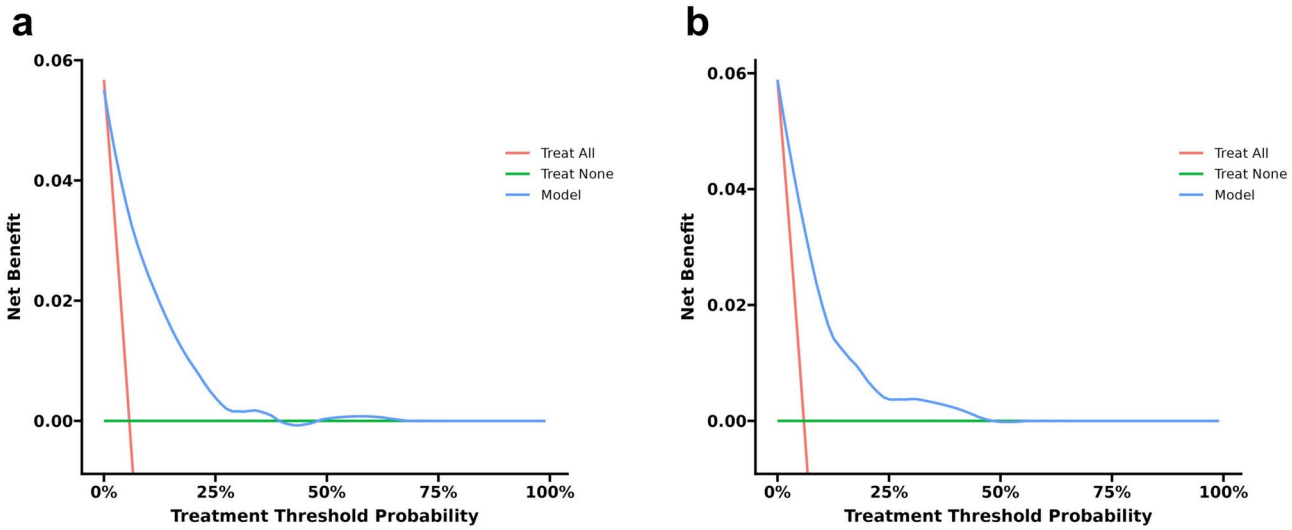

Fig. 6. Decision curve analysis of the nomogram for failure to collect oocytes in POSEIDON Groups 3 and 4. (**a**) and (**b**) are decision curves of the training cohort and the validation cohort, respectively.

(Fig. 5). Decision curve analysis (DCA) was used to analyze the clinical efficacy of the model. The DCA of the training and validation cohorts proved the potential clinical value of the model (Fig. 6).

Discussion

Our team is the first to successfully construct a quantifiable and comprehensive nomogram for the failure to collect oocytes in POSEIDON Groups 3 and 4 based on multivariate logistic regression. After internal validation, it was suggested that the model has good discrimination ability and good calibration. Using this prediction model, clinicians can identify risk groups with lower AMH levels as early as possible according to their baseline characteristics before patients start COS treatment. After entering COS treatment, clinicians can also identify the high-risk population for which oocytes cannot be retrieved according to the COS protocol, the number of follicles ≥ 14 mm on the day of trigger and the ΔE2. This model can provide patients with a visual consulting tool for determining oocyte retrieval prognosis and guide clinical decision-making.

Although the incidence of failure to collect oocytes in the whole population who received ART treatment was less than 1%[9]. However, in fact, failure to collect oocytes is more likely to occur in expected poor responders

classified by the POSEIDON criteria. Moreover, failure to collect oocytes results in the cancellation of treatment, which can cause economic losses and mental stress to patients. Although no specific factors were directly related to the inability to retrieve oocytes in Driscoll et al.'s study, poor ovarian reserve preceded 80% of these occurrences[9]. Poor ovarian reserve is associated with abnormalities in folliculogenesis, ovulation and oocyte structure and performance[20]. Previous studies have confirmed that in women with a diminished ovarian reserve (DOR), the steroidogenic potential of ovarian granulosa cells decreases, proliferation decreases and apoptosis increases[21,22]. The adverse influence of increasing basal FSH on cumulative granulosa cell viability was independent of patient age[23]. In this study, we found that the incidence of failure to collect oocytes in POSEIDON Groups 3 and 4 was 5.77%, which was much greater than that in the general population. This finding is consistent with previous research[11].

To date, the most sensitive markers of ovarian reserve have been identified as AMH and AFC[24,25]. AMH is a predictor of ovarian response in the in vitro fertilization (IVF) cycle[26]. In a mouse model with low AMH, primordial follicles are recruited at a faster rate, which leads to the depletion of the primordial follicular pool in younger mice[27]. Wang et al. reported that even if the number of mature follicles on the day of HCG trigger was similar, patients with DOR were more likely to have difficulty obtaining oocytes than patients with a normal ovarian reserve[28]. Similar to the above study, we found that AMH is an independent predictor of failure to collect oocytes in POSEIDON Groups 3 and 4. With a lower AMH and fewer dominant follicles on the day of trigger, the possibility of failure to collect oocytes is greater. This may be related to the deficit of maturity and/or healthiness of oocytes, cumulus cells, and mural granulosa cells[29]. Leung et al. also reported that cumulus–oocyte complexes in patients with POR exhibit reduced luteinizing hormone receptor responsiveness and that compared with those in normal responders, oocytes may not be released from the follicle wall as easily[30].

COS plays a critical role in the success of in vitro fertilization-embryo transfer (IVF-ET). It enables the recruitment of enough healthy fertilizable oocytes and, thereby, high-quality embryos to improve the cumulative live birth rate[31]. Although the COS protocol has made great progress, the modified protocol does not show overwhelming advantages for patients with POR[32]. Thus, the management of patients with POR is still challenging. There is controversy in previous studies on the effects of antagonist and agonist protocols on the outcome of oocyte retrieval. Most studies suggest that it is less difficult to collect oocytes via an agonist protocol[28]. In the antagonist protocol, the incidence of failure to collect oocytes is greater[33]. Some studies also consider that there is no difference in the cycle cancellation rate between the two protocols[34]. This may be related to the fact that the pituitary is not down-regulated in the antagonist protocol group; thus, the endogenous LH level in the antagonist protocol group was greater than that in the agonist protocol group, which is much closer to the physiological environment of follicular development. The PPOS protocol has been widely used in IVF/intracytoplasmic sperm injection (ICSI) treatment for POR in recent years because it can effectively inhibit spontaneous ovulation[35] and increase the percentage of high-quality embryos[36–38]. Turkgeldi et al. confirmed that the flexible PPOS protocol was as effective as the flexible GnRH antagonist protocol in preventing premature ovulation and oocyte yield in DOR women[39]. In our study, we found that the PPOS protocol and mild stimulation/natural cycle have a greater risk of oocyte collection failure than does the antagonist protocol. In recent years, several researchers have proposed the STOP-START protocol and Stop GnRH-agonist/GnRH-antagonist protocol, which may become effective, feasible and time-saving management options for patients in POSEIDON Groups 3 and 4[40,41]. This still requires a large-scale randomized controlled trial (RCT) for further verification.

Choosing the appropriate time to administer HCG to trigger ovulation is necessary for successful oocyte retrieval. Oocyte maturity parallels both progressive antral cavity enlargement and the production of E2 by granulosa cells. Generally, the E2 level on the day of trigger during COS treatment is regarded as the peak concentration of E2. A continuous increase in E2 before the trigger indicates a good IVF outcome[42]. Our results showed that in POSEIDON Groups 3 and 4, the decrease ($\Delta E2 < 0$ pg/ml) in E2 on the trigger day compared with that of the previous day, which was a risk factor for the failure to collect oocytes. This finding is consistent with those of previous studies. Decreasing E2 levels on the day of trigger or the day after trigger are predictive of more atretic oocytes and a greater polyspermic fertilization rate[43]. Previous studies have confirmed that a spontaneous reduction in E2 leads to a decrease in the number of retrieved oocytes[44,45]. This may be due to a decrease in the absolute number of granulosa cells or a decrease in aromatase activity in follicles, resulting in a reduction in E2 production. Before HCG administration, a plateau or decrease in E2 may indicate that the proliferation of granulosa cells is stagnant or that apoptosis is increased, thus negatively affecting oocyte retrieval.

Most of the previous studies on the failure to collect oocytes were observational studies or correlation analyses. Moreover, none of them restricted the study population[33,46]. Our study focused on expected low responders who are more prone to adverse pregnancy outcomes. In addition to this, we excluded all patients with premature ovulation of dominant follicles before oocyte pick-up (OPU), as they may have a different pathogenesis, which made our conclusions more rigorous. The clinical baseline characteristics and COS-related indicators of the patients were comprehensively considered. Through multivariate logistic regression, we constructed a nomogram based on 4 independent factors: AMH, the COS protocol, $\Delta E2$ and the number of follicles ≥ 14 mm on the day of trigger. In addition, the prediction result is more accurate. The AUCs of this model were greater than 0.8 in both the training cohort and validation cohort, indicating a high discriminative ability and good predictive accuracy and specificity. Our study is a real-world retrospective study based on clinical cases with a large sample size, which provides a more comprehensive reference for the formulation of clinical guidelines and medical decisions.

Our study has several limitations that should be acknowledged. First, the retrospective nature of the study may introduce some selection bias. Second, the exact diameter of follicles on the day of trigger and the time interval from trigger to OPU were not included in our study, which may also affect the results of oocyte retrieval. Finally, our model currently lacks effective external validation. Further research needs to include more possible influencing factors, and external validation should be performed with data from multiple regions and medical centers.

In conclusion, we found that AMH, the COS protocols, ΔE2 and the number of follicles ≥ 14 mm on the day of trigger were 4 independent factors for predicting failure to collect oocytes in POSEIDON Groups 3 and 4. Compared with traditional logistic regression models, nomograms are simpler, more intuitive, and more practical. However, it has greater value in clinical application. To improve the stability and universality of the model, prospective research and external validation are needed in the future.

Methods

Study population

This was a retrospective case–control study of patients receiving assisted reproduction treatments. We included female patients who underwent their first IVF/ICSI cycle at the Reproductive Center of the 1st Affiliated Hospital of Zhengzhou University from January 2016 to December 2023. All patients met the following criteria for POSEIDON Groups 3 or 4: AFC < 5 and AMH < 1.2 ng/ml. The exclusion criteria were: (i) incomplete COS cycles for personal reasons; (ii) incomplete clinical data and (iii) patients with premature ovulation of all dominant follicles before OPU after the HCG trigger. Patients whose oocytes could not be retrieved were defined as NOA, which included patients with no oocytes retrieved. Patients with > 0 oocytes were defined as the OA group. The flowchart of patient screening is shown in Fig. 7. This study was approved by the Ethics Committee of the 1st Affiliated Hospital of Zhengzhou University (Approval number: 2024-KY-0386–001). Written informed consent was obtained from all patients before IVF treatment. The research methods were carried out in accordance with relevant guidelines and regulations.

Data collection

Clinical data were collected from the Clinical Reproductive Medicine Management System/Electronic Medical Record Cohort Database (CCRM/EMRCD) of the Reproductive Medicine Center of the 1st Affiliated Hospital of Zhengzhou University. The clinical indicators included age, body mass index (BMI), type of infertility, infertility diagnosis, duration of infertility, gravidity, parity, AMH, bFSH, bLH, basal estradiol (bE2), basal progesterone (bP), thyroid stimulating hormone (TSH), AFC, COS protocol, total dose of Gn, duration of stimulation, fertilization method, hormone levels (LH, E2, P) one day before HCG trigger and on the day of trigger, number of follicles ≥ 14 mm on the day of trigger, and number of oocytes retrieved.

Controlled ovarian stimulation protocols

COS protocols include GnRH agonist (GnRH-a) protocols, the GnRH antagonist (GnRH-ant) protocol, the PPOS protocol, mild stimulation and the natural cycle.

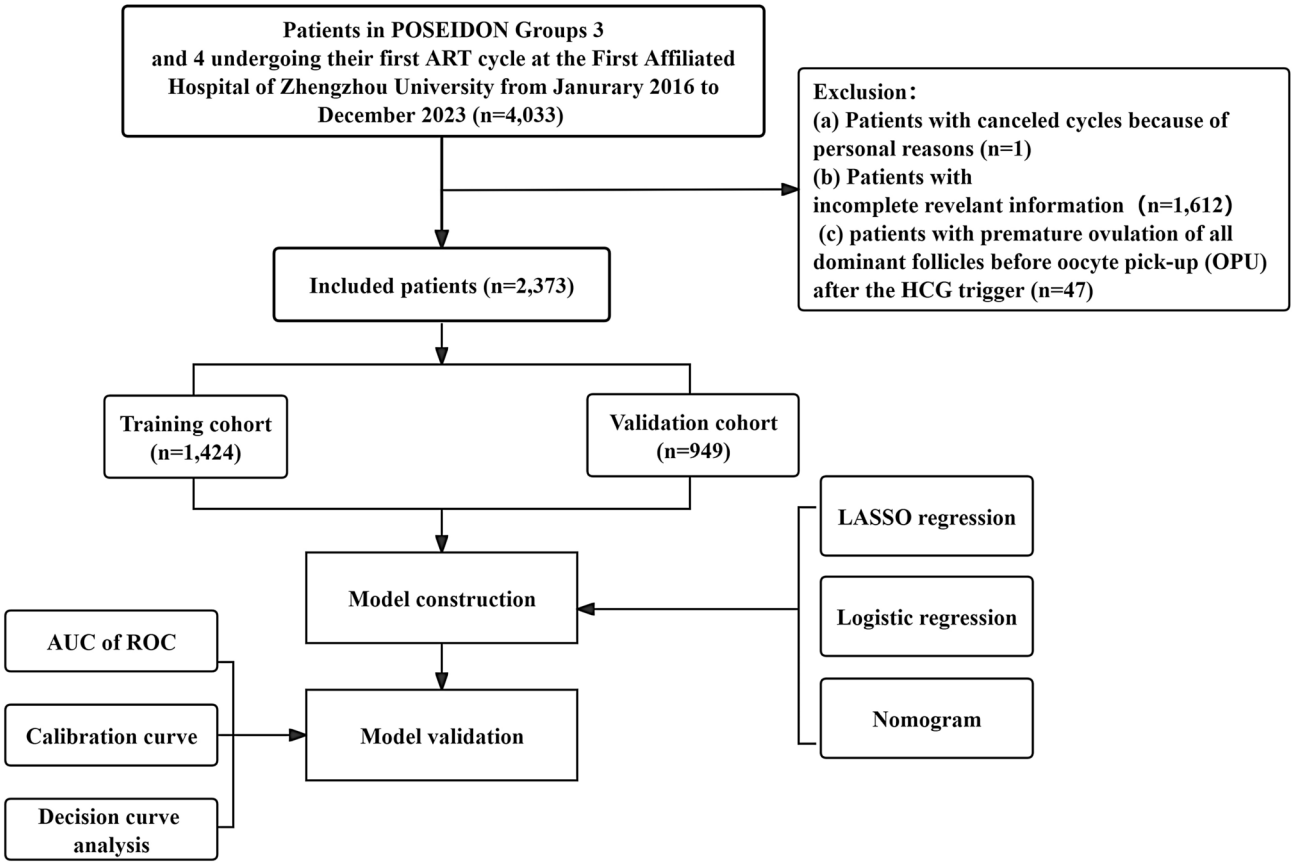

Fig. 7. Flowchart of patient screening.

(1) GnRH agonist protocols: Agonist protocols included the early-follicular phase long-acting GnRH-a long (EFLL) protocol and the luteal phase short-acting GnRH-a (LPS) protocol. The EFLL protocol and LPS protocol were performed according to our previous research from our team[47].

In EFLL protocol, patients underwent transvaginal ultrasound and serum sex hormone assessment on the 2^{nd}-3^{rd} day of their menstrual cycles. If no substantial follicular growth, cysts, or abnormalities in hormone levels were observed, long-acting GnRH-a (Diphereline, Ipsen) was administered at a dose of 3.75 mg for down-regulation. After 28 days, patients returned to the hospital for repeat transvaginal ultrasound and serum hormone evaluation. Ovarian stimulation was started by recombinant FSH (Gonal F, Merck Serono) when the pituitary down-regulation criteria were met (no functional cysts in the ovaries, follicle diameter 3–5 mm, E2 < 30 pg/ml, FSH < 5 mIU/ml, LH < 5 mIU/ml, endometrial thickness < 5 mm). The exogenous Gn dose was adjusted as needed, based on patient age, baseline AMH, and BMI, to facilitate follicular growth. When the dominant follicle reached a size of ≥ 20 mm, with another follicle ≥ 18 mm or more than 2/3 of the follicles had a size of ≥ 16 mm, HCG (Zhuhai Lizhu Group, Lizhu Pharmaceutical Factory) was administered to trigger ovulation. Oocyte retrieval was then scheduled 37 h after HCG trigger.

In LPS protocol, patients underwent transvaginal ultrasound and serum progesterone tests on the 19^{th}-21^{st} day of their menstrual cycles. If the serum progesterone level > 3 ng/ml, short-acting GnRH-a (Decapeptyl, Ferring Pharmaceuticals) was administered for 14 days for down-regulation. Ovarian stimulation was started by recombinant FSH (Gonal F, Merck Serono) when the pituitary down-regulation criteria were met (FSH < 5 mIU/ml, LH < 5 mIU/ml, E2 < 30 pg/ml, follicle diameter 4–7 mm, and endometrial thickness < 5 mm). Regular transvaginal ultrasound and serum hormone assessments were performed to adjust the Gn dose. The remaining procedure was performed as in the EFLL protocol.

(2) GnRH antagonist protocol: Ovarian stimulation was started by administering exogenous Gn on the 2^{nd}-4^{th} day of menstruation. Based on the personal experience of physicians, a fixed or flexible GnRH-ant protocol was performed using 0.25 mg daily of GnRH-ant (Cetrotide, Merck Serono) from Day 6 of stimulation or as soon as the diameter of the leading follicle reached 12–14 mm. When two dominant follicles reached a diameter of ≥ 18 mm or three follicles reached a diameter of ≥ 17 mm, HCG (Zhuhai Lizhu Group, Lizhu Pharmaceutical Factory) was administered to trigger ovulation. Oocytes were retrieved 36 h after HCG injection.

(3) PPOS: From the 2^{nd}-4^{th} day of menstruation, patients were orally administered 10 mg/d medroxyprogesterone acetate (Zhejiang Xianju Pharmaceutical Co., Ltd.) and 225–300 IU/d HMG (Zhuhai Lizhu Group, Lizhu Pharmaceutical Factory) until the trigger day. When at least one dominant follicle reached a diameter of ≥ 18 mm or two follicles reached a diameter of ≥ 17 mm, 0.1 mg of the trigger medicine triptorelin (Decapeptyl, Ferring Pharmaceuticals) and 1,000 IU of HCG (Zhuhai Lizhu Group, Lizhu Pharmaceutical Factory) were administered. Oocytes were retrieved 34–36 h after the trigger.

(4) Mild stimulation: From the 2^{nd}-4^{th} day of menstruation, patients were orally administered 2.5–5 mg/d letrozole (Jiangsu Hengrui Pharmaceutical Co., Ltd.) and injected with 150–225 IU/d HMG (Zhuhai Lizhu Group, Lizhu Pharmaceutical Factory). When the dominant follicle reached a diameter of > 15 mm, daily follicle tracking and serum hormone assessment were performed. 10,000 IU HCG (Zhuhai Lizhu Group, Lizhu Pharmaceutical Factory) was administered when appropriate. Oocytes were retrieved 33 h after triggering.

(5) Natural cycle: From the 6^{th}-8^{th} day of menstruation, patients returned periodically for cycle monitoring with an assessment of serum hormones and transvaginal sonography to monitor follicular growth. 10,000 IU HCG (Zhuhai Lizhu Group, Lizhu Pharmaceutical Factory) was administered when appropriate. Oocytes were retrieved 33 h after triggering. The oocytes were retrieved the day after the LH peak appeared on the trigger day.

Sex hormone assessment

A validated electrochemiluminescence immunoassay (Cobas 12,145,383) was used to detect the hormone. The detection limit and sensitivity of the method were 0.03 ng/ml and 0.15 ng/ml, respectively. The intra-assay and interassay coefficients of variation were 3.0 and 5.5%, respectively. The same detection method was utilized throughout the study, and the data were calibrated regularly to reduce unnecessary errors.

Oocyte collection

The cumulus-oocyte complexes (COCs) were collected by vaginal aspiration after the ovulatory trigger with a 30 cm, 16- or 17- gauge oocyte aspiration needle. Before OPU, transvaginal ultrasonography was performed. Oocyte retrieval was performed under transvaginal ultrasound guidance, with a suction pressure of 120–140 mmHg. A 2–3 ml flush with culture medium (G-MOPS, Vitrolife Sweden AB Göteborg) was used each time if no oocyte was retrieved via direct aspiration. If no oocyte was retrieved at the first flush, further flushes were performed up to a maximum of 6 flushes before moving to the next follicle[28]. Oocytes were picked up under a microscope by two experienced embryologists. The total number of oocytes retrieved was recorded.

Statistical analysis

The classified data are expressed as the frequency and percentage (%), and the median (interquartile distance) was used for continuous data that did not conform to a normal distribution. Overall, patients were randomly divided into a training cohort and a validation cohort at a ratio of 6:4. In the training cohort, the Mann–Whitney U test or χ^2 test was used for univariate analysis. Covariates with $P < 0.05$ were included in the LASSO regression. The covariates with nonzero regression coefficients were screened for further analysis via multivariate logistic regression. A nomogram was constructed based on the independent influencing factors with $P < 0.05$ in the multivariate logistic regression. The ROC curve was drawn, and the AUC was calculated to test the discrimination of the nomogram in the training and validation cohorts. Calibration curves were used to assess the consistency of the actual and predicted results. To evaluate the net benefit threshold of the prediction, DCA was conducted.

All the statistical analyses were performed with R (version 4.3.2) and MSTATA software. $P < 0.05$ was considered to indicate statistical significance in general situations.

Data availability

The data utilized and analyzed in the current study is accessible from the corresponding author upon reasonable request.

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Author contributions

TY was responsible for study design, data collection, data analysis, and manuscript drafting, revision and submission. WF and LD contributed to figures and manuscript revision and submission. ZB and JL contributed to data collection and statistical analysis. HK contributed to study design, manuscript revision and funding acquisition.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

This study involving human participants was reviewed and approved by the Ethics Committee of the 1st Affiliated Hospital of Zhengzhou University (Approval number: 2024-KY-0386–001). The procedures used in this study followed the principles of the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

Additional information

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