A Nomogram To Predict The Cumulative Live Birth Rate for Patients with Low Prognosis According To The POSEIDON Criteria: A Retrospective Observational Cohort Study of 4,395 Patients in Chinese Population

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Research Article

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Abstract

Purpose

A small number of risk prediction model have been previously reported to predict the infertility treatment success. While the studies of the risk prediction model for the patients with low prognosis are limited. This study aimed to construct and validate a nomogram for the prediction of cumulative live birth rate (CLBR) in patients with low prognosis from a single center database in Chinese population.

Methods

Clinical data of 4,395 patients with low prognosis, who received in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) therapy between 2014 and 2018, were retrieved and randomly divided into training (70%) and the external validation (30%) sets. Multivariate analysis with logistic regression model was conducted.

Results

Multivariate analyses showed that maternal age, body mass index (BMI), basal serum follicle-stimulating hormone (FSH) level, type of infertility, male factors, uterine factors, and usable embryos number at day 3 were risk factors for CLBR in patients with low prognosis. The area under the receiver operating characteristic curve (AUC) of the prediction model was 0.769 (95% confident interval (CI): 0.751, 0.787) in training set. The validation set presented good performance with an AUC of 0.749 (95% CI: 0.720, 0.778). In addition, Hosmer-Lemeshow chi-square value was 10.194 (P = 0.252).

Conclusion

We constructed and validated a nomogram for the prediction of CLBR in low prognosis patients with a single center database in Chinese population. The validated nomogram for the prediction of CLBR could be potentially applied in clinic for IVF counselling in patients with low prognosis.

Background

Although the assisted reproductive technology (ART) has been widely applied in clinical practice, and also the overall live birth rate has been greatly improved due to the improvement of technical methods during the recent decades[1], it is still a hard work for managing the poor ovarian response (POR) patients[2]. To distinguish these POR patients were not easy. Bologna criteria were most common accepted to stratify the POR patients[2], but there were still some limitations in clinical usage as the Bologna criteria were designed for clinical trials other than daily practice[3]. Clinicians had found it far from satisfactory on providing information for decision making. On the other hand, the application of Bologna criteria in clinical studies was not going smoothly either[4].

In 2016, the POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) group, which consists of reproductive endocrinologists and reproductive medicine experts with long-term clinical and/or research experiences from seven countries, proposed a new stratification according to the decreased ovarian reserve or unexpected POR to exogenous gonadotropins. By considering the influence of age, ovarian reserve parameters (AMH and AFC) and previous response to ovarian stimulation on in vitro fertilization (IVF) outcome, both qualitative and quantitative parameters were comprehensively evaluated and also take oocyte quantity and quality into account, patients with low prognosis were finally divided into four groups[5–6].

In order to better evaluate the clinical prognosis of Chinese low prognosis patients and help to develop therapeutic schedule, Chinese experts put forward some opinions and suggestions on the localization of POSEIDON criteria[7]. However, there were few studies using POSEIDON criteria to screen low prognosis patients and evaluate their prognosis in China. The treatment status and prognosis of patients in different stratification according to POSEIDON criteria were still unclear. Therefore, this study focuses on the clinical application of POSEIDON criteria. By case screening retrospectively and statistical analyzing, a scale tool for predicting cumulative live birth rate (CLBR) was developed on the basis of clinical data, which was used for the evaluation of the probability of expected cumulative live birth in low prognosis patients after ART.

Materials And Methods

Study design and population

The present study was a retrospective observational cohort study included all patients who received IVF/intracytoplasmic sperm injection (ICSI) therapy at Assisted Reproduction Center of Northwest Women's and Children's Hospital, Northwest China between 2014 and 2018. Patients underwent the first cycle and been defined as low prognosis according to the POSEIDON criteria were screened and enrolled in the statistics, but were excluded from this study if any of the following criteria occurred: (1) donated oocyte cycles; (2) PGS/PGD cycles; (3) cycles without live birth outcome but with remaining extra frozen embryos in this period; (4) lost to follow-up; (5) induced abortion.

Ethics statement

This study was approved by the Ethics Committee of the Clinical Application of Human Assisted Reproductive Technology of Northwest Women's and Children's Hospital (No. 2018002). Informed consent was not obtained for the present study was a retrospective observational cohort study. The study was performed according to the principles of the Declaration of Helsinki as well as its later amendments.

Clinical outcome

The primary outcome was the CLBR which was defined as the cumulative live birth per transvaginal oocyte aspiration accordant to terminology definition. The numerator for calculating CLBR was the sum of live births delivered from frozen-thawed embryo transfer (FETs) and live births from fresh cycles. If a patient received multiple deliveries, only the first delivery was taken into account in the analysis.

Treatment protocol

As a retrospective study, the treatment protocol were chosen by physicians according to the patients clinical situation, after discussion with the patients and her couple. There were three main protocols, including agonist protocol, antagonist protocol and progestin primed ovarian stimulation(PPOS) protocol. The detailed description of these protocols could be found in our previous reports[8,9].

Risk factors

Data were retrieved from an electronic system storing medical record (Wuhan Huchuang Co., Ltd., Version 9.2.5.8). The data at the baseline were collected for risk factor analysis, including maternal age, body mass index (BMI), previous gravidity, previous parity, duration of infertility, type of infertility, main etiology, antral follicle count (AFC), basal follicle-stimulating hormone (bFSH), and number of day 3 usable embryos. The age was stratified by 5 years old with a basic range of ≥ 25 and < 30. BMI was also stratified according to the pinched (< 18.5 kg/m^2), normal weight (≥ 18.5 kg/m^2 and < 24 kg/m^2), overweight (≥ 24 kg/m^2 and < 28 kg/m^2), and obesity (≥ 28 kg/m^2). The basic range (or normal, or first stratification in each variable) was used as a reference in statistical analysis. AFC and bFSH were stratified according to the clinical opinions, at the threshold of 4 and 9 for AFC, and 10 IU/L for bFSH.

Statistical analysis

4,395 eligible participants were randomly divided into training set (70% participants, 3,122 cases) and external validation set (30% participants, 1,273 cases). Categorical variables were described as frequency (percentage), and statistical differences between the groups were compared by using the $\chi 2$ test. In the training set, univariate and multivariate logistic regression analysis were conducted to determine the risk factors correlated with CLBR, and the correlations between the related factors and CLBR were reported as ORs with corresponding 95% confident intervals (CIs). Variables presenting statistical significance in the univariate analysis were tested with multivariate logistic regression analysis, followed by the selection of the variables which were eventually included in the model. A nomogram was constructed with the variables selected by multivariate logistic regression analysis, which were incorporated into the nomogram for the prediction of CLBR. The efficiency of the model was evaluated by the C statistic, which is equal to the area under the curve (AUC) of receiver operating characteristic curve (ROC) in the training set and validation set. The calibration efficiency (agreement between actual outcome frequencies and the predicted CLBR) was evaluated by Hosmer-Lemeshow $\chi 2$ statistics.

Statistical analysis was performed using SPSS software (version 23.0, USA), and R software (version 3.4.1, USA). Two-tailed analysis with $P < 0.05$ was considered significantly different.

Results

Patient demographics

Altogether, 54,714 cases were extracted, checked and verified. There were 4,635 cases in accordance with POSEIDEN criteria of low prognostic, and 4,395 cases finally enrolled in this study. For these female patients, they were 34.14 years old in average, the average BMI was 22.43 kg/m^2, with a average duration of infertility at 4.20 years, 42.71% of them were defined as primary infertility. According to the clinical outcome, 1,153 of them achieved the cumulative live birth (CLBR at 26.23%). After randomization, 3,122 of them were assigned into training set, and the reset 1,273 were assigned into validation set. (Fig. 1)

In the training set, there were 820 patients achieved cumulative live birth (CLB). According to the univariate results, almost all the factors were related with the CLB. But in the multivariate results, only the patients more than 35 years old, BMI ≥ 28kg/m^2, and those defined as secondary infertility, with uterine factors as cause of infertility, and bFSH more than 10IU/L will be less probability to achieving the CLB. Interestingly, those with BMI between 24kg/m^2 to 28kg/m^2, with male factors as cause of infertility, and had more usable embryos at day 3 indicates a better clinical outcome.

Nomogram development

According to the multivariate OR, the independent risk factors for CLB were used in the nomogram development (Fig. 2). The poorest stratification in each variable was defined as 0 point, and the best stratification get most points, for example the patients over 40 years old was recorded 0 point at the variable of age, while those at 25 to 29 years old get about 26 points. The total points in seven variables would be used to map to the scale of predictor. If a patient get more than 113 points, the estimated CLBR was > 90%; while an estimated CLBR < 10% would come if the total point was less than 39. The 50% probability was given when someone get 76 points.

Nomogram validation

By applying the nomogram on the training set, we could draw a ROC curve to show the predicting capability of the nomogram (Fig. 3A). The AUC was 0.769. And by applying the nomogram in validation set, the AUC was 0.749 (Fig. 3B). The Hosmer-Lemeshow chi-square statistic, which revealed calibration ability was 10.194, and the calibration plot is presented in Fig. 4 ($P = 0.252$). Furthermore, we also tested all the variables in the nomogram for their predicting capabilities of CLB(Table 2). It could be determined that the number of embryos usable at day 3 was the most correlated factors among the seven variables, but still not as accurate as the nomogram. Several variables, such as BMI and causes of infertility, were unable to predict the CLB alone in validation set.

Discussion

This was a study showing the cumulative live birth in patients with low prognosis by using POSEIDON criteria. In the present study, we constructed and validated a nomogram to predict CLBR, consist of age, BMI, type and causes of infertility, bFSH, and usable embryos number at day 3.

The usable embryos number at day 3 was the most important variable in the nomogram. According to the Fig. 2, we could see a huge weight of embryos number in the scoring, furthermore the predictor capability of it alone was also high (AUC 0.737 in Table 2). The variable reflecting quality or quantity of embryos were different among studies, such as number of embryos transferred[10,11], or good-quality embryos[12].In this study, we have chosen the usable embryos number at day 3 because it was not only a routine data in our center that could be most completely retrieved, and also it is a factor strongly related with CLBR or other clinical outcomes[13,14]. The usable embryos number at day 3 take account of both the high-quality and low-quality embryos, that the later ones were potential of live birth in subsequent transfer when the first transfer failed. It is more suitable for studies using CLBR as an endpoint. The number of embryos played such an important role in POSEIDON population[15], indicated that the treatment protocol should be carefully chosen as the other factors were less influential or hard to adjust in clinical. Several more embryos might be a decisive change for some couples.

Among reset six variables, age were always reported as important predictors in previous studies[16,17]. It is not surprising that age could affect the clinical outcome, but the detailed results showed that only > 35 year old will significantly impact the CLBR. The exact threshold of age to affect the live birth was still not established, but more and more studies choose the 35 years old as the threshold, and also it had been accept in the POSEIDON criteria[6]. The causes of infertility were also common in CLB prediction studies, especially the male factor which was quite reasonable as the application of ICSI technical. In this study, we also found uterine factors could be a disadvantage factor in IVF. But it need to mention that the predictor capability of infertility cause was not satisfactory in the validation set. It imply that the factors need further verification.

For BMI, it is interesting to see that overweight ($24kg/m^2 \leq BMI < 28\ kg/m^2$) achieved a better live birth rate than those with normal BMI. It is commonly believed that the BMI, or fat cells, is critical in estrogen secretion. But the results in previous studies were inconsistent with common sense. One large scale study focus on BMI found the overall live birth rate was decreased in women with BMI > 30 kg/m^2 [18], but no differences were seen in other groups. Other studies also indicated there was no correlation between BMI and live birth rate, or even negatively correlated with live birth rate[19]. But few study focus on POSEIDON patients had reported the relationship between CLBR and BMI, we suppose the endocrine changing were more sensitive in these patients and it might be a reason that BMI became one of the variables in the nomogram.

The management of POSEIDON patients was a challenging issue, the main reason was poor prognosis and it was the common cause of dropout[20]. In a recent studies in China, the POSEIDON patients got an approximate 24% of CLBR, significantly lower than that in non-POSEIDON patients, which was 44.5%[21]. In our study, the CLBR was about 26%, similar to that in the reference. The characteristics of the patients in several POSEIDON population were all similar. It indicated that the conclusion in our study could be applied and also validated by most POSEIDON population.

Treatment regimen decision might affect the clinical outcome, so it was always included in the multivariate analysis[21]. In the Chinese experts' opinions, antagonist protocol were recommended in both younger patients (< 35 years old) and elder patients (> 35 years old), as it could achieve good clinical outcomes in fresh cycle, and also reduce the Gn usage or shorten the treatment duration[7]. Even after the recommendation, an opinion was given that the protocol should be applied according to the situation of center and patients. But the treatment regimen was not included in the nomogram, as some further analyses would be applied to directly compare the effectiveness of different treatment protocols in POSEIDON population, and also in each subgroups. The comparison could directly reflect the difference of CLBR under both dimension of treatment regimens and dimension of POSEIDON subgroup, which is the first step for clinical application of the nomogram.

Limitation

It was a retrospective and single center study, bias could not be fully avoided. As shown in table 2, several variables showed different predict capability in training and validation set. The nomogram could be more accurate by expansion more samples. And the clinical outcome was chosen CLB only, some other common outcomes such as live birth in single cycle, clinical pregnancy rate were not shown in this study. One reason was the definition of CLB fits the criteria of POSEIDON best, another was that there were already extensive results by CLB.

Conclusion

In the present study, we constructed and validated a nomogram for the prediction of CLBR in patients with low prognosis from a single center database in Chinese population. The validated nomogram for the prediction of CLBR could be potentially applied in clinic for IVF counselling in patients with low prognosis.

Declarations

Acknowledgements

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Author contributions

LJ Chen: manuscript writing; PF Qu: data analysis; JF Wu: manuscript editing; JL Xie: data collection; H Wang: data collection; WH Shi: manuscript editing; JZ Shi: protocol development.

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Conflicts of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

The study was approved by the Ethics Committee for the Clinical Application of Human Assisted Reproductive Technology of Northwest Women's and Children's Hospital (No. 2018002). The study was conducted in accordance with the principles contained in the Declaration of Helsinki and its later amendments.

Consent to participate

Informed consent was not obtained as this was a retrospective cohort study.

Availability of data and material: not applicable

Code availability : not applicable

Consent for publication: not applicable

Author contributions:

LJ Chen: manuscript writing

PF Qu: data analysis

JF Wu: manuscript editing

JL Xie: data collection

H Wang: data collection

WH Shi: manuscript editing

JZ Shi: protocol development

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Tables

Due to technical limitations, table 1,2 is only available as a download in the Supplemental Files section.

Figures

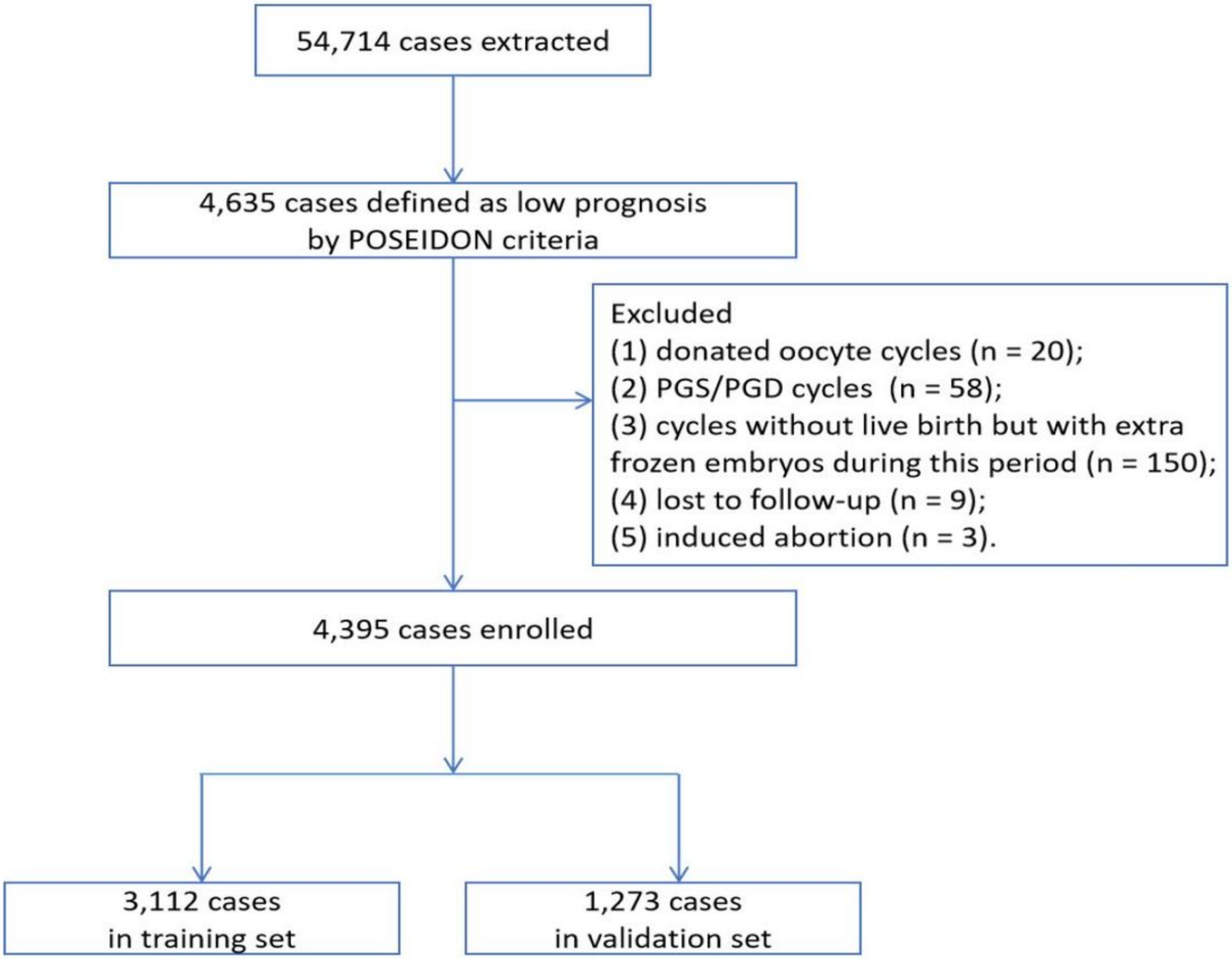

Figure 1

Patient flow chart

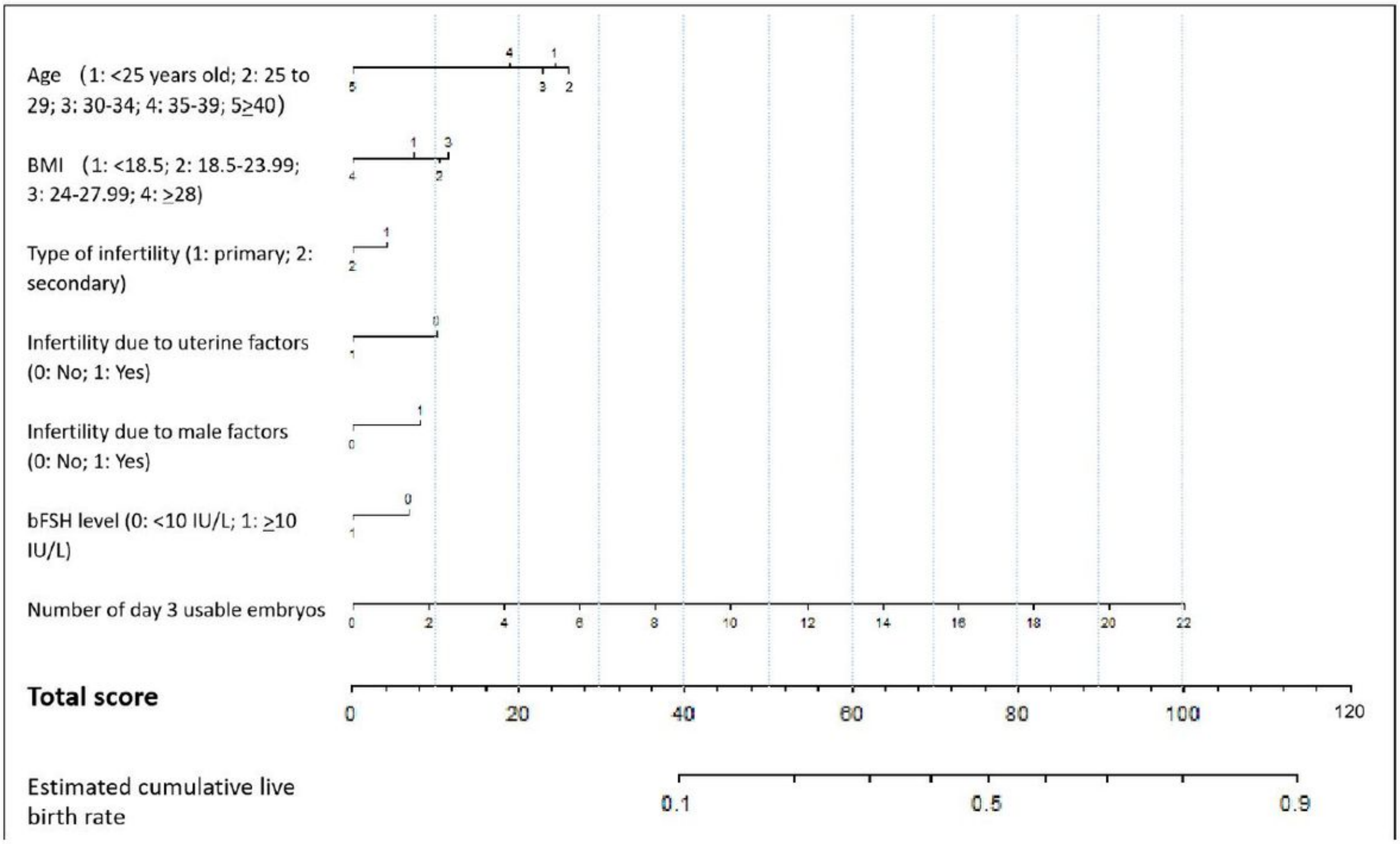

Figure 2

Nomogram for predicting cumulative live birth (CLB). All the factors in the nomogram, including age, BMI, type of infertility, cause of infertility (uterine factors and male factors), bFSH level and number of day 3 usable embryos, were scored according to the multivariate results. The total score of all the factors was used to count an estimated cumulative live birth rate for clinical prediction.

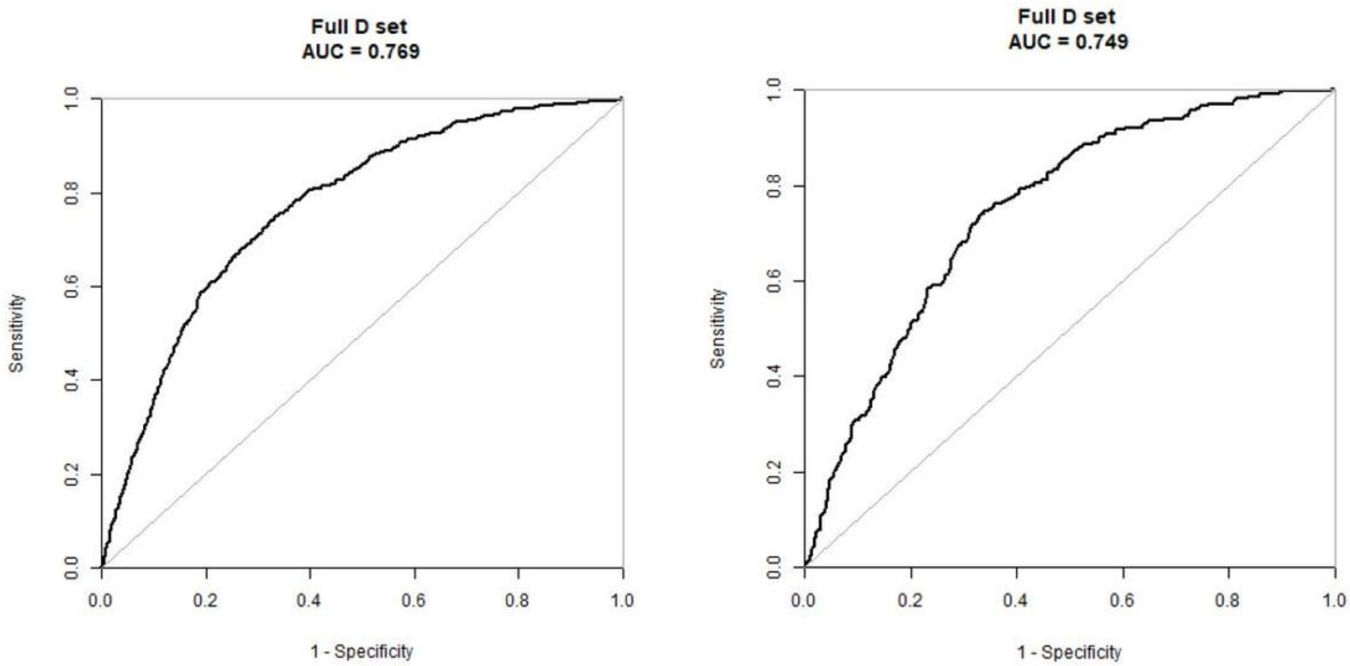

Figure 3

ROC curve in training cohort(A) and validation cohort (B).

Figure 4

Calibration plot

Supplementary Files

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- table.pdf