

## Prediction of Low Birth Weight From Quadruple Screening in Sanpatong Hospital, Chiang Mai

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### ABSTRACT

**OBJECTIVE** This study aimed to develop a predictive model for low birth weight (LBW) using maternal history and the second trimester biochemical quadruple screening test in singleton pregnancies delivered at Sanpatong Hospital, Chiang Mai, Thailand.

**METHODS:** This retrospective cohort study collected data from medical records of 873 singleton pregnancy women who underwent the quadruple test at 14–16 weeks of gestation and delivered at Sanpatong Hospital between October 1, 2016, and September 30, 2023. Data collected included maternal characteristics, quadruple test results, obstetric complications, and birth weight. Multivariable logistic regression was used to analyze associations between various factors and LBW. Model performance was evaluated using receiver operating characteristic (ROC) curve analysis.

**RESULTS:** The incidence of LBW was 6.76% (59 out of 873 deliveries). Significant factors associated with LBW in multivariable analysis included maternal body mass index (BMI) (AOR = 0.924,  $p = 0.018$ ), nulliparity (AOR = 0.524,  $p = 0.021$ ), high-risk quadruple test for aneuploidy (AOR = 16.061,  $p = 0.006$ ), preeclampsia (AOR = 3.573,  $p = 0.007$ ), preterm labor (AOR = 36.526,  $p < 0.001$ ), fetal growth restriction (AOR = 45.726,  $p < 0.001$ ), MoM of AFP (AOR = 2.598,  $p = 0.001$ ), and MoM of  $\beta$ -hCG (AOR = 1.352,  $p = 0.003$ ). Four predictive models were developed: history-only (AUC = 0.673), biochemical-only (MoM of AFP and  $\beta$ -hCG; AUC = 0.604), a combined model (history + biochemical; AUC = 0.707), and a full combined model (history + biochemical + complication; AUC = 0.902). The full combined model demonstrated superior performance in predicting LBW.

**CONCLUSIONS:** The full combined model incorporating clinical history and quadruple test biochemical markers (AFP and  $\beta$ -hCG) effectively predicts LBW. These findings suggest the potential for early identification of at-risk pregnancies, enabling timely interventions to improve maternal and neonatal outcomes.

**KEYWORDS** low birth weight, quadruple test, prediction model, alpha-fetoprotein,  $\beta$ -hCG

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## INTRODUCTION

Low birth weight (LBW), defined as a birth weight less than 2,500 grams, remains a significant global public health concern, contributing substantially to neonatal mortality and morbidity (1). Infants born with LBW face increased risks of short-term complications such as respiratory distress syndrome, hypothermia, and infections, as well as long-term health issues including developmental delays, chronic diseases in adulthood, and neurodevelopmental impairments (2). Globally, the incidence of LBW is estimated to be around 15.00-20.00% (1), with Thailand reporting an incidence of 9.91% in 2022 (3).

Early identification of pregnancies at high risk for LBW is crucial for implementing timely interventions, optimizing prenatal care, and preparing for appropriate delivery management. Various maternal characteristics and obstetric complications have been identified as risk factors for LBW, including poor maternal nutritional status, infections, preeclampsia (PE), preterm labor (PTL), and fetal growth restriction (FGR) (4-7).

Maternal serum biochemical markers, routinely used in second-trimester aneuploidy screening (e.g., quadruple test), have also been explored for their potential role in predicting adverse pregnancy outcomes, including LBW. The quadruple test typically measures alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and inhibin-A (Inh-A) (4, 8). While primarily designed for chromosomal abnormalities, deviations in these marker levels may reflect placental dysfunction or fetal growth disturbances (9).

Despite the established role of clinical factors and the potential utility of biochemical markers, comprehensive predictive models integrating both aspects are essential for improved risk stratification, particularly in specific regional populations. Data on the predictive value of the quadruple test in relation to LBW in Thailand, especially in provincial hospitals like Sanpatong Hospital, is limited.

This study aimed to develop a predictive model for LBW using maternal history and quadruple test biochemical screening in singleton pregnancies delivered at Sanpatong Hospital, Chiang Mai.

## METHODS

The study protocol was approved by the Sanpatong Hospital Ethical Committee (COE No.

18/2567, approved October 1, 2024). Patient confidentiality was maintained throughout the study. This was a retrospective cohort descriptive study conducted at Sanpatong Hospital, a community hospital in Chiang Mai Province, Thailand. Data were collected from the medical records of singleton pregnant women who received quadruple test screening at 14-16 weeks of gestation and delivered at Sanpatong Hospital between October 1, 2016, and September 30, 2023.

The sample size for this study was determined using the formula  $n = (k \times \text{EPV})/P$ , with a prevalence of LBW of 9.91%. The number of predictor variables (k) was set at 8, and the events per variable (EPV) was set at 10. This calculation yielded a required sample size of 808 participants. However, to enhance the robustness of the analysis, all eligible individuals who met the inclusion criteria were included, resulting in a total sample of 873 participants. Exclusion criteria included pregnant women with pre-existing medical conditions, pregnancies with known fetal chromosomal abnormalities, incomplete quadruple test data, and those who delivered at other hospitals.

Definitions used in this study are as follows: LBW was defined as a birth weight less than 2,500 grams. High risk for aneuploidy was determined by quadruple test screening results that indicated a risk exceeding the established cutoff of 1:250 for chromosomal abnormalities. Maternal obstetric complications were defined as PE (based on blood pressure of 140/90 mmHg or higher with proteinuria more than 300 mg in 24 hours), FGR (estimated fetal weight from ultrasound biometry less than 10th percentile for gestational age), abortion (fetal loss at less than 24 weeks), PTL (regular uterine contraction with cervical change before 37 complete weeks).

Data were extracted from medical records and included maternal characteristics (age, parity, body mass index at the time of the quadruple test, and gestational age at testing), quadruple test results (risk assessment for aneuploidy (high risk vs. low risk) and multiple of median values for AFP,  $\beta$ -hCG, Inh-A, and uE3, maternal obstetric complications (such as gestational diabetes, PE, PTL, and fetal growth restriction), and neonatal outcome (including infant sex, mode of delivery, gestational age at delivery, and birth weight).

Data were analyzed using SPSS software (version 16.0). Descriptive statistics were used to

summarize baseline characteristics: median and interquartile range (IQR) for continuous variables, and number and percentage (n, %) for categorical variables. Differences between the LBW and normal birth weight (NBW) groups were assessed using the Mann-Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables.

Multivariable logistic regression analysis was performed to identify independent factors associated with LBW. Variables with a  $p < 0.05$  in univariate analysis and those considered clinically important were included in the multivariable model. The adjusted odds ratios (AOR) with 95% confidence intervals (CI) were calculated. The performance of predictive models for LBW was evaluated using the receiver operating characteristic (ROC) curve. The area under the curve (AUC) was used to assess the discriminative ability of the model.

## RESULTS

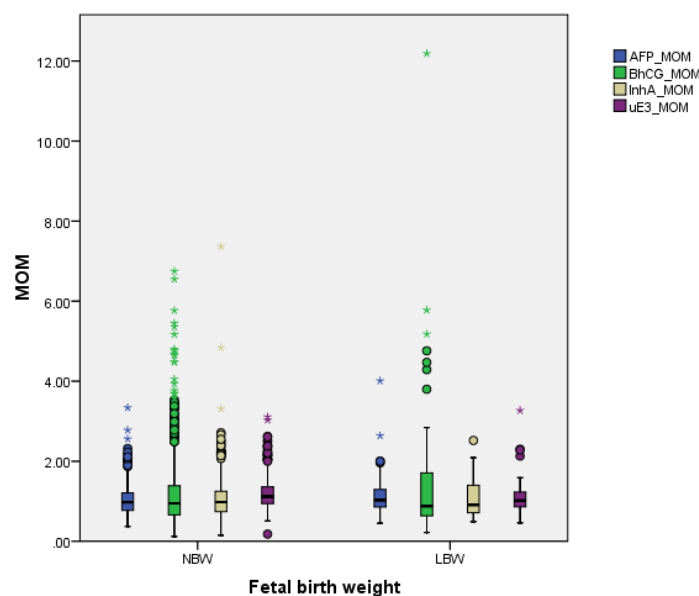
A total of 873 singleton pregnant women were included in this study. Among them, 59 (6.76%) infants were classified as LBW, while 814 (93.24%) were of NBW.

The baseline characteristics of the study population, described in Table 1 included the median maternal age of 27 years (IQR: 24–31), with no significant difference between LBW and NBW

groups ( $p = 0.220$ ). Maternal BMI at the quadruple test was significantly lower in the LBW group (median 21.2 kg/m<sup>2</sup>, IQR: 19.1–23.8) compared to the NBW group (median 22.9 kg/m<sup>2</sup>, IQR: 20.5–26.5) ( $p = 0.003$ ). Nulliparity was significantly more frequent in the LBW group (64.4% vs 48.6%,  $p = 0.019$ ). High-risk quadruple test for aneuploidy was also significantly higher in the LBW group (13.6% vs. 3.1%,  $p < 0.001$ ).

Regarding maternal obstetric complications, PE (10.2% vs. 3.1%,  $p = 0.004$ ), PTL (40.7% vs. 1.8%,  $p < 0.001$ ), and FGR (22.0% vs. 0.6%,  $p < 0.001$ ), were significantly more prevalent in mothers delivering LBW infants. The median gestational age at delivery was significantly lower in the LBW group (259 days, IQR: 250–269) compared to the NBW group (274 days, IQR: 269–279) ( $p < 0.001$ ).

The distributions of the maternal serum quadruple-test markers—AFP,  $\beta$ -hCG, Inh-A, and uE3, expressed as multiples of the median (MoM)—by birth weight group is presented in Figure 1. The median MoM of AFP was significantly higher in the LBW group (1.03, IQR: 0.86–1.30) than in the NBW group (0.98, IQR: 0.77–1.21) ( $p = 0.037$ ). Conversely, the median MoM of uE3 was significantly lower in the LBW group (1.02, IQR: 0.86–1.23) compared to the NBW group (1.12, IQR: 0.94–1.36) ( $p = 0.039$ ). No significant differences were observed for MoM of  $\beta$ -hCG and MoM of Inh-A in the univariable analysis (Table 1).



**Figure 1.** Box and whisker plots of maternal serum Quadruple test markers by fetal birth weight status (normal birth weight (NBW) and low birth weight (LBW))

AFP\_MOM, alpha-fetoprotein multiple of the median; B-hCG\_MOM, beta-human chorionic gonadotropin multiple of the median; InhA\_MOM, inhibin A multiple of the median; uE3\_MOM, unconjugated estriol multiple of the median

The multivariable logistic regression analysis (Table 2) identified several independent predictors for LBW, including maternal age (AOR = 0.937, 95%CI: 0.81-0.986,  $p = 0.021$ ), nulliparity (AOR = 0.524, 95%CI: 0.302-0.908,  $p = 0.021$ ), and BMI at the time of the quadruple test (AOR = 0.924, 95%CI: 0.866-0.987,  $p = 0.018$ ), all of which were significantly associated with an increased risk of LBW.

Factors associated with LBW from multivariable analysis (Table 2) identified several independent predictors for LBW. Maternal age (AOR = 0.937, 95%CI: 0.891-0.986,  $p = 0.021$ ), nulliparity (AOR = 0.524, 95%CI: 0.302-0.908,  $p = 0.021$ ), and BMI at quadruple test (AOR = 0.924, 95%CI: 0.866

- 0.987,  $p = 0.018$ ) were significantly associated with an increased risk of LBW.

Among quadruple test results, high risk for aneuploidy significantly increased the risk of LBW (AOR = 16.061, 95%CI: 2.215-116.455,  $p = 0.006$ ). Crucially, maternal obstetric complications such as PE (AOR = 3.573, 95%CI: 1.405-9.086,  $p = 0.007$ ), PTL (AOR = 36.526, 95%CI: 17.628-75.681,  $p < 0.001$ ), and FGR (AOR = 45.726, 95%CI: 15.632-133.754,  $p < 0.001$ ) were very strong predictors.

Regarding quadruple test biochemical markers in the multivariable model, MoM of AFP (AOR = 2.598, 95%CI: 1.458-4.631,  $p = 0.001$ ) and MoM of  $\beta$ -hCG (AOR = 1.352, 95%CI: 1.107-1.652,  $p = 0.003$ ) were significantly associated with LBW. MoM of

**Table 1.** Baseline characteristics of maternal and infant

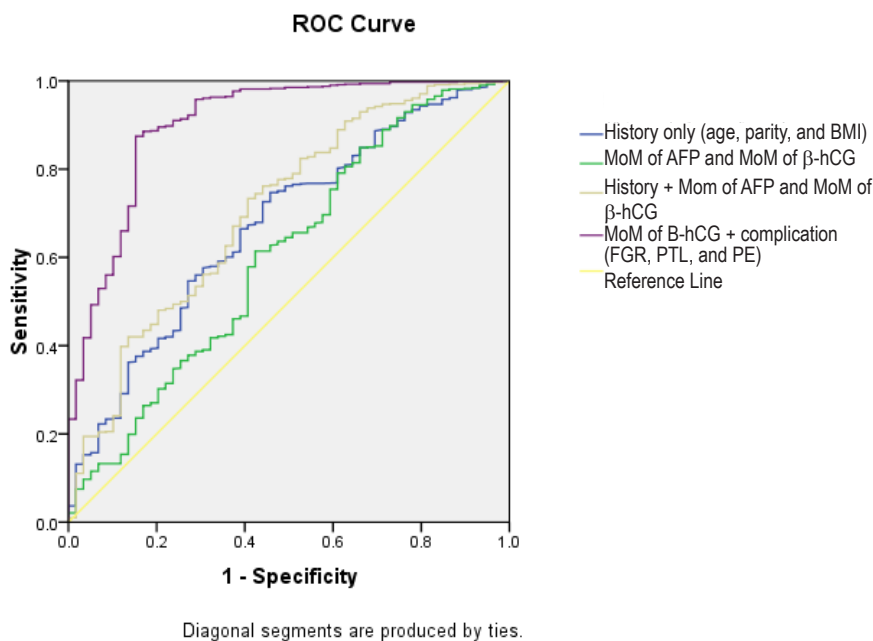
| Characteristics                                    | Total (N = 873)  | LBW (N = 59)     | NBW (N = 814)    | p-value |
|----------------------------------------------------|------------------|------------------|------------------|---------|
| Age, years, median (IQR)                           | 27 (24-31)       | 25 (21-31)       | 27 (24-31)       | 0.220   |
| Primigravida (G1), n (%)                           | 385 (44.1)       | 33 (55.9)        | 352 (43.2)       | 0.058   |
| Nulliparous (P0), n (%)                            | 434 (49.7)       | 38 (64.4)        | 396 (48.6)       | 0.019*  |
| BMI at Quad test, kg/m <sup>2</sup> , median (IQR) | 22.9 (20.4-26.4) | 21.2 (19.1-23.8) | 22.9 (20.5-26.5) | 0.003*  |
| GA at Quad test, days, median (IQR)                | 110 (106-115)    | 109 (106-115)    | 110 (106-115)    | 0.533   |
| Past history, n (%)                                |                  |                  |                  |         |
| Have history of preterm birth                      | 10 (1.1)         | 1 (1.7)          | 9 (1.1)          | 1.000   |
| Have history of preeclampsia                       | 1 (0.1)          | 0 (0.0)          | 1 (0.1)          | 0.505   |
| Quad test result, n (%)                            |                  |                  |                  |         |
| Low risk                                           | 836 (95.8)       | 49 (83.1)        | 787 (96.7)       | 0.000*  |
| HR for aneuploidy                                  | 33 (3.8)         | 8 (13.6)         | 25 (3.1)         |         |
| HR for NTD                                         | 4 (0.4)          | 2 (3.3)          | 2 (0.2)          |         |
| Maternal obstetric complication, n (%)             |                  |                  |                  |         |
| Gestational diabetes                               | 52 (6.0)         | 5 (8.5)          | 47 (5.8)         | 0.388   |
| Preeclampsia                                       | 31 (3.6)         | 6 (10.2)         | 25 (3.1)         | 0.004*  |
| Preterm labor                                      | 39 (4.5)         | 24 (40.7)        | 15 (1.8)         | 0.000*  |
| Fetal growth restriction                           | 18 (2.1)         | 13 (22.0)        | 5 (0.6)          | 0.000*  |
| Infant sex, n (%)                                  |                  |                  |                  |         |
| Male                                               | 474 (54.3)       | 30 (50.8)        | 444 (54.5)       | 0.582   |
| Female                                             | 399 (45.7)       | 29 (49.2)        | 370 (45.5)       |         |
| Route of delivery, n (%)                           |                  |                  |                  |         |
| Vaginal delivery (ND, VE, and breech)              | 622 (71.2)       | 48 (81.4)        | 574 (70.5)       | 0.076   |
| Cesarean section                                   | 251 (28.8)       | 11 (18.6)        | 240 (29.5)       |         |
| GA at delivery, days, median (IQR)                 | 273 (268-278)    | 259 (250-269)    | 274 (269-279)    | 0.000*  |
| Fetal birth weight, grams, median (IQR)            | 3115 (2830-3378) | 2290 (2153-2415) | 3150 (2895-3400) | 0.000*  |
| Quad test value, median (IQR)                      |                  |                  |                  |         |
| MoM of AFP                                         | 0.98 (0.77-1.23) | 1.03 (0.86-1.30) | 0.98 (0.77-1.21) | 0.037*  |
| MoM of $\beta$ -hCG                                | 0.95 (0.65-1.39) | 0.88 (0.64-1.71) | 0.95 (0.66-1.39) | 0.720   |
| MoM of Inh-A                                       | 0.97 (0.74-1.26) | 0.91 (0.72-1.40) | 0.95 (0.66-1.39) | 0.892   |
| MoM of uE3                                         | 1.12 (0.94-1.35) | 1.02 (0.86-1.23) | 1.12 (0.94-1.36) | 0.039*  |

BMI, body mass index; HR, high risk; NTD, neural tube defect; ND, normal delivery; VE, vacuum extraction; GA, gestational age; MoM, multiple of median; AFP, alpha feto-protein;  $\beta$ -hCG, beta-human chorionic gonadotropin; Inh-A, inhibin-A; uE3, unconjugated estriol; \*,  $p < 0.05$  indicates statistic significance.

**Table 2.** Factors associated with low birth weight

| Variable                        | Adjusted odds ratio | 95%CI          | p-value |
|---------------------------------|---------------------|----------------|---------|
| Age groups                      | 0.937               | 0.891-0.986    | 0.021*  |
| Parity                          | 0.524               | 0.302-0.908    | 0.021*  |
| BMI at Quad test                | 0.924               | 0.866-0.987    | 0.018*  |
| Quad test result                |                     |                |         |
| HR for aneuploidy               | 16.061              | 2.215-116.455  | 0.006*  |
| HR for NTD                      | 3.125               | 0.377-25.918   | 0.291   |
| Maternal obstetric complication |                     |                |         |
| Preeclampsia                    | 3.573               | 1.405-9.086    | 0.007*  |
| Preterm labor                   | 36.526              | 17.628-75.681  | 0.000*  |
| Fetal growth restriction        | 45.726              | 15.632-133.754 | 0.000*  |
| Quad test value                 |                     |                |         |
| MoM of AFP                      | 2.598               | 1.458-4.631    | 0.001*  |
| MoM of $\beta$ -hCG             | 1.352               | 1.107-1.652    | 0.003*  |
| MoM of Inh-A                    | 1.092               | 0.657-1.815    | 0.734   |
| MoM of uE3                      | 0.643               | 0.292-1.417    | 0.273   |

BMI, body mass index; HR, high risk; NTD, neural tube defect; ND, normal delivery; VE, vacuum extraction; GA, gestational age; MoM, multiple of median; AFP, alpha feto-protein;  $\beta$ -hCG, beta-human chorionic gonadotropin; Inh-A, inhibin-A; uE3, unconjugated estriol; \*,  $p < 0.05$  indicates statistic significance.

**Figure 2.** Receiver operating characteristic (ROC) curve for the prediction of low birth weight using maternal serum MoM of AFP and MoM of  $\beta$ -hCG

Inh-A and MoM of uE3 did not show significant associations in this model (Table 2).

Figure 2 illustrates the ROC curves for the four predictive models. The history-only model, which included maternal age, parity, and BMI, showed limited discriminative ability with an AUC of 0.673 (95%CI: 0.602-0.743,  $p < 0.001$ ). In contrast, the biochemical-only model, using only

MoM of AFP and MoM of  $\beta$ -hCG, demonstrated a lower discriminative ability with an AUC of 0.604 (95%CI: 0.523-0.685,  $p = 0.008$ ). The combined model, integrating history, MoM of AFP, and MoM of  $\beta$ -hCG, showed fair discriminative power with an AUC of 0.707 (95%CI: 0.635-0.779,  $p < 0.001$ ). At its optimal cut-off, this model yielded a sensitivity of 73.3% and a specificity of 59.3%. The

full combined model, integrating history, MoM of AFP, MoM of  $\beta$ -hCG, and complication (FGR, PTL, and PE), achieved the highest discriminative power, with an excellent AUC of 0.902 (95%CI: 0.855-0.949,  $p < 0.001$ ). At its optimal cut-off, this full model yielded a sensitivity of 88.1% and a specificity of 84.7%. This full combined model significantly outperformed the other models, highlighting the added value of integrating quadruple test markers with clinical factors for predicting LBW.

## DISCUSSION

This study aimed to investigate the association between quadruple test biochemical screening results and LBW in singleton pregnancies at Sanpatong Hospital, Chiang Mai, and to develop a comprehensive predictive model. The findings reveal several significant factors associated with LBW, contributing valuable insights for clinical practice, particularly within a regional hospital setting.

The observed LBW incidence of 6.76% in our study population is lower than global estimates (15.0-20.0%) (1) and the national average for Thailand (9.9% in 2022) (3). This difference may be attributed to the specific demographic characteristics of a district hospital population, which might differ from urban centers or national averages. Furthermore, the stringent inclusion and exclusion criteria, such as the exclusion of women with certain pre-existing medical conditions or those delivering at other facilities, could have contributed to a healthier study cohort.

Our findings that lower maternal BMI, nulliparity, and high-risk quadruple test for aneuploidy are significantly associated with LBW are consistent with existing literature (7-9). Importantly, obstetric complications such as PE, PTL, and FGR were found to be very strong independent predictors of LBW. These results reinforce the well-established understanding that preterm birth and FGR are primary determinants of LBW, both of which are linked to short-term and long-term adverse health outcomes for the infant (2, 10). Maternal nutritional status and infections are also acknowledged contributors to LBW, indirectly reflected through factors like BMI and complications (7).

Regarding the role of quadruple test biochemical markers, our study found that higher MoM of AFP and lower MoM of uE3 were significantly associated with LBW in univariable analysis (Table 1). Furthermore, higher MoM of AFP remained a significant predictor in the multivariable model (Table 2). This aligns with research indicating a negative correlation between AFP levels and birth weight (11), and studies suggesting AFP as a key marker within the triple test associated with birth weight (11). Elevated AFP levels have also been linked to various adverse pregnancy outcomes including pregnancy-induced hypertension, spontaneous abortion, preterm birth, FGR, oligohydramnios, and placental abruption (12).

While univariable analysis showed no significant difference in MoM of  $\beta$ -hCG and Inh-A between LBW and NBW groups, the multivariable model revealed a significant association between higher MoM of  $\beta$ -hCG and increased risk of LBW. This discrepancy might be due to the confounding effects of other clinical variables in the univariable setting, which are controlled for in the multivariable analysis. Literature supports the association of elevated  $\beta$ -hCG with increased risk of LBW (13), PE, fetal demise, preterm delivery, and FGR (14). The observed differences in findings across studies, including ours, could stem from variations in analytical methodologies, population characteristics, or the specific set of co-factors considered in statistical models.

The predictive performance evaluation demonstrated the significant utility of the developed logistic regression models. The full combined model, integrating clinical history (age, parity, BMI), biochemical markers (MoM of AFP and  $\beta$ -hCG), and complications (FGR, PTL, and PE), achieved an excellent discriminative ability with an AUC of 0.902. At its optimal cut-off, this model achieved a sensitivity of 88.1% and a specificity of 84.7%. This indicates that the model correctly identified 52 out of 59 (88.1%) actual LBW cases in the study population, highlighting the substantial value of a comprehensive assessment approach that incorporates quadruple test data alongside maternal clinical factors. In contrast, the model relying solely on MoM of AFP and  $\beta$ -hCG exhibited considerably lower predictive performance (AUC = 0.604). The model integrating history and the two biochemical markers (AUC = 0.707) showed

better performance than the biochemical-only model, and the history-only model (AUC = 0.673) was still outperformed by the combined models. These results underscore the limitations of using biochemical markers alone for LBW prediction, yet emphasize their incremental benefit when combined with relevant clinical information.

A key strength of this study is its focus on a specific population within a district hospital in rural Thailand, providing valuable local data where information on LBW prediction models is often limited. The retrospective design allowed for a relatively large sample size ( $N = 873$ ) and the use of real-world clinical data. However, the retrospective nature also presents limitations, including reliance on the completeness and accuracy of medical records and the potential for unmeasured confounding variables. The study was conducted in a single institution, which may limit the generalizability of findings to broader populations. Furthermore, while comprehensive, the predictive models did not include all potential risk factors for LBW that might be present in a prospective study design.

## CONCLUSIONS

This study demonstrates that combining quadruple test markers (AFP and  $\beta$ -hCG) with key maternal clinical factors can effectively predict LBW risk. Early identification allows timely interventions and targeted care, potentially improving maternal and neonatal outcomes in settings similar to Sanpatong Hospital.

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## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to report.

## AUTHOR CONTRIBUTIONS

The author confirms sole responsibility for the study conception and design, data collection, statistical analysis and interpretation of results, and manuscript preparation.

## DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality and institutional privacy policies of Sanpatong Hospital. However, they are available from the corresponding author upon reasonable request and with permission from the Sanpatong Hospital Ethical Committee (COE No. 18/2567).

## INSTITUTIONAL REVIEW BOARD STATEMENT

The study protocol was approved by the Sanpatong Hospital Ethical Committee (COE No. 18/2567, approved October 1, 2024). Patient confidentiality was maintained throughout the study.

## INFORMED CONSENT STATEMENT

Patient consent was waived due to the retrospective nature of the study, which utilized de-identified medical records. The study was conducted with the approval of the Sanpatong Hospital Ethical Committee, ensuring that all data were handled confidentially.

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