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Developing and validating a risk score for prediction of preterm birth at Felege Hiwot Comprehensive Specialized Hospital, Northwest, Ethiopia: Retrospective follow up study, 2021

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3 Developing and validating a risk score for prediction of preterm birth at Felege Hiwot
4 Comprehensive Specialized Hospital, Northwest Ethiopia: Retrospective follow- up study
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Objective: To develop and validate a risk score for the prediction of preterm birth using maternal characteristics.

Method: A retrospective follow-up study was conducted on March (1- 30) 2021 at Felege Hiwot comprehensive specialized hospital. The sample size was determined by assuming 10 events per predictor, based on this assumption total sample size was 1308. Data were collected using a structured checklist through chart review. Data were coded and entered into Epidata, version 3.02, and was analyzed by using R statistical programming language version 4.0.4 for further processing and analysis. Bivariable logistic regression was done to identify the relationship between each predictor and preterm birth. Variables with ($p \leq 0.25$) from the bivariable analysis were entered into a backward stepwise multivariable logistic regression model, and significant variables ($p < 0.05$) were retained in the multivariable model. Model accuracy and goodness of fit were assessed by computing the area under the ROC curve (discrimination) and calibration plot (calibration) respectively

Results: Residence, gravidity, hemoglobin < 11 mg/dl, early rupture of membranes, antepartum hemorrhage, and pregnancy-induced hypertension remained in the final multivariable prediction model. The AUC of the model was 0.816 (95% confidence interval: 0.779 – 0.856).

Conclusion: These results suggest the possibility of predicting preterm birth using a simple prediction model constructed from maternal characteristics.

Strength and Limitations of the study

- ✓ Adequate number of participants with the outcome, which helped us to construct the model using a sufficient number of predictor variables.
- ✓ Prediction model is constructed from easily obtainable maternal characteristics that make it applicable in primary care settings.
- ✓ A single-site study, it is confined to a single area, which needs external validation before using it in another context.
- ✓ Furthermore, data were collected from each mother's card; due to this, some important variables were missed, such as previously highlighted factors with preterm birth in different studies

Background

Preterm birth is described as babies that are born alive before the end of 37 weeks of pregnancy[1]. Preterm birth can be accidental (due to spontaneous preterm labor and/or preterm membrane rupture) or induced by the provider (by cesarean or labor induction)[2]. Most preterm births happen spontaneously[3].

An estimated 15 million babies worldwide are born too early per year. That's more than 1 in 10 infants. About 1 million newborns die per year because of preterm birth complications[4].

Across 184 countries, the rate of preterm birth ranges from 5% to 18% of babies born [5]. However, there are stark disparities in survival rates around the world. Half of the babies born at or below 32 weeks die in low-income settings due to a lack of practical, cost-effective, and critical care, such as comfort, breastfeeding assistance, basic infection care, and trouble Breathing[6].

In Ethiopia, every year, 320,000 babies are born too early and because of direct preterm complications, 24,400 children under five die [7]. According to the 2019 Mini Ethiopia Demographic and Health Survey, the neonatal mortality rate was 30 deaths per 1,000 live births and prematurity was the major cause of death[8]

Furthermore, the effect of preterm birth is also prolonged beyond the neonatal phase and throughout life[9]. Hence, the largest risk of severe health issues, including cerebral palsy, intellectual disability, chronic lung disease, and vision and hearing loss, is faced by babies born before maturity. This introduces a lifelong disability dimension. At some point in their lives, most people will face the struggles and potential disasters of preterm birth either directly in their families or indirectly through events for the nations[9, 10].

To alleviate this burden in the past few decades, numerous methods have been attempted internationally, including in Ethiopia, to prevent and enhance the treatment of preterm births [11-13]. Although several efforts were undertaken to prevent and reduce preterm birth, its rate appears to have increased over time [10, 14]. As part of the strategy, it is essential to diagnose or predict preterm birth earlier in pregnancy to take appropriate measures for high-risk groups.

There are clinical prediction models that attempt to predict the probability of preterm birth, however, all include laboratory tests that are generally not accessible in low-resource settings, like fetal fibronectin, insulin-like growth factor binding protein-1 (IGFBP-1), interleukin-6, and placental alpha-macroglobulin-1 to predict preterm birth[15-20].

Hence, because of limited resources, the use of easily accessible data to forecast preterm birth seems to be appealing in low- and middle-income areas. Although there are prediction models for preterm birth, variation in the occurrence of preterm birth globally is relevant, indicating variations in exposure to psychosocial, sociodemographic, and medical risk factors and genetic differences [21-23].

There is no prediction model for preterm birth in Ethiopia. Therefore, developing and validating a risk score for prediction of preterm birth using maternal (clinical and non-clinical) characteristics based on the available measurement is paramount to allow early preterm birth intervention such as utero transfer to tertiary care centers, appropriate corticosteroid administration while preventing excessive use, neuroprotective magnesium sulfate therapy, and antibiotic treatment in the event of infection [15, 24]

Methods and Materials

Study setting

This retrospective study was conducted among 1260 pregnant women who did prenatal care and finally delivered at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar city, Northwest Ethiopia from January 30, 2019, to January 30, 2021. Bahir Dar is the capital city of Amhara national regional state and is found 575 km northwest of Addis Ababa.

Felege Hiwot comprehensive specialized hospital was established with the German State government during the regime of Emperor H/ Selassie I in April 1963 G.C and is one of the oldest public hospitals in the Northwestern part of the country and located at the northern end of the city near Lake Tana and aspires to see a healthy, productive and prosperous society and become a center of medical service Excellency by 2029. During its establishment, it was planned to serve 25,000 people. The hospital has currently a total of 1431 manpower (5 obstetricians and gynecologists and 63 midwives among others) in different disciplines. It has a total of 500 formal beds, 11 wards (emergency ward and Inpatient wards such as Gynecological & Obstetric, Surgical, orthopedics, Medical, Pediatric, L&D, Eye unit, NICU, psychiatric, oncology, and 22 OPDS), 39 clinical and non-clinical departments /service units / providing laboratory, Diagnostic, curative & Rehabilitation service at outpatient & inpatient bases as well as disease prevention & health promotion services.

Sample size determination

The sample size required for model development was determined based on the minimum standard of 10 events per candidate predictor considered, according to the formula $N = (n \times 10)/I$ where N is the sample size, n is the number of candidate predictor variables and I is the estimated event rate in the population[25]. Since there were 17 candidate predictors considered and 10 events per candidate predictor, the estimated number of events for the study was 170. Based on a study done on the prevalence of preterm birth in Debre Tabor hospital was 13%[26], so taking into account this the required sample size was calculated as follows, $n = 170 \times 100 / 13 = 1308$.

Patient and public involvement

There was no direct interaction with patients in this study and no direct patient involvement in the design or conduct of this study.

Study Design and Participants

The theoretical design of the present study was; the incidence of preterm birth as a function of multiple predictors during pregnancy. The source population of the study was all pregnant mothers who gave birth at FHCSH. To be included in this study, mothers must meet all of the following eligibility criteria; All medical records of mothers who gave birth and had at least one ANC follow-up in FHCSH from January 30/2019 to January 30/2021.

Sampling method and procedures

A simple random sampling technique was employed to select participants using the medical registration number of a delivered mother from the delivery registration book. First, all mother delivered at FHCSH from January 30/2019 to January 30/2021 was identified from the delivery registration book. After that records of mothers who meet the inclusion criteria were included in the study. Subsequently, a sampling frame was prepared. Finally, the study unit was selected by using a computer-generated random number.

Data Collection

Outcome assessment: The outcome variable was attributed to women whose medical records indicated a physician or midwife diagnosis of preterm birth and delivery between 28 and 36 completed weeks of gestation. The gestational age (GA) was measured using either LNMP, which is found to be a more reliable measure of GA in a low-resource setting[27, 28], or an early ultrasound result.

Predictor assessment: Data was collected using a structured checklist through chart review. Checklists were developed after reviewing various relevant literature [29-33]. It consists of socio-demographic (Maternal age, Residence), Maternal obstetric characteristics : (History of preterm birth, History of abortion, history of stillbirth gravidity, Parity, Multiple pregnancy, APH, PROM, Gestational DM, and PIH), Maternal medical condition : (HGB level, Diabetic Mellitus, Chronic Hypertension, UTI and HIV).

Quality Assurance Mechanisms

To maintain the quality of data, the data collectors and supervisors were trained for a day on the objective of the study, the content of the checklists, how to fill the checklists. Afterward, reviewing 15 charts on medical records of mothers who gave birth at Felege Hiwot Comprehensive Specialized Hospital which is found in Northwest Ethiopia were done. After that, some adjustments were done accordingly. The checklist was developed in English.

Data Processing and Analysis

Data were entered into a software application (EPI DATA, version 3.02) and was analyzed by using R statistical programming language version 4.0.4 for further processing and analysis. There were 13(1%), 2(0.2 %), 11 (0.9 %),15 (2.5%), 21 (1.7%) ,29(2.3%),20(1.6%) and 20 (1.6%) missing values for premature rupture of membranes , residence, chronic hypertension, multiple pregnancy gestational diabetes Mellitus, pregnancy-induced hypertension ,antepartum hemorrhage and hemoglobin respectively. We assumed data were missing at random, and we, therefore, performed a multivariate imputation by chained equations for all variables evaluated in the prediction model [34]. Sensitivity analysis was performed to assess whether the assumption of missing at random (MAR) is valid or not, and the results were reasonably comparable (**Table1**). Descriptive statistics including median, inter-quartile range (IQR), and percentages, were carried out.

Table 1. Sensitivity analysis of the model to predict preterm birth: Comparison of the regression coefficients, standard errors (SE), and p-values for complete case analysis (CCA) and multiple imputed data (MI).

Predictor variables	Complete case analysis			Multiple imputations		
	B	SE	P value	B	SE	P value
Chronic hypertension	0.7313	0.6297	0.24	0.581	0.6285	0.92

(yes)						
Residence (rural)	0.815	0.1946	<0.001	1.154	0.1958	<0.001
GDM(yes)	0.709	0.4028	0.07	0.472	0.4236	0.26
HGB(<11g/dl)	0.497	0.2185	0.02	0.642	0.2153	0.001
PROM (yes)	1.898	0.2080	<0.001	2.097	0.2129	<0.001
APH (yes)	1.194	0.2858	<0.001	1.298	0.2874	<0.001
PIH (yes)	1.353	0.2600	<0.001	1.368	0.2523	<0.001
Multiple pregnancy (yes)	0.539	0.3173	0.08	0.446	0.3257	0.17
Gravidity(primigravida)	0.426	0.1944	0.02	0.711	0.1976	<0.001

Model Development and Validation

For model development, bivariable logistic regression was done to obtain insight into the association of each potential predictor and preterm birth. Variables with ($p < 0.25$) from the bivariable analysis were entered into a backward stepwise multivariable logistic regression model, and significant variables ($p < 0.05$) were retained in the multivariable model. The results of significant predictors were reported as coefficients with 95% confidence intervals (CI). To check for the model accuracy and goodness of fit, we computed the area under the ROC curve (discrimination) and calibration plot (calibration) using “classifierplots” and “givitiR” packages of R respectively. The AUC ranged from 0.5 (no predictive ability) to 1 (perfect discrimination)[35]. The regression coefficients and their 95% confidence levels, and the AUC were adjusted for overfitting or over-optimism using bootstrapping technique. To make internal validation, we computed 1000 random bootstrap [36]samples with the replacement on all predictors in the data. The model’s predictive performance after bootstrapping is considered as the performance that can be expected when the model is applied to future similar populations. To evaluate the clinical and public health impact of the model, we performed a decision curve analysis (DCA) [37] of standardized net benefit across a range of threshold probabilities (0 to 1). In the DCA, the model was compared against two extreme scenarios; “intervention for all” and “no intervention”. In our case, the intervention considered is the referral of high-risk pregnant women to facilities where appropriate corticosteroid administration, antibiotic treatment.

Risk Score Development

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3 To construct an easily applicable preterm birth prediction score, we transformed each coefficient
4 from the model to a rounded number by dividing it by the lowest coefficient. The number of
5 points was subsequently rounded to the nearest integer. We determined the total score for each
6 individual by assigning the points for each variable present and adding them up. The score was
7 transformed to a dichotomous, allowing each pregnant woman to be classified as having a high
8 or low risk of preterm birth. The receiver operating characteristic curve (ROC) was plotted and
9 the area under the curve (AUC) was calculated to measure the discriminatory power of the
10 scoring system.
11

12 **Ethical Approval**

13 Ethical clearance was obtained from the Institutional Review Boards (IRB) of Bahir Dar
14 University, College of Medicine and Health Sciences with Protocol number 083/ 2021) on
15 February 26, 2021. Confidentiality was maintained by omitting the personal identifier of the
16 participant during the data collection procedure and information was used only for research
17 purposes. Data were collected from the register, which was kept in a secure place and all data
18 were fully anonymized before we access them. After the collection of data, all the patient records
19 and patients' cards were placed back into a secure place. Data were entered into a password-
20 protected computer.
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Result

Demographic, Obstetric, and Clinical Characteristics of mothers who gave birth at Felege Hiwot Comprehensive Specialized Hospital.

A total of 1260 study cards were reviewed from a sample of 1308, about 48 cards were not reviewed due to the outcome of intrauterine fetal death, abortion. *Table (2)* shows the demographic, obstetric, and clinical characteristics of mothers who gave birth included in the analysis. The median age of the study participants was 26 years with IQR (24-30years); the majority of the participants 1086 (86.2%) were in the age group of 20-34 years.

More than three fourth of the participants 926 (73.49%) were urban residents. From the total of mothers who delivered at FHCSH, more than two-third 841 (66.7%) were multigravida. About parity, above half of them 713 (56.6%) were multipara. Concerning past obstetric history, 55 (6.5%) of them had a history of previous preterm birth, 76 (9%) of them had a previous history of stillbirth and 162 (19.3%) of them had a previous history of abortion.

Table 2. Demographic, obstetric, and clinical characteristics of mothers who gave birth at FHCSH from January 30/2019 to January 30/2021, in Northwest Ethiopia.

Characteristics	Category	Frequency	Percent
Gravidity	Primigravida	419	33.3
	Multigravida	841	66.7
Residence	Urban	926	73.5
	Rural	334	26.5
GDM	Yes	44	3.5
	No	1216	96.5
APH	Yes	84	6.7
	No	1176	93.3
PIH	Yes	110	8.73
	No	1150	91.27
HGB level	<11d/dl	236	18.7
	>=11g/dl	1024	81.3
Chronic hypertension	Yes	21	1.7
	No	1239	98.3

PROM	Yes	195	15.5
	No	1065	84.5
Multiple pregnancies	Yes	90	7.2
	No	1170	92.8

PROM: Premature rupture of membrane, HGB: hemoglobin, PIH: pregnancy-induced hypertension, APH: antepartum hemorrhage, GDM: gestational diabetes mellitus

Development of prediction model for preterm birth

Out of 1260 delivered neonates, 169 (13.4%) (95% CI (11.6%, 15.4%)) was preterm infants.

The bivariable logistic regression analysis found several factors were eligible to be included in the prediction model. Variables with $P \leq 0.25$ in the bivariable logistic regression analysis were hemoglobin level, Gravidity, residence, gestational diabetes mellitus, APH, PIH, chronic hypertension, PROM, and multiple pregnancies. Using the results, a prediction model was developed and an equation for the prediction model was obtained. (*Table 3*)

Table 3: Coefficients and risk-scores of each predictor included in the model to predict preterm birth ($n = 1260$)

Predictors Variables*	Multivariable analysis			
	Original β (95 % CI)	Bootstrap β	P- value	Risk score
Residence (rural)	1.161 (0.780, 1.545)	1.148	<0.001	2
Gravidity (primigravida)	0.675 (0.291, 1.061)	0.666	0.01	1
PROM (yes)	2.081 (1.669 , 2.50)	2.051	<0.001	3
APH (yes)	1.364 (0.806 , 1.915)	1.348	<0.001	2
PIH (yes)	1.387 (0.887 , 1.879)	1.368	<0.001	2
HGB <11g/dl	0.676 (0.255 , 1.09)	0.677	<0.001	1

*Variables retained in the reduced model are; residence, APH, hemoglobin, PIH, gravidity, and PROM. Both backward and forward selection showed the same results. β after internal validation with bootstrapping is shown. Simplified risk score: we divided the coefficient of predictors

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3 included in the reduced model by the smallest (0.666). The probability or risk of preterm birth = $1 / (1$
4 $+ \exp - (-3.517 + 1.148 * \text{Residence (rural)} + 0.666 * \text{gravity (primigravida)} + 2.051 * \text{PROM}$
5 $(\text{yes}) + 1.348 * \text{APH (yes)} + 1.387 * \text{PIH} + 0.677 * \text{HGB (<11g/dl)}..$
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8 The AUC of the final reduced model was 0.816 (95% confidence interval: 0.779 – 0.856)
9 **(Figure 1a)**. The calibration test had a p-value of 0.6228, indicating that the model does not
10 misrepresent the data or calibration of the model was visually accurate since observed and
11 predicted probabilities were similar **(Figure 1b)**.
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14 Validation of the model with the bootstrap technique showed hardly any indication of undue
15 influence by particular observations, with an optimism coefficient of 0.085, resulting AUC of
16 0.789 (corrected 95% CI: 0.748–0.83).
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19 Using the coefficients (β) the predicted risk cutoff point was a probability of (SpEqualSe >
20 0.1320), the model has a sensitivity of 75.74%, specificity of 72.87%, a positive predictive value
21 of 30.2%, and a negative predictive value of 95.1%.
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24 When applying DCA, we first evaluate whether our model understudy has a higher net benefit
25 than the default strategies (referring all and none). This model outperforms the default strategies
26 across the relevant threshold range. The model has the highest net benefit across the entire range
27 of threshold probabilities, which indicates that the model has the highest clinical and public
28 health value. Hence, referral decision made using the model has a higher net benefit than not
29 referring at all or referring all regardless of their risk thresholds as shown in **figure (2)**
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36 **Risk Classification Using a Simplified Risk Score**

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38 We created a simplified risk score from the model for practical use. The reduced model's
39 prediction score was simplified by rounding all regression coefficients. The simplified score had
40 a considerably comparable prediction accuracy with the original β coefficients, with an AUC of
41 0.786 (95%CI: 0.729–0.827) **(figure 3)**. The possible minimum and maximum scores a mother
42 can have are 0 and 11, respectively.
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46 When dichotomized to low risk (<3) and high risk (≥ 3) based on the risk score, 278 (14.36%)
47 were categorized as high risk and 982 (77.9%) as low risk for preterm birth. Using “SpEqualSe”,
48 the suggested threshold score to predict preterm birth using risk scores is ≥ 3 with a sensitivity of
49 75.14 % and specificity of 67.46% **(table 4)**.
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Table 4: Risk classification of preterm birth using simplified prediction score (n = 1260)

Score*(risk category)	Prediction Model Based on Maternal Characteristics	
	Number of mothers	Incidence of preterm birth
<3 (Low)	982 (77.9%)	72 (7.9%)
>=3 (High)	278 (14.36%)	97 (53.59%)
Total	1260 (100%)	169 (13.4%)

* $Score = (2*PIH) + (3*PROM) + (hemoglobin < 11 \text{ mg/dl}) + 2*residence + (2*APH) + gravidity.$

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Discussion

In this study, the incidence of preterm birth was found to be 13.4%. Maternal characteristics were identified in this retrospective study to build a preterm birth prediction risk score. The optimal combination of maternal factors to predict preterm birth include residency, gravidity, hemoglobin < 11 mg/dl, early rupture of membranes, antepartum hemorrhage, and pregnancy-induced hypertension, according to the prediction model. The model has an AUC of 0.816 (95%CI: 0.776 – 0.856). Predicting the probability of preterm birth in pregnant women is essential to take appropriate measures accordingly. Identifying women at risk of preterm birth is an important task for clinical care providers. However, in low and middle-income countries, there are only a few methods available for reliably predicting actual preterm labor in women. Previously, the focus of the research was to explain the maternal and fetal determinants of preterm birth. In recent years, the focus shifted to predicting preterm birth optimally using a combined set of characteristics.

Without any advanced laboratory or imaging testing, this study measured the predicted performance of a model based on maternal features during pregnancy. Furthermore, we discovered that utilizing SpEqualSe as an optimal cut point, the sensitivity and specificity of this prediction model achieved 75.14 percent and 67.46 percent, respectively, at the score threshold of 3.

In our study, a combination (residency, gravidity, hemoglobin < 11 mg/dl, early rupture of membranes, antepartum hemorrhage, and pregnancy-induced hypertension) of maternal characteristics results in an AUC of 0.816 (95%CI: 0.776 – 0.856), has an excellent accuracy according to diagnostic accuracy classification[38].

A study conducted in China showed that a model developed using advanced maternal age, lower maternal height, history of preterm delivery, amount of vaginal bleeding during pregnancy, and lack of folic acid intake before pregnancy for the prediction of overall preterm birth with AUC of (0.6)[39].

This difference may be due to some of the predictors they used such as lower maternal height, lack of folic acid intake before pregnancy, and advanced maternal age. However predictors they used such as lack of folic acid intake before pregnancy not easily obtainable information in routine clinical practice, which makes their model less practical in our setting. This prediction model constitutes variables that are easily obtainable and have reasonable accuracy to be used by

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3 both mid-and lower-level health professionals in the primary care settings. Among the maternal
4 characteristics included in our model, five can be easily found from history taking and one by
5 test for hemoglobin.
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8 The model's accuracy is consistent with a retrospective study done in China that established a
9 preterm birth prediction model based on maternal characteristics, including demographics and
10 clinical characteristics, and a model with predictors (gravidity, educational status, residency,
11 previous history of preterm birth, twin pregnancy, pre-gestational diabetes mellitus (type I or II),
12 chronic hypertension, and place of birth) with AUC of 0.749 (95%CI: 0.732–0.767) [40].
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15 On the other hand, a model incorporating four predictors (cervical length at admission,
16 gestational age, amniotic fluid glucose, and IL-6) has an area under the curve (AUROC) of
17 0.86[41] and similarly, the combination of biophysical, biochemical, immunological,
18 microbiological, fetal cell, exosomal, or cell-free RNA at different gestational ages, integrated as
19 part of a multivariable predictor model may be necessary to advance our attempts to predict
20 sPTL and preterm birth. In the prediction of spontaneous preterm birth within 48 hours, a
21 prognostic model including qfFN and clinical risk factors showed excellent results[42, 43]. Both
22 models have higher discriminatory performance. The reason for the lower discriminatory
23 performance in our study as compared to the studies described above could be because we used
24 secondary data available from the register and as this dataset is limited and some variables that
25 require advanced laboratory tests were not included in the model.
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36 Hence, predictors necessitate laboratory testing, which is often unavailable in low-resource
37 settings. As a result, such predictors are difficult to come by in ordinary clinical and public
38 health practice, making the model less useful.
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41 In our prediction score, using 3 as a cutoff point has an acceptable level of specificity,
42 sensitivity, PPV, and NPV to predict preterm birth. It is also possible to shift the cutoff point to
43 increase either of the accuracy measures depending on the program aim and availability of
44 resources.
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Conclusion and recommendation

This study shows the possibility of predicting preterm birth using a simple prediction model constructed from maternal characteristics. Thus, the optimal combination of maternal characteristics such as residence, gravidity, hemoglobin < 11 mg/dl, premature rupture of membrane, antepartum hemorrhage, and pregnancy-induced hypertension shows the possibility of predicting preterm birth using a simple prediction model constructed from maternal characteristics. In addition, risk score calculations based on a combination of predictors were effective and had comparable accuracy with the model-based approach of original β coefficients. This score may assist in clinical decision-making. In addition, incorporating this convenient and easily applicable score in the health care system to be used by clinicians to inform pregnant mothers about the future course of their outcome after external validation. Doing further research is needed to validate the prediction tool using prospective follow-up studies in another context before introducing it to the clinical and public health practices.

Data Sharing Statement

The data will be available upon request from the corresponding author.

Author Contributions: S.F.F. conceived the study and wrote the manuscript. Z.A.A, S.F.F, G.T.W, A.K.Y, and A.M.D, all contribute to data analysis, study design, and supervision of data collection. All authors participated in manuscript revision for intellectual content and approval of the final version. All authors have read and agreed to the published version of the manuscript.

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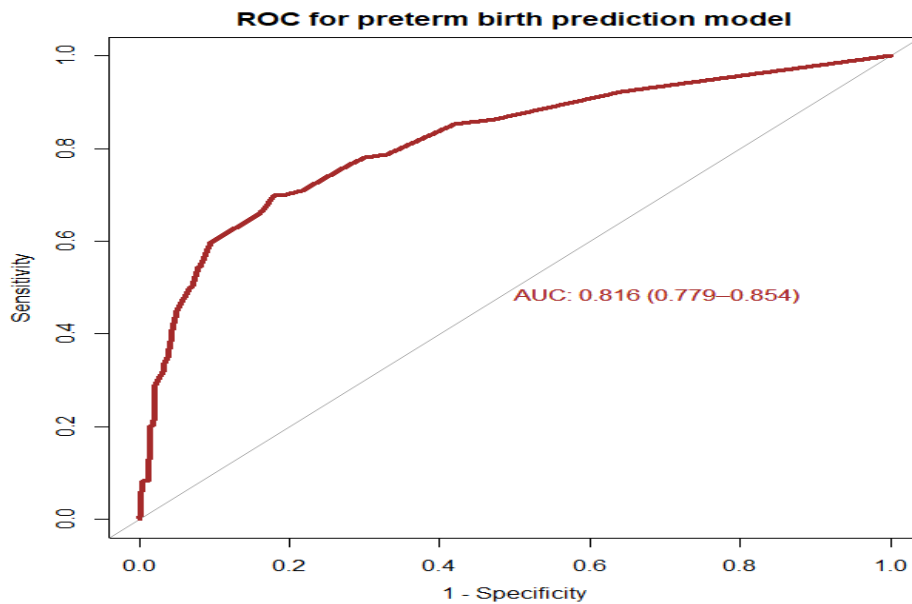
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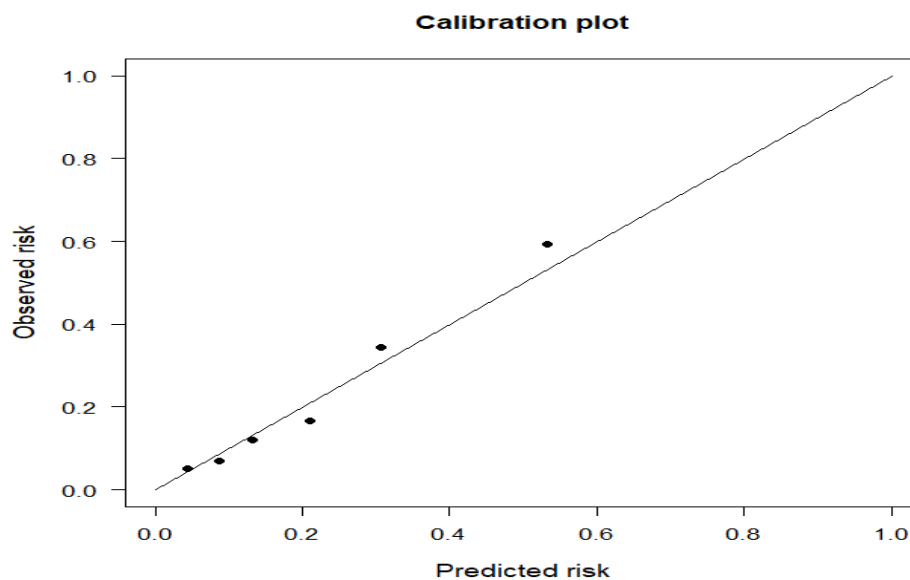
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Figure 1: (a) Area under the ROC curve for the prediction model, and (b) Predicted versus observed preterm birth probability in the sample. This analysis includes mothers who gave birth at FHCSH from January 30/2019 to January 30/2021(n = 1260). Calibration plot created using “plot Calibration” in R programming.

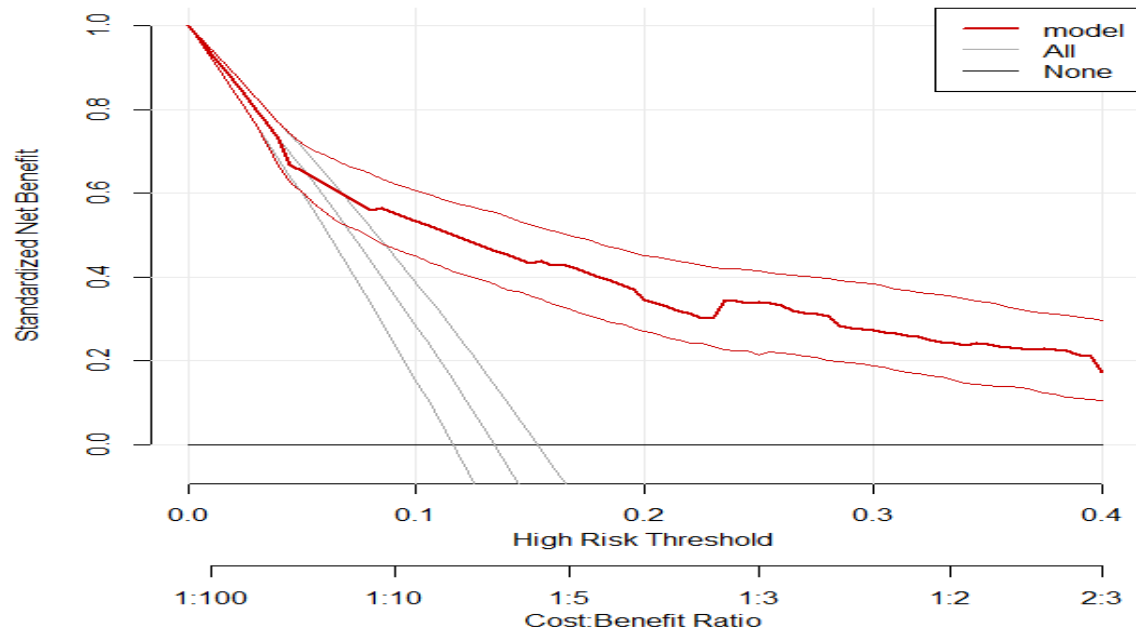


Figure 2: A decision curve plotting showing the net benefit of the model against threshold probability.

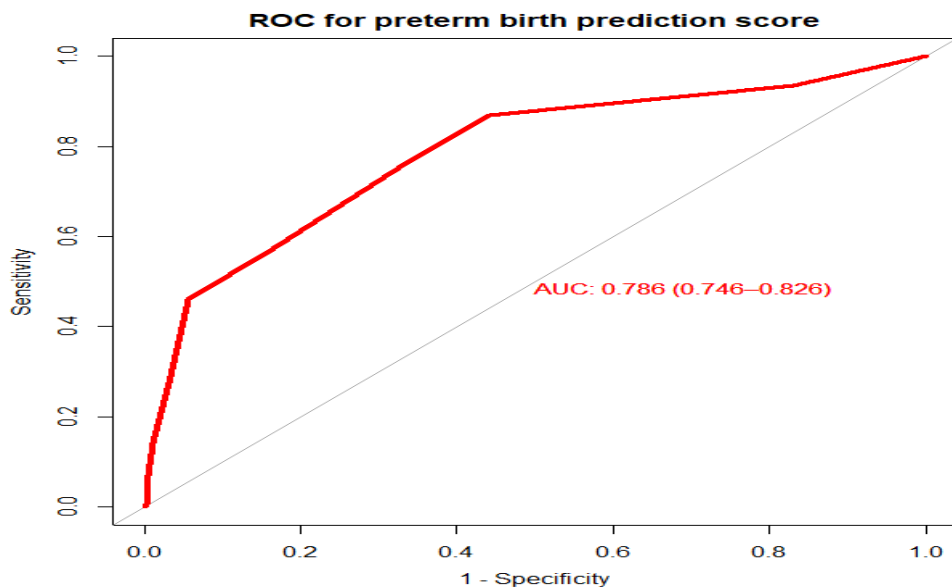


Figure 3: Area under the ROC curve for the simplified risk score to predict the risk of preterm birth among mothers who gave birth at FHCSH from January 30/2019 to January 30/2021.

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Developing and validating risk prediction model for preterm birth at Felege Hiwot comprehensive specialized hospital, Northwest Ethiopia: A retrospective follow-up study

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5 2 Developing and validating risk prediction model for preterm birth at Felege
6 3 Hiwot comprehensive specialized hospital, Northwest Ethiopia: A retrospective
7 4 follow-up study
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11 5 Sefineh F.Feleke*¹, Zelalem A.Anteneh², Gizachew T.Wassie², Anteneh K. Yalew³, Anteneh
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29 Abstract

30 **Objective:** To develop and validate a risk prediction model for the prediction of preterm birth
31 using maternal characteristics.

32 **Design:** A retrospective follow-up study was conducted. Data were coded and entered into
33 Epidata, version 3.02, and were analyzed by using R statistical programming language version
34 4.0.4 for further processing and analysis. Bivariable logistic regression was done to identify the
35 relationship between each predictor and preterm birth. Variables with ($p \leq 0.25$) from the
36 bivariable analysis were entered into a backward stepwise multivariable logistic regression
37 model, and significant variables ($p < 0.05$) were retained in the multivariable model. Model
38 accuracy and goodness of fit were assessed by computing the area under the ROC curve
39 (discrimination) and calibration plot (calibration) respectively.

40 **Setting and participants:** This retrospective study was conducted among 1260 pregnant women
41 who did prenatal care and finally delivered at Felege Hiwot Comprehensive Specialized
42 Hospital, Bahir Dar city, Northwest Ethiopia from January 30, 2019, to January 30, 2021.

43 **Results:** Residence, gravidity, haemoglobin < 11 mg/dl, early rupture of membranes, antepartum
44 haemorrhage, and pregnancy-induced hypertension remained in the final multivariable prediction
45 model. The AUC of the model was 0.816 (95% confidence interval: 0.779 – 0.856).

46 **Conclusion:** This study showed the possibility of predicting preterm birth using maternal
47 characteristics during pregnancy. Thus, using this model could help to identify pregnant women
48 at a higher risk of having a preterm birth to be linked to a center

49 **Keywords:** Prediction Model, Preterm birth, Risk score, Ethiopia

50 Strength and Limitations of the study

- 51 ✓ An adequate number of participants with the outcome helped us to construct the
52 model using a sufficient number of predictor variables and inclusion of sensitivity
53 analyses.
- 54 ✓ Multiple imputations was used to address missing data, which has been shown to be a
55 valid technique for dealing with missing data within logistic regression models, resulting
56 in less bias than excluding all women with missing data[1].
- 57 ✓ The prediction model is constructed from easily obtainable maternal characteristics that
58 make it applicable in primary care settings.

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3 59 ✓ A single-site study, it is confined to a single area, which needs external validation before
4 using it in another context.
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6 61 ✓ Furthermore, data were collected from each mother's card; due to this, some important
7 variables were missed, such as previously highlighted factors with preterm birth in
8 different studies.
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14 65 **Introduction**

15
16 66 Preterm birth is described as babies that are born alive before the end of 37 weeks of
17 pregnancy[2]. Preterm birth can be accidental (due to spontaneous preterm labor and/or preterm
18 membrane rupture) or induced by the provider (by cesarean or labor induction)[3]. Most preterm
19 births happen spontaneously[4].
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23 70 An estimated 15 million babies worldwide are born too early per year. That's more than 1 in 10
24 infants. About 1 million newborns die per year because of preterm birth complications[5].
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26 72 Across 184 countries, the rate of preterm birth ranges from 5% to 18% of babies born [6].
27
28 73 However, there are stark disparities in survival rates around the world. Half of the babies born at
29 or below 32 weeks die in low-income settings due to a lack of practical, cost-effective, and
30 critical care, such as comfort, breastfeeding assistance, basic infection care, and trouble
31 Breathing[7].
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35 77 Furthermore, the effect of preterm birth is also prolonged beyond the neonatal phase and
36 throughout life[8]. Hence, the largest risk of severe health issues, including cerebral palsy,
37 intellectual disability, chronic lung disease, and vision and hearing loss, is faced by babies born
38 before maturity. This introduces a lifelong disability dimension. At some point in their lives,
39 most people will face the struggles and potential disasters of preterm birth either directly in their
40 families or indirectly through events for the nations[8, 9].
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44 82 To alleviate this burden in the past few decades, numerous methods have been attempted
45 internationally, including in Ethiopia, to prevent and enhance the treatment of preterm births [10-
46 12]. As part of the strategy, it is essential to diagnose or predict preterm birth earlier in
47 pregnancy to take appropriate measures for high-risk groups.
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51 86 However, in most nations, predicting preterm birth is still largely based on subjective clinical
52 experience. This approach may increase unnecessary hospital admissions and unnecessary but
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89 potentially harmful treatments, such as the use of steroids for the maturation of the fetal lung and
90 tocolysis[13, 14]

91 There were clinical prediction models that aim to estimate the likelihood of preterm birth that
92 include laboratory tests that are typically inaccessible in low-resource settings, such as fetal
93 fibronectin, insulin-like growth factor binding protein-1 (IGFBP-1), interleukin-6, and placental
94 alpha-macroglobulin-1[15-20].

95 Although there were prediction models for preterm birth, variation in the occurrence of preterm
96 birth globally is relevant, indicating variations in exposure to psychosocial, sociodemographic,
97 and medical risk factors and genetic differences [21-23].

98 Hence, because of limited resources, the use of easily accessible data to forecast preterm birth
99 seems to be appealing in low- and middle-income areas.

100 Therefore, developing and validating a risk prediction model for prediction of preterm birth
101 using maternal(clinical and non-clinical) characteristics based on the available measurement is
102 paramount to allow early preterm birth intervention such as utero transfer to tertiary care centers,
103 appropriate corticosteroid administration while preventing excessive use, neuroprotective
104 magnesium sulfate therapy, and antibiotic treatment in the event of infection[15, 24]

105 **Methods and Materials**

106 **Study setting**

107 This retrospective study was conducted among 1260 pregnant women who did prenatal care and
108 finally delivered at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar city,
109 Northwest Ethiopia from January 30, 2019, to January 30, 2021. Bahir Dar is the capital city of
110 Amhara national regional state and is found 575 km northwest of Addis Ababa.
111 The hospital has currently a total of 1431 manpower (5 Obstetricians and Gynaecologists and 63
112 midwives among others) in different disciplines. It has a total of 500 formal beds, 11 wards
113 (emergency ward and Inpatient wards such as Gynecological & Obstetric, Surgical, Orthopaedics,
114 Medical, Pediatric, L&D, Eye unit, NICU, psychiatric, oncology, and 22 OPDS), 39 clinical and
115 non-clinical departments /service units / providing laboratory, Diagnostic, curative &
116 Rehabilitation service at outpatient & inpatient bases as well as disease prevention & health
117 promotion services.

121 **Sample size determination**

122 The sample size required for model development was determined based on the minimum
123 standard of 10 events per candidate predictor considered, according to the formula $N = (n \times 10)/I$
124 where N is the sample size, n is the number of candidate predictor variables and I is the
125 estimated event rate in the population[25]. Since there were 17 candidate predictors considered
126 and 10 events per candidate predictor, the estimated number of events for the study was 170.
127 Based on a study done on the prevalence of preterm birth in Debre Tabor hospital was 13%[26],
128 so taking into account this the required sample size was calculated as follows, $n = 170 \times 100 / 13 =$
129 1308.

130 **Study Design and Participants**

131 The theoretical design of the present study was; the incidence of preterm birth as a function of
132 multiple predictors during pregnancy. The source population of the study was all pregnant
133 mothers who gave birth at FHCSH. To be included in this study, mothers must meet all of the
134 following eligibility criteria; All medical records of mothers who gave live birth and had at least
135 one ANC follow-up in FHCSH from January 30/2019 to January 30/2021.

136 **Sampling method and procedures**

137 A simple random sampling technique was employed to select participants using the medical
138 registration number of a delivered mother from the delivery registration book. First, all mother
139 delivered at FHCSH in the last two years was identified from the delivery registration book.
140 After that records of mothers who meet the inclusion criteria were included in the study.
141 Subsequently, a sampling frame was prepared. Finally, the study unit was selected by using a
142 computer-generated random number.

143 **Data Collection**

144 Outcome assessment: The outcome variable was attributed to women whose medical records
145 indicated a physician or midwife diagnosis of preterm birth and delivery between 28 and 36
146 completed weeks of gestation. The gestational age (GA) was measured using either LNMP,
147 which is found to be a more reliable measure of GA in a low-resource setting[27, 28], or an early
148 ultrasound result(12 weeks).

149 Predictor assessment: Data were collected using a structured checklist through chart review.
150 Checklists were developed after reviewing various relevant literatures [29-33]. It consists of
151 socio-demographic (Maternal age, Residence), Maternal obstetric characteristics : (History of

152 preterm birth, History of abortion, history of stillbirth gravidity, Parity, Multiple pregnancy,
 153 APH, PROM, Gestational DM, and PIH), Maternal medical condition : (HGB level, Diabetic
 154 Mellitus, Chronic Hypertension, UTI and HIV).

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156 **Quality Assurance Mechanisms**

157 To maintain the quality of data, the data collectors and supervisors were trained for a day on the
 158 objective of the study, the content of the checklists, how to fill the checklists. Afterward,
 159 reviewing 15 charts on medical records of mothers who gave birth at Felege Hiwot
 160 Comprehensive Specialized Hospital which is found in Northwest Ethiopia were done. After
 161 that, some adjustments (removing variables that were not available in medical record of mothers)
 162 were done accordingly. The checklist was developed in English.

163 **Data Processing and Analysis**

164 Data were entered into a software application (EPI DATA, version 3.02) and was analyzed by
 165 using R statistical programming language version 4.0.4 for further processing and analysis.
 166 There were 13(1%), 2(0.2 %), 11 (0.9 %),15 (2.5%), 21 (1.7%) ,29(2.3%),20(1.6%) and 20
 167 (1.6%) missing values for premature rupture of membranes , residence, chronic hypertension,
 168 multiple pregnancy gestational diabetes Mellitus, pregnancy-induced hypertension ,antepartum
 169 hemorrhage and hemoglobin respectively.

170 We assumed data were missing at random, and we, therefore, performed a multivariate
 171 imputation by chained equations for all variables evaluated in the prediction model [34].
 172 Sensitivity analysis was performed to assess whether the assumption of missing at random
 173 (MAR) is valid or not, and the results were reasonably comparable table (1). Descriptive
 174 statistics including median, inter-quartile range (IQR), and percentages, were carried out.

175 **Table 1. Sensitivity analysis of the model to predict preterm birth: Comparison of the**
 176 **regression coefficients, standard errors (SE), and p-values for complete case analysis**
 177 **(CCA) and multiple imputed data (MI).**

178 Predictor variables	179 Complete case analysis			180 Multiple imputations		
	181 B	182 SE	183 P value	184 B	185 SE	186 P value
187 Chronic hypertension 188 (yes)	189 0.7313	190 0.6297	191 0.24	192 0.581	193 0.6285	194 0.92

Residence (rural)	0.815	0.1946	<0.001	1.154	0.1958	<0.001
GDM(yes)	0.709	0.4028	0.07	0.472	0.4236	0.26
HGB(<11g/dl)	0.497	0.2185	0.02	0.642	0.2153	0.001
PROM (yes)	1.898	0.2080	<0.001	2.097	0.2129	<0.001
APH (yes)	1.194	0.2858	<0.001	1.298	0.2874	<0.001
PIH (yes)	1.353	0.2600	<0.001	1.368	0.2523	<0.001
Multiple pregnancy (yes)	0.539	0.3173	0.08	0.446	0.3257	0.17
Gravidity(primigravida)	0.426	0.1944	0.02	0.711	0.1976	<0.001

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179 Model Development and Validation

180 For model development, bivariable logistic regression was done to obtain insight into the
 181 association between each potential predictor and preterm birth. Variables with ($p \leq 0.25$) from
 182 the bivariable analysis were entered into a backward stepwise multivariable logistic regression
 183 model, and significant variables ($p < 0.05$) were retained in the multivariable model. The results
 184 of significant predictors were reported as coefficients with 95% confidence intervals (CI). To
 185 check for the model accuracy and goodness of fit, we computed the area under the ROC curve
 186 (discrimination) and calibration plot (calibration) using “classifierplots” and “givitiR” packages
 187 of R respectively. The AUC ranged from 0.5 (no predictive ability) to 1 (perfect
 188 discrimination)[35]. The regression coefficients and their 95% confidence levels, and the AUC
 189 were adjusted for overfitting or over-optimism using bootstrapping technique. To make internal
 190 validation, we computed 1000 random bootstrap [36]samples with the replacement on all
 191 predictors in the data. The model’s predictive performance after bootstrapping is considered as
 192 the performance that can be expected when the model is applied to future similar populations. To
 193 evaluate the clinical and public health impact of the model, we performed a decision curve
 194 analysis (DCA) [37] of standardized net benefit across a range of threshold probabilities (0 to 1).
 195 In the DCA, the model was compared against two extreme scenarios; “intervention for all” and
 196 “no intervention”. In our case, the intervention considered is the referral of high-risk pregnant
 197 women to facilities where appropriate corticosteroid administration, antibiotic treatment.

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201 **Risk Score Development**

202 To construct an easily applicable preterm birth prediction score, we transformed each coefficient
203 from the model into a rounded number by dividing it by the lowest coefficient. The number of
204 points was subsequently rounded to the nearest integer. We determined the total score for each
205 individual by assigning the points for each variable present and adding them up. The score was
206 transformed to a dichotomous, allowing each pregnant woman to be classified as having a high
207 or low risk of preterm birth. The receiver operating characteristic curve (ROC) was plotted and
208 the area under the curve (AUC) was calculated to measure the discriminatory power of the
209 scoring system.

210 **Patient and public involvement**

211 There was no direct interaction with patients in this study and no direct patient involvement in
212 the design or conduct of this study.

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229 Result

230 Demographic, Obstetric, and Clinical Characteristics of mothers

231 A total of 1260 study cards were reviewed from a sample of 1308, about 48 cards were not
 232 reviewed due to the outcome of intrauterine fetal death, and abortion. Table (2) shows the
 233 demographic, obstetric, and clinical characteristics of mothers who gave birth included in the
 234 analysis. The median age of the study participants was 26 years with IQR (24-30years); the
 235 majority of the participants 1086 (86.2%) were in the age group of 20-34 years.
 236 More than three fourth of the participants 926 (73.49%) were urban residents. Of the total of
 237 mothers who delivered at FHCSH, more than two-thirds of 841 (66.7%) were multigravida.
 238 About parity, above half of them 713 (56.6%) were multipara. Concerning past obstetric history,
 239 55 (6.5%) of them had a history of previous preterm birth, 76 (9%) of them had a previous
 240 history of stillbirth and 162 (19.3%) of them had a previous history of abortion.

241 **Table 2. Demographic, obstetric, and clinical characteristics of mothers who gave birth at**
 242 **FHCSH , Northwest Ethiopia, 2021.**

Characteristics	Category	Frequency	Percent
Gravidity	Primigravida	419	33.3
	Multigravida	841	66.7
Residence	Urban	926	73.5
	Rural	334	26.5
GDM	Yes	44	3.5
	No	1216	96.5
APH	Yes	84	6.7
	No	1176	93.3
PIH	Yes	110	8.73
	No	1150	91.27
HGB level	<11d/dl	236	18.7
	>=11g/dl	1024	81.3
Chronic hypertension	Yes	21	1.7
	No	1239	98.3
PROM	Yes	195	15.5

	No	1065	84.5
Multiple pregnancies	Yes	90	7.2
	No	1170	92.8

243 *PROM: Premature rupture of membrane, HGB: hemoglobin, PIH: pregnancy-induced*
 244 *hypertension, APH: antepartum hemorrhage, GDM: gestational diabetes mellitus*

245

246 **Development of prediction model for preterm birth**

247 Out of 1260 delivered neonates, 169 (13.4%) (95%, CI (11.6%, 15.4%) was preterm infants.

248 The bivariable logistic regression analysis found several factors were eligible to be included in
 249 the prediction model. These variables were haemoglobin level, Gravidity, residence, gestational
 250 diabetes mellitus, APH, PIH, chronic hypertension, PROM, and multiple pregnancies. Using the
 251 results, a prediction model was developed an equation for the prediction model was obtained
 252 table (3).

253 **Table 3: Coefficients and risk-scores of each predictor included in the model to predict**
 254 **preterm birth ($n = 1260$)**

Predictors Variables*	Multivariable analysis			
	Original β (95 % CI)	Bootstrap β	P- value	Risk score
Residence (rural)	1.161 (0.780, 1.545)	1.148	<0.001	2
Gravidity (primigravida)	0.675 (0.291, 1.061)	0.666	0.01	1
PROM (yes)	2.081 (1.669 , 2.50)	2.051	<0.001	3
APH (yes)	1.364 (0.806 , 1.915)	1.348	<0.001	2
PIH (yes)	1.387 (0.887 , 1.879)	1.368	<0.001	2
HGB <11g/dl	0.676 (0.255 , 1.09)	0.677	<0.001	1

255 **Variables retained in the reduced model are; residence, APH, hemoglobin, PIH, gravidity, and PROM.*
 256 *Both backward and forward selection showed the same results. β after internal validation with*
 257 *bootstrapping is shown. Simplified risk score: we divided the coefficient of predictors included in the*

reduced model by the smallest (0.666). The probability or risk of preterm birth = $1 / (1 + \exp(-3.517 + 1.148 * \text{Residence (rural)} + 0.666 * \text{gravity (primigravida)} + 2.051 * \text{PROM (yes)} + 1.348 * \text{APH (yes)} + 1.387 * \text{PIH} + 0.677 * \text{HGB (<11g/dl)}))$.

The AUC of the final reduced model was 0.816 (95% confidence interval: 0.779 – 0.856) (**Figure 1a**). The calibration test had a p-value of 0.492, indicating that the model does not misrepresent the data or calibration of the model was visually accurate since observed and predicted probabilities were similar (**Figure 1b**).

Validation of the model with the bootstrap technique showed hardly any indication of undue influence by particular observations, with an optimism coefficient of 0.085, resulting AUC of 0.789 (corrected 95% CI: 0.748–0.83).

Using the coefficients (β) the predicted risk cutoff point was a probability of (SpEqualSe > 0.1320), the model has a sensitivity of 75.74%, specificity of 72.87%, a positive predictive value of 30.2%, and a negative predictive value of 95.1%.

When applying DCA, we first evaluate whether our model understudy has a higher net benefit than the default strategies (referring all and none). This model outperforms the default strategies across the relevant threshold range. The model has the highest net benefit across the entire range of threshold probabilities, which indicates that the model has the highest clinical and public health value. Hence, referral decision made using the model has a higher net benefit than not referring at all or referring all regardless of their risk thresholds as shown in *figure (2)*.

Risk Classification Using a Simplified Risk Score

We created a simplified risk score from the model for practical use. The reduced model's prediction score was simplified by rounding all regression coefficients. The simplified score had a considerably comparable prediction accuracy with the original β coefficients, with an AUC of 0.786 (95%CI: 0.729–0.827) (**figure 3**). The possible minimum and maximum scores a mother can have are 0 and 11, respectively.

Using “SpEqualSe”, the suggested threshold score to predict preterm birth using risk scores is ≥ 3 with a sensitivity of 75.14 % and specificity of 67.46% table (4).

When dichotomized to low risk (<3) and high risk (≥ 3) based on the risk score, 278 (14.36%) were categorized as high risk and 982 (77.9%) as low risk for preterm birth.

Table 4: Risk classification of preterm birth using simplified prediction score (n = 1260)

Score*(risk	Prediction Model Based on Maternal Characteristics
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category)	Number of mothers	Incidence of preterm birth
<3 (Low)	982 (77.9%)	72 (7.9%)
>=3 (High)	278 (14.36%)	97 (53.59%)
Total	1260 (100%)	169 (13.4%)

* $Score = (2*PIH) + (3*PROM) + (hemoglobin < 11 \text{ mg/dl}) + 2*residence + (2*APH) +$
gravidity.

Discussion

In this study, the incidence of preterm birth was found to be 13.4%. Maternal characteristics were identified in this retrospective study to build a preterm birth prediction risk score. The optimal combination of maternal factors to predict preterm birth include residency, gravidity, hemoglobin < 11 mg/dl, early rupture of membranes, antepartum hemorrhage, and pregnancy-induced hypertension, according to the prediction model. The model has an AUC of 0.816 (95%CI: 0.776 – 0.856). Predicting the probability of preterm birth in pregnant women is essential to take appropriate measures accordingly. Identifying women at risk of preterm birth is an important task for clinical care providers. However, in low and middle-income countries, there are only a few methods available for reliably predicting actual preterm labor in women. Previously, the focus of the research was to explain the maternal and fetal determinants of preterm birth. In recent years, the focus shifted to predicting preterm birth optimally using a combined set of characteristics.

Without any advanced laboratory or imaging testing, this study measured the predicted performance of a model based on maternal features during pregnancy. Furthermore, we discovered that utilizing SpEqualSe as an optimal cut point, the sensitivity and specificity of this prediction model achieved 75.14 percent and 67.46 percent, respectively, at the score threshold of 3.

In our study, a combination (residency, gravidity, hemoglobin < 11 mg/dl, early rupture of membranes, antepartum hemorrhage, and pregnancy-induced hypertension) of maternal characteristics results in an AUC of 0.816 (95%CI: 0.776 – 0.856), has an excellent accuracy according to diagnostic accuracy classification[38].

A study conducted in China showed that a model developed using advanced maternal age, lower maternal height, history of preterm delivery, amount of vaginal bleeding during pregnancy, and lack of folic acid intake before pregnancy for the prediction of overall preterm birth with AUC of (0.6)[39].

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3 316 This difference may be due to some of the predictors they used such as lower maternal height,
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5 317 lack of folic acid intake before pregnancy, and advanced maternal age. However predictors they
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7 318 used such as lack of folic acid intake before pregnancy not easily obtainable information in
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9 319 routine clinical practice, which makes their model less practical in our setting. This prediction
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11 320 model constitutes variables that are easily obtainable and have reasonable accuracy to be used by
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13 321 both mid-and lower-level health professionals in the primary care settings. Among the maternal
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15 322 characteristics included in our model, five can be easily found from history taking and one by
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17 323 test for hemoglobin.

17 324 The model's accuracy is consistent with a retrospective study done in China that established a
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19 325 preterm birth prediction model based on maternal characteristics, including demographics and
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21 326 clinical characteristics, and a model with predictors (gravidity, educational status, residency,
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23 327 previous history of preterm birth, twin pregnancy, pre-gestational diabetes mellitus (type I or II),
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25 328 chronic hypertension, and place of birth) with AUC of 0.749 (95%CI: 0.732–0.767) [40].

25 329 On the other hand, a model incorporating four predictors (cervical length at admission,
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27 330 gestational age, amniotic fluid glucose, and IL-6) has an area under the curve (AUROC) of
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29 331 0.86[41] and similarly, the combination of biophysical, biochemical, immunological,
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31 332 microbiological, fetal cell, exosomal, or cell-free RNA at different gestational ages, integrated as
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33 333 part of a multivariable predictor model may be necessary to advance our attempts to predict
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35 334 sPTL and preterm birth. In the prediction of spontaneous preterm birth within 48 hours, a
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37 335 prognostic model including qfFN and clinical risk factors showed excellent results[42, 43]. Both
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39 336 models have higher discriminatory performance. The reason for the lower discriminatory
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41 337 performance in our study as compared to the studies described above could be because we used
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43 338 secondary data available from the register and as this dataset is limited and some variables that
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45 339 require advanced laboratory tests were not included in the model.

44 340 Hence, predictors necessitate laboratory testing, which is often unavailable in low-resource
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46 341 settings. As a result, such predictors are difficult to come by in ordinary clinical and public
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48 342 health practice, making the model less useful.

49 343 A study conducted in the UK found that data on maternal characteristics and obstetric history at
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51 344 11–13 weeks of gestation were predictive of spontaneous early preterm deliveries; this model
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53 345 had an AUC of 0.67[44] which had lower discriminatory performance than the present study.

54 346 This difference may be difference in study population.

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3 347 A model that predict a risk of preterm delivery in women with a multiple pregnancy
4 348 incorporates previous preterm delivery, monochorionicity, smoking, educational level, and triplet
5 349 pregnancy for preterm and very preterm delivery had a c-index of 0.68 (95% CI 0.63 to 0.72) and
6 350 0.68 (95% CI 0.62 to 0.75) respectively[45]. It had lower discriminatory performance than the
7 351 present study. This might be due to study population difference. In the present study the study
8 352 populations were both women who had multiple pregnancies and singleton pregnancy.

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13 353 In our prediction score, using 3 as a cutoff point has an acceptable level of specificity,
14 354 sensitivity, PPV, and NPV to predict preterm birth. It is also possible to shift the cutoff point to
15 355 increase either of the accuracy measures depending on the program aim and availability of
16 356 resources.

20 357 **Conclusion and recommendation**

21
22 358 This study shows the possibility of predicting preterm birth using a simple prediction model
23 359 constructed from maternal characteristics. Thus, the optimal combination of maternal
24 360 characteristics such as residence, gravidity, haemoglobin < 11 mg/dl, premature rupture of
25 361 membrane, antepartum haemorrhage, and pregnancy-induced hypertension shows the possibility
26 362 of predicting preterm birth using a simple prediction model constructed from maternal
27 363 characteristics. In addition, risk score calculations based on a combination of predictors were
28 364 effective and had comparable accuracy with the model-based approach of original β coefficients.
29 365 This score may assist in clinical decision-making. In addition, incorporating this convenient and
30 366 easily applicable score in the health care system to be used by clinicians to inform pregnant
31 367 mothers about the future course of their outcome after external validation. Doing further research
32 368 is needed to validate the prediction tool using prospective follow-up studies in another context
33 369 before introducing it to the clinical and public health practices.

43 370 **Data Sharing Statement**

44 371 The data will be available upon request from the corresponding author.

45 372 **Author Contributions:** S.F.F. conceived the study and wrote the manuscript. Z.A.A, S.F.F,
46 373 G.T.W, A.K.Y, and A.M.D, all contribute to data analysis, study design, and supervision of data
47 374 collection. All authors participated in manuscript revision for intellectual content and approval of
48 375 the final version. All authors have read and agreed to the published version of the manuscript.

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50 377 (2500ETB).

378 **Competing interest's statement:** The author reports no conflicts of interest in this work.

379 **Ethical approval**

380 Ethical clearance was obtained from the Institutional Review Boards (IRB) of Bahir Dar
 381 University, College of Medicine and Health Sciences with Protocol number 083/ 2021) on
 382 February 26, 2021. Confidentiality was maintained by omitting the personal identifier of the
 383 participant during the data collection procedure and information was used only for research
 384 purposes. Data were collected from the register, which was kept in a secure place and all data
 385 were fully anonymized before we access them. After the collection of data, all the patient records
 386 and patient cards were placed back in a secure place. Data were entered into a password-
 387 protected computer.

388 **References**

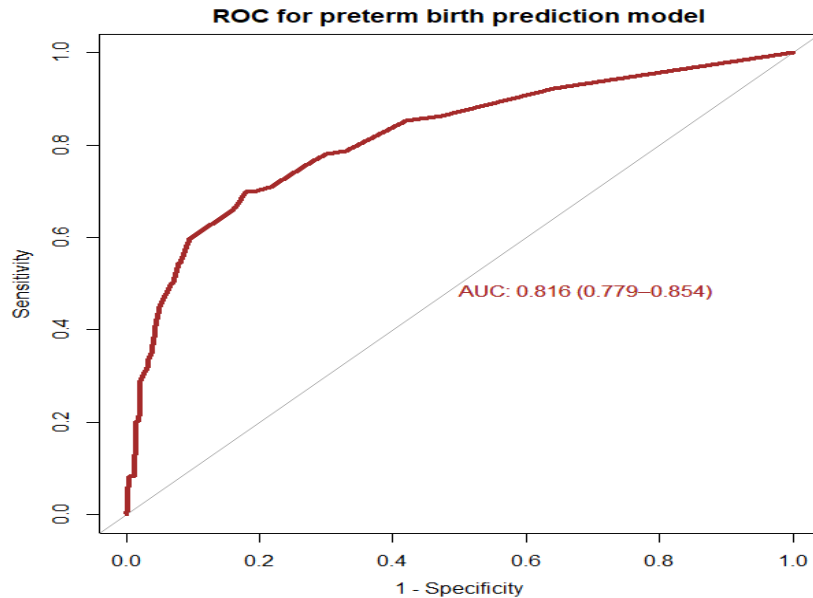
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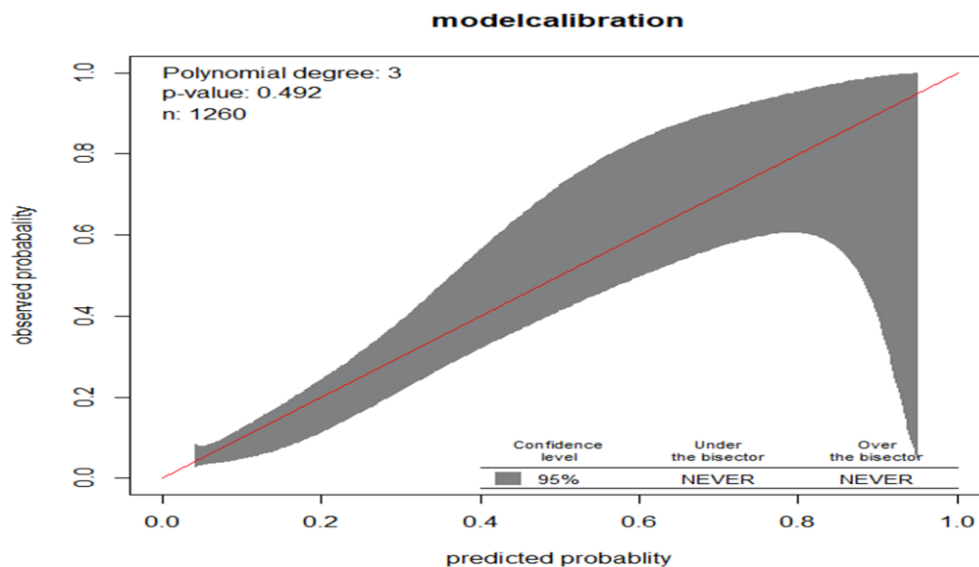
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Figure 1: (a) Area under the ROC curve for the prediction model, and (b) Predicted versus observed preterm birth probability in the sample. This analysis includes mothers who gave birth at FHCSH, 2021(n = 1260). Calibration plot created using “givitiCalibrationBelt” in R programming.

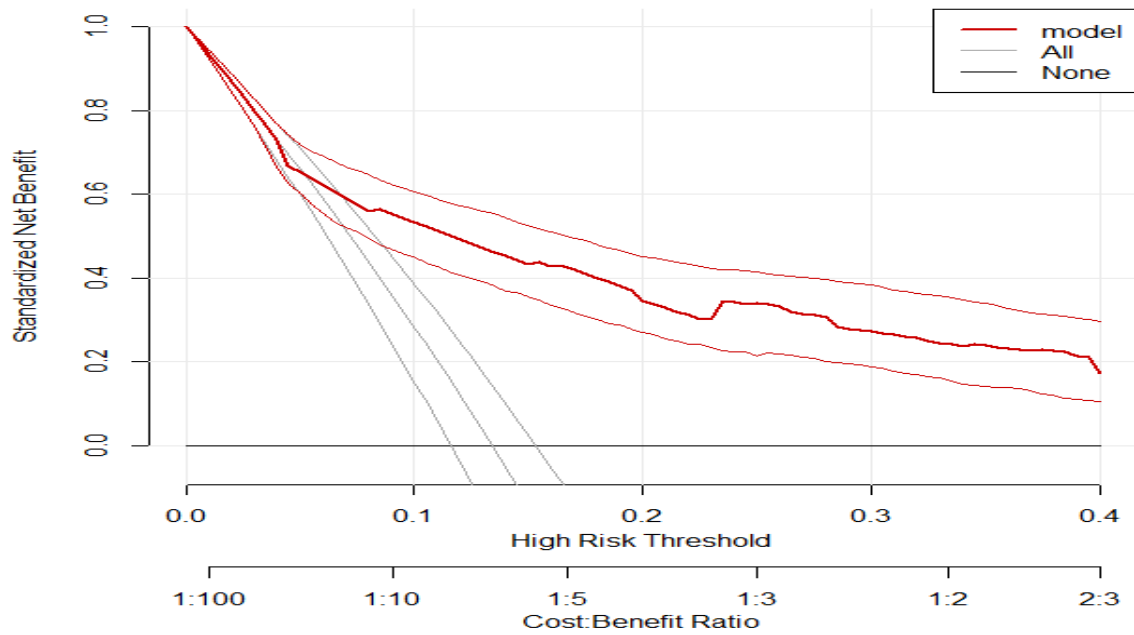


Figure 2: A decision curve plotting the net benefit of the model against threshold probability.

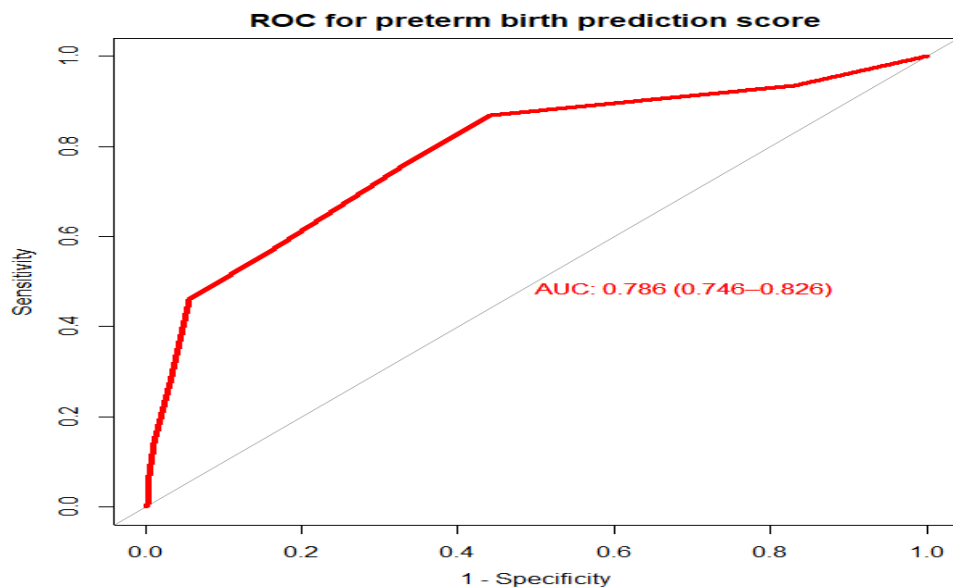


Figure 3: Area under the ROC curve for the simplified risk score to predict the risk of preterm birth among mothers who gave birth at FHCSH, 2021.

The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Line 1-59	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Line 1-59
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Line 60-100		
Objectives	3	State specific objectives, including any prespecified hypotheses	Line 96-98		
Methods					
Study Design	4	Present key elements of study design early in the paper	Line 103		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Line 103-113 Line 123-128		
Participants	6	(a) <i>Cohort study</i> - Give the eligibility criteria, and the	Line 123-128	RECORD 6.1: The methods of study population selection (such as codes or	Line 129-135

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25		<p>sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p><i>(b) Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>		<p>algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.</p> <p>RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.</p> <p>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.</p>		
26 27 28 29 30 31 32	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Line 137-147	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Line 137-147
33 34 35 36 37 38 39 40	Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Line 142-147		
41 42	Bias	9	Describe any efforts to address potential sources of bias	Line 123-141		
43 44	Study size	10	Explain how the study size was	Line 114-122		

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		arrived at			
1 2 3 4 5 6	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Line 155-198	
7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Line 155-198	
31 32 33 34 35 36 37 38 39 40 41	Data access and cleaning methods		Line 148-154		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.
42 43 44	Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-
					Line 130-132

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (<i>e.g.</i> , numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Line 130-135	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Line 130-135
Descriptive data	14	(a) Give characteristics of study participants (<i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i> , average and total amount)	Line 232-241		
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures	Line 247		
Main results	16	(a) Give unadjusted estimates	Line 246-286		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Line 162-166		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Line 351-362		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Line 50-59	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Line 351-362		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Line 351-362		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Line 369		
Accessibility of protocol, raw data, and programming code		Line 364		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Line 364

*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Developing and validating risk prediction model for preterm birth at Felege Hiwot comprehensive specialized hospital, Northwest Ethiopia: A retrospective follow-up study

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6 2 Developing and validating risk prediction model for preterm birth at Felege
7 3
8 3 Hiwot Comprehensive Specialized Hospital, Northwest Ethiopia: A
9 4
10 4 retrospective follow-up study

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29 Abstract

30 **Objective:** To develop and validate a risk prediction model for the prediction of preterm birth
31 using maternal characteristics.

32 **Design:** A retrospective follow-up study was conducted. Data were coded and entered into
33 Epidata, version 3.02, and were analyzed by using R statistical programming language version
34 4.0.4 for further processing and analysis. Bivariable logistic regression was done to identify the
35 relationship between each predictor and preterm birth. Variables with ($p \leq 0.25$) from the
36 bivariable analysis were entered into a backward stepwise multivariable logistic regression
37 model, and significant variables ($p < 0.05$) were retained in the multivariable model. Model
38 accuracy and goodness of fit were assessed by computing the area under the ROC curve
39 (discrimination) and calibration plot (calibration), respectively.

40 **Setting and participants:** This retrospective study was conducted among 1260 pregnant women
41 who did prenatal care and finally delivered at Felege Hiwot Comprehensive Specialized
42 Hospital, Bahir Dar city, Northwest Ethiopia, from January 30, 2019, to January 30, 2021.

43 **Results:** Residence, gravidity, haemoglobin < 11 mg/dl, early rupture of membranes, antepartum
44 haemorrhage, and pregnancy-induced hypertension remained in the final multivariable prediction
45 model. The AUC of the model was 0.816 (95% confidence interval: 0.779 – 0.856).

46 **Conclusion:** This study showed the possibility of predicting preterm birth using maternal
47 characteristics during pregnancy. Thus, using this model could help to identify pregnant women
48 at a higher risk of having a preterm birth to be linked to a center

49 **Keywords:** Prediction Model, Preterm birth, Risk score, Ethiopia

50 Strength and Limitations of the study

- 51 ✓ An adequate number of participants with the outcome helped us to construct the
52 model using a sufficient number of predictor variables and the inclusion of sensitivity
53 analyses.
- 54 ✓ Multiple imputation were used to address missing data, which has been shown to be a
55 valid technique for dealing with missing data within logistic regression models, resulting
56 in less bias than excluding all women with missing data.
- 57 ✓ The prediction model is constructed from easily obtainable maternal characteristics that
58 make it applicable in primary care settings.

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3 59 ✓ A single-site study, it is confined to a single area, which needs external validation before
4 using it in another context.
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6 61 ✓ Furthermore, data were collected from each mother's card; due to this, some important
7 variables were missed, such as previously highlighted factors of preterm birth in
8 62 different studies.
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65 **Introduction**

66 Preterm birth is described as babies that are born alive before the end of 37 weeks of
67 pregnancy[1]. Preterm birth can be accidental (due to spontaneous preterm labor and/or preterm
68 membrane rupture) or induced by the provider (by cesarean or labor induction)[2]. Most preterm
69 births happen spontaneously[3].

70 An estimated 15 million babies worldwide are born too early per year. That is more than 1 in 10
71 infants. About 1 million newborns die per year because of preterm birth complications[4].

72 Across 184 countries, the rate of preterm birth ranges from 5% to 18% of babies born [5].
73 However, there are stark disparities in survival rates around the world. Half of the babies born at
74 or below 32 weeks die in low-income settings due to a lack of practical, cost-effective, and
75 critical care, such as comfort, breastfeeding assistance, basic infection care, and trouble
76 Breathing[6].

77 Furthermore, the effect of preterm birth is also prolonged beyond the neonatal phase and
78 throughout life[7]. Hence, the largest risk of severe health issues, including cerebral palsy,
79 intellectual disability, chronic lung disease, and vision and hearing loss, is faced by babies born
80 before maturity. This introduces a lifelong disability dimension. At some point in their lives,
81 most people will face the struggles and potential disasters of preterm birth either directly in their
82 families or indirectly through events for the nations[7, 8].

83 To alleviate this burden, in the past few decades, numerous methods have been attempted
84 internationally, including in Ethiopia, to prevent and enhance the treatment of preterm births [9-
85 11]. As part of the strategy, it is essential to diagnose or predict preterm birth earlier in
86 pregnancy to take appropriate measures for high-risk groups. However, in most nations,
87 predicting preterm birth is still largely based on subjective clinical experience. This approach
88 may increase unnecessary hospital admissions and unnecessary but potentially harmful
89 treatments, such as the use of steroids for the maturation of the fetal lung and tocolysis[12, 13].

1
2
3 90 There were clinical prediction models that aim to estimate the likelihood of preterm birth that
4 91 include laboratory tests that are typically inaccessible in low-resource settings, such as fetal
5 92 fibronectin, insulin-like growth factor binding protein-1 (IGFBP-1), interleukin-6, and placental
6 93 alpha-macroglobulin-1[14-19]. Most current research on PTB prediction focuses on finding PTB
7 94 risk factors using a hypothesis-testing methodology in highly controlled environments. PTB has
8 95 been linked to a number of risk factors, including previous preterm labor, multiple gestation
9 96 (carrying several children), and diabetes, problems with the cervix, uterus, or placenta, smoking,
10 97 and infections [20-22]. However, women who have preterm delivery often have no known risk
11 98 factors[23]. In addition, some of the predictors (such as prior PTB) do not apply for first-time
12 99 mothers.

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20 100 Predicting the risk of PTB in pregnant women has been the subject of numerous studies[24], but
21 101 no model exists that is accurate enough to be used in clinical settings. Most research (e.g.,
22 102 cervical length or fetal fibronectin) have concentrated on predictors during the second or third
23 103 trimester[25]. These predictors, however, can only forecast PTB at intermediate risk and have
24 104 only been shown to be reliable in high-risk populations. Unfortunately, the majority of women
25 105 who give birth early have no evident risk factors, and more than half of PTBs happen in low-risk
26 106 pregnancies, indicating the limited usefulness of using fetal fibronectin or cervical length in the
27 107 general population[26].

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34 108 Due to scarce resources, using readily available data to predict PTB seems appealing in low- and
35 109 middle-income communities. But relatively few models have been made public. The
36 110 considerable range in PTB occurrence across the globe, which suggests differences in exposure
37 111 to psychosocial, sociodemographic, and medical risk factors as well as genetic variations, is also
38 112 significant [27-29]. As a result, it is necessary to develop and evaluate PTB prediction models in
39 113 various populations.

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44 114 Therefore, developing and validating a risk prediction model for the prediction of preterm birth
45 115 using maternal (clinical and nonclinical) characteristics based on the available measurements is
46 116 paramount to allow early preterm birth interventions such as in utero transfer to tertiary care
47 117 centers, appropriate corticosteroid administration while preventing excessive use,
48 118 neuroprotective magnesium sulfate therapy, and antibiotic treatment in the event of infection[14,
49 119 30]

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121 **Methods and Materials**

122 **Study setting**

123 This retrospective study was conducted among 1260 pregnant women who did prenatal care and
124 finally delivered at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar city,
125 Northwest Ethiopia, from January 30, 2019, to January 30, 2021. Bahir Dar is the capital city of
126 Amhara national regional state and is found 575 km northwest of Addis Ababa.
127 The hospital has currently a total of 1431 manpower (5 Obstetricians and Gynaecologists and 63
128 midwives among others) in different disciplines. It has a total of 500 formal beds, 11 wards
129 (emergency ward and Inpatient wards such as Gynecological & Obstetric, Surgical, Orthopaedics,
130 Medical, Pediatric, L&D, Eye unit, NICU, psychiatric, oncology, and 22 OPDS), 39 clinical and
131 non-clinical departments /service units / providing laboratory, Diagnostic, curative &
132 Rehabilitation service at outpatient & inpatient bases as well as disease prevention & health
133 promotion services.

134 **Sample size determination**

135 The sample size required for model development was determined based on the minimum
136 standard of 10 events per candidate predictor considered, according to the formula $N = (n \times$
137 $10)/I$, where N is the sample size, n is the number of candidate predictor variables and I is the
138 estimated event rate in the population[31]. Since there were 17 candidate predictors considered
139 and 10 events per candidate predictor, the estimated number of events for the study was 170.
140 Based on a study done on the prevalence of preterm birth in Debre Tabor hospital was 13%[32],
141 so taking into account this the required sample size was calculated as follows, $n = 170 * 100 / 13 =$
142 1308.

143 **Study Design and Participants**

144 The theoretical design of the present study was; the incidence of preterm birth as a function of
145 multiple predictors during pregnancy. The source population of the study was all pregnant
146 mothers who gave birth at FHCSH. To be included in this study, mothers must meet all of the
147 following eligibility criteria; all medical records of mothers who gave live birth and had at least
148 one ANC follow-up in FHCSH from January 30/2019 to January 30/2021.

149 **Sampling method and procedures**

150 A simple random sampling technique was employed to select participants using the medical
151 registration number of a delivered mother from the delivery registration book. First, all mothers

1
2
3 152 delivered at FHCSH in the last two years was identified from the delivery registration book.
4
5 153 After that, records of mothers who met the inclusion criteria were included in the study.
6
7 154 Subsequently, a sampling frame was prepared. Finally, the study unit was selected by using a
8
9 155 computer-generated random number.

10 156 **Data Collection**

11
12 157 Outcome assessment: The outcome variable was attributed to women whose medical records
13
14 158 indicated a physician or midwife diagnosis of preterm birth and delivery between 28 and 36
15
16 159 completed weeks of gestation. The gestational age (GA) was measured using either LNMP,
17
18 160 which is found to be a more reliable measure of GA in a low-resource setting[33, 34], or an early
19
20 161 ultrasound result(12 weeks).

21
22 162 Predictor assessment: Data were collected using a structured checklist through chart review.
23
24 163 Checklists were developed after reviewing various relevant literatures [35-39]. It consists of
25
26 164 socio-demographic (Maternal age, Residence), Maternal obstetric characteristics : (History of
27
28 165 preterm birth, History of abortion, history of stillbirth, gravidity, Parity, Multiple pregnancy,
29
30 166 APH, PROM, Gestational DM, and PIH), Maternal medical condition : (HGB level, Diabetic
31
32 167 Mellitus, Chronic Hypertension, UTI and HIV).

32 169 **Quality Assurance Mechanisms**

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34 170 To maintain the quality of data, the data collectors and supervisors were trained for a day on the
35
36 171 objective of the study, the content of the checklists, and how to fill the checklists. Afterward,
37
38 172 reviewing 15 charts medical records of mothers who gave birth at Felege Hiwot Comprehensive
39
40 173 Specialized Hospital which is found in Northwest Ethiopia were done. After that, some
41
42 174 adjustments (removing variables that were not available in the medical records of mothers) were
43
44 175 done accordingly. The checklist was developed in English.

44 176 **Data Processing and Analysis**

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46 177 Data were entered into a software application (EPI DATA, version 3.02) and was analyzed by
47
48 178 using R statistical programming language version 4.0.4 for further processing and analysis.
49
50 179 There were 13(1%), 2(0.2 %), 11 (0.9 %),15 (2.5%), 21 (1.7%) ,29(2.3%),20(1.6%) and 20
51
52 180 (1.6%) missing values for premature rupture of membranes , residence, chronic hypertension,
53
54 181 multiple pregnancy gestational diabetes Mellitus, pregnancy-induced hypertension ,antepartum
55
56 182 hemorrhage and hemoglobin respectively.

183 We assumed the data were missing at random, and we, therefore, performed a multivariate
 184 imputation by chained equations for all variables evaluated in the prediction model [40].
 185 Sensitivity analysis was performed to assess whether the assumption of missing at random
 186 (MAR) is valid or not, and the results were reasonably comparable table (1). Descriptive
 187 statistics including median, interquartile range (IQR), and percentages, were carried out.

188 **Table 1. Sensitivity analysis of the model to predict preterm birth: Comparison of the**
 189 **regression coefficients, standard errors (SE), and p-values for complete case analysis**
 190 **(CCA) and multiple imputed data (MI).**

Predictor variables	Complete case analysis			Multiple imputations		
	B	SE	P value	B	SE	P value
Chronic hypertension (yes)	0.7313	0.6297	0.24	0.581	0.6285	0.92
Residence (rural)	0.815	0.1946	<0.001	1.154	0.1958	<0.001
GDM(yes)	0.709	0.4028	0.07	0.472	0.4236	0.26
HGB(<11g/dl)	0.497	0.2185	0.02	0.642	0.2153	0.001
PROM (yes)	1.898	0.2080	<0.001	2.097	0.2129	<0.001
APH (yes)	1.194	0.2858	<0.001	1.298	0.2874	<0.001
PIH (yes)	1.353	0.2600	<0.001	1.368	0.2523	<0.001
Multiple pregnancy (yes)	0.539	0.3173	0.08	0.446	0.3257	0.17
Gravidity(primigravida)	0.426	0.1944	0.02	0.711	0.1976	<0.001

191

192 Model Development and Validation

193 For model development, bivariable logistic regression was done to obtain insight into the
 194 association between each potential predictor and preterm birth. Variables with ($p \leq 0.25$) from
 195 the bivariable analysis were entered into a backward stepwise multivariable logistic regression
 196 model, and significant variables ($p < 0.05$) were retained in the multivariable model. The results
 197 of significant predictors were reported as coefficients with 95% confidence intervals (CI). To
 198 check for the model accuracy and goodness of fit, we computed the area under the ROC curve
 199 (discrimination) and calibration plot (calibration) using “classifierplots” and “givitiR” packages
 200 of R respectively. The AUC ranged from 0.5 (no predictive ability) to 1 (perfect

1
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3 201 discrimination)[41]. The regression coefficients and their 95% confidence levels, and the AUC
4
5 202 were adjusted for overfitting or over optimism using the bootstrapping technique. To make
6
7 203 internal validation, we computed 1000 random bootstrap [42]samples with the replacement of all
8
9 204 predictors in the data. The model's predictive performance after bootstrapping is considered as
10
11 205 the performance that can be expected when the model is applied to future similar populations. To
12
13 206 evaluate the clinical and public health impact of the model, we performed a decision curve
14
15 207 analysis (DCA) [43] of standardized net benefits across a range of threshold probabilities (0 to
16
17 208 1). In the DCA, the model was compared with two extreme scenarios; "intervention for all" and
18
19 209 "no intervention". In our case, the intervention considered is the referral of high-risk pregnant
20
21 210 women to facilities where appropriate, corticosteroid administration, antibiotic treatment.

211 **Risk Score Development**

212 To construct an easily applicable preterm birth prediction score, we transformed each coefficient
213 of the model into a rounded number by dividing it by the lowest coefficient. The number of
214 points was subsequently rounded to the nearest integer. We determined the total score for each
215 individual by assigning points for each variable present and adding them up. The score was
216 transformed to dichotomous, allowing each pregnant woman to be classified as having a high or
217 low risk of preterm birth. The receiver operating characteristic curve (ROC) was plotted and the
218 area under the curve (AUC) was calculated to measure the discriminatory power of the scoring
219 system.

220 **Patient and public involvement**

221 There was no direct interaction with patients in this study and no direct patient involvement in
222 the design or conduct of this study.

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231 Result

232 Demographic, Obstetric, and Clinical Characteristics of mothers

233 A total of 1260 study cards were reviewed from a sample of 1308, about 48 cards were not
 234 reviewed due to the outcome of intrauterine fetal death, and abortion. Table (2) shows the
 235 demographic, obstetric, and clinical characteristics of mothers who gave birth included in the
 236 analysis. The median age of the study participants was 26 years with IQR (24-30years); the
 237 majority of the participants 1086 (86.2%) were in the age group of 20-34 years.
 238 More than three-fourth of the participants 926 (73.49%) were urban residents. Of the total of
 239 mothers who delivered at FHCSH, more than two-thirds of 841 (66.7%) were multigravida.
 240 About parity, above, half of them 713 (56.6%) were multipara. Concerning past obstetric history,
 241 55 (6.5%) of them had a history of previous preterm birth, 76 (9%) of them had a history of
 242 stillbirth and 162 (19.3%) of them had a history of abortion.

243 **Table 2. Demographic, obstetric, and clinical characteristics of mothers who gave birth at**
 244 **FHCSH , Northwest Ethiopia, 2021.**

Characteristics	Category	Frequency	Percent
Gravidity	Primigravida	419	33.3
	Multigravida	841	66.7
Residence	Urban	926	73.5
	Rural	334	26.5
GDM	Yes	44	3.5
	No	1216	96.5
APH	Yes	84	6.7
	No	1176	93.3
PIH	Yes	110	8.73
	No	1150	91.27
HGB level	<11d/dl	236	18.7
	>=11g/dl	1024	81.3
Chronic hypertension	Yes	21	1.7
	No	1239	98.3
PROM	Yes	195	15.5

	No	1065	84.5
Multiple pregnancies	Yes	90	7.2
	No	1170	92.8

245 *PROM: Premature rupture of membrane, HGB: hemoglobin, PIH: pregnancy-induced*
 246 *hypertension, APH: antepartum hemorrhage, GDM: gestational diabetes mellitus*

247 Development of prediction model for preterm birth

248 Out of 1260 delivered neonates, 169 (13.4%) (95%, CI (11.6%, 15.4%)) was preterm infants.
 249 The bivariable logistic regression analysis found several factors were eligible to be included in
 250 the prediction model. These variables were haemoglobin level, Gravidity, residence, gestational
 251 diabetes mellitus, APH, PIH, chronic hypertension, PROM, and multiple pregnancies. Using the
 252 results, a prediction model was developed, and equation for the prediction model was obtained
 253 table (3).

254 **Table 3: Coefficients and risk scores of each predictor included in the model to predict**
 255 **preterm birth (n = 1260)**

Predictors Variables*	Multivariable analysis			
	Original β (95 % CI)	Bootstrap β	P- value	Risk score
Residence (rural)	1.161 (0.780, 1.545)	1.148	<0.001	2
Gravidity (primigravida)	0.675 (0.291, 1.061)	0.666	0.01	1
PROM (yes)	2.081 (1.669 , 2.50)	2.051	<0.001	3
APH (yes)	1.364 (0.806 , 1.915)	1.348	<0.001	2
PIH (yes)	1.387 (0.887 , 1.879)	1.368	<0.001	2
HGB <11g/dl	0.676 (0.255 , 1.09)	0.677	<0.001	1

256 **Variables retained in the reduced model are; residence, APH, hemoglobin, PIH, gravidity, and PROM.*
 257 *Both backward and forward selection showed the same results. β after internal validation with*
 258 *bootstrapping is shown. Simplified risk score: we divided the coefficient of predictors included in the*
 259 *reduced model by the smallest (0.666). The probability or risk of preterm birth = $1 / (1 + \exp - (-$*

260 $3.517 + 1.148 * \textit{Residence (rural)} + 0.666 * \textit{gravity (primigravida)} + 2.051 * \textit{PROM (yes)} + 1.348$
261 $* \textit{APH (yes)} + 1.387 * \textit{PIH} + 0.677 * \textit{HGB (<11g/dl)}$.

262 The AUC of the final reduced model was 0.816 (95% confidence interval: 0.779 – 0.856)
263 **(Figure 1a)**. The calibration test had a p-value of 0.492, indicating that the model does not
264 misrepresent the data or the calibration of the model was visually accurate since the observed
265 and predicted probabilities were similar **(Figure 1b)**.

266 In addition, to verify whether any maternal characteristics were used as a specific predictor of
267 preterm birth we performed an ROC analysis. The analysis indicated that, residence
268 (AUC=0.604, 95% CI 0.564 to 0.643), gravity (AUC=0.59, 95% CI 0.571 to 0.628), PROM
269 (AUC=0.580, 95% CI 0.544 to 0.616), APH (AUC= 0.695, 95% CI 0.661 to 0.729), PIH (AUC=
270 0.721, 95% CI 0.685 to 0.757), and HGB (AUC=0.630, 95% CI 0.591 to 0.668) emerged as
271 better predictors of preterm birth **(Figure 2)**.

272 Validation of the model with the bootstrap technique showed hardly any indication of undue
273 influence by particular observations, with an optimism coefficient of 0.085, resulting AUC of
274 0.789 (corrected 95% CI: 0.748–0.83).

275 Using the coefficient (β), the predicted risk cutoff point was a probability of (SpEqualSe >
276 0.1320), the model has a sensitivity of 75.74%, specificity of 72.87%, a positive predictive value
277 of 30.2%, and a negative predictive value of 95.1%.

278 When applying DCA, we first evaluate whether our model understudy has a higher net benefit
279 than the default strategies (referring all and none). This model outperforms the default strategies
280 across the relevant threshold range. The model has the highest net benefit across the entire range
281 of threshold probabilities, which indicates that the model has the highest clinical and public
282 health value. Hence, the referral decision made using the model has a higher net benefit than not
283 referring at all or referring all regardless of their risk threshold as shown in **figure (3)**.

284 **Risk Classification Using a Simplified Risk Score**

285 We created a simplified risk score from the model for practical use. The reduced model's
286 prediction score was simplified by rounding all regression coefficients. The simplified score had
287 a considerably comparable prediction accuracy to the original β coefficients, with an AUC of
288 0.786 (95%CI: 0.729–0.827) **(figure 4)**. The possible minimum and maximum scores a mother
289 can have are 0 and 11, respectively.

Using “SpEqualSe”, the suggested threshold score to predict preterm birth using risk scores is ≥ 3 with a sensitivity of 75.14 % and specificity of 67.46% table (4).

When dichotomized into low risk (< 3) and high risk (≥ 3) based on the risk score, 278 (14.36%) were categorized as high risk and 982 (77.9%) as low risk for preterm birth.

Table 4: Risk classification of preterm birth using simplified prediction score (n = 1260)

Score*(risk category)	Prediction Model Based on Maternal Characteristics	
	Number of mothers	Incidence of preterm birth
< 3 (Low)	982 (77.9%)	72 (7.9%)
≥ 3 (High)	278 (14.36%)	97 (53.59%)
Total	1260 (100%)	169 (13.4%)

* $Score = (2*PIH) + (3*PROM) + (hemoglobin < 11 \text{ mg/dl}) + 2*residence + (2*APH) + gravidity.$

Discussion

In this study, the incidence of preterm birth was found to be 13.4%. Maternal characteristics were identified in this retrospective study to build a preterm birth prediction risk score. We intended to employ maternal features that are easily accessible and pertinent to clinical practice in countries with constrained resources, including Ethiopia. These nations may not have the financial resources to pay for ultrasound exams and laboratory tests. The optimal combination of maternal factors to predict preterm birth includes residency, gravidity, and hemoglobin < 11 mg/dl, early rupture of membranes, antepartum hemorrhage, and pregnancy-induced hypertension, according to the prediction model. The model has an AUC of 0.816 (95%CI: 0.776 – 0.856). Predicting the probability of preterm birth in pregnant women is essential to take appropriate measures accordingly. Identifying women at risk of preterm birth is an important task for clinical care providers. However, in low and middle-income countries, there are only a few methods available for reliably predicting actual preterm labor in women. Previously, the focus of the research was to explain the maternal and fetal determinants of preterm birth. In recent years, the focus shifted to predicting preterm birth optimally using a combined set of characteristics.

Without any advanced laboratory or imaging testing, this study measured the predicted performance of a model based on maternal features during pregnancy. Furthermore, we discovered that utilizing SpEqualSe as an optimal cut point, the sensitivity and specificity of

1
2
3 316 this prediction model achieved 75.14 percent and 67.46 percent, respectively, at the score
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5 317 threshold of 3.

6
7 318 In our study, a combination (residency, gravidity, hemoglobin < 11 mg/dl, early rupture of
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9 319 membranes, antepartum hemorrhage, and pregnancy-induced hypertension) of maternal
10
11 320 characteristics resulted in an AUC of 0.816 (95%CI: 0.776 – 0.856), has an excellent accuracy
12
13 321 according to diagnostic accuracy classification[44].

14
15 322 We found that early rupture of membrane is strong predictors of preterm birth. Similar evidence
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17 323 was found in different studies [36, 37, 45, 46]. The effect of a burst membrane on uterine
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19 324 contraction could explain this. Existing scientific evidence confirms that when a membrane
20
21 325 ruptures, natural uterotonic chemicals are released, and these uterotonic chemicals drive uterine
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23 326 contraction, resulting in PTB. This finding suggested that due attention should be given to
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25 327 women with premature rupture of membrane.

26
27 328 In our study, pregnancy-induced hypertension is strong predictors of preterm birth. Similar
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29 329 studies have demonstrated that pregnancy-induced hypertension was predictive of subsequent
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31 330 preterm birth[47, 48]. This could be related to vascular injury to the placenta caused by
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33 331 pregnancy-induced hypertension issues or iatrogenesis caused by the severity of hypertension or
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35 332 its complications. As a result, the oxytocin receptors are activated, resulting in preterm labor and
36
37 333 delivery. Or else this conclusion could be explained by current scientific evidence suggesting
38
39 334 that PIH is linked to vascular and placental injury, which causes oxytocin receptors to be
40
41 335 activated, resulting in PTB. Therefore, it is imperative to identify populations at risk pregnancy-
42
43 336 induced hypertension and introduce risk lowering interventions.

44
45 337 Another strong predictor of preterm birth is the place of residence. Existed evidence shows that
46
47 338 there is an association between preterm birth and rural residence [49-53]. This gap may be
48
49 339 explained by the greater accessibility and availability of maternal health service in metropolitan
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51 340 regions. It has long been understood that social deprivation and the nuanced interactions between
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53 341 them affect prenatal outcomes, including premature birth[54]. Hence, accessing maternal health
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55 342 services targeted to rural women could improve prenatal outcomes including the risk of preterm
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57 343 birth.

58
59 344 Antepartum hemorrhage is the predictor of preterm birth which is supported by different
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345 studies[55]. Identification of groups at risk for antepartum hemorrhage and the introduction of
346 risk-reducing measures are therefore essential. Other predictors of preterm birth are gravidity and

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3 347 hemoglobin <11 g/dl (anemia) which is in line with different studies[32, 56]. The molecular
4
5 348 factors that could explain how anemia, iron deficiency, or both, could result in preterm delivery.
6
7 349 In reality, a number of plausible molecular processes have linked anemia to a higher risk of
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9 350 premature birth. Accordingly, maternal and fetal stress can be caused by anemia (by resulting in
10
11 351 hypoxia) and iron deficiency (by increasing serum nor-epinephrine concentrations), which in
12
13 352 turn induces the production of corticotrophin-releasing hormone (CRH). Additionally, iron
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15 353 deficiency may raise the risk of maternal infections, which can again boost the synthesis of CRH.
16
17 354 High levels of CRH are known to be a risk factor for PTB since they increase the likelihood of
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19 355 PTB [57]. Thus, we can conclude that, in order to prevent PTB, routine ANC services need to
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21 356 place a greater emphasis on anemia prevention.

22
23 357 A study conducted in China showed that a model developed using advanced maternal age, lower
24
25 358 maternal height, history of preterm delivery, amount of vaginal bleeding during pregnancy, and
26
27 359 lack of folic acid intake before pregnancy for the prediction of overall preterm birth with AUC of
28
29 360 (0.6)[58]. Which had lower discriminatory performance than the present study, this difference
30
31 361 may be due to some of the predictors they used such as lower maternal height, lack of folic acid
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33 362 intake before pregnancy, and advanced maternal age. However, the predictors they used such as
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35 363 lack of folic acid intake before pregnancy are not easily obtainable information in routine clinical
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37 364 practice, which makes their model less practical in our setting. This prediction model constitutes
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39 365 variables that are easily obtainable and have reasonable accuracy to be used by both mid-and
40
41 366 lower-level health professionals in primary care settings. Among the maternal characteristics
42
43 367 included in our model, five can be easily found by history taking and one by test for hemoglobin.
44
45 368 The model's accuracy is consistent with a retrospective study done in China that established a
46
47 369 preterm birth prediction model based on maternal characteristics, including demographics and
48
49 370 clinical characteristics, and a model with predictors (gravidity, educational status, residency,
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51 371 history of preterm birth, twin pregnancy, pre-gestational diabetes mellitus (type I or II), chronic
52
53 372 hypertension, and place of birth) with AUC of 0.749 (95%CI: 0.732–0.767) [48].

54
55 373 On the other hand, a model incorporating four predictors (cervical length at admission,
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57 374 gestational age, amniotic fluid, glucose, and IL-6) has an area under the curve (AUROC) of
58
59 375 0.86[59] and similarly, the combination of biophysical, biochemical, immunological,
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376 microbiological, fetal cell, exosomal, or cell-free RNA at different gestational ages, integrated as
377 part of a multivariable predictor model may be necessary to advance our attempts to predict

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3 378 sPTL and preterm birth. In the prediction of spontaneous preterm birth within 48 hours, a
4
5 379 prognostic model including qfFN and clinical risk factors showed excellent results[60, 61]. Both
6
7 380 models have higher discriminatory performance. The reason for the lower discriminatory
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9 381 performance in our study compared to the studies described above could be because we used
10
11 382 secondary data available from the register and as this dataset is limited and some variables that
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13 383 require advanced laboratory tests were not included in the model.

14 384 Hence, predictors necessitate laboratory testing, which is often unavailable in low-resource
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16 385 settings. As a result, such predictors are difficult to come by in ordinary clinical and public
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18 386 health practice, making the model less useful.

19 387 A study conducted in the UK found that data on maternal characteristics and obstetric history at
20
21 388 11–13 weeks of gestation were predictive of spontaneous early preterm delivery; this model had
22
23 389 an AUC of 0.67[62] which had lower discriminatory performance than the present study. This
24
25 390 difference may be the difference in the study population.

26 391 A model that predicts a risk of preterm delivery in women with multiple pregnancy
27
28 392 incorporating previous preterm delivery, monochorionicity, smoking, educational level, and
29
30 393 triplet pregnancy for preterm and very preterm delivery had a c-index of 0.68 (95% CI 0.63 to
31
32 394 0.72) and 0.68 (95% CI 0.62 to 0.75) respectively[63]. It had lower discriminatory performance
33
34 395 than the present study. This might be due to the study population difference. In the present study,
35
36 396 the study populations were both women who had multiple pregnancies and singleton pregnancy.

37 397 In our prediction score, using 3 as a cutoff point has an acceptable level of specificity,
38
39 398 sensitivity, PPV, and NPV to predict preterm birth. It is also possible to shift the cutoff point to
40
41 399 increase either of the accuracy measures depending on the program aim and availability of
42
43 400 resources.

44 401 The strength of the study was using an adequate number of participants with the outcome, which
45
46 402 helped us to construct the model using a sufficient number of predictor variables. In addition, our
47
48 403 prediction model was constructed from easily obtainable maternal characteristics that make it
49
50 404 applicable in primary care setting and multiple imputation were used to address missing data,
51
52 405 which has been shown to be a valid technique for dealing with missing data within logistic
53
54 406 regression models, resulting in less bias than excluding all women with missing data.

55 407 However, the findings from this study should be interpreted with the perspective of the following
56
57 408 limitations. As a single-site study, it is confined to a single area, which needs external validation

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3 409 before using it in another context. Furthermore, data were collected from each mother's card; due
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5 410 to this, some important variables were missed, such as previously highlighted factors with
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7 411 preterm birth in different studies.

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11 415 **Conclusions and recommendations**

12 416 This study shows the possibility of predicting preterm birth using a simple prediction model
13 417 constructed from maternal characteristics. Thus, the optimal combination of maternal
14 418 characteristics such as residence, gravidity, haemoglobin < 11 mg/dl, premature rupture of
15 419 membrane, antepartum haemorrhage, and pregnancy-induced hypertension shows the possibility
16 420 of predicting preterm birth using a simple prediction model constructed from maternal
17 421 characteristics. In addition, risk score calculations based on a combination of predictors was
18 422 effective and had comparable accuracy with the model-based approach of the original β
19 423 coefficients. This score may assist in clinical decision-making. In addition, incorporating this
20 424 convenient and easily applicable score in the health care system to be used by clinicians to
21 425 inform pregnant mothers about the future course of their outcome after external validation.
22 426 Doing further research is needed to validate the prediction tool using prospective follow-up
23 427 studies in another context before introducing it to clinical and public health practices.

24 428 **Data Sharing Statement**

25 429 Data will be available upon request from the corresponding author.

26 430 **Author Contributions:** S.F.F. conceived the study and wrote the manuscript. Z.A.A, S.F.F,
27 431 G.T.W, A.K.Y, and A.M.D, all contribute to data analysis, study design, and supervision of data
28 432 collection. All authors participated in manuscript revision for intellectual content and approval of
29 433 the final version. All authors have read and agreed to the published version of the manuscript.

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32 436 **Competing interest's statement:** The author reports no conflicts of interest in this work.

33 437 **Ethical approval**

34 438 Ethical clearance was obtained from the Institutional Review Board (IRB) of Bahir Dar
35 439 University, College of Medicine and Health Sciences with Protocol number 083/ 2021) on

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2
3 440 February 26, 2021. It is a retrospective study of medical records and personal identifiers were not
4
5 441 used on the data collection checklist. So, the IRB waived the requirement for informed consent
6
7 442 from each participant. Confidentiality was maintained by omitting the personal identifier of the
8
9 443 participant during the data collection procedure and the information was used only for research
10
11 444 purposes. Data were collected from the register, which was kept in a secure place and all data
12
13 445 were fully anonymized before we accessed them. After the collection of data, all patient records
14
15 446 and patient cards were placed back in a secure place. Data were entered into a password-
16
17 447 protected computer.
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3 638 **Figure 1:** (a) Area under the ROC curve for the prediction model, and (b) Predicted versus
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5 639 observed preterm birth probability in the sample. This analysis includes mothers who gave birth
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7 640 at FHCSH, 2021(n = 1260). Calibration plot created using “givitiCalibrationBelt” in R
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9 641 programming.

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12 642 **Figure 2:** Receiver operating characteristic curve of maternal parameters for prediction of
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14 643 postpartum glucose intolerance. Residence, PROM, APH, PIH, HGB and Gravidity.

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17 644 **Figure 3:** A decision curve plotting the net benefit of the model against threshold probability.

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19 645 **Figure 4:** Area under the ROC curve for the simplified risk score to predict the risk of preterm
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21 646 birth among mothers who gave birth at FHCSH, 2021.

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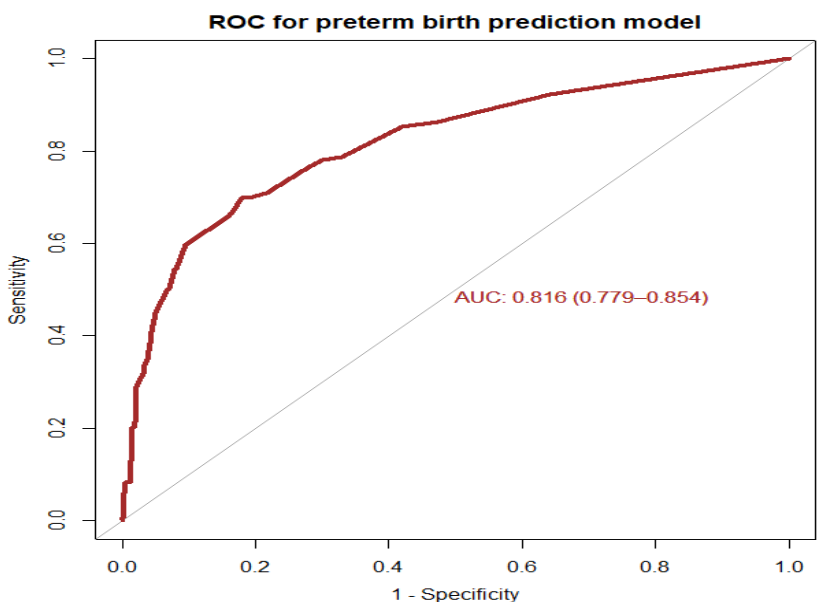
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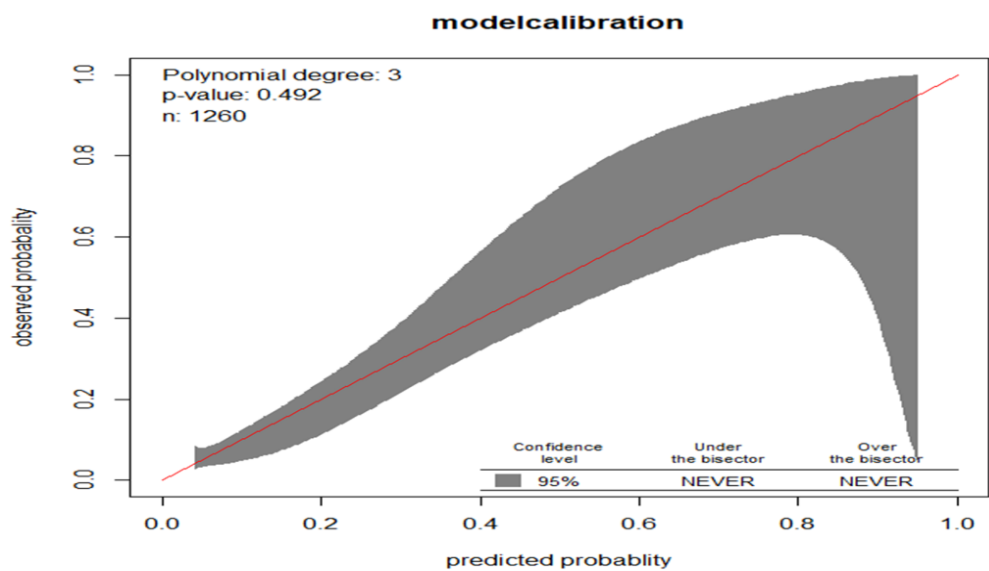
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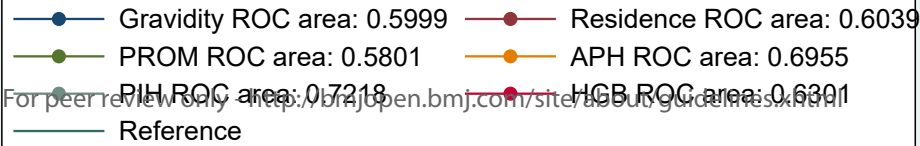
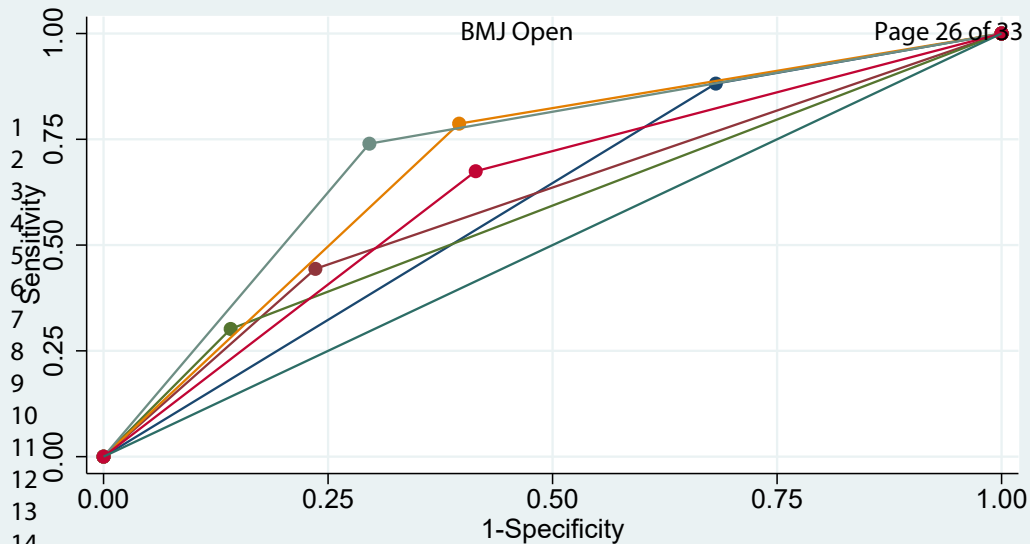
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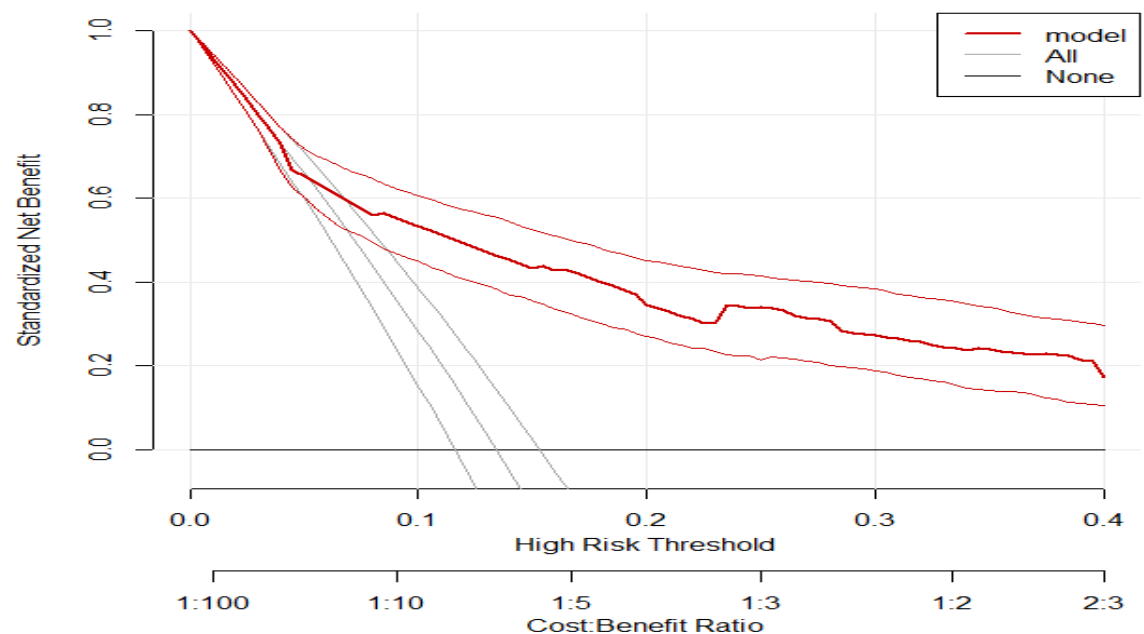


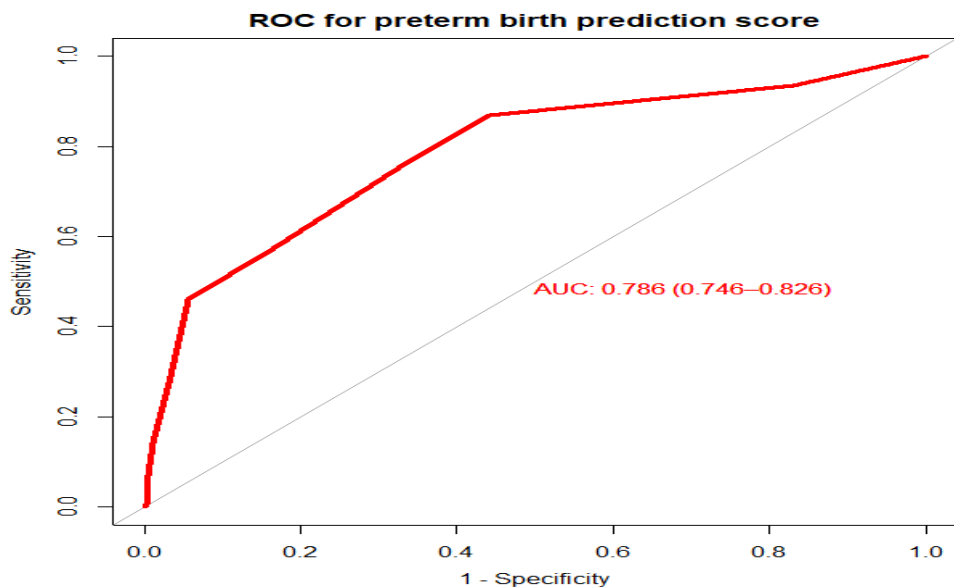
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The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Line 1-59	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Line 1-59
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Line 60-100		
Objectives	3	State specific objectives, including any prespecified hypotheses	Line 96-98		
Methods					
Study Design	4	Present key elements of study design early in the paper	Line 103		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Line 103-113 Line 123-128		
Participants	6	(a) <i>Cohort study</i> - Give the eligibility criteria, and the	Line 123-128	RECORD 6.1: The methods of study population selection (such as codes or	Line 129-135

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25		sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case		algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.		
26 27 28 29 30 31 32	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Line 137-147	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Line 137-147
33 34 35 36 37 38 39 40	Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Line 142-147		
41 42	Bias	9	Describe any efforts to address potential sources of bias	Line 123-141		
43 44 45 46 47	Study size	10	Explain how the study size was	Line 114-122		

		arrived at			
1 2 3 4 5 6	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Line 155-198	
7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Line 155-198	
31 32 33 34 35 36 37 38 39 40 41	Data access and cleaning methods		Line 148-154		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.
42 43 44	Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-
					Line 130-132

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (<i>e.g.</i> , numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Line 130-135	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Line 130-135
Descriptive data	14	(a) Give characteristics of study participants (<i>e.g.</i> , demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i> , average and total amount)	Line 232-241		
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures	Line 247		
Main results	16	(a) Give unadjusted estimates	Line 246-286		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Line 162-166		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Line 351-362		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Line 50-59	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Line 351-362		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Line 351-362		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Line 369		
Accessibility of protocol, raw data, and programming code		Line 364		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Line 364

*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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