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Maternal Near-Miss Prediction Model Development Among Pregnant Women in Bahir Dar City Administration, Northwest Ethiopia: A study protocol

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ABSTRACT

Introduction: A maternal near-miss is a woman who nearly died but survived from complications that happened during pregnancy, childbirth, or within 42 days of delivery. This problem is major challenge of global population specifically developing nations. The individual predictor effects on maternal near-miss were investigated whereas shared characteristic of prognostic predictor, that directly indicate risk stratification of obstetric patients, were overlooked in Ethiopia. Hence, this needs maternal near-miss clinical prediction model development in Ethiopia.

Aim: The aim of this study is to develop and validate (internal) prognostic prediction model, and produce the risk score of maternal near-miss among pregnant women in Bahir Dar City Administration, Northwest Ethiopia 2023/24.

Methods and analysis: Prospective follow up study design will be used to develop prognostic prediction model of maternal near-miss among 2110 randomly selected pregnant women in Bahir Dar City Administration from May 2023 to October 2024. The study participants will be randomly selected pregnant women at first antenatal visit. The selected pregnant women will be followed from 16 weeks of gestational age to 42 days after delivery. Data will be collected by validated structured questionnaire, extraction checklists and measuring tools. Cox proportional hazard regression analysis will be applied to develop prognostic prediction model of maternal near-miss. The model performance will be checked by its discrimination ability using c-index and calibration ability using calibration plot and slope. Internal validation of model will be checked using bootstrapping approach. Finally, the model will be presented by nomogram and decision tree for potential users.

Ethics and dissemination: Ethical approval has been obtained from the Institutional Review Board of the College of Health Sciences, Bahir Dar University (protocol number 704/2023). Findings will be disseminated through scientific publications, conference presentations, community meetings and policy briefs.

Keywords: Maternal near-miss, clinical prediction, prognostic model, risk stratification

Strength and imitation of the study

This is the first study on the clinical prediction model development on maternal near-miss in Ethiopian context. This study is also the first in sub-Saharan countries to develop and validate (internal) prognostic clinical prediction model of women with near-miss using prospective follow up study. However, results from institutional based studies may not be generalizable to the underlying characteristics in the general population. In addition, application of WHO maternal near-miss screening criteria may under estimate the detection of maternal near-miss.

INTRODUCTION

Sever maternal outcome is a life threatening condition that can result in maternal mortality or maternal near-miss during pregnancy, childbirth, or within 42 days after delivery (1). A maternal near-miss is defined as a woman who nearly died but survived from a condition that happened during pregnancy, childbirth, or within 42 days of delivery (2, 3). Severe acute maternal morbidity (SAMM) is another name for maternal near-miss (4).

The concept of maternal near-miss was developed by World Health Organization (WHO) to identify life-threatening conditions throughout pregnancy, labor and puerperium (1). Based on such concept the interventions can concentrate on the series of circumstances that led to a woman's near-death experience or death (5, 6). The health system flaws or priorities in maternal health can be more quickly identified using maternal near-miss statistics than maternal death (1, 7). In order to apply such concept in different parts of the world, WHO developed maternal near-miss diagnosis tools that includes clinical, laboratory and management-based criteria (8, 9). Such tool was also adapted and validated in Sub-Saharan Africa (SSA) (10).

Maternal death and maternal near-miss are major health problems globally, but particularly in impoverished nations. An estimated 303,000 women die each year owing to complications during childbirth and pregnancy around the world (11). In 2017, the maternal mortality rates (MMR) was 211 per 100,000 live births worldwide (12). A woman dies due to pregnancy or childbirth-related problems every two minutes, according to a 2017 report by the United Nations Population Fund (13). Ninety-nine percent of all maternal deaths take place in low-resource nations (14). According to the 2019 Mini-EDHS, the MMR in Ethiopia was 412 per 100,000 live births (15). This number is significantly higher than average MMR for the world (211 per 100,000 live births), but lower than MMR in SSA (553 per 100,000 live births) (12).

The burden of maternal near-miss also varied from 0.80 to 8.23% in disease-specific measures, and 0.01 to 2.99% in management-based criteria (16). The maternal near-miss ratio was 18.57 per 1000 live-births in the world (17). The smallest maternal near-miss ratio was found in Europe (3.10 per 1000 live birth) (17) whereas the highest-burden of maternal near-miss was found in African and Asian middle- and low-income countries (18). In SSA, the maternal near-miss ratio was 24.2

per 1000 live births (19). The prevalence of maternal near-miss in Ethiopia was 12.57% with the highest magnitude, (26.5%), in the Amhara region (20).

The high burden of maternal death and maternal near-miss due to direct or indirect causes are influenced by a multitude of complex risk factors such as socio-economic and cultural features. Most significantly, delays in seeking care, reaching to care, receiving adequate and appropriate care (21) and community's accepting responsibility (22) can indirectly cause maternal near-miss or maternal death. Delay in seeking care is associated with failure to recognize signs of complications, failure to perceive severity of illness, cost consideration, negative experience with health system, transportation difficulties and needing permission from family members (21, 23). The factors which bring delay in reaching care are lengthy distance to a facility, conditions of roads, and lack of available transportation (24). Delay in receiving adequate and appropriate care is occurred due to uncaring attitudes of providers, shortages of supplies and basic equipment, non-availability or poor skills of health personnel, and lack of urgency or understanding of emergency (21). A community's delay to take responsibility can also contribute to maternal mortality as a result of absence of a community based and community drive comprehensive approach to maternal health/well-being. This problem includes lack of community members engagement based on community knowledge, political will, mobilization, accountability and empowerment (22).

Various initiatives have been put into place to lower the burden, complications, causes, and risk factors associated with maternal death and maternal near-miss. The WHO launched a program of work in 2012 on the definition, conceptualization, and assessment of maternal morbidity. This effort aimed to compile the numerous definitions of the condition (25, 26). In 2013, WHO also developed Maternal Mortality Surveillance and Response (MPDSR) team, which focuses on ongoing analysis of the causes and contributors to maternal death (27).

In addition to the above global efforts, the individual risk stratification research such as prognostic prediction model is also very important by informing the healthcare professionals, patients and their relatives about outcome risk, with the aim to facilitate (shared) medical decision making and improve maternal health outcomes.

Different researchers investigated the burden and determinants of maternal near-miss in Ethiopia (20, 28-35). These studies focused on the individual predictor effects on maternal near-miss. But

they did not focus shared characteristic of prognostic predictor as a whole, and did not directly indicate the risk stratification of obstetric patients. The researchers in other area developed and validated the clinical prediction models of maternal death or severe obstetric morbidity among admitted patients (36-39). There was also a clinical risk prediction study on severe maternal outcome in SSA among admitted obstetric patients (40). The previous clinical prediction research on maternal outcomes in SSA predominantly uses traditional case control study, hardly suitable for risk prediction model development and validation. Hence the development and validation of prognostic prediction model of maternal near-miss among pregnant women is required in Ethiopia using a prospective cohort study. Therefore, this study aims to develop and validate (internal) prognostic prediction model of maternal near-miss among pregnant women in Bahir Dar City Administration, Northwest Ethiopia, 2023/24.

Aim and objectives

The aim is to conduct longitudinal study for the development, and validation of (internal) the prognostic clinical prediction model of maternal near-miss among pregnant women. The objectives are:

1) To develop the prognostic model of maternal near-miss among pregnant women in Bahir Dar city, Northwest Ethiopia Administration, 2023/24
2) To validate (internal) the prognostic model of maternal near-miss among pregnant women in Bahir Dar city Administration, Northwest Ethiopia, 2023/24
3) To create the risk score of maternal near-miss among pregnant women in Bahir Dar city Administration, Northwest Ethiopia, 2023/24

METHODS AND ANALYSIS

Study setting, and period

This study will be conducted in Bahir Dar city administration, Northwest Ethiopia. Bahir Dar is found 450 km from the capital city of Addis Ababa. Bahir Dar city is one of Ethiopia's biggest and fastest-growing city. It serves as the political, economic, and cultural hub of Amhara National Regional State, the second-most populous region in the nation. The city is also one of the main tourist destinations in the nation due to its cultural history (such as the Lake Tana Monasteries and religious festivals) and natural beauties (such as the Blue Nile Falls, birds, and hippos). The United Nations Educational, Scientific and Cultural Organization has designated the Bahir Dar city as a

Biosphere Reserve due to its extensive biodiversity. Approximately 350,000 people lived in the city as of 2017, according to data from the Central Statistics Agency (41). The city is situated on the southern coasts of Lake Tana, the largest lake in Ethiopia, at 11°36′ N latitude and 37°23′ E longitude. The study will be carried out from 1 May 2023 to May 1 2024.

Study design

Prospective follow up study will be used to develop prognostic prediction model of maternal near-miss. These models estimate the probability of developing maternal near-miss. The focus of prognostic prediction models is on predicting a future health outcome that occurs after the moment of prediction, using predictors available at the moment of prediction. Prospective follow up study is suitable for development of prognostic prediction model development. Hence, prospective follow up study is selected to develop prognostic prediction model of maternal near-miss in this study.

Maternal near-miss in the follow up period (O)=f (D1, D2, D3, …Dn)

Where:

O=occurrence of maternal near-miss

D1…Dn=the predictors

The occurrence of maternal near-miss (O) in the follow up period will be diagnosed based on WHO diagnostic tool. The individual-level variables that are known or assumed to be related to the maternal near-miss will be studied as prognostic predictors. The occurrence of maternal near-miss among pregnant women as a function of individual level predictors is expressed as =f (age, height, weight…Dn).

Source and study population

All pregnant women who will have confirmed pregnancy at 1st antenatal care (ANC) (<=16 weeks) in the selected health facilities will be the source population. A sample of pregnant woman at or less than 16 weeks of gestational age will be the study population. The event group will be the women who will develop maternal near-miss whereas the censoring group will be the women who will be referred, withdraw against ANC visit, transfer out from the selected health facility, loss to follow up and died during the follow up period. Participants who have no plans to move out of the study area; and will be well enough to be interviewed, as judged by the interviewer will be included

in the study. The pregnant women who have confirmed maternal near-miss at outset of the cohort and after 42 days of delivery will be excluded from the study participants.

Study variables and measurements

Dependent variable

The maternal near-miss, dependent variable, will be assessed based on WHO screening criteria (1) from 16 weeks of gestational age to 42 days after delivery. The woman who will face at least one component of clinical, laboratory or management-based criteria will be considered as women with maternal near-miss whereas others will be considered as censored. The trained MSc clinical midwifery will identify the suspected life-threatening event and linked the participants to nearest hospital for confirmation of the maternal near-miss.

Prognostic predictors

The prognostic predictors of maternal near-miss that are used to develop prognostic prediction model will include the individual level predictors. These are age (in year), height (in cm), residence (coded as '0' rural and '1'urban), weight (measured in kg), as well as obstetric factors like parity (measured in number), plurality (coded as '0' singleton and '1' multiple), desire of pregnancy (coded as '0' non-planned and '1'planned), gestational age (in week), inter-pregnancy interval (in months), responsible for decision making (coded as '1'self, '2' husband, '3' relatives and '4' jointly) and history of cesarean section (C/S) (coded as '0' and '1' yes). Other factors include preeclampsia (coded as '0' and '1' yes), eclampsia (coded as '0' and '1' yes), sepsis (coded as '0' and '1' yes), hemorrhage (coded as '0' and '1' yes), obstructed labor (coded as '0' and '1' yes), medical morbidity (coded as '0' and '1' yes), history of stillbirth (coded as '0' and '1' yes), history of abortion (coded as '0' and '1' yes), distance from health facility (measured in kilo-meter), and birth-preparedness and complication readiness (coded as '0' no and '1' yes). Additionally, base line clinical indices such as blood pressure (measured in mmHg), temperature (measured in °C), pulse rate (measured in beat/minute), respiratory rate (measured in breath/minute) and hematocrit measurement (measured in ml/dl).

Sample size determination

The sample size of development of prognostic prediction model of maternal near-miss will be calculated using two methods. First, the rule of thumb is used. This rule stated that at least

there could be 10 events per candidate parameters. Based on such criteria, the rule of thumb formula is $n = \frac{10K}{P}$ (42).

Where

K is the number of candidate parameters

P is the proportion of maternal near-miss

Around 25 candidate variables were selected from the previous studies, and using 26.6% the of maternal near-miss from previous study (32). Then, $n = 25 * \frac{10}{0.266} = 940$. By adding 10% non-response rate, the final sample size will be 1,034.

The second sample size determination method of prognostic prediction model is based on the minimum sample size calculation criteria of time to event study. The minimum criteria to be meet in this calculation are 1) minimum heuristic shrinkage factor, S ≥ 0.9 (target < 10 % overfitting), 2) a small difference in Nagelkerke's R^2_{app} and R^2_{adj} (target < 0.05 absolute difference), and 3) a small margin of error in overall risk estimate (target <0.05 absolute error). The criteria such as the number of parameters (P), heuristic shrinkage factor (S), the overall risk in the population and model's anticipated Cox-Snell R^2 (or C-statistics) are reviewed from previous studies. Around 25 candidate parameters, 26.6% of maternal near-miss (32) and C-statistics of 0.11 (40) are used to calculate the sample size. Then the sample size is calculated using Stata command "pmsampsize, type (b) rsquared (0.11) parameter (25) prev (0.266)". Finally, the sample size is 1918 (Table 1).

Table 1: Sample size calculation for prognostic prediction model development of maternal near-miss using minimum criteria of event-to-time method in Bahir Dar city, Ethiopia 2023/24.

Criteria	Sample size	Shrinkage	Parameter	Rsq	Max-Rsq	EPP
Criteria1	1918	0.90	25	0.11	0.52	9.21
Criteria 2	895	0.81	25	0.11	0.52	4.30
Criteria 3	162	0.90	25	0.11	0.52	0.78
Final	1918	0.90	25	0.11	0.52	9.21

Minimum sample size required for new model development based on the inputs is 1918. The sample size calculated by minimum criteria for event-time is greater than the sample size calculated by rule of thumb. Finally, by considering 10% non-response rate, the sample size for prognostic prediction model development of maternal near-miss will be 2110.

Sampling technique

First, health facilities in Bahir Dar City Administration that provide ANC service will be identified. Second, the health facility that provide ANC will be selected randomly. Third, the total sample size will be proportionally allocated to each health facility based on last year's reports of first antenatal care visit. Fourth, the mothers who will come for 1st ANC visit will be selected randomly by considering the 1st comers first, and then every other interval. Fifth, all pregnant women who will develop maternal near-miss will be considered as event whereas women who are referred out of Bahir Dar city, withdrawal against the follow up schedule, not develop event and dead during the follow up period will be selected as censoring participants in the follow up period (Figure 1).

Data collection tools

The validated WHO near-miss data abstraction tool will be utilized to measure the maternal near-miss (1). In addition to this tool, structured questionnaire, data extraction check lists and direct measurements will be used to collect the data of independent variables. The interview questionnaire that consists of sociodemographic characteristics, wealth index, reproductive related factors, birth preparedness and complication readiness, health service utilization, and health service accessibility related factors will be used to collect data directly from the participants. The data extraction check lists will be used to collect data on obstetric morbidities, medical problems, maternal near-miss, birth outcomes, and laboratory results from participants' cards. The data collectors will also use measurements to collect data on gestational age, weight, middle upper arm circumference, height, blood pressure, respiration rate, pulse rate and temperature from the participants.

Data collection process

The data will be collected by trained data collectors using validated data collection tools via epi-collections -5 software. In general, the data collection process will have baseline, and follow up phases.

Base line procedure

The base line data will be collected by thirteen trained data collectors. First, the data collectors will identify women who come at 16th weeks of gestational age by communicating with the ANC providers at ANC clinic. Second, last normal menstrual period, expected date of delivery,

gestational age, weight, middle upper arm circumference, height, systolic and diastolic blood pressure, respiration rate, pulse rate and temperature will be directly measured from the participants. Third, confirmation of pregnancy, obstetric history, medical history, laboratory findings and utilized health service will be abstracted from ANC charts. Fourth, data on socio-demographic characteristics, wealth index, and health access related factors will be collected via interview. Finally, the scheduled for the next subsequent contact will be informed to the participants in addition to the exchange of their phone numbers for further communication if obstetric morbidities are happened before the next data collection phase.

Follow up procedure

At the second data collection period, the service given, clinical indices, laboratory investigations, pregnancy danger signs, maternal near-miss, referral, withdrawal against medical advice, transfer out, death, laboratory investigations, and any complication will be extracted from ANC chart whereas data on birth preparedness and complication readiness will be collected via interview at health facility. Similar approach will be used at third and fourth data collection period. During delivery time, mode of delivery, duration of labor, maternal near-miss, maternal death, birth outcomes, laboratory findings and clinical indices will be extracted from delivery charts. After delivery at 10 and 42 days, obstetric complications including maternal near-miss will be collected from maternal cards.

If the women will not available during the follow up schedule, the reasons for absence will be ruled out via home-to-home visit. If the woman is referred to the other health facility in Bahir Dar city Administration, the facility will be identified and the final outcomes will be assessed by the data collectors.

Data quality assurance

Input from study participants and subject-matter experts will be used to construct and validate the questionnaire in terms of face and content validity. After tool validation, data collectors and supervisors will receive two days of training to become familiar with the questionnaires, the data collection processes, the ethical considerations, and the study's purpose. A pretest will be undertaken to ensure the accuracy of the data and check for ambiguities in the language after switching from the English version to the Amharic version. The tools will be changed in light of the pretest's results. The daily supervision of data collectors and daily verification of all collected

data will be done by the supervisor. The data will be regularly checked for completeness, and any problems during data collection will be addressed appropriately.

Data processing and management

The data from epi-collect5 will be downloaded and transferred to the Microsoft excel. The illogical values and steps will be checked during designing of questionnaire/abstraction sheet in the epi-collect5. The collected data will be examined for consistency and completeness.

The missing data will be handled carefully. Instead of excluding all missing data, mean, median, mode imputation or multiple imputation are vital techniques to handle the missing data. Specifically, in this study, exclusion and multiple imputation will be applied to handle the missing data.

Multicollinearity between each independent predictor will be checked by using variance inflation factor (VIF). In this regard, if VIF is greater than 10, there is no multicollinearity. During the pre-processing, transformation and standardization of categorical data will be performed.

The distribution of continuous variables will be examined graphically using a histogram and statistically by the Shapiro-Wilk test. Finally, R 4.2.2 software will be used for the final analysis.

Data analysis

Model development

The maternal-near miss will be an event while referral, withdrawal against medical treatment and death will be considered censoring. The overall survival of the study subject will be depicted using the Kaplan-Meier curve. The median time will be reported using 95% CI. Cox proportional hazard regression model will be used. First, bivariable proportional hazard regression will be done. Variables that will be significant in bivariable analysis ($p < 0.25$) will be entered into the multivariable cox proportional hazard model using the backwards stepwise method. The strength of the association will be measured in terms of hazard ratio at 95% confidence limits. The Cox proportional hazard model assumption will be checked using scaled Schoenfeld residual test and

graphically with log-log Cox adjusted survival estimate. The model fitness will be checked using Cox –snell residuals test. Finally, the multivariable cox proportional hazard model will declare a p-value < 0.05 with 95% CI as statistical significance.

Assessing model performance

Calibration and discrimination are two important factors in evaluating the predictive performance of the model. On a group level, calibration evaluates how well the absolute anticipated hazards match the actual dangers (43). The ability of a model to distinguish between patients who have and do not have the relevant event is called discrimination.

Using the concordance index, the model's ability to discriminate may be evaluated (C-index). To calculate the C-index, all potential pairs of patients with and without the result are examined. If the patient with the outcome has a higher expected risk than the patient without the outcome, the pair is said to be concordant. The C-index is equivalent to the area under the curve (44). The AUC values between 0.9 and 1.0, 0.8 and 0.9, 0.7 and 0.8, 0.6 and 0.7, and 0.5 and 0.6 are leveled as excellent (A), good (B), fair (C), poor (D), and fail (F), respectively to evaluate the model's discrimination capacity.

A time-to-event C-index, such as Harrel's C-index or Uno's C-index, can be estimated for Cox proportional hazards prediction models (45). Two patients who both experience the outcome can be paired together in these measurements, and if the patient who experiences the outcome first has the greater predicted risk, they are deemed to be a concordant pair. Due to the survival-related aspect of this project, the time-to-event C-index approach will be utilized to evaluate the model's capacity for discriminating.

Calibration determines whether the absolute predicted risks are similar to the observed risks (45). Calibration can be measured by calibration plot and calibration slope. By calculating a Cox proportional hazards model using the prognostic index, the calibration slope is calculated. The calibration slope is the regression coefficient applied to the prognostic index.

Internal validation

There are various methods for internal validation of prognostic prediction models, such as cross-validation, bootstrapping, and split-sample validation (46). Bootstrapping method overcomes optimism better than the split-sample and cross-validation methods. Hence, 10,000 random bootstrap samples with replacement on all predictors in the data will be employed in this study to validate the model. The C-index with 95% CI, sensitivity and specificity will be used applied in-conjunction with Hosmer-Lemeshow statistic.

Model accuracy

With the aid of a Brier score, the precision of a group of probabilistic predictions will be assessed. The Brier score is simply the mean of squared differences between those probabilistic forecasts and the corresponding event scores, where the probabilistic predictions are given for those events.

Clinical and public health impact assessment

An approach that is frequently used to assess the usefulness of clinical prediction models is decision curve analysis (DCA). The clinical value of a particular model is not taken into account by conventional measures of diagnostic performance like sensitivity, specificity, and area under the receiver operating characteristic curve, which simply compare the diagnostic accuracy of one prediction model to another (47). Therefore, DCA will evaluate the maternal near-miss model's clinical and public health effects in this study.

Model presentation

After model development and validation, the risk score for maternal near-misses will be created. Based on individual level predictors, the easily usable prediction score of maternal near-miss will be created. Each predictor coefficient that will be statistically significant in the multivariable cox proportional hazard regression model will be transformed to produce the risk scores in this process. The Youden index value (sensitivity + specificity − 1) of each risk category will be used to determine the risk score cut point and develop nomogram. The clinical prediction model will be also presented to the potential user with a decision tree.

Ethics and dissemination

Ethical approval has been obtained from the Institutional Review Board of the College of Health Sciences, Bahir Dar University (protocol number 704/2023). Findings will be disseminated through scientific publications, conference presentations, community meetings and policy briefs

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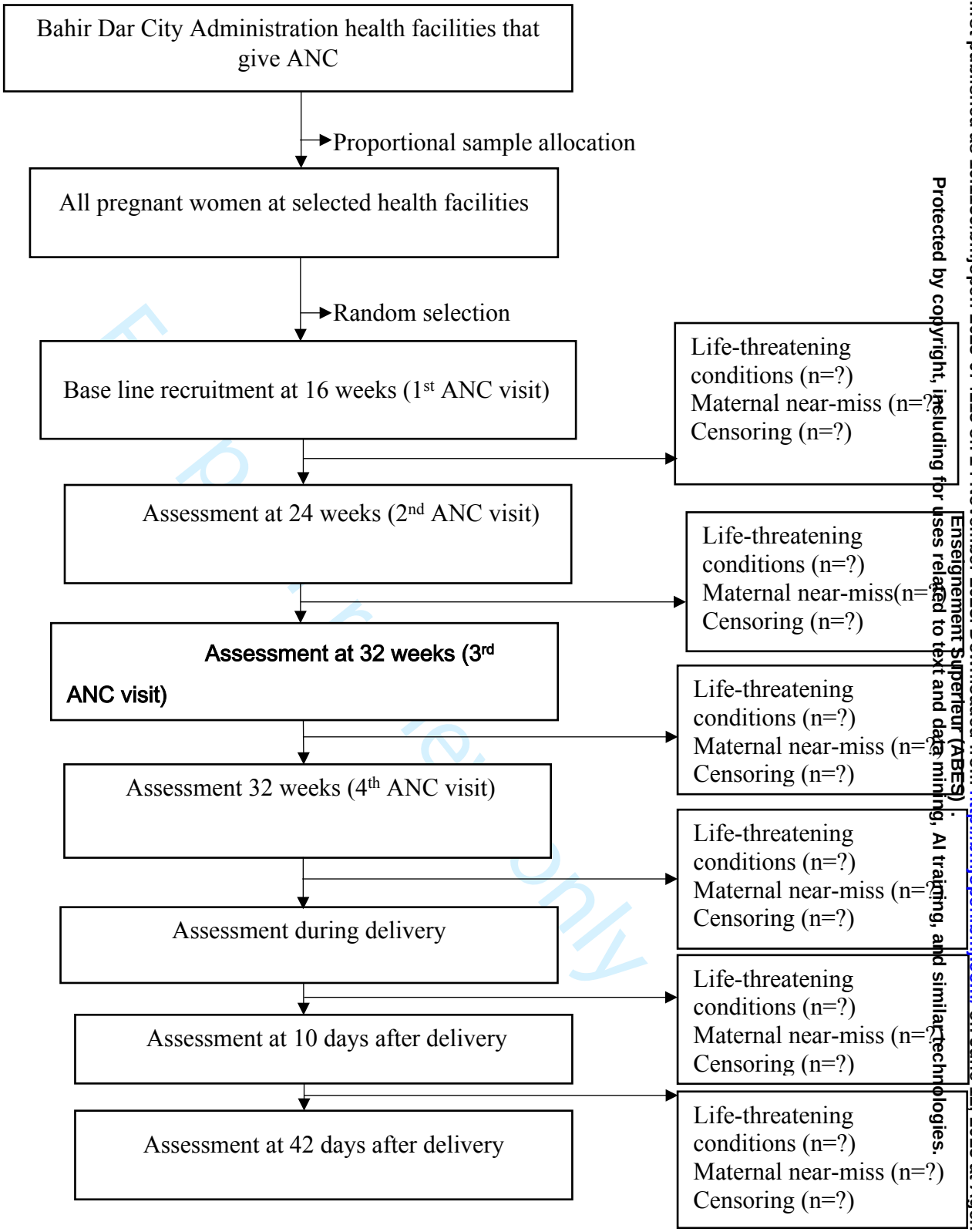

Figure 1: Flow chart for study participants selection in Bahir Dar city administration, Northwest Ethiopia, 2023

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Maternal Near-Miss Prediction Model Development Among Pregnant Women in Bahir Dar City Administration, Northwest Ethiopia: A Study Protocol

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BSTRACT

Introduction: Maternal near-miss is a condition when a woman nearly died but survived from complications that happened during pregnancy, childbirth, or within 42 days of delivery. Maternal near-miss is more prevalent among women in developing nations. Previous studies identified the impact of each predictor variable on maternal near-miss but shared prognostic predictors are not adequately explored in Ethiopia. It is therefore necessary to build a clinical prediction model for maternal near-misses in Ethiopia. Hence, the aim of this study is to develop and validate prognostic prediction model, and generate risk score for maternal near-miss among pregnant women in Bahir Dar City Administration.

Methods and analysis: A prospective follow-up study design will be employed among 2110 selected pregnant women in the Bahir Dar City Administration from 1st May 2023 to 1st April 2024. At the initial antenatal visit, pregnant women will be systematically selected. Then they will be followed until 42 days following birth. Data will be collected using structured questionnaires and data extraction sheet. The model will be created using Cox proportional hazard regression analysis. The performance of the model will be assessed based on its capacity for discrimination using c-index and calibration using calibration plot, incept and slope. The model's internal validity will be evaluated through the implementation of the bootstrapping method. Ultimately, the model will be illustrated through a nomogram and decision tree, which will be made available to prospective users.

Ethics and dissemination: Ethical approval is obtained from the Institutional Review Board of the College of Health Sciences, Bahir Dar University (protocol number 704/2023). Findings will be published in peer reviewed journals, and presented in national and internal conferences, and community meetings. In addition, policy briefs will be prepared and disseminated.

Strengths and limitations of the study

- The data will be collected prospectively to minimize missing data.
- The model will be developed based on easily and quickly identifiable individual level factors at the entrance of antenatal contact
- Recall bias related to last normal mensural period may potentially affect the results.
- Application of WHO maternal near-miss screening criteria may under estimate the detection of maternal near-miss.

INTRODUCTION

Maternal near-miss refers to a woman who almost lost her life but survived from a severe obstetric complication that occurred during pregnancy, childbirth, or within 42 days following delivery (1, 2). Severe acute maternal morbidity (SAMM) is a synonymous term for maternal near-miss (3).

The notion of maternal near-miss was devised by the World Health Organization (WHO) to pinpoint life-threatening situations during pregnancy, childbirth, and postpartum (4). This concept allows for interventions to focus on the sequence of events that led to a woman with near to death or actual death (5, 6). By using maternal near-miss statistics instead of maternal mortality rates, healthcare system deficiencies or maternal health priorities can be more swiftly identified (4, 7). To apply this concept globally, WHO created diagnostic tools for maternal near-miss that encompass clinical, laboratory, and management-based criteria (8, 9). This tool was adapted and validated for Sub-Saharan Africa (SSA) countries (10).

Maternal mortality and maternal near-miss are prominent health concerns on a global scale, especially in underprivileged countries. Roughly 303,000 women die annually due to complications during pregnancy and childbirth across the world (11). The 2017 United Nations Population Fund reported that every two minutes a woman died due to pregnancy or childbirth-related complications (12). Low-resource countries account for 99% of all maternal mortalities (13). According to the 2019 Mini-EDHS report, Ethiopia's MMR stood at 412 per 100,000 live births (14). This number is considerably higher than the average MMR worldwide (211 per 100,000 live births), but lower than the MMR in SSA (553 per 100,000 live births) (15).

Maternal near-miss ranged from 0.80 to 8.23% based on disease specific criteria, and 0.01 to 2.99% based on management related criteria (16). The maternal near-miss ratio was 18.57 per 1000 live-births globally (17). The smallest maternal near-miss ratio was found in Europe (3.10 per 1000 live birth) (17) whereas the highest-burden of maternal near-miss was found in African and Asian countries (18). In SSA, the maternal near-miss ratio was 24.2 per 1000 live births (19). The prevalence of maternal near-miss in Ethiopia was 12.57% with the highest, (26.5%), in the Amhara region (20).

The high burden of maternal near-miss is influenced by a multitude of complex risk factors. Delays in seeking care, reaching to care, receiving adequate and appropriate care (21) are some of the risk

factors for maternal near miss. The delay in seeking care is linked to failure to recognize signs of complications, failure to perceive severity of illness, cost consideration, negative experience with health system, transportation difficulties and needing permission from family members (21, 22). The reasons for the delay in accessing healthcare services include a considerable distance to the medical facility, poor road conditions, and a shortage of transportation options (23). The uncompassionate demeanor of healthcare providers, inadequacy of supplies and essential equipment, unavailability or inadequate proficiency of medical staff, and absence of urgency or comprehension of emergency situations are the reasons for delay in receiving adequate and appropriate care (21). A community's delay to take responsibility can also contribute to maternal mortality as a result of absence of a community based and community driven comprehensive approach to maternal health/well-being (24).

Several measures have been implemented to reduce the load, complications, causes, and risk factors linked to maternal mortality and maternal near-miss. In 2012, WHO defined, conceptualized and evaluated severe maternal morbidity. The objective of this effort was to compile numerous definition of maternal morbidity (25, 26). In 2013, WHO established the Maternal Mortality Surveillance and Response (MPDSR) unit, which concentrates on continuous evaluation of the reasons and factors that lead to maternal mortality (27).

In addition to the aforementioned global initiatives, individualized risk assessment studies like clinical prediction models are important in enhancing maternal health. These prediction model can guide 1) clinical researchers to select appropriate study subjects 2) patients to choose more beneficial steps for themselves; 3) doctors to make better clinical decisions; and 4) health management departments to monitor and manage the quality of medical services better and allocate medical resources more rationally (28).

The effects of clinical prediction models can be nearly mirrored in any of the three-level prevention system of diseases including the primary (health promotion, prevention and control), secondary (early screening, early diagnosis, and early treatment), and tertiary (rehabilitation programs, preventing disease relapse, reducing mortality and disability, and promoting functional recovery and quality of life). Prognostic predictive models can provide patients and doctors with a numerical risk value (probability) of identifying a specific illness in the future based on current health

condition, providing a more visual and potent scientific tool for health education and behavioral intervention (29).

Different researchers investigated the burden and determinants of maternal near-miss in Ethiopia (20, 30-37). These studies focused on the individual predictor effects on maternal near-miss. They did not identify shared characteristic of prognostic predictor as a whole, and did not directly indicate the risk stratification of obstetric patients. The researchers in other area developed and validated the diagnostic prediction models for maternal death or severe obstetric morbidity among admitted patients (38-41). The diagnostic prediction model was developed for severe maternal outcome in SSA among admitted obstetric patients (42). But there are no prognostic prediction models for maternal near-miss. Hence the development and validation of prediction model for maternal near-miss among pregnant women is required in Ethiopia. Therefore, aims of this study are the development and (internal) validation of prognostic prediction model, as well as the generation of a risk score for maternal near-miss among pregnant women. The specific objectives are:

1) To develop prognostic model for maternal near-miss among pregnant women in Bahir Dar city Administration, Northwest Ethiopia 2023-2024
2) To validate (internal) the prognostic model of maternal near-miss among pregnant women in Bahir Dar city Administration, Northwest Ethiopia, 2023-2024
3) To create risk score for maternal near-miss among pregnant women in Bahir Dar city Administration, Northwest Ethiopia, 2023-2024

METHODS AND ANALYSIS

Study design and period

Prospective follow up study will be used to develop prognostic prediction model of maternal near-miss. The focus of the model is to predict a future occurrence of maternal near-miss using predictors available at the moment of prediction.

Maternal near-miss in the follow up period (O)=f (D1, D2, D3, …Dn)

Where:

O=occurrence of maternal near-miss

D1…Dn=the predictors

Individual-level variables will be used as prognostic predictors (Dn) to forecast the incidence of maternal near-miss (O) during the follow-up period. The occurrence of maternal near-miss among pregnant women as a function of individual level predictors is expressed as =f (age, height, weight…Dn).

The study will be conducted from 1st May 2023 to 1st April 2024. The requirement of participants and data collection on prognostic predictors will be performed from 1st May 2023 to 5th August 2023 (base line period). The follow up assessment of the outcome will be at any time after the enrolment of the participants. Hence, identification of the outcome will be carried out from 2nd May 2023 to April 2024 (end line period).

Study setting and participants

The study will be carried out in Bahir Dar city administration in Northwest Ethiopia. Bahir Dar is 450 km away from Addis Ababa. Both urban and rural populations inhabit this city. There are three public hospitals, eleven healthcare centers, fifteen health posts, four private hospitals, fifty-six private specialty clinics, and thirteen private medium clinics in the city (43).

First, health facilities in Bahir Dar City Administration that provide ANC service will be identified. Second, the health facility that provide ANC will be selected randomly. Third, the total sample size will be proportionally allocated to each health facility based on last year's reports of first antenatal care visit. Fourth, the mothers who will come for 1st ANC visit will be selected systematic approach by considering the 1st comers first, and then every other interval. Lastly, the selected pregnant women will be followed until they develop the event or censorship (Figure 1). The event group will consist of women who experience maternal near-miss, while the censoring group will include women who will withdraw from ANC visits, transfer out from the selected healthcare facility, are lost to follow-up, or die during the follow-up period.

Eligibility criteria

Participants who have no plans to relocate from the study area and are deemed well enough to be interviewed by the interviewer will be included in the study. Pregnant women who experienced maternal near-miss at the beginning of the cohort and after 42 days of delivery, and do not remember the last normal menstrual period will be excluded from the study participants.

Predictors and their measurements

Individual-level data on all predictors will be collected by trained midwives using interview administer questionnaire and extraction sheet. These variables are socio-demographic characteristics such as age (in year), residence (coded as '0' rural and '1' urban), decision-making for healthcare (coded as '1' self, '2' spouse, '3' relatives, and '4' jointly), height (in centimeters), weight (measured in kilograms), and mid-upper arm circumference (MUAC) (measured in centimeters), as well as obstetric factors like parity (measured in number), plurality (coded as '0' single and '1' multiple), pregnancy intention (coded as '0' unplanned and '1' planned), gestational age (in weeks), inter-pregnancy interval (in months), and history of cesarean section (C/S) (coded as '0' and '1' yes). Other factors include history preeclampsia (coded as '0' and '1' yes), eclampsia (coded as '0' and '1' yes), sepsis (coded as '0' and '1' yes), hemorrhage (coded as '0' and '1' yes), obstructed labor (coded as '0' and '1' yes), medical morbidity (coded as '0' and '1' yes), history of stillbirth (coded as '0' and '1' yes), history of abortion (coded as '0' and '1' yes), distance from health facility (measured in kilo-meter), timing of initial antenatal contact (expressed in weeks) and birth-preparedness and complication readiness (coded as '0' no and '1' yes). Additionally, base line clinical indices such as systolic blood pressure (measured in mmHg), and hematocrit measurement (measured in ml/dl).

Outcome

The maternal near-miss will be diagnosed using the WHO screening criteria (4) during the follow up phase by trained health professionals. Women who meet at least one of the clinical, laboratory, or management-based criteria will be classified as event group (maternal near-miss), while the rest will be classified as censoring group. In addition to maternal near-miss, pregnancy danger signs, referral, withdrawal against medical advice, transfer out, death, and any complications will be extracted from maternal card during the follow up period.

Blinding assessment of predictors and outcome

Blinding reduces the risk of bias that may be introduced in the model development. This will be done by measuring the predictors at the base line and outcome at the follow up period. The data collectors for the baseline and end line surveys will be different.

Sample size determination

The sample was determined based on the minimum sample size calculation criteria for a time to event study. The minimum criteria for this calculation are: 1) a minimum heuristic shrinkage factor, S, greater than 0.9 (targeting less than 10% overfitting), 2) a small difference between Nagelkerke's R2app and R2adj (targeting less than 0.05 absolute difference), and 3) a small margin of error in the overall risk estimate (targeting less than 0.05 absolute error). These criteria, including the number of parameters (P), heuristic shrinkage factor (S), overall risk in the population, and the model's anticipated Cox-Snell R2 (or C-statistics), were reviewed from previous studies. Approximately 25 candidate parameters, 26.6% of maternal near-miss (34) and C-statistics of 0.11 (42) were utilized to calculate the sample size.. The sample size was then calculated using the Stata command "pmsampsize, type (b) rsquared (0.11) parameter (25) prev (0.266)". The resulting sample size was 1918 (Table 1).

Table 1: Sample size calculation for prognostic prediction model development of maternal near-miss using minimum criteria of event-to-time method in Bahir Dar city, Ethiopia 2023-2024.

Criteria	Sample size	Shrinkage	Parameter	Rsq	Max-Rsq	EPP
Criteria1	1918	0.90	25	0.11	0.52	9.21
Criteria 2	895	0.81	25	0.11	0.52	4.30
Criteria 3	162	0.90	25	0.11	0.52	0.78
Final	1918	0.90	25	0.11	0.52	9.21

Finally, taking into account a non-response rate of 10%, the sample size for the development of a predictive model for maternal near-miss will be 2110.

Data quality assurance

Input from study participants and subject-matter experts will be used to construct and validate the questionnaire in terms of face and content validity. After tool validation, data collectors and supervisors will receive two days of training to become familiar with the questionnaires, the data collection processes, the ethical considerations, and the study's purpose. Similarly, health professionals who work at antenatal, delivery and postnatal departments will be trained on the screening criteria of maternal near-miss. A pretest will be undertaken to ensure the accuracy of the data and check for ambiguities in the language after switching from the English version to the

Amharic version. The tools will be changed in light of the pretest's results. The daily supervision of data collectors and daily verification of all collected data will be done by the supervisor. The data will be regularly checked for completeness, and any problems during data collection will be addressed appropriately.

Data processing and management

The data from epi-collect5 will be downloaded and transferred to the Microsoft excel. The illogical values and steps will be checked during designing of questionnaire/abstraction sheet in the epi-collect5. The collected data will be examined for consistency and completeness. Then the data will be exported to R 4.2.2 software for analysis.

Statistical analysis methods

Missing data handling

Once the data is prepared for analysis, a thorough evaluation, based on inspection of the data, will be conducted to determine if statistical methods should be employed to address any missing data. Then the missing data will be addressed using the technique of multiple imputation. If the amount of missing data is less than 10%, the missing values will be imputed. This imputation process will be repeated 5 times. The overall procedure for multiple imputation in this study will be 1) replacing the missing values with randomly selected values from certain distributions to create complete case datasets; 2) conducting the same analysis on each of these datasets; and 3) pooling the results in the same fashion.

Data pre-processing

The dichotomization or categorization of the continuous will be based on widely accepted clinical cut-off value grouping. Additionally, restricted cubic splines, or fractional polynomials will be applied for the nonlinear relation if there are no clinical cut points.

The distribution of continuous variables will be examined graphically using a histogram and statistically by the Shapiro-Wilk test. If the data will not normally distribute, transformation and standardization of data will be performed. Multicollinearity between each independent predictor will be checked by using variance inflation factor (VIF). In this regard, if VIF is greater than 10, there is no multicollinearity.

Model building

Predictor selection

The prognostic predictors will be selected by considering existing knowledge of previously established predictors; applicability and costs of predictor measurement relevant to the targeted setting; and statistical power.

Model estimation and specification

Cox proportional hazard regression model will be used. The strength of the association will be measured in terms of hazard ratio at 95% confidence limits. The Cox proportional hazard model assumption will be checked using scaled Schoenfeld residual test and graphically with log-log Cox adjusted survival estimate. The model fitness will be checked using Cox –snell residuals test. Finally, the multivariable cox proportional hazard model will declare a p-value < 0.05 with 95% CI as statistical significance.

Model performance

Calibration and discrimination are two crucial factors in assessing the prognostic accuracy of the model. At a group level, calibration assesses how accurately the absolute predicted risks align with the real hazards (44). Discrimination refers to the model's capacity to differentiate between patients who experience the relevant event and those who do not.

By utilizing the concordance index, the model's capacity for differentiation can be assessed (C-index). To compute the C-index, all possible pairs of patients with and without the outcome are examined. If the patient with the result has a higher expected risk than the patient without the result, the pair is considered to be in agreement. The C-index is equivalent to the area under the curve(45). The AUC values ranging from 0.9 to 1.0, 0.8 to 0.9, 0.7 to 0.8, 0.6 to 0.7, and 0.5 to 0.6 are classified as excellent (A), good (B), fair (C), poor (D), and fail (F), respectively in order to evaluate the model’s ability to differentiate.

A time-to-event C-statistic, such as Harrel's C-statistic or Uno's C-statistic, can be calculated for Cox proportional hazards prediction models (46). Two patients who both have the event can be matched together in these calculations, and if the patient who has the event first has the higher predicted risk, they are considered to be a concordant pair. Because this project is focused on

survival, the time-to-event C-statistic method will be used to assess the model's ability to discriminate.

Calibration assesses if the predicted hazards are comparable to the actual hazards (46). Calibration can be evaluated through a calibration plot, intercept and slope. By computing a Cox proportional hazards model utilizing the prognostic indicator, the calibration slope is determined. The calibration slope represents the coefficient of regression applied to the prognostic indicator.

Internal validation

There exist different techniques for internal verification of prognostic forecasting models, including cross-validation, bootstrapping, and split-sample validation (47). The bootstrapping approach surpasses the split-sample and cross-validation methods in addressing optimism. Therefore, this study will utilize 10,000 random bootstrap samples with replacement on all predictors in the dataset to validate the model. The C-index with a 95% confidence interval, as well as sensitivity and specificity, will be employed in conjunction with the Hosmer-Lemeshow statistic.

Model accuracy

Using a Brier score, the accuracy of a set of probabilistic forecasts will be evaluated. The Brier score is the average of the squared disparities between the probabilistic predictions and the actual event outcomes, with the probabilistic forecasts being provided for those specific events.

Clinical and public health impact assessment

Decision curve analysis (DCA) is a commonly employed method to evaluate the efficacy of clinical prediction models. Traditional measures of diagnostic performance, such as sensitivity, specificity, and area under the receiver operating characteristic curve, do not consider the clinical value of a specific model. Instead, these measures only compare the diagnostic accuracy of different prediction models (48). Therefore, in this study, DCA will be utilized to assess the clinical and public health impacts of the maternal near-miss model.

Model presentation

Once the model is developed and validated, a risk score will be generated for maternal near-misses. This score will be based on predictors at the individual level and will be user-friendly. The

coefficients of each predictor that are statistically significant in the multivariable cox proportional hazard regression model will be adjusted to calculate the risk scores. The cut-off point for the risk score and the development of a nomogram will be determined using the Youden index value (sensitivity + specificity - 1) for each risk category. Additionally, a decision tree will be presented to potential users as part of the clinical prediction model.

Patient and Public Involvement

No patient or public has been involved while developing this study protocol.

Ethics and dissemination

The Institutional Review Board of the College of Health Sciences, Bahir Dar University has granted ethical clearance (protocol number 704/2023) for this study. The results will be shared via scientific publications, conference presentations, community meetings, and policy briefs.

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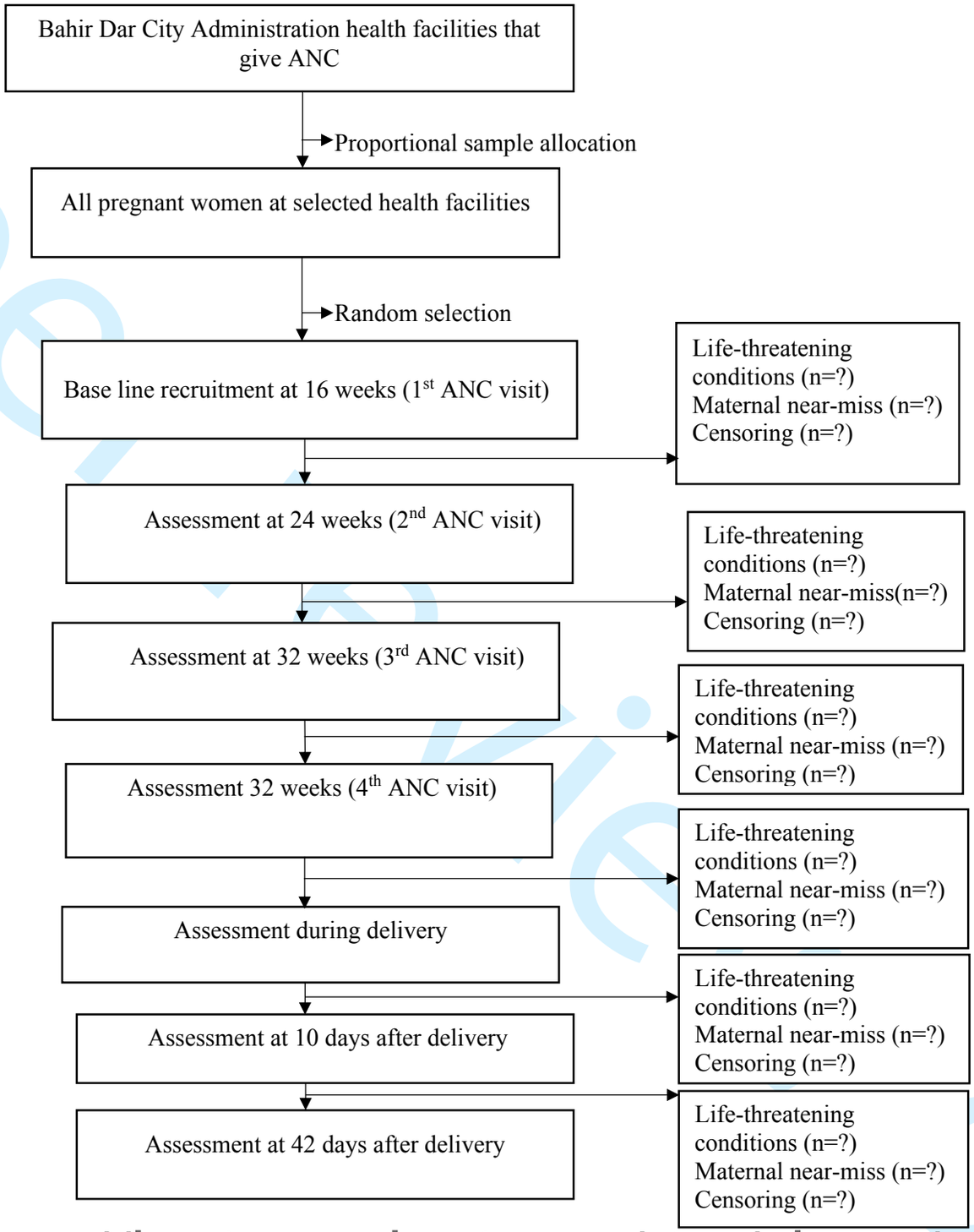
Figure Legend

Figure 1: Flow chart for study participants selection in Bahir Dar city administration, Northwest Ethiopia, 2023



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Maternal Near-Miss Prediction Model Development among Pregnant Women in Bahir Dar City Administration, northwest Ethiopia: A Study Protocol

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ABSTRACT

Introduction: Maternal near-miss is a condition when a woman nearly died but survived from complications that happened during pregnancy, childbirth, or within 42 days after delivery. Maternal near-miss is more prevalent among women in developing nations. Previous studies have identified the impact of different predictor variables on maternal near-miss but shared prognostic predictors are not adequately explored in Ethiopia. It is therefore necessary to build a clinical prediction model for maternal near-misses in Ethiopia. Hence, the aim of this study is to develop and validate a prognostic prediction model, and generate a risk score for maternal near-miss among pregnant women in Bahir Dar City Administration.

Methods and analysis: A prospective follow-up study design will be employed among 2110 selected pregnant women in the Bahir Dar City Administration from 1st May 2023 to 1st April 2024. At the initial antenatal visit, pregnant women will be systematically selected. Then they will be followed until 42 days following birth. Data will be collected using structured questionnaires and data extraction sheet. The model will be created using Cox proportional hazard regression analysis. The performance of the model will be assessed based on its capacity for discrimination using c-index and calibration using calibration plot, intercept and slope. The model's internal validity will be evaluated through the bootstrapping method. Ultimately, the model will be illustrated through a nomogram and decision tree, which will be made available to prospective users.

Ethics and dissemination: Ethical approval has been obtained from the Institutional Review Board of the College of Medicine and Health Sciences, Bahir Dar University (protocol number 704/2023). Findings will be published in peer reviewed journals and local and international seminars, conferences, symposiums and workshops. Manuscripts will be prepared and published in scientifically reputable journals. In addition, policy briefs will be prepared.

Strengths and limitations of the study

- The data will be collected prospectively to minimize missing data.
- The model will be developed based on easily and quickly identifiable individual level factors at the entrance of antenatal contact.
- Recall bias related to last normal menstrual period may potentially affect the results.
- Application of WHO maternal near-miss screening criteria may under estimate the detection of maternal near-miss.

INTRODUCTION

Maternal near-miss refers to a woman who almost lost her life but survived from a severe obstetric complication that occurred during pregnancy, childbirth, or within 42 days following delivery (1, 2). Severe acute maternal morbidity (SAMM) is a synonymous term for maternal near-miss (3).

The notion of maternal near-miss was devised by the World Health Organization (WHO) to pinpoint life-threatening situations during pregnancy, childbirth, and postpartum (4). This concept allows for interventions focusing on the sequence of events that led to a woman with near to death or actual death (5, 6). By using maternal near-miss statistics instead of maternal mortality rates, maternal healthcare system deficiencies and health priorities can be more swiftly identified (4, 7). To apply this concept globally, WHO created diagnostic tools for maternal near-miss that encompass clinical, laboratory, and management-based criteria (8, 9). This tool was adapted and validated for Sub-Saharan Africa (SSA) countries (10).

Maternal mortality and maternal near-miss are prominent health concerns on a global scale, especially in underprivileged countries. Roughly 303,000 women die annually due to complications during pregnancy and childbirth across the world (11). The 2017 United Nations Population Fund reported that every two minutes a woman died due to pregnancy or childbirth-related complications (12). Low-resource countries account for 99% of all maternal mortalities (13). According to the 2019 Mini-Ethiopian Demographic Health Survey (EDHS) report, Ethiopia's maternal mortality rate (MMR) stood at 412 per 100,000 live births (14). This number is considerably higher than the average MMR worldwide (211 per 100,000 live births), but lower than the MMR in SSA (553 per 100,000 live births) (15).

Maternal near-miss ranged from 0.80 to 8.23% based on disease specific criteria, and 0.01 to 2.99% based on management related criteria (16). The maternal near-miss ratio was 18.57 per 1000 live-births globally (17). The smallest maternal near-miss ratio was found in Europe (3.10 per 1000 live birth) (17) whereas the highest-burden of maternal near-miss was found in African and Asian countries (18). In SSA, the maternal near-miss ratio was 24.2 per 1000 live births (19). The prevalence of maternal near-miss in Ethiopia was 12.57% with the highest (26.5%) in the Amhara region (20).

The high burden of maternal near-miss is influenced by a multitude of complex risk factors. Delays in seeking care, reaching to care, receiving adequate and appropriate care (21) are some of the risk factors for maternal near- miss. The delay in seeking care is linked to failure to recognize signs of complications, failure to perceive severity of illness, cost consideration, negative experience with health system, transportation difficulties and need of permission from family members (21, 22). The reasons for the delay in accessing healthcare services include a considerable distance to the medical facility, poor road conditions, and a shortage of transportation options (23). The uncompassionate demeanor of healthcare providers, inadequacy of supplies and essential equipments, unavailability or inadequate proficiency of medical staff, and absence of urgency or comprehension of emergency situations are the reasons for delay in receiving adequate and appropriate care (21). A community's delay to take responsibility can also contribute to maternal mortality as a result of absence of a community based and community driven comprehensive approach to maternal health/well-being (24).

Several measures have been implemented to reduce the load, complications, causes, and risk factors linked to maternal mortality and maternal near-miss. In 2012, WHO defined, conceptualized and evaluated severe maternal morbidity. The objective of this effort was to compile numerous definition of maternal morbidity (25, 26). In 2013, WHO established the Maternal Mortality Surveillance and Response (MPDSR) unit, which concentrates on continuous evaluation of the reasons and factors that lead to maternal mortality (27).

In addition to the aforementioned global initiatives, individual risk assessment studies like clinical prediction models are important in enhancing maternal health. These prediction models can guide 1) clinical researchers to select appropriate study subjects; 2) patients to choose more beneficial steps for themselves; 3) doctors to make better clinical decisions; and 4) health management departments to monitor and manage the quality of medical services and to allocate medical resources more rationally (28).

The effects of clinical prediction models can be nearly mirrored in any of the three-level prevention system of diseases including the primary (health promotion, prevention and control), secondary (early screening, early diagnosis, and prompt treatment), and tertiary (rehabilitation programs, preventing disease relapse, reducing mortality and disability, and promoting functional recovery and quality of life). Prognostic predictive models can provide patients and doctors with a numerical

risk value (probability) of identifying specific illness in the future based on current health condition (29).

The prediction model we are going to develop will be used in daily clinical practice and obstetric patients. It will help pregnant women to identify themselves as a risk group or not. In daily clinical practice, this model will provide clues for obstetricians to select high-risk obstetric patients for further screening, diagnosis, and management. In general, the development of numerical and visual maternal near-miss model will assist obstetricians or other healthcare professionals, obstetric patients, and their relatives to facilitate shared medical decision-making for diagnostic testing, initiating or discontinuing treatments, or making lifestyle changes throughout the perinatal period.

Different researchers investigated the burden and determinants of maternal near-miss in Ethiopia (20, 30-37). These studies focused on the individual predictor effects on maternal near-miss. They did not identify shared characteristics of prognostic predictors as a whole, and did not directly indicate the risk stratification of obstetric patients. Researchers in other areas developed and validated the diagnostic prediction models for maternal death or severe obstetric morbidity among admitted patients (38-41). The diagnostic prediction model was developed for severe maternal outcome in SSA among admitted obstetric patients (42). But there are few prognostic prediction models for maternal near-miss. Hence the development and validation of a prediction model for maternal near-miss among pregnant women is required in Ethiopia. Therefore, the aims of this study are the development and (internal) validation of a prognostic prediction model, as well as the generation of a risk score for maternal near-miss among pregnant women. The specific objectives are:

1) To develop a prognostic model for maternal near-miss among pregnant women in Bahir Dar city Administration, Northwest Ethiopia 2023-2024
2) To validate (internal) the prognostic model of maternal near-miss among pregnant women in Bahir Dar city Administration, Northwest Ethiopia, 2023-2024
3) To create risk score for maternal near-miss among pregnant women in Bahir Dar city Administration, Northwest Ethiopia, 2023-2024

METHODS AND ANALYSIS

The components of this protocol were reported based on the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline or checklists (43) (supplementary file 1).

Study design and period

Prospective follow up study will be conducted to develop prognostic prediction model of maternal near-miss. The focus of the model is to predict a future occurrence of maternal near-miss using individual level factors at the entrance of antenatal contact (ANC).

Maternal near-miss in the follow up period (O)=f (D1, D2, D3, …Dn)

Where:

O=occurrence of maternal near-miss

D1…Dn=the predictors

Individual-level variables will be used as prognostic predictors (Dn) to forecast the incidence of maternal near-miss (O) during the follow-up period. The occurrence of maternal near-miss among pregnant women as a function of individual level predictors is expressed as =f (age, height, weight…Dn).

The study will be conducted from 1st May 2023 to 1st April 2024. The requirement of participants and data collection on prognostic predictors will be performed from 1st May 2023 to 5th August 2023 (base line period). The follow up assessment of the outcome will be at any time after the enrolment of the participants. Hence, identification of the outcome will be carried out from 2nd May 2023 to April 2024 (end line period).

Study setting and participants

The study will be carried out in Bahir Dar city administration in Northwest Ethiopia. Bahir Dar is 450 km away from Addis Ababa. Both urban and rural populations inhabit this city. There are three public hospitals, eleven healthcare centers, fifteen health posts, four private hospitals, fifty-six private specialty clinics, and thirteen private medium clinics in the city (44).

First, health facilities in Bahir Dar City Administration that provide ANC service will be identified. Second, the health facilities to be included in the study will be selected randomly. Third, the total

sample size will be proportionally allocated to each health facility based on last year's reports of first antenatal care visit. Fourth, pregnant women who come for their first ANC visit will be selected using a systematic sampling method. In this regard, in each data collection day, the woman who will arrive first in the ANC clinic will be selected as a starting participant. Then, every other ANC visitor will be selected. Lastly, the selected pregnant women will be followed until they either experience the event or reach a state of censorship (Figure 1). The event group will consist of women who experience maternal near-miss, while the censoring group will include women who withdraw from ANC visits, transfer out from the selected healthcare facility, are lost to follow-up, or pass away during the follow-up period.

Eligibility criteria

Participants who have no plans to relocate from the study area and are considered well enough to be interviewed by the interviewer will be included in the study. Pregnant women who experienced maternal near-miss at the beginning of the cohort and after 42 days of delivery, and who do not remember their last normal menstrual period will be excluded from the study participants.

Predictors and their measurements

Individual-level data on all predictors will be collected by trained midwives using an interview-administered questionnaire and an extraction sheet. These variables include socio-demographic characteristics such as age (in years), residence (coded as '0' for rural and '1' for urban), decision-making for healthcare (coded as '1' for self, '2' for spouse, '3' for relatives, and '4' for jointly), height (in centimeters), weight (in kilograms), and mid-upper arm circumference (MUAC) (measured in centimeters). Additionally, obstetric factors such as parity (measured in number), plurality (coded as '0' for single and '1' for multiple), pregnancy intention (coded as '0' for unplanned and '1' for planned), gestational age (in weeks), inter-pregnancy interval (in months), and history of cesarean section (C/S) (coded as '0' for no and '1' for yes) will be recorded. Other factors to be considered include the history of preeclampsia (coded as '0' for no and '1' for yes), eclampsia (coded as '0' for no and '1' for yes), sepsis (coded as '0' for no and '1' for yes), hemorrhage (coded as '0' for no and '1' for yes), obstructed labor (coded as '0' for no and '1' for yes), medical morbidity (coded as '0' for no and '1' for yes), history of stillbirth (coded as '0' for no and '1' for yes), history of abortion (coded as '0' for no and '1' for yes), distance from the health facility (measured in kilometers), timing of initial antenatal contact (expressed in weeks), and birth preparedness and complication readiness (coded as '0' for no and '1' for yes). Additionally, baseline clinical indices such as blood

pressure (measured in mmHg) and hematocrit measurement (measured in percentage) will be recorded.

Outcome

Maternal near-miss will be diagnosed during the follow-up phase by trained health professionals using the WHO screening criteria (4).Women who meet at least one of the clinical, laboratory, or management-based criteria will be classified as the event group (maternal near-miss), while the remaining women will be classified as the censoring group. In addition to identifying maternal near-miss cases, pregnancy danger signs, referrals, withdrawals against medical advice, transfers out, deaths, and any complications will be extracted from the maternal card during the follow-up period..The survival time will be measured in week (s) from the last date of normal menstrual period to the occurrence of maternal near-miss or censorship.

Blinding assessment of predictors and outcome

Blinding reduces the risk of bias that may be introduced in the model development. This will be done by measuring the predictors at the base line and outcome at the follow up period. The data collectors for the baseline and end line surveys will be different.

Sample size determination

The sample was determined based on the minimum sample size calculation criteria for a time to event study. The minimum criteria for this calculation are: 1) a minimum heuristic shrinkage factor, S, greater than 0.9 (targeting less than 10% overfitting), 2) a small difference between Nagelkerke's R2app and R2adj (targeting less than 0.05 absolute difference), and 3) a small margin of error in the overall risk estimate (targeting less than 0.05 absolute error). These criteria, including the number of parameters (P), heuristic shrinkage factor (S), overall risk in the population, and the model's anticipated Cox-Snell R2 (or C-statistics) were reviewed from previous studies. Approximately 25 candidate parameters, 26.6% of maternal near-miss (34) and C-statistics of 0.11 (42) were utilized to calculate the sample size. The sample size was then calculated using the Stata command "pmsampsize, type (b) rsquared (0.11) parameter (25) prev (0.266)". The resulting sample size was 1918 (Table 1).

Table 1: Sample size calculation for prognostic prediction model development of maternal near-miss using minimum criteria of event-to-time method in Bahir Dar city, Ethiopia 2023-2024.

Criteria	Sample size	Shrinkage	Parameter	Rsq	Max-Rsq	EPP
Criteria1	1918	0.90	25	0.11	0.52	9.21
Criteria 2	895	0.81	25	0.11	0.52	4.30
Criteria 3	162	0.90	25	0.11	0.52	0.78
Final	1918	0.90	25	0.11	0.52	9.21

Finally, taking into account a non-response rate of 10%, the sample size for the development of a predictive model for maternal near-miss will be 2110.

Data quality assurance

Input from study participants and subject-matter experts will be used to construct and validate the questionnaire in terms of face and content validity. After tool validation, data collectors and supervisors will receive a two days of training to become familiar with the questionnaires, the data collection processes, the ethical considerations, and a purpose of the study. Similarly, health professionals who work at antenatal, delivery and postnatal departments will be trained on the screening criteria of maternal near-miss. Then a pretest will be conducted by four data collectors (Bachelor degree in Midwifery) and one supervisor (Epidemiologist). This pretest will be undertaken to ensure the accuracy of the data and to check for ambiguities in language after switching from English to Amharic. Data collection tools will be changed in light of the pretest's results. Daily supervision of data collectors and daily verification of all collected data will be done by the supervisor. The data will be regularly checked for completeness, and any problems during data collection will be addressed appropriately.

Statistical analysis methods

Data processing

The data from Epi-Collect5 will be downloaded and transferred to Microsoft Excel. The illogical values and steps will be checked during the design of the questionnaire/abstraction sheet in Epi-Collect5. The collected data will be examined for consistency and completeness. Then the data will be exported to R 4.2.2 software for analysis.

Data cleaning will be performed to check the completeness of the data, remove or correct noise, outliers, and missing values in order to prepare the data for the subsequent steps of model

development and validation. The cleaned data will be further processed using feature selection and extraction algorithms, which will involve deriving new attributes and summarizing the data. Data transformations, such as normalization, will be applied to remove noise and correct inconsistencies in the data.

For continuous variables, dichotomization or categorization will be performed based on widely accepted clinical cutoff values. If there are no clinical cutoff points, restricted cubic splines or fractional polynomials will be applied to model non-linear relationships.

The distribution of continuous variables will be examined graphically using a histogram and statistically using the Shapiro-Wilk test. If the data does not follow a normal distribution, data transformation and standardization will be performed. Multicollinearity between each independent predictor will be checked using the variance inflation factor (VIF). If the VIF is greater than 10, there is no multicollinearity.

Missing data handling

Once the data is prepared for analysis, a thorough evaluation will be conducted to identify missing data. Missing data is a common problem that can impact the accuracy of classification and the models generated from data mining algorithms.

The first step in dealing with missing data is to understand the patterns of missing values. The Hmisc library's "naclus" and "naplot" functions, as well as the recursive partitioning library of Atkinson and Therneau, will be applied for this purpose. The "naclus" function identifies variables that tend to be missing for the same participants and computes the proportion of missing values for each variable. The "rpart" function builds a tree to predict which types of participants tend to have missing values.

After understanding the patterns of missing values, statistical methods will be employed to handle the missing values. One common method is complete case analysis, which involves excluding all subjects with missing values for any potential predictor or outcome. Complete case analysis considers subjects with complete data for a specific predictor, even if they have missing values for other covariates not included in the specific model. This method discards information from subjects who have information on some predictors but not all, making it statistically inefficient.

Therefore, methods that replace missing values with substituted values based on various criteria are preferred. These methods include: 1) replacing the missing value with a constant, 2) replacing the missing value with the mean of the field, and 3) replacing the missing values with randomly generated values from the observed variable distribution.

In the current model development, missing values will be handled by replacing them with randomly generated values from the observed variable distribution. Specifically, multiple imputation techniques will be used when the amount of missing data is less than 10%. The steps of multiple imputation involve: 1) replacing missing values with randomly selected values from specific distributions to create complete case datasets, 2) conducting the same analysis on each of these datasets, and 3) pooling the results together. This imputation process will be repeated 5 times.

Model building

Predictor selection

The prognostic predictors will be selected by considering existing knowledge of previously established predictors; applicability and costs of predictor measurement relevant to the targeted setting; and statistical power.

Model estimation and specification

Cox proportional hazard regression model will be used. The strength of the association will be measured in terms of hazard ratio at 95% confidence limits. The Cox proportional hazard model assumption will be checked using scaled Schoenfeld residual test and graphically with log-log Cox adjusted survival estimate. The model fitness will be checked using Cox –snell residuals test. Finally, the multivariable cox proportional hazard model will declared be at a p-value < 0.05 with 95% CI as statistical significance.

Model performance

Calibration and discrimination are two crucial factors in assessing the prognostic accuracy of the model. At a group level, calibration assesses how accurately the absolute predicted risks align with the real hazards (45). Discrimination refers to the model's capacity to differentiate between patients who experience the relevant event and those who do not.

By utilizing the concordance index, the model's capacity for differentiation can be assessed (C-index). To compute the C-index, all possible pairs of patients with and without the outcome are

examined. If the patient with the result has a higher expected risk than the patient without the result, the pair is considered to be in agreement. The C-index is equivalent to the area under the curve(46). The AUC values ranging from 0.9 to 1.0, 0.8 to 0.9, 0.7 to 0.8, 0.6 to 0.7, and 0.5 to 0.6 are classified as excellent (A), good (B), fair (C), poor (D), and fail (F), respectively in order to evaluate the model's ability to differentiate.

A time-to-event C-statistic, such as Harrel's C-statistic or Uno's C-statistic, can be calculated for Cox proportional hazards prediction models (47). Two patients who both have the event can be matched together in these calculations, and if the patient who has the event first has the higher predicted risk, they are considered to be a concordant pair. Because this project is focused on survival, the time-to-event C-statistic method will be used to assess the model's ability to discriminate.

Calibration assesses if the predicted hazards are comparable to the actual hazards (47). Calibration can be evaluated through a calibration plot, intercept and slope. By computing a Cox proportional hazards model utilizing the prognostic indicator, the calibration slope is determined. The calibration slope represents the coefficient of regression applied to the prognostic indicator.

Internal validation

Different techniques exist for internal verification of prognostic forecasting models, including cross-validation, bootstrapping, and split-sample validation (48). The bootstrapping approach surpasses the split-sample and cross-validation methods in addressing optimism. Therefore, this study will utilize 10,000 random bootstrap samples with replacement on all predictors in the data-set to validate the model. The C-index with a 95% confidence interval, as well as sensitivity and specificity, will be employed in conjunction with the Hosmer-Lemeshow statistic.

Model accuracy

Using a Brier score, the accuracy of a set of probabilistic forecasts will be evaluated. The Brier score is the average of the squared disparities between the probabilistic predictions and the actual event outcomes, with the probabilistic forecasts being provided for those specific events.

Clinical and public health impact assessment

Decision curve analysis (DCA) is a commonly employed method to evaluate the efficacy of clinical prediction models. Traditional measures of diagnostic performance, such as sensitivity, specificity, and area under the receiver operating characteristic curve do not consider the clinical value of a specific model. Instead, these measures only compare the diagnostic accuracy of different prediction models (49). Therefore, in this study, DCA will be utilized to assess the clinical and public health impacts of the maternal near-miss model.

Model presentation

Once the model is developed and validated, a risk score will be generated for maternal near-misses. This score will be based on predictors at the individual level and will be user-friendly. The coefficients of each predictor that are statistically significant in the multivariable cox proportional hazard regression model will be adjusted to calculate the risk scores. The cut-off point for the risk score and the development of a nomogram will be determined using the Youden index value (sensitivity + specificity - 1) for each risk category. Additionally, a decision tree will be presented to potential users as part of the clinical prediction model.

Patient and Public Involvement

No patient or public has been involved while developing this study protocol.

Ethics and dissemination

The Institutional Review Board of the College of Medicine and Health Sciences, Bahir Dar University has granted ethical clearance (protocol number 704/2023) for this study. Results will be shared via scientific publications, conference presentations, community meetings, and policy briefs.

Authors' contribution: YW, GD, and GA contributed equally to the design of the study. YW drafted the manuscript and all the authors revised and approved the manuscript.

Competing interests: The authors declared that there is no any competing interest.

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Data statement: The data to be collected in this study will be published in appropriate data repositories.

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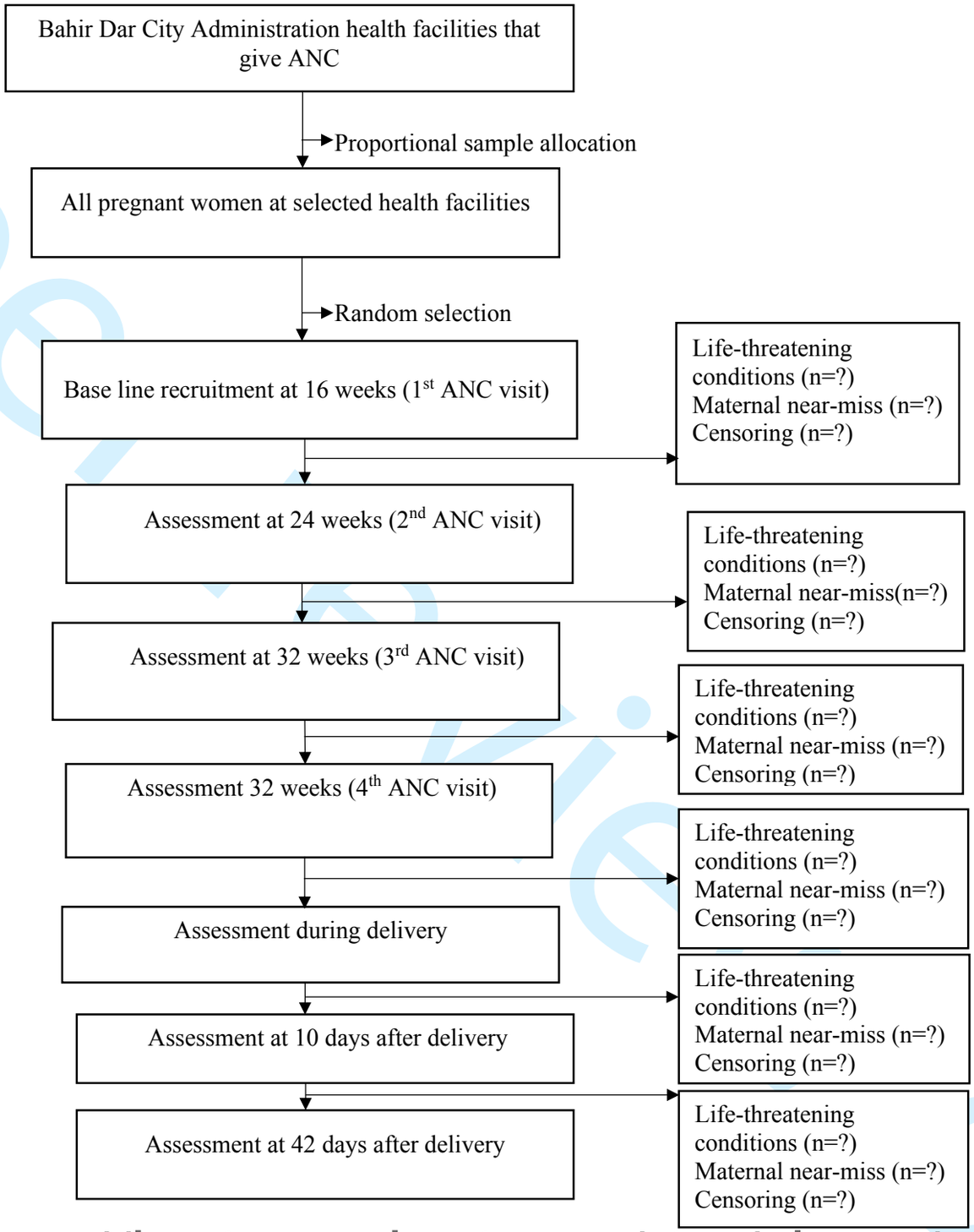
Figure Legend

Figure 1: Flow chart for study participants selection in Bahir Dar city administration, Northwest Ethiopia, 2023



TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4-6
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	Describe eligibility criteria for participants.	8
	5c	Give details of treatments received, if relevant.	NA
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	9
	6b	Report any actions to blind assessment of the outcome to be predicted.	9
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	8
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	9
Sample size	8	Explain how the study size was arrived at.	9
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	11
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	12
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	12
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	12-13
Risk groups	11	Provide details on how risk groups were created, if done.	14
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	NA
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	NA
Model development	14a	Specify the number of participants and outcome events in each analysis.	NA
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	NA
	15b	Explain how to the use the prediction model.	NA
Model performance	16	Report performance measures (with CIs) for the prediction model.	NA
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	3
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	NA
Implications	20	Discuss the potential clinical use of the model and implications for future research.	NA
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	Give the source of funding and the role of the funders for the present study.	14

NA-Not applicable

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.