Statistical risk prediction models for adverse maternal and neonatal outcomes in severe preeclampsia in a low-resource setting, Mpilo Central Hospital, Bulawayo, Zimbabwe. A PhD Research Proposal.

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Abstract

This research proposal is for a PhD research project that is being done under the National University of Science and Technology in Bulawayo, Zimbabwe. Hypertensive disorders in pregnancy are a leading cause of maternal and perinatal morbidity and mortality especially in low-resource settings. This study will address the need to develop and test statistical risk prediction models for adverse maternal and neonatal outcomes in low-resource settings. This will be the first time such research to produce risk prediction models would be carried out at a local or national level setting in Zimbabwe. Critically, new risk prediction models introduced for our clinical setting may reduce avoidable maternal and neonatal morbidity and mortality at local, national, regional and international level.

1 Introduction

German authors reported that the first reports referring to eclampsia date from 2200 BC, observed in papyri of ancient Egypt [1,2]. It is an age old disease. The incidence of preeclampsia remains underestimated due to underreporting [3]. This disorder has life-threatening, life-altering and life-ending consequences.

Preeclampsia occurs only in human pregnancy and is characterised by high blood pressure and significant proteinuria after 20 weeks' gestation [2]. von Dadelszen et al. defined preeclampsia as occurring after 20 weeks' gestation with high blood pressure (i.e. BP>160–170/100–110), significant proteinuria of >3–5g/24 hours, and/or the occurrence of symptomatology, such as headache or visual disturbances [4]. Severe preeclampsia causes significant adverse impact on maternal, fetal and neonatal health. Avoidable maternal and neonatal morbidity and mortality may result particularly in cases of severe disease. Mpilo Central Hospital is a teaching tertiary referral centre, located in Bulawayo. Bulawayo is located in Matabeleland, and is the second largest city in Zimbabwe after the capital city Harare, with a population of 653, 337 [5]. It is a1000-bedded hospital and its maternity unit delivers 8 000–10 000 babies per year.

Hypertensive disorders of pregnancy present as part of the spectrum of disorders in pregnancy. According to Tranquilli et al. [6], Tranquilli [7] and Mayrink et al.[3], there is a general agreement to define preeclampsia as severe if blood pressure was ≥160mmHg systolic or 110mmHg diastolic. These conditions pose serious consequences for both maternal and neonatal health, with 50,000–100,000 annual maternal deaths attributable to these conditions globally, as well as 500 000 fetal and neonatal deaths as reported by Brown et al.[8], including increased risks of fetal growth restriction and stillbirth according to Oyston et al.[9].

According to Say et al., the three most common causes of maternal deaths globally as of 2010 are haemorrhage, hypertensive disorders and sepsis, accounting for more than half of maternal deaths [10]. In2015 developing countries accounted for approximately 99% (302,000) of the global maternal deaths, with sub-Saharan Africa alone accounting for roughly 66% (201,000) as reported by the WHO et al.[11].

The same WHO report states that critically most of the deaths were avoidable if they had care and access to healthcare.

In Zimbabwe, hypertensive disorders were the third leading cause of maternal deaths [12]. The overall incidence of severe preeclampsia and eclampsia at Mpilo Central Hospital in 2017 was 1.3% [13]. The incidence of early-onset severe preeclampsia has been reported to be 0.38% in the USA, with chronic hypertension and congenital anomalies strongly associated with early-onset preeclampsiaas found by Lisonkova etal. and 13% by Pettit et al.[14,15]. Abalos et al. found that the overall incidence of preeclampsia in Brazil was 1.5% [16].

Iacobelli et al. and Robillard et al. reported that the predominance of early- or late onset preeclampsia has huge geographical differences [17,18]. Ratsiatosika et al. in a study in Madagascar found a high overall incidence of early-onset preeclampsia of 37% versus approximately 10% in the international literature [19]. The study also found high rates of early-onset preeclampsia in Guadeloupe (31%), Reunion (31%), Mauritius (34%), Cameroon (37.4%), China (38%), Zimbabwe (58%), Thailand (34%), Turkey (29%) and India (26%). Sansone et al. found that HIV-infected women were at an increased risk of preeclampsia [20].

Despite all the research published in the last three decades on screening and prevention of preeclampsia, the condition remains one of the main causes of maternal and perinatal morbidity and mortality, both in low and high-income countries. Rolnik et al. reported that preeclampsia affects 2–8% of pregnancies [21]. Dekker and Sibai noted that proper antenatal care and timed delivery are of utmost importance in tertiary prevention of preeclampsia [22]. The Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) suggested that aspirin could be effective in reducing the risk of recurrent early-onset preeclampsia, if started before 32 weeks gestation as reported by de Swiet[23]. Too often in low-resource settings women with identifiable risk factors for developing hypertensive disorders of pregnancy are cared for in inappropriate city health clinics or rural areas. They do not receive antenatal therapy such aspirin therapy where this is clearly indicated. They are usually referred as dire emergencies and this results in poor perinatal outcomes.

Consequently, a better understanding of predictors of severe preeclampsia may improve maternal and neonatal morbidity by facilitating access to aspirin, focused antenatal care or timely delivery. Against this background, the literature shows that models have been developed to help mitigate the effects of severe preeclampsia on maternal and neonatal health.

2 Problem Statement

Severe preeclampsia has very poor outcomes for women and neonates in low-resource settings. Hypertensive disorders cause a huge burden on the healthcare as they were the third leading cause of maternal deaths in Zimbabwe in 2007[12].However, there are a few such predictive models which are applicable to the local population and there are no locally developed or evaluated statistical risk prediction models. However, there is paucity of data derived from low-resource settings to study this

important subject even though the disease mainly adversely affects pregnant women from low-resource settings such as those in Bulawayo.The non-availability of predictive models is one of the precipitating factor in adverse outcome. This inability to predict women whose pregnancy will end in adverse maternal and neonatal outcome, deprives pregnant women and their babies' potential preventative treatment and management strategies that will promote timely intervention.

3 Justification Of The Study

Hypertensive disorders in pregnancy are a leading cause of maternal and perinatal morbidity and mortality especially in low-resource settings. Preeclampsia risk prediction models can help in triaging and managing patients promptly hence potentially saving lives. The best available models such as the fullPIERS model (*P*reeclampsia *I*ntegrated *E*stimate of *RiS*k) were developed in high-resource settings and used variables which are unavailable in low-resource countries and subsequent developments including miniPIERS used data from low- and middle- income countries (LMICs). However, there are no such risk prediction models that have been developed for our local settings in Bulawayo or Zimbabwe. This study will address the need to develop and test statistical risk prediction models in a relevant local population.

This will be the first time such research to produce risk prediction models would be carried out at a local or national level setting in Zimbabwe. It is anticipated that remote rural areas in our setting could use such a model to predict preeclampsia risks and refer patients early. Implementation of predictive models could then be prospectively evaluated to determine whether this improves outcomes for women and their babies.

For practical reasons the models will be developed using data which are already routinely and easily collected and are available for use. Due to resource constraints, there will be no expensive laboratory tests needed for developing the models appropriate in our low-resource setting. Therefore, this makes the development of such models achievable. Clinicians will likely find the models useful as the predictor variables are encountered in their daily work.

Crucially, new risk prediction models introduced for our clinical setting may reduce avoidable maternal and neonatal morbidity and mortality at local, national, regional and international level.

3.1 Aim

To develop and validate simple clinical risk prediction models for predicting adverse maternal and neonatal outcomes in severe preeclampsia in a low-resource setting.

4 Objectives

- To investigate the demographic contributions of severe preeclampsia in a low-resource setting to poor maternal and neonatal outcomes.

- To determine the incidence and associated risk factors of severe preeclampsia in a low-resource setting.
- To develop statistical risk prediction models for predicting adverse maternal and neonatal outcomes in severe preeclampsia in a low-resource settings.
- To compare and validate the developed maternal model to the miniPIERS.

5 Literature Review

Al-Rubaie et al. noted that statistical risk prediction models are valuable in identifying women at risk of preeclampsia to guide management [24]. Schummers et al. reported that compelled by the intuitive appeal of predicting each individual woman's risk of an adverse outcome, there is a growing interest in risk prediction models [25]. However, there are no such risk prediction models for preeclampsia in our low-resource setting developed by local researchers at Mpilo Central Hospital or in Zimbabwe. Models developed elsewhere where resources are rich may not be appropriate for our setting as many patients may come from rural settings. Models developed in rich-resourced settings also used predictor variables such as laboratory markers which are not routinely done in low-resource settings.

Risk prediction models can use routinely collected maternal characteristics to predict risks. Routinely collected maternal characteristics include maternal age, parity, marital status and history of hypertensive disorders some of which are known to be associated with the development of hypertensive disorders of pregnancy. Most of the prediction models for preeclampsia focus on maternal outcomes and with no mention on neonatal outcomes.

Ukah et al. concluded that the ability to predict severe early-onset preeclampsia using simple tests could aid in the management of severe preeclampsia and improve outcomes [26]. In low-resource settings, such risk prediction models could help rural healthcare workers predict disease progression and refer patients earlier rather than later in emergency situations.

von Dadelszen et al. produced the best known model to predict adverse maternal outcomes in hypertensive disorders of pregnancy called the fullPIERS model [27]. It was developed for predicting adverse maternal outcomes from 2023 women with preeclampsia using data from tertiary centres in high-income countries(Canada, New Zealand, Australia and the UK), and used maternal demographics, signs, symptoms and laboratory tests as predictors. It had good discrimination with an area under receiver operating characteristic curve (AUC ROC) of0.88, 95% CI 0.84–0.92, sensitivity 76% and specificity 87%. fullPIERS accurately predicted adverse maternal outcomes for up to 48 hours, a clinically useful period that allows corticosteroids administration, in-utero transfer or induction. It showed both internal and external validities for predicting adverse maternal outcomes within 48 hours for women admitted with preeclampsia at any gestational age. Ukah et al. found that the ability to recognize women at highest risk of complications earlier could aid in preventing these adverse outcomes through improved management [28,29].

The miniPIERS model was developed for low- and middle- income countries using data of 2081 women from Fiji, Uganda, South Africa, Brazil and Pakistan. Payne et al. produced a model that included parity, gestational age on admission, headache/visual disturbances, chest pain/dyspnoea, vaginal bleeding with abdominal pain, systolic blood pressure and urine proteinuria [30]. It had good discrimination with an area under curve of receiver operating characteristic (AUC ROC) of 0.768, 95% CI 0.735–0.801, sensitivity 41.4% and specificity 91.9%. Individual country analysis showed neighboring South Africa had an AUC ROC of 0.762, 95% CI 0.702–0.821 and Uganda the AUC ROC was 0.656, 95% CI 0.523–0799. This logistic regression model was developed to provide a simple, evidence-based tool to identify pregnant women in LMICs at increased risk of death or major hypertensive-related complications.

Thangaratinam et al. did a (Prediction of complications in early-onset pre-eclampsia-logistic regression)PREP-L model with data from 946 women from 53 hospitals in England and Wales [31]. The model included maternal age, gestation, medical history, systolic blood pressure, deep tendon reflexes, urine protein creatinine ratio, platelets, serum alanine amino transaminase and creatinine in their model. The model showed an optimism-adjusted c-statistic of 0.82 (95% CI 0.80 to 0.84) for composite adverse maternal outcomes by 48 hours. The model used estimated fetal weight and liquor volume by ultrasound scan, uterine artery Doppler, cardiotogography findings and administration of steroids for prediction of fetal outcome. Thangaratinam et al. noted that preeclampsia models have a potential role in triaging high risk mothers who may need transfer to tertiary units for intensive maternal and neonatal care [31].

Onwudiwe et al. used multiple regression analysis to demonstrate that various maternal characteristics such as uterine artery Doppler and mean arterial pressure provided significant independent contribution in the prediction of preeclampsia with a false-positive rate of 10%, the estimated detection rates of early- and late-onset preeclampsia were 100% and 56.4% respectively [32]. Al-Rubaie et al. validated simple preeclampsia risk models and demonstrated good risk discrimination achieving the highest AUC ROC (0.76, 95% CI 0.74–0.77) [24].

Ukah et al. found that the most promising prediction was with multivariable models [29]. von Dadelszen et al. used a multiple logistic regression model that revealed gestational age on admission to hospital (OR, 0.91), dipstick proteinuria (OR, 1.31), and mean platelet volume: platelet ratio (OR, 391.0) independently predicted adverse maternal outcomes in preeclampsia [33].

Thangaratinam et al. used logistic regression models to assess the overall risk of any maternal or neonatal outcome and a survival analysis model to obtain individual risk estimates [34]. Other researchers have used statistical models including maternal age, gestation, medical history, systolic blood pressure, deep tendon reflexes, and urine protein to creatinine ratio, platelets, serum alanine amino transaminase, urea, creatinine, oxygen saturation and treatment with antihypertensives or magnesium sulphate. In low-resource settings due to limited funding in healthcare, some of biochemical characteristics are not routinely measured hence some cannot be included in the risk prediction models for our locally developed models.

Payne et al. included parity, gestational age on admission, headaches/visual disturbances, chest pain/dyspnea, vaginal bleeding with abdominal pain, systolic blood pressure and urine proteinuria in their model [30]. Gabbay-Benziv et al. found probability scores considering nulliparity, prior preeclampsia, body mass index, diastolic blood pressure and placental growth factor had an AUC ROC of 0.784 (95% CI = 0.721–0.847) [35].

Almedia et al., validated the fullPIERS and showed an AUC ROC of 0.72 (p<0.001), determining a cut-off point for fullPIERS probability of 1.7% [36]. Sensitivity was 60.0% and specificity was 65.1%; the positive likelihood ratio was 1.72 and the negative likelihood ratio was 0.61, sensitivity still means that 40% of cases of preeclampsia are not predicted at all. The miniPIERS model was well-calibrated and had an AUC ROC of 0.768 (95% CI 0.735–0.801) with an average optimism of 0.037. Caradeux et al. did a risk prediction model for early-onset preeclampsia with a 5% false positivity and achieving a sensitivity of 62.5% and specificity of 95.5% [37].

The fullPIERS model performed well in the prediction of adverse maternal outcomes in women with preeclampsia but crucially did not attempt to predict neonatal outcome. It is easy to use. The model by Agrawal and Maitra was based on important clinical and biochemical parameters and does not require extensive laboratory testing [38]. This research will develop models for low-resource-settings using patients' data from Bulawayo to predict risks applicable to patients in a low-resource setting.

Examples of predictive models on adverse maternal or neonatal outcomes

Author	Year	Country	Predictor variables	Outcome	AUC ROC	Sensitivity	Specificity
von Dadelszen, P. et al.	2011	Canada, New Zealand Australia UK	Demographic characteristics Clinical Interventions Pregnancy outcomes	Maternal	0.880	76%	87%
Payne, B.A. et al.	2014	Fiji Uganda South Africa Brazil Pakistan	Demographic characteristics Symptoms Signs	Maternal	0.768	41.4%	91.9%
Thangaratinam, S. et al.	2017	England Wales	Demographic characteristics Medical history Signs Laboratory tests Oxygen saturation Antihypertensives Magnesium sulphate	Maternal Neonatal	0.840	82%	-

This research's predictor variables will include maternal characteristics, simple bedside and laboratory tests, therapeutic interventions and foetal characteristics similar to the fullPIERS except expensive laboratory tests like detailed renal and liver tests. It will also be similar to the miniPIERS in terms of low- and middle-income countries settings and the fact that this research will have some basic laboratory tests (haemoglobin, platelets and alanine transaminase) and therapeutic interventions that were not included in the miniPIERS. The model by Thangaratinam et al. was similar in terms of most characteristics but differing in the inclusion of oxygen saturation [31]. Crucially, all these other models only predicted adverse maternal outcome except the one by Thangaratinam et al. This research will predict both adverse maternal and neonatal outcomes in a low-resource setting for the first time using less laboratory tests than those done by Thangaratinam et al. due to the difference in the availability of resources [34]. This research will be published as mpiloPIERS, after Mpilo Central Hospital where it is being carried out.

6 Methodology Design

6.1 Study type, setting and participants

The study will employ a retrospective cross-sectional design and will be carried out at Mpilo Central Hospital, a government teaching and tertiary referral centre. Some of the participants will overlap with published studies on the same subject [2,13]. This research proposal is for a PhD research project that is being done under the National University of Science and Technology. It will cover the period from January 1, 2016 to December 31, 2018. The method of the study will be quantitative.

6.2 Inclusion and exclusion criteria

Participants will be included in the study if they have a diagnosis of severe preeclampsia. Both singleton and twin/higher order pregnancies will be included. Severe preeclampsia will be defined as high blood pressure (systolic blood pressure (SBP) ≥160, diastolic blood pressure(DBP) ≥110mmHg) and or either severe headaches, epigastric pains and deranged biochemical/haematological blood indices. Women with mild or moderate preeclampsia or less than 20 weeks' of gestation and those with epilepsy will be excluded from the study.

6.3 Main outcome measure

The outcome of interest for this study will be maternal death or serious morbidity (composite adverse maternal outcome) and perinatal death (stillbirth + early neonatal death (defined as death within 7 days of birth) or serious morbidity (composite adverse neonatal outcome).

6.4 Data collection and tool

Data collection will be done using a paper data collection tool. It will be used to collect secondary data from the labour ward delivery registers, perinatal registers and mortality registers. The data will be collected primarily by the researcher and double entered to prevent errors. Data will also be collected from neonatal intensive care unit and special care baby unit. Hospital case notes will be retrieved and the clinical data collected.

Data Collection Sheet

Maternal characteristics

Hospital Number…… Date/time of entry in labour ward register.....

Age ...../years

14-19	1
20-24	2
25-29	3
30-34	4
35-39	5
>40	6

Gravidity……

Parity……..

Gestational age at admission .....weeks ……days (decimals)

$20\text{-}26^{+6}$	1	0.14
$27\text{-}29^{+6}$	2	0.28
$30\text{-}33^{+6}$	3	0.42
$34\text{-}36^{+6}$	4	0.57
37-40	5	0.71
$>40^{+1}$	6	0.86

Number of foetuses: Single 0 Multiple 1

Marital status: Single 0 Married 1 Divorced 2

Level of education: Nil 0 Primary 1 Secondary 2 College 3 University 4

HIV status: -ve 0 +ve 1 unknown 2

ARV's: No 0 Yes 1

Booked status: No 0 Yes 1

Referred cases: No 0 Yes 1

Unbooked: No 0 Yes 1

Past obstetric history

Aspirin therapy: No 0 Yes 1

Past obstetric history of hypertension: No 0 Yes 1

Past medical history

Pre-existing medical conditions: No 0 Yes 1

Hypertension: No 0 Yes 1

Diabetes: No 0 Yes 1

Kidney disease: No 0 Yes 1

Area of dwelling

Place of dwelling: urban 0 rural 1

Symptoms

Symptoms: No 0 Yes 1

Nausea/vomiting: No 0 Yes 1

Frontal headaches: No 0 Yes 1

Epigastric pains No 0 Yes 1

Visual disturbances: No 0 Yes 1

Right upper quadrant pains: No 0 Yes 1

Vaginal bleeding with abdominal pains: No 0 Yes 1

Chest pains: No 0 Yes 1

Cardiovascular tests

Presenting BP

SBP……..mmHg

<160	1
160-180	2
181-200	3
201-220	4
221-240	5
241-260	6
>260	7

DBP……..mmHg

<110	1
110-130	2
131-150	3
151-170	4
171-190	5
191-220	6
>220	7

Simple bedside renal test

Dipstick proteinuria: nil/trace 0 + 1 ++ 2 +++ 3 ++++ 4 not done 99

0	1
+	2
++	3
+++	4
++++	5
99	6

Haematological tests

Haemoglobin (Hb) .....g/dl

0-4.99	1
5-9.99	2
10-14.99	3
>15	4

Platelet count (PLT)……../10^9/l

0-49	1
50-99	2
100-149	3
>150	4

Hepatic test

Alanine amino transaminase (ALT) .....IU/l

Therapeutic interventions

Antihypertensives: No 0 Yes 1

Magnesium sulphate: No 0 Yes 1

Corticosteroid therapy: No 0 Yes 1

Complications

Complications: No 0 Yes 1

Convulsions/CNS:No 0 Yes 1

APH: No 0 Yes 1

PPH: No 0 Yes 1

HELLP: No 0 Yes 1

Renal failure: No 0 Yes 1

CVA: No 0 Yes 1

DIC: No 0 Yes 1

Liver dysfunction: No 0 Yes 1

Liver rupture: No 0 Yes 1

ICU ventilation: No 0 Yes 1

Renal dysfunction No 0 Yes 1

Renal dialysis: No 0 Yes 1

Blood transfusion: No 0 Yes 1

FFP/Plat transfusion: No 0 Yes 1

Pulmonary oedema: No 0 Yes 1

Any other morbidity: No 0 Yes 1

Maternal death: No 0 Yes 1

Cause of death:

HELLP: No 0 Yes 1

Renal failure: No 0 Yes 1

CVA: No 0 Yes 1

DIC: No 0 Yes 1

APH: No 0 Yes 1

PPH: No 0 Yes 1

Liver rupture: No 0 Yes 1

Other cause No 0 Yes 1

Composite adverse maternal outcomes-final model

Maternal mortality or one or more serious complication of major organs morbidity in renal, hepatic, cardiac, respiratory, cerebral and haematological systems, ventilator support, pulmonary oedema, renal dialysis, transfusion of any blood product, abruption placenta and postpartum haemorrhage within 48 hours of admission to 7 days post-delivery.

Maternal death or other serious complications: No 0 Yes 1

Foetal/neonatal characteristics

Foetal heart beat present: No 0 Yes 1

Outcome Live: No 0 Yes 1

Apgar score 5 minute <7:No 0 Yes 1

Sex: Male1Female 2

Birth weight……../g

0-500	1
501-1000	2
1001-1500	3
1501-2000	4
2001-2500	5
>2500	6

Complications: No 0 Yes 1

NICU admission: No 0 Yes 1

RDS:No 0 Yes 1

ENND: No 0 Yes 1

Cause of ENND

RDS: No 0 Yes 1

Prematurity: No 0 Yes 1

Very low birth weight: No 0 Yes 1

Sepsis: No 0 Yes 1

Congenital malformation: No 0 Yes 1

Discharged home: No 0 Yes 1

Composite adverse neonatal outcomes-final model

The composite adverse neonatal outcome will be defined as one or more of perinatal mortality, 5 minute Apgar score <7, respiratory distress syndrome and admission to neonatal intensive unit.

Perinatal death or any complication No 0 Yes 1

6.5 Study design and initial analysis

6.5.1Sample size

Simple proportion formula will be used to calculate the sample size, with the following assumptions95% Confidence Interval (CI) and a margin of error of 5%. In the 5 years (2014–2018) to be studied roughly40 000 deliveries will be analysed. The overall incidence of severe preeclampsia/eclampsia was 1.3% in the unit [13]. The final sample will be around 500 but may be more as all the available cases during the study period will be included.

6.5.2 Variables to be considered for the models

Some of these variables are similar to those considered under the miniPIERS and fullPIERS models. This will allow some comparisons to be made to the models developed from this research.

Maternal characteristics

Maternal age (years)

Parity

Gravidity

Gestational age on admission

Marital status

Number of foetuses

Level of education

HIV status

Antiretroviral therapy

Booking status

Past obstetric history

Aspirin therapy

History of previous hypertensive disorder

Past medical history

Pre-existing disease of hypertension

Pre-existing disease of diabetes mellitus

Pre-existing renal disease

Area of dwelling

Urban/rural

Symptoms/signs

Nausea/vomiting

Frontal headaches

Epigastric pains

Visual disturbances

Right upper quadrant pains

Vaginal bleeding with abdominal pains

Chest pains

Convulsions

Cardiovascular signs

Systolic blood pressure on at diagnosis (mmHg)

Diastolic blood pressure on at diagnosis (mmHg)

Haematological tests

Haemoglobin level (g/dl)

Platelet count ($x10^9$/l)

Renal tests

Urine dipstickprotenuira

Hepatic tests

Alanine transaminase (U/L)

Therapeutic

Antihypertensive therapy

Magnesium sulphate therapy

Corticosteroid therapy

Foetal characteristics

Foetal heart rate

Apgar scores

Admission to neonatal intensive care unit

Respiratory distress syndrome

Candidate predictor variables for the final model development will be those variables that will be either of i) available and easy to collect in our settings including in rural health centres, ii) those that are known to be associated with preeclampsia and iii) those that are measurable, simple and reliable methods even in rural health clinics, like in the miniPIERS model by Payne et al. [30].

6.5.3 General statistical analysis

The data will be entered into a Microsoft Excel Inc. spreadsheet. Data will be exported to the SPSS Version 20 (IBM Corp., Armonk, NY, USA) for analysis. Univariate statistical analysis will be used and presented as frequencies and percentages for categorical variables. Continuous variables will be checked for normal distribution using Shapiro Wilk test and mean and standard deviation (SD) will be reported for all data. For variables not normally distributed, non-parametric tests like the Wilcoxon tests will be used. Bivariate statistical analysis will be used to test for association between independent and dependent variables, using the Pearson or Spearman two-tailed chi-square tests. This will test any statistical associations between the explanatory variables with the composite maternal and neonatal outcomes. A *P* value of <0.05 would be considered statistically significant.

6.6.0 Risk prediction regression model development

6.6.1 Predictor variables

Predictor variables will include the maternal characteristics, simple bedside and laboratory tests, therapeutic interventions and foetal characteristics outlined in section 6.5.2 above. Continuous variables like maternal age will be put in groups for analysis before logistic regression. Multiple imputation will be used for missing data. Multiple imputation will allow for the uncertainty about missing data, a process found in SPSS Version 20 package.

6.6.2 Composite adverse maternal and neonatal outcomes

The composite adverse maternal outcome to be predicted by the model will be determined by the Delphi consensus as described by Brown et al. and will include maternal mortality or one or more serious complication of major organ morbidity in renal, hepatic, cardiac, respiratory, cerebral and haematological systems, renal dialysis, transfusion of any blood product, abruption placenta, antepartum haemorrhage and postpartum haemorrhage within 48 hours of admission to 7 days post-delivery [39]. The composite

adverse neonatal outcome will be determined by the Delphi consensus and defined as one or more of perinatal mortality, 5 minute Apgar score <7, respiratory distress syndrome and admission to neonatal intensive unit. The relationship between each predictor variable and the composite adverse maternal or neonatal outcome will first be assessed by binary logistic regression. The Hosmer-Lemeshow goodness-of- fit for logistic regression models with be used. Backward elimination regression models will be used to build models with a stopping rule of $p<0.20$. Predictor variables with a *P* value of < 0.2 will be considered for the final binary logistic regression models. Binary logistic regression models will be used to predict the adverse maternal outcome or neonatal outcome. Standard methods will be used to calculate the area under the curve (AUC) of the receiver operating characteristic (ROC) as found in SPSS Version 20.

6.6.3 The final models

In developing the final binary logistic regression models (logit), the predictor variables with a *P* value of < 0.2 will be considered for the following models;

$$\text{logit } y = e^{\beta_0 + \sum_{i=1}^{k} \beta_i x_i}$$

where y = binary dependent variable (adverse maternal outcome or neonatal outcome)

β_0 = is a constant when all variables are equated to zero

β_i = is a the i^{th} coefficient for variable i, i = 1,2,3…,k.

x_i = is the i^{th} independent variable.

6.6.4 Assessment of model's performance and validation

Calibration ability of the model will be assessed visually by plotting deciles of predicted probability of an adverse maternal outcome against the observed rate in each decile and fitting a smooth line as done by Harrell et al., and Steyerberg et al.[40,41]. Performance of the models will be assessed using the area under the curve (AUC) of the receiver operating characteristic (ROC). Standard bootstrapping techniques will be used to assess potential over-fitting. Discrimination ability will be evaluated on the basis of area under curve of the receiver operating characteristic (AUC ROC) as stated by Hanley and McNeil [42]. Internal validation of the model will be assessed using Efron's enhanced bootstrap method described by Efron and Tibsherani [43]. External validation will be assessed using the miniPIERS model.

7.0 Declarations

Ethics approval and consent to participate

A waiver by the Ethics Committee at Mpilo Central Hospital was given to all retrospective and non-intervention studies to go ahead in the institution in 2016 as long as the data remained anonymous. No ethical issues will arise during the study as all the data will remain anonymous with no identifying personal data. Patient consent will be not be necessary as this will use secondary data. This study being a PhD research will be registered with the Medical Research Council of Zimbabwe. The study will be conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) as reported by von Elm et al. [44]. The study will be registered with Clinical Trials at http//www.clinicaltrials.gov

Consent for publication

There will be no patient consent necessary as the study will be retrospective using secondary data from case notes retrieved from the Hospital Records Department. There will be no identifying information to identify a particular patient.

Availability of data and materials

Not applicable

Competing interests

None

Funding

None

Author’s contribution

SN is the PhD student who conceived the idea and wrote the research proposal. BJ and AEPH are the supervisors for the PhD thesis at the National University of Science and Technology. BJ, AEPH and DM gave critical analysis and suggestions from conception of the PhD research. All authors read and approved the final proposal.

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8.0 References

1. Chesley L. Chesley's Hypertensive Disorders in Pregnancy, Elsevier, 4th
2. Ngwenya S, Jones B, Mwembe D. Determinants of adverse maternal and perinatal outcomes in severe preeclampsia and eclampsia in a low-resource setting, Mpilo Central Hospital, Bulawayo, Zimbabwe. BMC Res Notes. 2019.
3. Mayrink J, CostaM.L,Cecatti G. Preeclampsia in 2018: Revisiting Concepts, Physiopathology, and Prediction. ScientificWorldJournal, 2018:6268276.
4. vonDadelszenP, Menzies J.M, Payne B, Magee L.A. Predicting Adverse Outcomes in Women with Pre-eclampsia. SeminPerinatol 33:152-157.
5. ZIMDAT; Census Report 2012. [Online]. Available from: http//www.zimstat.co.zw [Accessed 20 December 2018]
6. Tranquilli A.L, Brown M.A, Zeeman G.G, Dekker G,Sibai B.M. The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Pregnancy Hypertens, 3(1):44-7.
7. Tranquilli A.L. Early and late-onset pre-eclampsia. Pregnancy Hypertens, 4(3):241.
8. Brown M.A, Magee L.A, Kenny L.C, Karumanchi S.A, McCarthy F.P, Saito S, Hall D.R, Warren C.E,AdoyiG, Salisu I. The hypertension disorder of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension, 13,291-310.
9. Oyston C.J, Stanley J.L, Baker P.N. Potential targets for the treatment of preeclampsia. Expert OpinTher Targets, 19(11):1517-30.
10. Say L, Chou D, Gemmill A, Tuncalp O, Moller A.B, Daniels J, Gulmezoglu A.M, TemmermanM,Alkema L. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health, 2:e323-33.
11. Trends in maternal mortality 1990 to 2015. WHO, UNICEF, UNFPA, World Bank and the United Nations Population Division Nov 2015 WHO/RHR/15.23[online]. Available from: http//www.who.int [Accessed 20 April 2018].
12. Munjanja S. Zimbabwe Maternal and Perinatal Mortality Study. Ministry of Health and Child Welfare/Unicef 2007[online]. Available from: http//unicef.org [Accessed 20 December 2018].
13. Ngwenya S. Severe preeclampsia and eclampsia: incidence, complications, and perinatal outcomes at a low-resource setting, Mpilo Central Hospital, Bulawayo, Zimbabwe. IntJWomens Health, 9:353-357.

14. LisonkovaS, Joseph K.S. Incidence of preeclampsia: risk factors and outcomes associated with early-versus late-onset disease. Am J ObstetGynecol, 209(6):544.

15. Pettit F, Mangos G, Davis G, Henry A, Brown M.A. Pre-eclampsia causes adverse maternal outcomes across the gestational spectrum. Pregnancy Hypertens, 5(2):198-204.

16. Abalos E, Cuesta C, Grosso A.L, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J ObstetGynecolReprodBiol, 170(1):1-7.

17. IacobelliS, Bonsante F, Robillard P.Y. Pre-eclampsia and preterm birth in Reunion Island: a 13 years cohort-based study. Comparison with international data. J Matern Fetal Neonatal Med, (18):3035-40.

18. Robillard P.Y, Dekker G, Iacobelli S, Chaouat G. An essay of reflection: Why does preeclampsia exist in humans, and why are there such huge geographical differences in epidemiology? J ReprodImmunol, 114:44-7.

19. Ratsiatosika A.T, Razafimanantsoa E, Andriantoky V.B, Ravoavison N, Andrianampanalinarivo H.R, BoukerrouM,IacobelliS,Robillard P.Y. Incidence and natural history of preeclampsia/eclampsia at the university maternity of Antananarivo, Madagascar: high prevalence of the early-onset condition. J Matern Fetal Neonatal Med, 22:1-6.

20. Sansone M, Sarno L, Saccone G, Berghella V, Maruotti G.M, Migliucci A, Capone A, Martinelli P. Risk of Preeclampsia in Human Immunodeficiency Virus-Infected Pregnant Women. ObstetGynecol, 127(6):1027-32.

21. Rolnik D.L, O'Gorman N, Roberge S, Bujold E, Hyett J, Uzan S, Beaufils M, da Silva Costa F. Early screening and prevention of preterm preeclampsia with aspirin: time for clinical implementation. Ultrasound ObstetGynecol, 50(5):551-556.

22. Dekker G, Sibai B. Primary, secondary, and tertiary prevention of pre-eclampsia. Lancet, 357(9251):209-15.

23. deSwiet M. Pre-eclampsia: III: The role of aspirin in prevention. Mod Midwife, 4(12):20-2.

24. Al-Rubaie Z, Askie L.M, Ray J.G, Hudson H.M, Lord S.J. The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialized tests and with clinical guideline decision rules: a systematic review. BJOG, 123(9):1441-52.

25. Schummers L, Himes K.P, BodnarL.M,Hutcheon J.A. Predictor characteristics necessary for building a clinically useful risk prediction model: a simulation study. BMC Med Res Methodol, 16(1):123.

26. Ukah U.V, Payne B, Hutcheon J.A, Ansermino J.M, ThangaratinamS,Magee L.A, von Dadelszen P. Assessment of the fullPIERS Risk Prediction Model in Women With Early-Onset Preeclampsia.

Hypertension, 71(4):659-665.

27. von Dadelszen P, Payne B, Jing L, Ansermino J.M, Pipkin F.B, CoteA.M,Douglas M.J, Gruslin A, Hutcheon J.A, Joseph K.S, Kyle P.M, Lee T, Loughna P, Menzies J.M, Merialdi M, Millman A.L, Moore M.P, Moutquin J.M, Quellet A.B, Smith G.N, Walker J.J, Wlley K.R, Wlters B.N, Widmer M, Lee S.K, Russell J.A, Magee L.A. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet 377:219-27.

28. Ukah U.V, Payne B, Lee T, Magee L.A, von Dadelszen P. External Validation of the fullPIERS Model for Predicting Adverse Maternal Outcomes in Pregnancy Hypertension in Low- and Middle-Income Countries. Hypertension, (4):705-711.

29. Ukah U.V, De Silva D.A, Payne B, Magee L.A, Hutcheon J.A, Brown H,Ansermino J.M, Lee T, von Dadelszen P. Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review. Pregnancy Hypertens, 11:115-123.

30. Payne B.A, Hutcheon J.A, Ansermino J,M, Hall D.R, Bhutta Z.A, BhuttaS.Z,Biryabarema C, Grobman W.A, Groen H, Haniff F, Li J, MageeL.A,Merialdi M, Nakimuli A, Qu Z, Sikandar R, Sass N, Sawchuck D, Steyn D.W, Widmer M, Zhou J, von Dadelszen P. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) multi-country prospective cohort study. PLoS Med, 11(1):e1001589.

31. Thangaratinam S, Allotey J, Marlin N, Mol BW, von Dadelszen P, Ganzevoort W, Akkermans J, Ahmed A, Daniels J,DeeksJ, Ismail K, Barnard A.M, Dodds J, Kerry S, Moons C, Riley R.D, Khan K.S. Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study. Health Technol Assess, 21(18):1-100.

32. Onwudiwe N, Yu C.K, Poon L.C, Spiliopoulos I, Nicolaides K.H. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. Ultrasound ObstetGynecol, 32(7):877-83.

33. von Dadelszen P, Magee L.A, Devarakonda R.M, Hamilton T, Ainsworth L.M, Yin R, Norena M, Wlley K.R, Gruslin A, Moutquin J.M, Lee S.K, Russell J.A. The prediction of adverse maternal outcomes in preeclampsia. J ObstetGynaecol, 26(10):871-9.

34. Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-SeeF, von DadelszenP,Ganzevoort W, Akkermans J, Kerry S, Mol B.W, Moons K.G, Riley R.D, Khan K.S.Prediction of complications in early-onset pre-eclampsia (PREP):development and external multinational validation of prognostic models. BMC Med, 15(1):68.

35. Gabbay-Benziv, R, Oliveira N, Baschat A.A. Optimal first trimester preeclampsia prediction: a comparision of multimarker algorithm, risk profiles and their sequential application. PrenatDiagn,

36(1):34-9.

36. Almedia S.T, Katz, L, Coutinho I, Amorim M.M.R. Validation of fullPIERS model for prediction of adverse outcomes among women with severe pre-eclampsia. Int J GynaecolObstet, 138(2):142-147.

37. Caradeux J, Serra R, Nien J.K, Perez-Sepulveda A, Schepeler M, Guerra F, Gutierrez J, Martinez J, Cabrera C, Figueroa-Diesel H, Soothill P, Illanes S.E. First trimester prediction of early onset preeclampsia using demographic, clinical, and sonographic data: a cohort study. PrenatDiagn, 33(8):732-6.

38. Agrawal S, Maitra N. Prediction of Adverse Maternal Outcomes in Preeclampsia Using a Risk Prediction Model. J ObstetGynaecol India, 66(Suppl 1);104-11.

39. Brown B, Cochran S.W, Helmer O. An evaluation of methodology of Delphi Technique. Biometrics 23: 600-606.

40. Harrell F.E, Lee K.l, Mark D.B. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med, 15: 361-387.

41. Steyerberg E.W, Vickers A.J, CookN.R,Gerds T, GonenM,Obuchowski N, Pencina M.J, Kattan M.W. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 21: 128-138.

42. Hanley J.A, McNeil B.J. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology, 143:29-36.

43. Efron B, Tibsherani R. An introduction to the bootstrap. New York: Chapman and Hall.

44. von Elm E, Altman D.G, Egger M, Pocock S.J, Gotzsche P.C, Vandenbroucke, J.P. The strengthening of the reporting of observational studies inepidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ, 335:806-8.