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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SUBJECT AREAS
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Abstract
A PhD Research Proposal submitted to the National University of Science and Technology

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

Preeclampsia is a multi-systemic disorder of pregnancy 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), heavy proteinuria of >3-5g/24 hours, and/or the occurrence of symptoms, such as headache or visual disturbances [4]. Severe preeclampsia has considerable adverse impact on maternal, fetal and neonatal health especially in low-resource countries. Significant avoidable maternal and neonatal morbidity and mortality may result particularly in cases of severe disease. Mpilo Central Hospital is a tertiary referral centre, located in Bulawayo. Bulawayo is the second largest city in Zimbabwe after the capital city Harare, with a population of 653,337 as of the 2012 census according to a ZIMDAT report [5]. It delivers 8 000-10 000 babies per year.

Severe preeclampsia and eclampsia are part of the spectrum of hypertensive disorders of 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.

Severe preeclampsia and eclampsia have dire 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].

Globally, the three most common causes of maternal deaths are haemorrhage, hypertensive disorders and sepsis, accounting for more than half of maternal deaths worldwide as of 2010 as reported by Say et al. [10]. Developing countries accounted for approximately 99%(302,000) of the
global maternal deaths in 2015, 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.

Munjanja found that in Zimbabwe, hypertensive disorders were the third leading cause of maternal deaths [12]. Ngwenya noted that the overall incidence of severe preeclampsia and eclampsia at Mpilo Central Hospital 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 preeclampsia as found by Lisonkova et al. 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 as 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 in city health clinics or rural areas. They do not receive antenatal therapy such as 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 risk 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.

Problem Statement
Severe preeclampsia has very poor outcomes for women and neonates in low-resource settings. 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 our setting. Low-resourced countries lack funding for research hence research outputs from these areas is very scant. One precipitating factor in adverse outcome is the inability to predict women whose pregnancy will end in adverse maternal and neonatal outcome, depriving them of potential preventative treatment, or management strategies that will promote timely intervention. Without good research output, it is very difficult to tackle problems associated with poor outcomes in low-resourced countries. 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.

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 (Preeclampsia Integrated Estimate of RiSk) were developed in high-resource settings and used variables which are unavailable in low-resource countries, 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.

Routine collected maternal characteristics are readily available for use to develop these models. These maternal characteristics will include maternal age, parity, gravidity, gestational age on...
admission, marital status and level of education. Other independent variables may include HIV status, booking status, history of previous hypertensive disorder, pre-existing disease, referral distance, systolic blood pressure and diastolic blood pressure at diagnosis, urine dipstick protenuira, haemoglobin, alanine aminotransaminase and platelet count. Antihypertensive, magnesium sulphate, corticosteroid therapy and mode of delivery will be other independent variables. 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 a predictive model could then be prospectively evaluated to determine whether this improves outcomes for women and their babies.

For practical reasons the model 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, regional and national 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.

Objectives

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

To analyse 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.
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 were resources are rich may not be appropriate for our setting as many patients may come from rural setting. Models developed in rich-resourced settings also used predictor variables such as laboratory markers which are not routinely done in our setting.

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 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 uses maternal demographics, signs, symptoms and laboratory tests as predictors. It had good discrimination with an area under receiver operating characteristic curve (AUC ROC) of 0.88, 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 corticosteroid administration, 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 BA 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 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 aminotransaminase and creatinine in the 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 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 multiple logistic regression that revealed gestational age on admission to hospital (odds ratios [OR], 0.91), dipstick proteinuria (OR, 1.31), and mean platelet volume: platelet ratio (OR, 391.0) independently predicted the 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, 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 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 area under the curve of the receiver operating characteristic of 0.784 (95% CI=0.721-0.847) [35]. Almedia et al., validated the fullPIERS and showed the area under the curve was 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 area under curve of the receiver operating characteristic (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 that for early-onset preeclampsia with a 5% false positive 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 our setting, developed using patients’ data from here to predict risks applicable to patients in 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 the maternal, simple bedside and laboratory tests, therapeutic and fetal 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 characteristics that were not included in the miniPIERS. The model by Thangaratinam et al. will be similar in terms of most characteristics but differing 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 outcome in low-resource setting for the first time using less laboratory
tests than those done by Thangaratinam et al. due to difference in availability of resources [34]. This research will be published as either nustPIERS or mpiloPIERS or nustmpiloPIERS or simply lowPIERS.

Methodology Design

6.1 Ethical considerations

The Ethics Committee at Mpilo Central Hospital gave a waiver for 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. No patient consent will be necessary. This study being a PhD research will be registered with the Medical Research Council. 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.[39]. The study will be registered with Clinical Trials at http://www.clinicaltrials.gov.

6.2 Data collection

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]. Data will be extracted from cases which meet the inclusion criteria from 1 January 2014 to 31 December 2018. The method of the study will be quantitative. Participants will be included in the study if they have a diagnosis of severe preeclampsia and/or eclampsia. 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 either severe headaches, epigastric pain and deranged biochemical/haematological blood indices. Eclampsia will be diagnosed in women who will have a generalised seizure with features of preeclampsia and no previous history of a seizure disorder such as epilepsy. Women with such history will be excluded from the study. All women that will meet the above criteria will be included in the study. The outcome of interest for this study is maternal death or serious morbidity and perinatal death (stillbirth + early neonatal death (defined as death within 7 days of birth) or serious morbidity.

A paper data collection tool 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 be also be collected from neonatal intensive care unit and special care baby unit. Hospital case notes will be retrieved.

6.3 Study design and initial analysis
6.3.1 Sample size
The sample size will be estimated by using simple proportion formula, with the following assumptions: 95% Confidence interval (CI), a margin of error of 5%. In the 5 years (2014-2018) to be studied 40 000 deliveries will be analysed. The overall incidence of severe preeclampsia/eclampsia was 1.3% as reported by Ngwenya in the unit [13]. The final sample will be around 500.

6.3.2 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 model developed from this research.

Demographic 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
Nausea/vomiting
Frontal headaches
Epigastric pains
Visual disturbances
Right upper quadrant
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 dipstick protenuira
Hepatic tests
Alanine transaminase (U/L)
Therapeutic
Antihypertensive therapy
Magnesium sulphate therapy
Corticosteroid therapy
Fetal characteristics
Fetal 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 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].

6.3.3 General statistical analysis
The data will be entered into Microsoft Excel Inc., coded, cleaned and exported to the SPSS Version 20 (IBM Corp., Armonk, NY, USA) for analysis. Univariate statistics 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 analysis will be used to test for association between binary variables, using the Pearson chi-square or Fisher exact tests. A $P$ value of $<0.05$ would be considered statistically significant.

6.4.0 Risk prediction regression model development
6.4.1 Predictor variables
Predictor variables will include the maternal, simple bedside and laboratory tests, therapeutic and fetal characteristics outlined in section 6.3.2 above. Linear variables like maternal age will be put in groups for analysis before logistic regression. Multiple imputation will be used for missing data.

6.4.2 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 [40]. 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 bivariate logistic regression. The Hosmer-Lemeshow goodness-of-fit for logistic regression models will 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 multivariable logistic regression models. Multivariable 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.  

6.4.3 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.[41,42]. 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 [43]. Internal validation of the model will be assessed using Efron’s enhanced bootstrap method described by Efron and Tibshirani [44].External validation will be assessed using the miniPIERS model.  

Declarations  
Ethics approval and consent to participate  
The Ethics Committee at Mpilo Central Hospital made a ruling for all retrospective studies to go ahead in the institution from 2016 onwards 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. Minutes of the Committee’s inaugural meeting held on the 13th October 2016 set out the requirements of all the studies at the institution. This is the same ethics approval as in the published paper [2].
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

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None

Author’s contribution
SN is the PhD student who conceived the idea, and wrote the research proposal. BJ and DM gave critical analysis and suggestions. All authors read and approved the final proposal submitted to the National University of Science and Technology.

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