Development and validation of a predictive model for composite adverse outcomes in primary postpartum haemorrhage in a low-resource setting, Mpilo Central Hospital, Bulawayo, Zimbabwe.

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Postpartum haemorrhage, multivariable predictive model, composite adverse outcomes, low-resource settings
Abstract

Background

Primary postpartum haemorrhage remains an important cause of maternal mortality and morbidity globally. It is difficult to predict. There are very few predictive models on composite adverse outcomes on postpartum haemorrhage that are available in the literature. The aim of this study was to develop and validate multivariable predictive model to assist clinicians in decision-making after a diagnosis of postpartum haemorrhage is made, and to prevent the development of composite adverse outcomes.

Methods

This was a retrospective cross-sectional study that covered the period from 1 July 2016 to 30 November 2019, at Mpilo Central Hospital. The study included participants that had a diagnosis of postpartum haemorrhage within 24 hours of delivery at Mpilo Central Hospital.

The independent variables included socio-demographic factors, laboratory tests, clinical outcomes, causes and the management of PPH. The outcome of interest for this research was composite adverse outcome in PPH. Predictor variables that had a $p<0.2$ from the bivariate correlations analyses were considered for the multivariable stepwise backward logistic regression.

Performance of the model was assessed with a calibration slope. Discrimination ability was evaluated using the area under curve of the receiver operating characteristic (AU ROC). Internal validation of the model was assessed using bootstrap method.

Results
The final predicted probability model for composite adverse maternal outcomes was; \( \text{logit (logarithm of the odds)} (p_i) = 0.141 + (2.35 \times 10^{-1} \times \text{blood loss}) + (-1.18 \times 10^{-1} \times \text{platelets}) + (0.57 \times 10^{-1} \times \text{parity}) + (2.27 \times 10^{-1} \times \text{ruptured uterus}). \)

The model was well calibrated. The discrimination ability of the model was excellent. The AU ROC curve was 0.890 (95% CI 0.830-0.949, \( p < 0.0001 \)). Internal validation was by bootstrapping, and the model was still a good fit for the data with a \( p < 0.0001 \).

**Conclusions**

A predictive model for composite adverse outcomes in PPH was developed. It had a good discriminatory ability, with an AU ROC of 0.890 (95% CI 0.830-0.949). This predictive model for composite adverse outcomes could help clinicians to be alerted to which women with PPH are most likely to develop composite adverse outcomes thereby preventing maternal deaths.

**Background**

Primary postpartum haemorrhage (PPH) is defined as a cumulative blood loss from the genital tract of \( \geq 500 \) mL or more following a normal vaginal delivery or \( \geq 1,000 \) mL or more following a cesarean section within 24 hours of delivery evidenced by a rise in the pulse rate, and falling blood pressure [1, 2, 3].

PPH is a major contributor to maternal death figures worldwide. In 2017, according to the World Health Organisation (WHO) statistics, PPH was amongst the top three causes of maternal deaths together with sepsis and hypertensive disorders of pregnancy [4]. Sub-Saharan Africa (SSA) accounted for roughly two-thirds of maternal deaths according to the same WHO report.

PPH is difficult to predict. Prata et al. found that post model probability estimates
showed that even among women with three or more risk factors, PPH could only be predicted in 10% of the cases [5]. Despite the use of uterotonics agents as preventive measures, it remains a challenge to identify those women who are at increased risk of PPH [6]. There are no known predictive models to predict PPH or its adverse outcomes unlike the work that has been done for another leading cause of maternal death, preeclampsia.

Predictive models are developed to aid health care providers in estimating the probability or risk that a specific disease or condition is present (diagnostic models) or that a specific event will occur in the future (prognostic models), to inform in their decision making [7]. The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative developed a set of recommendations for the reporting of studies developing, validating, or updating a prediction model, whether for diagnostic or prognostic purposes [7]. The TRIPOD Initiative came up with a TRIPOD Checklist of 22 items [8] to help standardize reporting of predictive models as this had been found to be poor before.

The work on developing and validating the models through the fullPIERS(Preeclampsia Integrated Estimate of RiSk)[9] and miniPIERS [10] for preeclampsia has been extensive. This has been great efforts to raising clinical awareness, triaging women to higher referral centres, and giving prompt treatment.

There is scant data on predictive models for PPH since the condition is difficult to predict. Rubio-Alvarez et al. developed and validated a predictive model for excessive postpartum blood loss [6]. They found that the predictive factors in their final model were maternal age, primiparity, duration of the first and second stages of labour, neonatal birth weight and antepartum haemoglobin levels.

This research aims to develop and validate a diagnostic multivariable predictive
model for composite adverse outcomes in PPH using multivariable stepwise backward elimination logistic regression. The rationale being that once PPH is diagnosed, we could have a parsimonious multivariable predictive model for composite adverse outcomes since not all women with PPH develop composite adverse outcomes. Such a parsimonious predictive model can be clinically useful just as the miniPIERS and fullPIERS model for preeclampsia to help prevent composite adverse outcomes in PPH, and help save maternal lives. Crucially, a parsimonious multivariable predictive model for composite adverse outcomes could help clinicians to be alerted to which women with PPH are most likely to develop composite adverse outcomes thereby preventing maternal deaths.

Methods

**Study type, setting and participants**

This was a retrospective cross-sectional study that covered the period from 1 July 2016 to 30 November 2019, at Mpilo Central Hospital, a government teaching and tertiary referral centre. Mpilo Central Hospital is located in the township of Mzilikazi in Bulawayo. Bulawayo, located in Matabeleland is the second largest city in Zimbabwe after the capital city Harare, with a population of 653,337 as of the 2012 census [11]. Mpilo Central Hospital is a 1000-bedded hospital and its maternity unit delivers 8000-10 000 babies per year. The objective of the study was to develop and validate a diagnostic multivariable parsimonious predictive model for composite adverse outcomes in PPH.

**Inclusion and exclusion criteria**

The study included participants that had a diagnosis of postpartum haemorrhage of ≥500ml blood loss after the delivery of the baby or ≥1000ml for caesarean section
within 24 hours of delivery at Mpilo Central Hospital. Both singleton and twin/higher order pregnancies were included. Women who delivered outside the hospital were excluded from the study even if they had PPH since their birth records were kept at the place of their delivery.

**Independent variables**

The independent variables included socio-demographic factors, known risk factors for PPH, current obstetric history, antenatal haemoglobin levels, mode of delivery, fetal outcome and birth weight, estimated blood loss, post-delivery haemoglobin and platelet count, causes of PPH and the management of PPH.

**Main outcome measure**

The outcome of interest for this research was composite adverse outcome. This was defined as maternal death or serious morbidity (either of hypovolaemic shock or haemoglobin <4g/dL or massive blood transfusion >4 units or hysterectomy or admission to ICU or coagulopathy or major organ dysfunction). Some of these outcome measures were part of the core outcome sets for prevention and treatment of postpartum haemorrhage in the Delphi consensus study [12].

**Sample size calculation**

The Cochran sample size formula was used to calculate the sample size as follows;

\[ n_0 = \frac{z^2pq}{e^2} \]

where \( n_0 \) = sample size

\( z \) = is the selected critical value of desired confidence level

\( p \) = is the estimated proportion of an attribute that is present in the population

\( q \) = is 1-p and \( e \) is the desired level of precision

Assuming the maximum variability, which is equal to 50% \( (p = 0.5) \) and taking 95%
confidence level with ±5% precision, the calculation for the required sample size was as follows;

\[ p = 0.5 \text{ and hence } q = 1 - 0.5 = 0.5, \ e = 0.05; \ z = 1.96 \]

So, \[ n_0 = (1.96)^2 (0.5)(0.5)/(0.05)^2 \]

\[ = 384.16 \]

\[ = 385 \]

**Data collection**

A paper-based data collection tool was used to collect data for the above study. This was used to collect secondary data from the labour ward delivery registers, and mortality registers. Patients’ hospital case notes were retrieved from the Hospital Records Department using hospital numbers obtained from the above registers. Clinical information was then collected onto the paper data collection sheet.

**Data analysis**

Prior to analysis the data were cleaned, coded and entered into a Microsoft Excel spreadsheet, then exported to SPSS Version 20 (IBM, Armonk, NY, USA) for analysis. Multiple imputation was used for missing data. Bivariate correlations of association between main independent variables and the outcome measures were performed using Pearson 2-tailed chi-square test.

**Candidate predictor variables considered for the model**

Table 1 shows the candidate predictor variables collected for the predictive model.

**Model building**

Those variables that had a \( p < 0.2 \) from the bivariate correlations analyses, were considered for the multivariable stepwise linear logistic regression. Stepwise backward elimination on SPSS, was used to produce a predictive model that was
parsimonious and accurate as this excluded variables that do not contribute to explaining differences in the dependent variable, with a stopping rule of \( p < 0.20 \).

Continuous variables were checked for non-collinearity. Co-linearity was avoided by determining correlation between variables and only those clinically relevant pairs of highly related pairs were retained.

**The final model**

In developing the final logistic regression model (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)

\( \beta_0 \) = is a constant when all variables are equated to zero

\( \beta_i \) = is a the \( i^{th} \) coefficient for variable \( i \), \( i = 1,2,3..., k \).

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

**Assessment of model’s performance and validation**

Performance of the models was assessed using a calibration slope. Discrimination ability was evaluated on the basis of area under curve of the receiver operating characteristic (AU ROC). Internal validation of the model was assessed using Efron’s enhanced bootstrap method [13].

**Results**

**Characteristics of participants**

The 25-29 year old age group constituted the largest group with 27.7%. The gestational age group 37-40 weeks’ of gestation had the highest percentage at 60.1%. 76.1% of women were HIV negative, 20.5% were positive and 3.4% were
unknown. 87.0% were from urban settings while 13% were from rural areas. 67.9% delivered vaginally, 31.3% by Caesarean section and 0.5% and 0.3% by vacuum and forceps delivery, respectively. The commonest risk factor was preeclampsia at 25.1%. 71.7% of the babies weighed 2501-4000 g. 73.6% of women lost 500-1000 ml of blood. Uterine atony was the commonest cause of PPH at 78.8% of women. 43/386 (11.1) of women had composite adverse outcomes. Receiving a massive blood transfusion constituted the 6.2%, hysterectomy 5.7% and admission to ICU 5.7%.

The model

The multivariable stepwise backward elimination logistic regression for the composite adverse outcomes, SPSS ran 4 models. In this model, $R^2$ was 0.380 that meant independent variables explained 38.0% of the variability of the dependent variable. In this model adjusted $R^2$ was 36.6%, this accurately reported data. In the ANOVA results, the $F$ ratio was; $F(4, 168) = 25.770, p<0.0001$. The regression model was a good fit for the data.

A multivariable stepwise backward elimination logistic regression was run to predict composite adverse maternal outcomes. The variables statistically significantly predicted composite adverse maternal outcomes, $F(4, 168) = 25.770, p<0.0001, R^2 = 0.380$. All seven variables added statistically significantly to the prediction of composite adverse outcomes.

The final predicted probability model for composite adverse maternal outcomes was; \[ \text{logit (logarithm of the odds) } (\pi) = 0.141 + (2.35 \times 10^{-1} \times \text{blood loss}) + (-1.18 \times 10^{-1} \times \text{platelets}) + (0.57 \times 10^{-1} \times \text{parity}) + (2.27 \times 10^{-1} \times \text{ruptured uterus}). \]

Calibration plot for the model


A regression analysis between the observed outcome variable and the predicted model was done. A curve estimation was done and a perfect calibration curve fit was inserted into the graph as shown in Figure 1 below. The calibration slope was 0.45

**Discrimination ability**

The discrimination ability of the maternal model was evaluated on the basis of the AU ROC curve. This is shown in Figure 2 below. The area under the ROC curve was 0.890 (95% CI 0.830-0.949, p<0.0001). Standard error 0.030. This was an excellent AU ROC curve. The sensitivity was 94.7% and a specificity of 48.1%. The positive predictive value was 0.663. The negative predictive value was 0.901.

**Internal validation**

The best method was internally validated by bootstrapping, using Efron’s enhanced bootstrap method by SPSS using 1000 iterations/re-samplings. The model remained valid with $R^2$ of 0.349 that meant independent variables explained 34.9% of the variability of the dependent variable, and an adjusted $R^2$ of 34.7%. The ANOVA results, $F(1, 298) = 159.860$, p<0.0001. The bootstrapped model was still a good fit for the data with a p<0.0001 as seen in Tables 4 & 5.

**Discussion**

As far as we know, this is the first attempt to develop and validate a predictive model on composite adverse outcomes in PPH. This will make it difficult to compare this model with those in the published literature. This developed predictive model for composite adverse outcomes in PPH had a good discriminatory ability, with an AU ROC of 0.890 (95% CI 0.830-0.949).

The strength of this research is that it used a fairly large homogenous group of
women with PPH from Sub-Saharan Africa where the disease is a major contributor to maternal deaths. This makes the finding relevant. The limitation of the study is that it was a retrospective study that used secondary data. Such data from clinical case notes could vary from care giver to care giver. Being retrospective in nature means that some data were missing for certain variables as care givers could have forgotten to record them.

The model had an $R^2$ of 0.380 that meant independent variables explained 38.0% of the variability of the dependent variable. In this model adjusted $R^2$ was 36.6%, this accurately reported data. In the ANOVA results, the $F$ ratio was; $F(4, 168) = 25.770$, $p<0.0001$. The regression model was a good fit for the data. The variables statistically significantly predicted composite adverse maternal outcomes, $F(4, 168) = 25.770$, $p<0.0001$, $R^2 = 0.380$. All seven variables added statistically significantly to the prediction of composite adverse outcomes.

The final predicted probability model for composite adverse maternal outcomes was; logit (logarithm of the odds) ($\pi$) = 0.141 + ($2.35 \times 10^{-1} \times$ blood loss) + ($-1.18 \times 10^{-1} \times$ platelets) + ($0.57 \times 10^{-1} \times$ parity) + ($2.27 \times 10^{-1} \times$ ruptured uterus). This parsimonious predictive model means that clinicians should bear in mind that once PPH has been diagnosed, blood loss, platelet counts, parity and ruptured uterus are predictive of composite adverse outcomes in PPH. This is a useful diagnostic tool in decision-making by healthcare workers.

The performance of a predictive model is done by calibration and discriminatory ability. The model was well calibrated with a slope of 0.45. The discrimination ability of the maternal model was evaluated on the basis of the AU ROC curve. The area under the ROC curve was 0.890 (95% CI 0.830-0.949, $p<0.0001$). This was an
excellent AU ROC curve. The sensitivity was 94.7% and a specificity of 48.1%. The positive predictive value was 0.663. The negative predictive value was 0.901.

The model remained valid with an \( R^2 \) of 0.349 that meant independent variables explained 34.9% of the variability of the dependent variable, and an adjusted \( R^2 \) of 34.7%. The ANOVA results, \( F(1, 298) = 159.860, p<0.0001 \). The bootstrapped model was still a good fit for the data with a \( p<0.0005 \).

Conclusions

It was possible to develop and internally validate a parsimonious multivariable predictive model for composite adverse outcomes in PPH. The model was well calibrated and had a good discriminatory ability with an AU ROC of 0.890 (95\% CI 0.830-0.949).

This parsimonious multivariable predictive model for composite adverse outcomes presented here could be a useful decision-making tool to help clinicians to be alerted to which women with PPH are most likely to develop composite adverse outcomes thereby preventing maternal deaths.

Future research should involve a multicountry prospective study with larger numbers of patients since this study has revealed that it is possible to develop and validate a multivariable predictive model for composite adverse outcomes in PPH. Such research will go a long way in helping reduce maternal deaths from PPH.

List of Abbreviations

ANOVA: Analysis of variance
APH: Antepartum haemorrhage
AU ROC: Area under the receiver operating characteristic
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.

Consent for publication

There was no patient consent necessary as the study was retrospective from case
notes retrieved from the Hospital Records Department. There would not be any identifying information to identify a particular patient.

**Availability of data and materials**

All data generated and analysed during this study are included in this published article. The dataset can be made available to any researcher upon reasonable request.

**Competing interests**

None

**Funding**

None

**Author’s contribution**

SN conceived the idea, collected the data, carried out the statistical analysis and wrote the article.

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Tables
Table 1: Variables collected for the predictive model.
| Characteristic                          | Maternal demographic characteristics                                                                 | Pregnancy characteristics                                                                 |
|----------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
|                                        | Maternal age(years)                                                                                     | Booking status                                                                            |
|                                        | Gravidity                                                                                                | Referred                                                                                  |
|                                        | Parity                                                                                                   | Unbooked                                                                                  |
|                                        | Marital status                                                                                            | Gestation on admission                                                                    |
|                                        | Level of education                                                                                       | Number of fetuses                                                                          |
| HIV status                             | Anti-retroviral status                                                                                    |                                                                                           |
| Past obstetrics history                | Past obstetric history of postpartum haemorrhage (PPH)                                                  | Past obstetric history of antepartum haemorrhage (APH)                                    |
|                                        |                                                                                                         | Previous Lower segment caesarean section (LSCS)                                             |
| Current obstetric history              |                                                                                                         |                                                                                           |
|                                        | Preeclampsia                                                                                            |                                                                                           |
|                                        | Presence of fibroids                                                                                     |                                                                                           |
|                                        | Large for dates                                                                                         |                                                                                           |
|                                        | Intrauterine death (IUD)                                                                                 |                                                                                           |
|                                        | Induction of labour (IOL)                                                                               |                                                                                           |
|                                        | Prolonged labour                                                                                        |                                                                                           |
|                                        | Oxytocin augmentation                                                                                   |                                                                                           |
| Area of dwelling                       |                                                                                                         | Urban/rural                                                                               |
| Mode of delivery                       | Normal vaginal delivery (NVD)                                                                            |                                                                                           |
|                                        | Vacuum                                                                                                   |                                                                                           |
|                                        | Forceps                                                                                                  |                                                                                           |
|                                        | LSCS                                                                                                     |                                                                                           |
| Fetal outcome                          |                                                                                                         | Dead/Alive                                                                                 |
|                                        |                                                                                                         | Birth weight                                                                               |
| Third stage                            |                                                                                                         |                                                                                           |
|                                        | Active management                                                                                       |                                                                                           |
|                                        | Blood loss                                                                                                |                                                                                           |
|                                        | Haemoglobin levels g/dL                                                                                  |                                                                                           |
|                                        | Platelet count X10^9/L                                                                                  |                                                                                           |
| Causes of PPH                          |                                                                                                         |                                                                                           |
|                                        | Perineal trauma                                                                                         |                                                                                           |
|                                        | Retained placenta                                                                                        |                                                                                           |
|                                        | Uterine atony                                                                                            |                                                                                           |
|                                        | Bleeding disorder                                                                                       |                                                                                           |
|                                        | Ruptured uterus                                                                                        |                                                                                           |
| Management                             | Extra oxytocins                                                                                         |                                                                                           |
|                                        | Misoprostol                                                                                              |                                                                                           |
|                                        | IV fluids                                                                                                |                                                                                           |
|                                        | Blood transfusion                                                                                       |                                                                                           |
|                                        | Platelet/Fresh frozen plasma (FFP) transfusion                                                          |                                                                                           |
|                                        | Vaginal packing                                                                                        |                                                                                           |
|                                        | Repair of perineal tears                                                                                 |                                                                                           |
|                                        | Manual removal of placenta                                                                              |                                                                                           |
| Adverse outcomes                       |                                                                                                         |                                                                                           |
|                                        | Hypovolaemic shock                                                                                      |                                                                                           |
|                                        | Haemoglobin <4g/dL                                                                                      |                                                                                           |
|                                        | Massive blood transfusion >4 units of blood products                                                    |                                                                                           |
|                                        | Hysterectomy                                                                                           |                                                                                           |
|                                        | Admission to intensive care unit (ICU)                                                                  |                                                                                           |
|                                        | Mortality                                                                                               |                                                                                           |
| Composite adverse outcomes             | Any 1 or more of the adverse outcomes above                                                              |                                                                                           |

Table 2: Bivariate correlations between independent variables and composite adverse outcome.
| Variable                                      | P-value |
|-----------------------------------------------|---------|
| Age                                           | <0.0001 |
| Gravidity                                     | 0.01    |
| Parity                                        | 0.004   |
| Gestational age                               | 0.03    |
| HIV status                                    | 0.01    |
| Antiretroviral therapy                        | 0.05    |
| Booked                                        | 0.01    |
| Referred                                      | 0.31    |
| Unbooked                                      | 0.025   |
| Place of dwelling                             | <0.0001 |
| Past history of PPH                          | 0.31    |
| Past history of APH                           | 0.38    |
| Previous LSCS                                 | 0.001   |
| Preeclampsia                                  | 0.24    |
| APH                                           | 0.01    |
| Presence of fibroids                          | 0.05    |
| Large for gestational age                     | 0.01    |
| IUD                                           | 0.01    |
| Prolonged labour                              | 0.35    |
| Oxytocin augmentation                         | 0.48    |
| Antenatal haemoglobin                         | 0.04    |
| Birth weight                                  | <0.0001 |
| Blood loss                                    | <0.0001 |
| Post PPH haemoglobin                          | <0.0001 |
| Platelet counts                               | <0.0001 |
| Perineal trauma                               | 0.09    |
| Retained placenta                             | 0.03    |
| Uterine atony                                 | 0.10    |
| Bleeding disorder                             | 0.72    |
| Ruptured uterus                               | 0.02    |
| Oxytocin drip                                 | 0.04    |
| Rectal misoprostol                            | 0.32    |
| Vaginal packing                               | 0.26    |
| Perineal repairs                              | 0.09    |
| Manual removal of placenta                    | 0.75    |

Table 3: Composite adverse outcomes Coefficients table

| Model 4 | Unstandardized coefficients | Standardized coefficients | t     | P-value | 95% Confidence Interval | Lower Bound | Upper Bound |
|---------|-----------------------------|----------------------------|-------|---------|-------------------------|-------------|-------------|
|         | B                   | St Error    | Beta       |       |            |             |             |             |
| Constant| 0.141               | 0.140       | 0.505      | 1.007 | 0.315       | -0.135      | 0.416       |
| Blood loss | 0.235              | 0.029       | 0.505      | 8.170 | <0.0001     | 0.178       | 0.292       |
| Platelets | -0.118             | 0.033       | -0.221     | -3.628| <0.0001     | -0.182      | -0.054      |
| Parity   | 0.057              | 0.028       | 0.127      | 2.069 | 0.04        | 0.003       | 0.112       |
| Ruptured uterus | 0.243         | 0.120       | 0.125      | 2.020 | 0.05        | 0.005       | 0.480       |

Table 4: Coefficients table for the validated model

| Model 1 | Unstandardized coefficients | Standardized coefficients | t     | P-value | 95% Confidence Interval | Lower Bound | Upper Bound |
|---------|-----------------------------|----------------------------|-------|---------|-------------------------|-------------|-------------|
|         | B                   | St Error    | Beta       |       |            |             |             |             |
| Constant| -0.009              | 0.018       | 0.591      | 12.644| <0.0001     | 1.000       | -0.036      |

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Table 5: Bootstrap Coefficients table for the validated model

| Model       | B   | Bootstrap^a |   |   |   |   |
|-------------|-----|-------------|---|---|---|---|
|             |     | Bias        | Std. Error | P-value | Bca Interval |
| Constant    | -0.009 | 0.001 | 0.039 | 0.600 | 1.020 |
| Model       | 1.000 | 0.001 | 0.080 | 0.001 | 0.830 |

Figures

Figure 1

Calibration plot of the development model. Red line = Observed, Black line = Perfect calibration line.
Figure 2

Receiver operating characteristic curve of the development model developed in 386 women in the development cohort.