External Validation of the fullPIERS Model for Predicting Adverse Maternal Outcomes in Pregnancy Hypertension in Low- and Middle-Income Countries

U. Vivian Ukah, Beth Payne, Tang Lee, Laura A. Magee, Peter von Dadelszen;
for the fullPIERS and miniPIERS Working Groups

Abstract—The hypertensive disorders of pregnancy are leading causes of maternal mortality and morbidity, especially in low- and middle-income countries. Early identification of women with preeclampsia and other hypertensive disorders of pregnancy at high risk of complications will aid in reducing this health burden. The fullPIERS model (Preeclampsia Integrated Estimate of Risk) was developed for predicting adverse maternal outcomes from preeclampsia using data from tertiary centers in high-income countries and uses maternal demographics, signs, symptoms, and laboratory tests as predictors. We aimed to assess the validity of the fullPIERS model in women with the hypertensive disorders of pregnancy in low-resourced hospital settings. Using miniPIERS data collected on women admitted with hypertensive disorders of pregnancy between July 2008 and March 2012 in 7 hospitals in 5 low- and middle-income countries, the predicted probability of developing an adverse maternal outcome was calculated for each woman using the fullPIERS equation. Missing predictor values were imputed using multivariate imputation by chained equations. The performance of the model was evaluated for discrimination, calibration, and stratification capacity. Among 757 women with complete predictor data (complete-case analyses), the fullPIERS model had a good area under the receiver-operating characteristic curve of 0.77 (95% confidence interval, 0.72–0.82) with poor calibration (P<0·001 for the Hosmer–Lemeshow goodness-of-fit test). Performance as a rule-in tool was moderate (likelihood ratio: 5.9; 95% confidence interval, 4.23–8.35) for women with ≥30% predicted probability of an adverse outcome. The fullPIERS model may be used in low-resourced setting hospitals to identify women with hypertensive disorders of pregnancy at high risk of adverse maternal outcomes in need of immediate interventions. **(*Hypertension*. 2017;69:705-711. DOI: 10.1161/HYPERTENSIONAHA.116.08706.)**

● **Online Data Supplement**

Key Words: hypertension ■ mortality ■ preeclampsia ■ pregnancy ■ prognosis

Hypertension during pregnancy is one of the top 3 causes of maternal morbidity and mortality worldwide.[1,2] The hypertensive disorders of pregnancy (HDPs), which include preeclampsia, superimposed preeclampsia, gestational hypertension, and chronic hypertension, complicate ≈5% to 10% of pregnancies.[1,3] Maternal complications that result from HDPs include stroke, eclampsia, and renal dysfunction; and adverse fetal outcomes include stillbirth, preterm delivery, and cerebral palsy.[4] These severe consequences of the HDPs make them a global health burden, especially in the low- and middle-income countries (LMICs) where >90% of HDP-related deaths occur.[2,5] To reduce this burden, there is a need to correctly identify women at high risk of developing adverse outcomes in time to avoid their occurrence. Accurate risk assessment can aid decision making around the management of HDPs, including timing of delivery, administration of antenatal corticosteroids for acceleration of fetal pulmonary maturity or Magnesium sulfate for seizure prophylaxis, and maternal transfer to a higher level of care.[1,3]

To facilitate risk stratification and improve the management of HDPs, the fullPIERS model (Preeclampsia Integrated Estimate of Risk) was developed to predict adverse maternal outcomes occurring in the 48 hours after hospital admission with preeclampsia in high-income countries. The adverse outcomes predicted by the model included major organ dysfunction and death.[6] The fullPIERS model is based on maternal demographics, signs, symptoms, and laboratory tests, with the final model consisting of 6 predictor variables: gestational

Received November 4, 2016; first decision December 2, 2016; revision accepted January 6, 2017.

From the Department of Obstetrics and Gynaecology (U.V.U., T.L.) and Department of Anaesthesiology (B.P.), University of British Columbia, Vancouver, Canada; Healthy Starts Theme, BC Children's Hospital Research, Vancouver, Canada (U.V.U., B.P., T.L.); Molecular and Clinical Sciences Research Institute, St George's, University of London, United Kingdom (L.A.M., P.v.D.); and Department of Obstetrics and Gynaecology, St George's University Hospitals, NHS Foundation Trust, London, United Kingdom (L.A.M., P.v.D.).

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.116.08706/-/DC1.

Correspondence to U. Vivian Ukah, Department of Obstetrics and Gynaecology, University of British Columbia, 950 W 28th Ave, Vancouver, British Columbia, V5Z 4H4, Canada. E-mail vivian.ukah@cw.bc.ca

age, chest pain or dyspnoea, oxygen saturation (Spo_2), platelet count, serum creatinine, and serum aspartate aminotransferase (AST). On internal validation, the fullPIERS model predicted an adverse maternal outcome within 48 hours of hospital admission with an area under the receiver-operating characteristic curve (AUC ROC) of 0.88 (95% confidence interval [CI], 0.84–0.92).[6,7] A preliminary external validation using the PETRA study (Preeclampsia Eclampsia Trial) cohort of high-risk women was also reassuring (AUC ROC: 0.97; 95% CI, 0.94–0.99).[8]

To ensure the generalizability of the fullPIERS model before it is implemented into clinical practice to improve maternal care,[9,10] we sought to assess the model's potential for use in a LMIC setting where the majority of HDP-related morbidity and mortality occur. The objective of this study was to use data from the miniPIERS cohort,[11] collected prospectively in LMICs, to assess the broader validity of the fullPIERS model.

Methods

Ethical approval for this validation study was obtained from the Research Ethics Board of the University of British Columbia (CREB no: H07-02207). The PIERS projects were undertaken as a consented research and as a continuous quality improvement project depending on local ethics committee requirements.[6]

fullPIERS Cohort (Development Cohort)

The methods and results of the fullPIERS model have been published.[6] In brief, the cohort consists of 2023 women diagnosed with preeclampsia who were admitted into tertiary hospital units, from September 2003 to January 2010 in 4 well-resourced countries: Canada, New Zealand, Australia, and the United Kingdom.[6] Preeclampsia was defined as hypertension and one of proteinuria, hyperuricemia, or HELLP syndrome (Hemolysis Elevated Liver enzyme Low Platelet).[6] An adverse maternal outcome referred to a composite of maternal death or morbidity, as determined by Delphi consensus for the fullPIERS study[6] and outlined in Table S1 in the online-only Data Supplement. Women were excluded if they had already experienced an adverse maternal outcome before hospital admission or data collection or if they were admitted in spontaneous labor.

miniPIERS Cohort (Validation Cohort)

The methods and results of the miniPIERS study have been published.[11] In brief, the cohort consists of 2081 women who were admitted to a participating hospital unit with a HDP (ie, preeclampsia, gestational hypertension, or chronic hypertension) and who had not yet experienced an adverse maternal outcome, from July 2008 to March 2012 in 5 LMICs: Fiji, Uganda, South Africa, Brazil, and Pakistan. Preeclampsia was defined as in the fullPIERS cohort; gestational hypertension was defined as blood pressure ≥140/90 mm Hg (at least one component, twice, ≥4 hours apart, $\geq 20^{+0}$ weeks) without significant proteinuria, and chronic hypertension as blood pressure ≥140/90 mm Hg (at least one component, twice, ≥4 hours apart, $<20^{+0}$ weeks' gestation). Adverse maternal outcomes were defined as in fullPIERS (Table S1). Women were excluded from the cohort if they experienced an adverse outcome before hospital admission or data collection or if they were admitted in spontaneous labor.

Further details of the development and validation cohorts have been described elsewhere.[6,11]

Statistical Analyses

The distribution of patient characteristics in the development (fullPIERS) and validation (miniPIERS) cohorts were compared using χ^2 test for nominal data and Mann–Whitney *U* test for continuous data. Univariate comparison of patient characteristics between the women in the validation cohort who experienced an adverse outcome and those who did not was also performed. A *P* value <0.05 was considered to be statistically significant.

The fullPIERS logistic regression equation for the prediction of adverse maternal outcomes from preeclampsia: log it(pi)=2.68+(−5.41×10^{-2}; gestational age at eligibility)+1.23(chest pain or dyspnea)+(−2.71×10^{-2}; creatinine)+(2.07×10^{-1}; platelets)+(4.00×10^{-5}; platelets2)+(1.01×10^{-2}; aspartate transaminase)+(−3.05×10^{-6}; AST2)+(2.50×10^{-4}; creatinine×platelet)+(−6.99×10^{-5}; platelet×aspartate transaminase)+(−2.56×10^{-3}; platelet×Spo_2).

Using the worst values (predefined in the model development study as the highest or lowest where appropriate)[7] for the model predictors recorded within 24 hours of admission to HDP, the fullPIERS equation was applied to the miniPIERS data, and the predicted probability of adverse outcomes for each individual with complete predictor data (complete case) was calculated. Before assessing the performance of the model, the model intercept was updated (baseline adjustment)[10] because of the difference in the adverse maternal outcome rates between the fullPIERS (6.5%) and the miniPIERS population (12.5%).[6,11]

Missing Data and Sensitivity Analyses

To be consistent with the fullPIERS study, missing Spo_2 values were imputed with 97%, the population median for women without adverse outcomes.[6]

After imputation of missing Spo_2 data, complete-case analysis was used to assess model performance in the validation cohort, meaning only women with complete predictor data were included. However, to determine whether any bias in the model performance was present because of missing data, sensitivity analyses were performed using multiple imputations by chained equations to generate plausible values for the missing variables.[12–20] More details on the imputation technique are given in the online-only Data Supplement.

We also conducted a sensitivity analysis using data of women admitted with only preeclampsia to assess the discriminatory performance of the model in this subgroup.

Performance Evaluation in the Final Validation Cohort

The performance of the model was evaluated based on discrimination and calibration ability and stratification accuracy.[13,14] Discriminative ability was assessed using the AUC ROC and was interpreted using the following criteria: noninformative (AUC≤0.5), poor discrimination (0.5<AUC≤0.7), and good discrimination (AUC>0.7).[15] Calibration was assessed by estimating the slope on a calibration plot of predicted versus observed outcome rates in each decile of predicted probability.[13] Similar to the AUC ROC, a calibration slope of 1 was interpreted as ideal, >0.5 to <0.7 as poor, and ≤0.5 as noninformative. Calibration was also assessed based on the fit of the model in the validation cohort using the Hosmer–Lemeshow goodness-of-fit test, in which a *P* value >0·05 signifies a good fit between the model and data.[14] The stratification capacity of the model to classify the women into low- and high-risk categories was assessed using a classification table with generated risk groups (defined based on categories established in the model development study).[16,17] The true and false positive rates, negative predictive values, and positive predictive values were computed for each group. The likelihood ratios were calculated for each group using the Deeks and Altman method for a multicategory diagnostic test.[18]

All statistical analyses were performed using R version 3.1.3 (The R Project for Statistical Computing).

Sample Size

Simulation studies recommend at least 100 events and 100 nonevents for adequate power in validation studies.[19] This number of events was calculated to give 80% power at the 5% significance level. We used this guideline to determine whether we had adequate statistical power in our study.

Results

Description

Of the 2081 women in the miniPIERS cohort, 261 women (12.5%) developed an adverse maternal outcome(s) within 48 hours of hospital admission with a HDP. Seven hundred and fifty-seven women (36.4%) women had information for all variables in the fullPIERS model, and these women were used for this validation study (complete-case analysis).

Of the 757 complete cases, 109 women (14.4%) had an adverse maternal outcome(s) within 48 hours of hospital admission. The most common adverse outcomes encountered were blood transfusion (52 women), eclampsia (14 women), and pulmonary edema (18 women). Other notable outcomes are listed in Table S2. There was no case of maternal death recorded in the validation data set.

Women in the miniPIERS validation cohort versus the fullPIERS development cohort were different with regard to demographics and pregnancy characteristics (ie, slightly younger, more often parous, and less likely to be a smoker or have a multiple pregnancy), clinical measures (ie, lower dipstick proteinuria, lower platelet count, and lower creatinine), interventions (ie, more likely to receive antenatal corticosteroids, antihypertensive therapy, and $MgSO_4$), and outcomes (ie, shorter admission to delivery interval, higher infant birth weight but a higher infant mortality before hospital discharge; Table 1).

Within the miniPIERS validation data set, women who had adverse outcome (versus those who did not) were slightly younger, were more often nulliparous, and had hypertensive disorders of greater severity, including higher blood pressure, more frequent antihypertensive therapy and $MgSO_4$, early gestational age at delivery, and lower infant birth weight compared with women without an adverse outcome (Table 2).

Data Completeness and Imputation Analysis

Seven hundred and fifty-seven women (36.4%; 568 preeclampsia and 189 with other HDPs) in the miniPIERS data set had complete fullPIERS variables. All women in the miniPIERS cohort had data for the gestational age at eligibility and chest pain/dyspnea; missing Spo_2 values (1423, 68.3%) were substituted with

Table 1. Maternal Characteristics Within 48 h of Eligibility for the Development (fullPIERS) and Validation (Complete-Case miniPIERS) Cohorts*

Characteristics	miniPIERS Cohort (Complete Cases, Validation; 757 Women)	fullPIERS Cohort (Development; 2023 Women)	*P* Value†
Demographics and pregnancy characteristics			
Maternal age at EDD, y	28 (24–33)	31 (27–36)	<0.0001
Parity ≥1	406 (53.6)	581 (28.7)	<0.0001
Gestational age at eligibility, wk*	36.6 (33.1–38.1)	36 (33–38.3)	0.43
Multiple pregnancy	18 (2.4)	192 (9.5)	<0.0001
Smoking in this pregnancy	48 (6.3)	249 (12.3)	<0.0001
Clinical measures			
Systolic BP, mm Hg	160 (150–170)	160 (150–176)	0.58
Diastolic BP, mm Hg	100 (100–110)	102 (97.8–110)	0.53
Worst dipstick proteinuria	+2 (+1–+3)	+2 (+1–+4)	<0.0001
Chest pain/dyspnea†	30 (4.0)	90 (4.4)	0.65
Lowest platelet count ($\times 10^9$ per L)*	187 (150–231)	192 (150–241.5)	0.04
Highest AST, U/L†	30 (20–35)	28 (21–41)	0.51
Interventions during admission			
Corticosteroids	253 (33.4)	550 (27.2)	<0.0001
Antihypertensive therapy	704 (92.9)	1381 (68.3)	<0.0001
$MgSO_4$	376 (49.7)	690 (34.1)	<0.0001
Pregnancy outcomes			
Admission to delivery interval (gestational age <34 wk), d	1 (1–3)	2 (1–5)	0.0029
Gestational age at delivery, wk	37.1 (34.4–38.6)	36.9 (34.1–38.6)	0.15
Birth weight, g	2500 (1896–2433)	2141 (1441–2807)	<0.0001
Infant death (before discharge)	26 (3.4)	26 (1.3)	<0.0001

Values are represented as n (%) or median (interquartile range). AST indicates aspartate aminotransferase; BP, blood pressure; EDD, estimated date of delivery; fullPIERS, Preeclampsia Integrated Estimate of Risk from high-income countries; $MgSO_4$, magnesium sulfate; and miniPIERS, Preeclampsia Integrated Estimate of Risk from low- and middle-income countries.

*Variables included in the model.

†*P* values calculated using χ^2 test for categorical variables and Mann–Whitney *U* test for continuous variables.

Table 2. Demographics of the 757 Women in the miniPIERS Complete-Case Validation Cohort According to the Occurrence of the Adverse Maternal Outcomes

Characteristics	Women With an Adverse Outcome (109 Women)	Women Without an Adverse Outcome (648 Women)	*P* Value*
Demographics			
Maternal age at EDD, y	27 (±5.82)	29 (±6.46)	0.03
Parity ≥1	46 (42.2)	360 (55.6)	0.01
Gestational age at eligibility, wk	36.5 (31.3–37.9)	36.6 (33.4–38.2)	0.16
Multiple pregnancy	1 (0.9)	17 (2.6)	0.49
Smoking in this pregnancy	4 (3.7)	44 (6.8)	0.29
Clinical measures (within 24 h of eligibility)			
Systolic BP, mm Hg	170 (156–190)	151 (145–170)	<0.0001
Diastolic BP, mm Hg	110 (107–120)	100 (100–110)	<0.0001
Worst dipstick proteinuria	+3 (+2–+3)	+2 (+0.5–+3)	0.84
Interventions at any time during admission			
Corticosteroids	35 (32.1)	218 (33.6)	0.09
Antihypertensive therapy	106 (97.2)	598 (92.3)	<0.0001
$MgSO_4$	83 (76.1)	293 (45.2)	<0.0001
Pregnancy outcomes			
Admission to delivery interval, d	1 (1–1)	2 (1–5)	<0.0001
Gestational age on delivery, wk	36.6 (31.3–38.1)	37.1 (34.7–38.1)	<0.0001
Birth weight, g	2390 (1380–2820)	2500 (1950–3000)	<0.0001
Infant death before discharge	4 (3.7)	22 (3.4)	0.78

Values are represented as n (%) or median (interquartile range). AST indicates aspartate aminotransferase; BP, blood pressure; EDD, estimated date of delivery; $MgSO_4$, magnesium sulfate; and miniPIERS, Preeclampsia Integrated Estimate of Risk from low- and middle-income countries.

*P values calculated using χ^2 test for categorical variables and Mann–Whitney U for continuous variables.

97% similar to the fullPIERS model development, and multiple imputations were performed for missing platelet count (1297, 62.3%), serum creatinine (1282, 61.6%), and AST (923, 44.4%). Imputation of missing values did not seem to alter the model performance significantly (online-only Data Supplement).

External Validation

Within 48 hours of eligibility, the fullPIERS model predicted an adverse maternal outcome in the miniPIERS validation cohort with good discriminative performance as indicated by an AUC ROC of 0.77 (95% CI, 0.72–0.82; Figure 1). There was no significant change in the model performance using only cases with preeclampsia.

Figure 2 shows the calibration plot of the fullPIERS model when applied to the miniPIERS validation cohort. The calibration performance of the model was poor with a slope of 0.67 and intercept of −0.53, showing underestimation of risk at the lower risk ranges and overestimation of risks at the high-risk ranges. The Hosmer–Lemeshow test indicated a poor fit of the model's expected outcomes with those observed in the validation cohort (P<0·05).[13] Table 3 presents tabular information about calibration and classification accuracy. In the fullPIERS development cohort, more women (35%) fell into the predicted risk category of <1.0% than any other category, whereas in the miniPIERS complete-case validation cohort, the 5.0% to 9.9% range was the most common (with 23.5% of women). The majority of women who experienced an adverse outcome in both cohorts were in the predicted risk category of ≥0.30 (ie, 59% for fullPIERS and 50% for miniPIERS). Thus, the model classified a greater proportion of women without outcomes

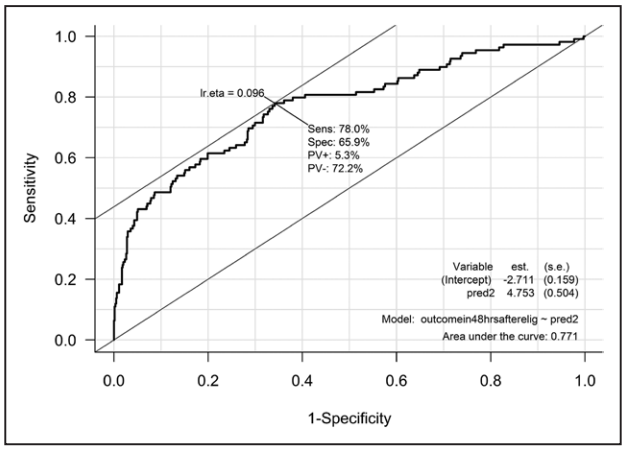

Figure 1. Receiver-operating characteristic curve for performance of the fullPIERS model (Preeclampsia Integrated Estimate of Risk from high-income countries) in predicting adverse maternal outcome in the miniPIERS (complete case, low- and middle-income countries) cohort within 48 h after admission. PV indicates predictive value.

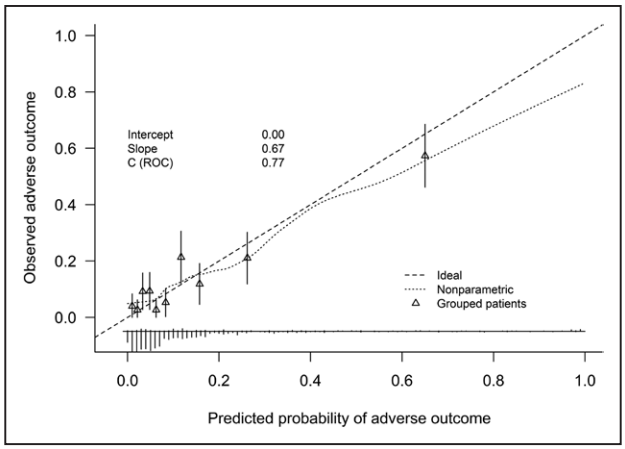

Figure 2. Calibration plot of the fullPIERS model (Preeclampsia Integrated Estimate of Risk from high-income countries) performance in the miniPIERS (complete case, low- and middle-income countries) cohort.

into the middle group, indicating lower stratification accuracy for the low-risk groups, although stratification accuracy remained good for the high-risk group in the validation cohort.

Table 4 presents the negative and positive predictive values and the true and false positive rates for the different risk groups. Using the highest predicted probability cutoff of 0.30, the category into which most women with adverse outcomes fell, the likelihood ratio was moderate at 5.9 (95% CI, 4.2–8.4), with a positive predictive value of 50% (95% CI, 0.40–0.60). Overall, the negative predictive values remained high (>90%) across all the risk.

Discussion

Main Findings

We externally validated the fullPIERS model using the miniPIERS cohort of women in low-resourced settings for the prediction of adverse maternal outcomes related to the HDP within 48 hours of hospital admission. The model had good discriminative ability with AUC ROC of 0.77 (95% CI, 0.72–0.82) within 48 hours of admission, but this was significantly lower than its original performance in the development cohort (AUC ROC: 0.88; 95% CI, 0.84–0.92). Despite updating the model intercept to account for the baseline differences in adverse outcomes between the development and validation cohorts, the fullPIERS model had a poor fit in the miniPIERS data set reflected by the poor calibration performance. However, the fullPIERS model performed moderately as a rule-in test in the highest probability risk group with likelihood ratio of 5.9 (95% CI, 4.23–8.35).[18]

The decrease in the discriminative performance of the model in this study is in contrast with the fullPIERS validation study by Akkermans et al,[8] which reported a high discriminative performance of the model with AUC ROC of 0.97 (95% CI, 0.94–0.99). The study used the PETRA cohort collected in the Netherlands, which is similar to the fullPIERS development cohort in that both cohorts were derived from tertiary centers in high-income settings, with similar management for women with HDPs. Compared with our validation cohort and the development cohort, the prevalence of adverse maternal outcomes in their study was also high (34%).

A possible reason for the decrease in the performance of the fullPIERS model in our study was the heterogeneity between the development cohort and our validation cohort. Differences between the development cohort and our validation cohort existed in the inclusion criteria, outcome prevalence, data collection settings (high-resourced versus low-resourced countries), and predictor distribution such as AST and platelet count (Table 1). Such low- and middle-income settings as our validation cohort settings are more likely to have more comorbidity, lower socioeconomic status, less availability of resources, and differences in disease management compared with high-income settings (reflected by more cointerventions and the shorter admission to delivery interval in the validation cohort shown in Table 1). Such factors may result in case-mix differences and may also alter the effect of the predictors on the outcome.[2,7] Therefore, the extreme predictions observed in the calibration slope may have been as a result of differences in the predictor effects in the validation and development cohorts.[10] These factors may have resulted in the reduced performance of the model.[10,13]

Table 3. Distribution of Women With and Without an Adverse Maternal Outcome Within 48 h Across Categories of the Predicted Scores in the Development and Validation Cohorts

Prediction Score Range	No. Women in Range		No. Women With Outcome	
	fullPIERS Development Cohort (1935 Women)	miniPIERS Complete-Case Validation Cohort (757 Women)	fullPIERS Development Cohort (98 Women)	miniPIERS Complete-Case Validation Cohort (109 Women)
0–0.99%	671 (34.7)	30 (4.0)	3 (0.4)	2 (6.7)
1.0–2.4%	586 (30.3)	107 (14.1)	11 (1.9)	3 (2.8)
2.5–4.9%	314 (16.2)	140 (18.5)	9 (2.9)	12 (8.6)
5.0–9.9%	160 (8.3)	178 (23.5)	8 (5.0)	8 (4.5)
10.0–19.0%	98 (5.1)	157 (20.9)	14 (14.3)	26 (16.6)
20.0–29.9%	32 (1.7)	47 (6.1)	9 (28.3)	9 (19.2)
≥30.0%	74 (3.8)	98 (12.9)	44 (59.5)	49 (50)

Values are represented as n (%) of women. fullPIERS indicates Preeclampsia Integrated Estimate of Risk from high-income countries; and miniPIERS, Preeclampsia Integrated Estimate of Risk from low- and middle-income countries.

Table 4. Risk Stratification Table to Assess the Performance of the fullPIERS Model for Predicting Maternal Outcome at Varying Predicted Probability Cutoff Values Within 48 h

Prediction Score Range	No. Observed Events/n in Range, % (95% CI)	LR (95% CI)	NPV, % (95% CI)	PPV, % (95% CI)	True Positive Rate, % (95% CI)*	False Positive Rate, % (95% CI)
1.0–2.4%	2.8 (0.96–7.92)	0.17 (0.06–0.53)	93 (0.76–0.99)	15 (0.12–0.18)	98.0 (0.93–0.99)	95.6 (0.94–0.97)
2.5–4.9%	8.6 (4.97–14.38)	0.56 (0.32–0.97)	96 (0.91–0.99)	17 (0.14–0.20)	95.4 (0.89–0.98)	79.6 (0.76–0.83)
5.0–9.9%	4.5 (2.29–8.61)	0.28 (0.14–0.55)	94 (0.90–0.96)	19 (0.16–0.23)	84.4 (0.76–0.90)	59.9 (0.56–0.64)
10.0–29.9%	16.6 (11.56–23.16)	1.23 (0.91–1.67)	95 (0.92–0.96)	28 (0.23–0.33)	77.1 (0.68–0.84)	33.6 (0.30–0.37)
≥30.0%	50.0 (40.29–59.71)	5.9 (4.23–8.35)	91 (0.88–0.93)	50 (0.40–0.60)	45.0 (0.36–0.55)	7.6 (0.06–0.10)

CI indicates confidence interval; fullPIERS, Preeclampsia Integrated Estimate of Risk from high-income countries; LR, likelihood ratio; NPV, negative predictive value; and PPV, positive predictive value.

*True positive rate (or sensitivity), false positive rate (1-specificity).

Another study by Agrawal and Maitra that assessed the validity of the fullPIERS model in a low-income setting reported a high likelihood ratio (17.53) for ruling out adverse outcomes.[21] However, the rate of adverse outcomes (18.3%) and management of HDPs in their study cohort differed from the fullPIERS development cohort and our cohort. In addition, the study was underpowered and did not report AUC ROC.

Strengths

A strength of our study is that this the first study to externally validate the fullPIERS model in a broader population (in a low-resourced setting with any HDP) using a fully powered sample size. Although internal and external validation using a similar patient cohort are important, validating a model in a different geographical setting is needed to evaluate the generalizability of the prediction model in other settings with a more diverse group of patients.[10] This external validation study conducted using data from LMICs is particularly useful as most of the global burden of mortality and morbidity from the HDPs is borne by low-resourced settings.

The observed likelihood ratio (5.9) at the highest classification group suggests that the fullPIERS model can be used as a moderate rule-in tool for adverse outcomes from preeclampsia and other HDPs in low-resourced settings. For clinical practice in these settings, the recommended predicted probability of 0.3 can also be used as the optimal cutoff point to guide decisions around the need for immediate interventions. Half of the women with an adverse outcome fell in this risk category while the model still maintained a good likelihood ratio at a low false positive rate (7.6%). This has the added advantage of focusing limited resources on those who most need assistance in LMICs.

Limitations

The major limitation of this study is the high proportion of missing values because the miniPIERS data were not originally collected explicitly for the purpose of this study. Using only complete-case analysis can lead to biased estimates of the predictions if the validation subset is not truly representative of the population at risk.[20,22] Imputation of all missing values did not show any significant change in the model performance. Therefore, it is unlikely that selection bias contributed significantly to the drop in performance of the fullPIERS model in the complete-case analysis compared with the development performance. Even when missing values were excluded, the complete-case analysis had sufficient power (109 outcomes) to externally validate the model as recommended by simulation studies.[19]

Of note, most of the variables were missing because laboratory measurements for preeclampsia and the other HDPs are usually ordered based on the severity of other clinical measurements. This clinical management practice reflects the scarcity of resources in LMIC public hospitals and should draw attention to the need for lower cost point-of-care laboratory measurement techniques for these important laboratory measures. In the validation cohort, we demonstrated that there were worse clinical measures and pregnancy outcomes observed in the women with complete laboratory data compared with those with missing laboratory results (Table S4). This suggests that clinicians in these settings are able to identify higher risk women based on clinical assessment alone but that there remains a delay in timely intervention, so women continue to experience poor outcomes. Reducing the delay between assessments of laboratory measures and intervening when indicated should improve these women's outcomes.

Perspectives

The fullPIERS model showed moderate utility for the prediction of adverse maternal outcomes in women with HDPs in our validation cohort collected in low-resourced setting hospitals, with some limitations in the lower risk groups. The stratification accuracy and discriminative ability of the fullPIERS model within the highest risk group makes it a valuable tool to aid clinicians in the identification of women at highest risk of adverse outcomes and allow for timely delivery of appropriate interventions such as transfer to a higher level of care for delivery and administration of antenatal corticosteroids.[3] To determine applicability of the model in other well-resourced settings, future validation studies using more similar cohorts to that in which the model was developed are still needed.[19,23]

Acknowledgments

We are grateful to the members of the miniPIERS working group.[11]

Sources of Funding

This study was supported by the Canadian Institutes of Health Research (CIHR operating grants). The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the article for publication.

Disclosures

None.

References

1. von Dadelszen P, Magee LA. Pre-eclampsia: an update. *Curr Hypertens Rep*. 2014;16:454. doi: 10.1007/s11906-014-0454-8.
2. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet*. 2006;367:1066–1074. doi: 10.1016/S0140-6736(06)68397-9.
3. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P; Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertens*. 2014;4:105–145. doi: 10.1016/j.preghy.2014.01.003.
4. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:391–403. doi: 10.1016/j.bpobgyn.2011.01.006.
5. Wulf S, Johns N, Lozano R. Non-fatal burden of maternal conditions: Country-level results from the GBD 2010 study. *Lancet*. 2013;381:149–149.
6. von Dadelszen P, Payne B, Li J, et al; PIERS Study Group. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet*. 2011;377:219–227. doi: 10.1016/S0140-6736(10)61351-7.
7. Payne B, Hodgson S, Hutcheon JA, Joseph KS, Li J, Lee T, Magee LA, Qu Z, von Dadelszen P; PIERS Study Group. Performance of the fullPIERS model in predicting adverse maternal outcomes in pre-eclampsia using patient data from the PIERS (Pre-eclampsia Integrated Estimate of RiSk) cohort, collected on admission. *BJOG*. 2013;120:113–118. doi: 10.1111/j.1471-0528.2012.03496.x.
8. Akkermans J, Payne B, von Dadelszen P, Groen H, Vries Jd, Magee LA, Mol BW, Ganzevoort W. Predicting complications in pre-eclampsia: external validation of the fullPIERS model using the PETRA trial dataset. *Eur J Obstet Gynecol Reprod Biol*. 2014;179:58–62. doi: 10.1016/j.ejogrb.2014.05.021.
9. Moons KG, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, Woodward M. Risk prediction models: II. External validation, model updating, and impact assessment. *Heart*. 2012;98:691–698. doi: 10.1136/heartjnl-2011-301247.
10. Steyerberg E. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. New York, NY: Springer-Verlag; 2009.
11. Payne BA, Hutcheon JA, Ansermino JM, et al; miniPIERS Study Working Group. 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*. 2014;11:e1001589. doi: 10.1371/journal.pmed.1001589.
12. van Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45:1–67.
13. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010;21:128–138. doi: 10.1097/EDE.0b013e3181c30fb2.
14. Van Hoorde K, Vergouwe Y, Timmerman D, Van Huffel S, Steyerberg EW, Van Calster B. Assessing calibration of multinomial risk prediction models. *Stat Med*. 2014;33:2585–2596. doi: 10.1002/sim.6114.
15. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36. doi: 10.1148/radiology.143.1.7063747.
16. Pepe MS, Feng Z, Janes H, Bossuyt PM, Potter JD. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: standards for study design. *J Natl Cancer Inst*. 2008;100:1432–1438. doi: 10.1093/jnci/djn326.
17. Janes H, Pepe MS, Gu W. Assessing the value of risk predictions by using risk stratification tables. *Ann Intern Med*. 2008;149:751–760.
18. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ*. 2004;329:168–169. doi: 10.1136/bmj.329.7458.168.
19. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. *J Clin Epidemiol*. 2005;58:475–483. doi: 10.1016/j.jclinepi.2004.06.017.
20. Cummings P. Missing data and multiple imputation. *JAMA Pediatr*. 2013;167:656–661. doi: 10.1001/jamapediatrics.2013.1329.
21. Agrawal S, Maitra N. Prediction of adverse maternal outcomes in pre-eclampsia using a risk prediction model. *J Obstet Gynaecol India*. 2016;66:104–112. doi: 10.1007/s13224-015-0779-5.
22. Clark TG, Altman DG. Developing a prognostic model in the presence of missing data: an ovarian cancer case study. *J Clin Epidemiol*. 2003;56:28–37.
23. Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. *BMC Med Res Methodol*. 2013;13:33. doi: 10.1186/1471-2288-13-33.

Novelty and Significance

What Is New?

- In this article, we have externally validated the fullPIERS model (Pre-eclampsia Integrated Estimate of Risk from high-income countries) for predicting maternal adverse outcomes from preeclampsia using data from multiple settings in low- and middle-income countries.
- Our study is adequately powered and shows a moderate prediction performance of the model at the prerecommended predicted probability cutoff of ≥30%.
- We have also assessed the performance of the model after imputation, which has not been done by the previous studies. Even on imputation of missing values, the model still identified high-risk women moderately.

What Is Relevant?

- Hypertension in pregnancy is a major contributor to maternal morbidity and mortality, especially in low- and middle-income countries. Identifying the women at highest risk of adverse maternal outcome from hypertensive disorders of pregnancy is crucial in the settings to avert severe complications.

Summary

This study supports the existing literature and provides evidence that the fullPIERS model might be a useful tool in low-resourced settings. This finding is important to aid in reducing maternal morbidity and mortality resulting from hypertensive disorders of pregnancy in such areas where these events occur the most.

Hypertension
Journal of the American Heart Association

External Validation of the fullPIERS Model for Predicting Adverse Maternal Outcomes in Pregnancy Hypertension in Low- and Middle-Income Countries

U. Vivian Ukah, Beth Payne, Tang Lee, Laura A. Magee and Peter von Dadelszen
for the fullPIERS and miniPIERS Working Groups

Hypertension. 2017;69:705-711; originally published online February 6, 2017;
doi: 10.1161/HYPERTENSIONAHA.116.08706
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

EXTERNAL VALIDATION OF THE FULLPIERS MODEL FOR PREDICTING ADVERSE MATERNAL OUTCOMES IN PREGNANCY HYPERTENSION IN LOW-AND-MIDDLE-INCOME COUNTRIES.

U. Vivian Ukah, MPH[1,2*], Beth Payne, PhD [3], Tang Lee, Msc[1,2], Laura A. Magee, Professor[4,5], Peter von Dadelszen, Professor[4,5], for the fullPIERS and miniPIERS Working Groups.

Affiliations:

1. Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver, BC, Canada

2. Department of Anaesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada

3. Healthy Starts Theme, BC Children's Hospital Research, Vancouver, BC, Canada

4. Molecular & Clinical Sciences Research Institute, St George's, University of London, London, UK

5. Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, London, UK

Address for correspondence: U. Vivian Ukah, 950 W 28th Avenue, Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver BC, V5Z 4H4, Canada; Telephone: +1604-875-2424x6112; Email: Vivian.Ukah@cw.bc.ca

Short title: fullPIERS validation in low-and-middle-income countries

Imputation Method

Before carrying out imputation of missing values, we compared the complete case cohort (validation cohort) with the total miniPIERS cohort to assess if the complete case was representative of the whole dataset. There were no significant differences between the cohorts except for gestational age at eligibility and delivery (S3). We also assessed the pattern of missingness by comparing the complete case cohort with the cases missing at least one predictor variable. Women in the complete case cohort had worse clinical measures and pregnancy outcomes compared to those with missing predictor values (S4). Based on our comparison of the complete case and incomplete miniPIERS dataset, we assumed that the pattern of missingness was "missing at random".[1-2] Therefore, multiple imputation technique which works optimally for this pattern of missingness, was used in this study.[3-4]

Multiple imputation analyses were carried out to generate plausible values using the Multiple Imputation by Chained Equations (MICE) package in R program.[5] Predictive mean matching based on Rubin's formula[2] was used to generate the missing numeric values for AST, platelet and creatinine variables. This method produces possible values using chained equation models based on specified variables.[4] It is recommended to include as many variables as possible and outcomes to get more reliable values.[3-4] Therefore for our study, we included all the model variables and outcomes as well as auxillary variables such as maternal age, parity, dipstick value etc. To account for the uncertainties of the imputed values, due to the large proportion of missing data, this imputation technique was carried out ten times resulting in ten datasets. The predicted risk of developing an adverse outcome was calculated in each of the ten derived datasets using the published fullPIERS equation. The final predicted risks were combined by averaging the ten calculated predicted risks for each individual. This average predicted probability was then used to evaluate the predictive performance of the model (in the imputed dataset) based on discrimination as described in the main document.

Imputation Results

After imputation of missing values, the AUC ROC did not change significantly (0·73, 95% CI 0·69-0·77).

References

(1) Cummings P. Missing Data and Multiple Imputation. *JAMA Pediatrics*. 2013; 167:656-661.

(2) Rubin DB. Multiple imputation for nonresponse in surveys. *Journal of Marketing Research*. 1989; 26:485-486.

(3) Buuren V, Stef, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*. 2011; 45:1-67.

(4) Rippe RCA, den Heijer M, le Cessie S. Imputation of missing data. *Ned Tijdschr Geneeskd*. 2013; 157:A5539.

S1. List and definitions of PIERS Maternal Adverse Outcomes

Outcome	Definition
Maternal Mortality	Maternal death occurring within six weeks of pregnancy or if later, attributable to complications of pre-eclampsia
Hepatic dysfunction	INR >1.2 in the absence if DIC or treatment of Warfarin (DIC is defined as having both: abnormal bleeding and consumptive coagulopathy (i.e., low platelets, abnormal peripheral blood film, or one or more of the following: increased INR, increased PTT, low fibrinogen, of increased fibrin degradation products that are outside normal non-pregnancy ranges))
Hepatic hematoma or rupture	Blood collection under the hepatic capsule as confirmed by ultrasound or laparotomy
Glasgow Coma Scale (GCS) < 13	Based on GCS scoring system: Teasdale G, Jennet B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974; **2**:81-83
Stroke	Acute neurological event with deficits lasting longer than 48 hours
Cortical Blindness	Loss of visual acuity in the presence of intact papillary response to light
Reversible Ischaemic Neurologic Deficit (RIND)	Cerebral ischaemia lasting longer than 24 hrs but less than 48 hours revealed through clinical examination
Retinal detachment	Separation of the inner layers of the retina from the underlying retinal pigment epithelium (RPE, choroid) and is diagnosed by opthamological exam
Acute renal insufficiency	For women with an underlying history of renal disease: defined as creatinine >200 uM; for patients with no underlying renal disease: defined as creatinine >150 uM
Dialysis	Including haemodialysis and peritoneal dialysis
Platelet count < 50,000 without blood transfusion	Measurement of platelet count recorded as less than 50,000 without patient being given a blood transfusion
Transfusion of blood products	Includes transfusion of any units of blood products: fresh frozen plasma (FFP), platelets, red blood cells (RBCs), cryoprecipitate

	(cryo) or whole blood
Positive inotropic support	The use of vasopressors to maintain a sBP > 90 mmHg or Mean Arterial pressure > 70 mmHg
Myocardial ischaemia/infarction	ECG changes (ST segment elevation or depression) without enzyme changes AND/OR any one of the following: 1)Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed. 2) Pathological findings of an acute, healed or healing MI 3) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischaemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischaemia (ST segment elevation or depression); or d) coronary artery intervention (e.g., coronary angioplasty)
Require >50% oxygen for greater than one hour	Oxygen given at greater than 50% concentration based on local criteria for longer than 1 hour
Intubation other than for Caesarean section	Intubation may be by ventilation, EIT or CPAP
Pulmonary Oedema	Clinical diagnosis with x-ray confirmation or requirement of diuretic treatment and SaO_2 <95%

S2. Maternal adverse outcomes occurring in the complete-case miniPIERS cohort; outcome counts listed are not mutually exclusive.

One or More of Maternal Morbidity or Mortality within 48 h: Total *n* (%)	**Validation Cohort (*N* = 757) Outcomes *n* = 109 (14.4%)**
CENTRAL NERVOUS SYSTEM	
Eclampsia	14
Glasgow coma score <13	5
Stroke	1
Cortical blindness or retinal detachment	2
CARDIORESPIRATORY	
Positive inotropic support	1
Infusion of a 3rd parenteral antihypertensive	4
Myocardial ischaemia/infarction	3
SpO2 <90%	5
Intubation (other than for cesarean section)	3
Pulmonary oedema	18
HAEMATOLOGICAL	
Transfusion of any blood product	52
Platelets $<50 \times 10^9$/l with no transfusion	5
HEPATIC	
Dysfunction	4
RENAL	
Acute renal insufficiency	3
Dialysis	1
PLACENTAL OUTCOMES	
Placental abruption	2

S3. Comparison of demographics between the total miniPIERS (*n*= 2081) and the complete-case miniPIERS (*n*= 757) data.

Characteristics	Total miniPIERS cohort (*n* = 2081 women)	Complete-case cohort (*n*= 757 women)	*p*-Value*
DEMOGRAPHICS			
Maternal age at EDD (years) median [interquartile range]	28 [24, 33]	28 [24, 33]	0·6450
Parity ≥1 n (%)	1122 (53·9%)	406 (53·6%)	0·9271
Gestational age at eligibility (wk) median [interquartile range]	36.8 [33·5, 38·7]	36·6 [33·1, 38·1]	0·0044
Multiple pregnancy n (%)	74 (3·6%)	18 (2·4%)	0·1478
Smoking in this pregnancy n (%)	97 (4·7%)	48 (6·3%)	0·0890
CLINICAL MEASURES (WITHIN 24 H OF ELIGIBILITY)			
Systolic BP (mm Hg) median [interquartile range]	160 [140, 170]	160 [150, 170]	0.0600
Diastolic BP (mm Hg) median [interquartile range]	100 [95, 110]	100 [100, 110]	0·0044
Worst dipstick proteinuria median [interquartile range]	+2 [+0.5, +3]	+2 [+1, +3]	<0·0001
Chest pain/dyspnoea n (%)	94 (4·5%)	30 (4·0%)	0·5928
INTERVENTIONS AT ANY TIME DURING ADMISSION			
Corticosteroid administration n (%)	705 (33·9%)	253 (33·4%)	0·8551
Antihypertensive medications administered n (%)	1946 (93·5%)	704 (92·9%)	0·6880
$MgSO_4$ administered n (%)	948 (45·6%)	376 (49·7%)	0·0537
PREGNANCY OUTCOMES			
GA on delivery (wk) median [interquartile range]	37·4 [34·6, 39·1]	37·1 [34·4, 38·6]	0·0072
Birth weight (g) median [interquartile range]	2600 [1900, 3100]	2500 [1896, 2433]	0·0670
Infant death (before discharge) n (%)	68 (3·3%)	26 (3·4%)	0·9194

** p-Values calculated using chi-squared test for categorical variables and Mann-Whitney U for continuous variables.*

S4. Comparison of demographics between the complete-case miniPIERS (*n*= 757) and the incomplete (*n*= 1324) subsets of the miniPIERS data.

Characteristics	Complete-case subset (*n*= 757 women)	Incomplete subset (*n* = 1324 women)	*p*-Value*
DEMOGRAPHICS			
Maternal age at EDD (years) median [interquartile range]	28 [24, 33]	28 [24, 32]	0·5021
Parity ≥1 n (%)	406 (53·6%)	716 (54.1%)	0·8444
Gestational age at eligibility (wk) median [interquartile range]	36·6 [33·1, 38·1]	37.1 [33.7, 39.0]	<0·0001
Multiple pregnancy n (%)	18 (2·4%)	56 (4.2%)	0·0335
Smoking in this pregnancy n (%)	48 (6·3%)	49 (3.7%)	0·0083
CLINICAL MEASURES (WITHIN 24 H OF ELIGIBILITY)			
Systolic BP (mm Hg) median [interquartile range]	160 [150, 170]	160 [140, 171]	0·0124
Diastolic BP (mm Hg) median [interquartile range]	100 [100, 110]	100 [90, 114]	<0·0001
Worst dipstick proteinuria median [interquartile range]	+2 [+1, +3]	+1 [Trace, +3]	<0·0001
Chest pain/dyspnoea n (%)	30 (4·0%)	64 (4.8%)	0·4176
INTERVENTIONS AT ANY TIME DURING ADMISSION			
Corticosteroid administration n (%)	253 (33·4%)	452 (34.1%)	0·7760
Antihypertensive medications administered n (%)	704 (92·9%)	1242 (93.8%)	0·5304
$MgSO_4$ administered n (%)	376 (49·7%)	572 (43.2%)	0·0050
PREGNANCY OUTCOMES			
GA on delivery (wk) median [interquartile range]	37·1 [34·4, 38·6]	37.6 [34.7, 39.3]	<0·0001
Birth weight (g) median [interquartile range]	2500 [1896, 2433]	2654 [1900, 3200]	0·0142

Infant death (before discharge) n (%)	26 (3·4%)	42 (3.2%)	0·8448

** p-Values calculated using chi-squared test for categorical variables and Mann-Whitney U for continuous variables.*