CLINICAL ARTICLE

Obstetrics

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Retrospective validation study of miniPIERS prediction model in Zanzibar

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Abstract

Objective: To perform a retrospective external validation of miniPIERS in Zanzibar's referral hospital.

Methods: From February to December 2017, data were collected retrospectively on all cases of hypertensive disorders of pregnancy (HDP) admitted to Mnazi Mmoja Hospital, Zanzibar, Tanzania. The primary outcome was the predictive performance of miniPIERS by examining measures of discrimination, calibration, and stratification accuracy. The secondary outcome was the applicability of miniPIERS within the referral hospital setting.

Results: During this period, 2218 of 13 395 (21%) patients were identified with HDP, of whom 594 met the inclusion criteria. Sixty per cent of patients with adverse outcomes were excluded because they had experienced one of the adverse outcomes before admission. The discriminative ability of miniPIERS was inaccurate. It was not likely to aid risk stratification because of low sensitivity and low positive predictive value. The model showed fair discrimination in HDP before 34 weeks of gestation (area under the receiver operating characteristics curve 0.72, 95% confidence interval 0.63–0.82).

Conclusions: The benefit of miniPIERS appeared to be limited, although clinical conditions make any validation challenging. Its application for risk stratification in preterm pregnancies should be further investigated.

KEYWORDS
eclampsia, HELLP, hypertensive disorders of pregnancy, miniPIERS, pre-eclampsia, Tanzania

1 | INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are a major cause of maternal morbidity and mortality, complicating 2%–10%[1-3] of pregnancies globally and accounting for 30 000–50 000 maternal deaths annually.[1,2] This is accompanied by increased risks of perinatal morbidity and mortality. A majority of 90% occur in low- and middle-income countries, with the burden concentrated in South Asia and sub-Saharan Africa. Approximately 10% of maternal deaths in Africa can be attributed to HDP.[2,4-6]

Early identification of patients at increased risk of life-threatening complications of HDP would be of great value to reduce maternal and perinatal mortality[1,7-9]; either by enabling prompt referral to adequate health care, or by improving the allocation of care in

low-resource settings. It could also help to decide between delivery and expectant management in preterm HDP.

In 2014, Payne et al[10] developed the miniPIERS (Pre-eclampsia Integrated Estimate of Risk) prediction model to identify pregnant women in low- and middle-income countries at increased risk of hypertension-related organ failure and death. Predictor variables are based on patient characteristics (gestational age [GA] and parity) and manifestations of disease (hypertension, proteinuria, visual changes, chest pain and/or shortness of breath, vaginal bleeding with abdominal pain) on admission. MiniPIERS is a follow up to the fullPIERS prediction model, designed to predict adverse maternal outcomes of pre-eclampsia in high-income countries.[11,12] MiniPIERS has been validated using the fullPIERS data set and performs accurately (area under the receiver operating characteristics curve [AUROC] 0.77, 95% confidence interval [CI] 0.72–0.82).[10] However, the applicability in the context of a low-resource referral setting has not yet been confirmed, nor has its performance been validated outside the context of a prospective trial.

This study aims to perform a retrospective external validation of miniPIERS in Zanzibar's referral hospital. In addition, it investigates the potential of miniPIERS in supporting decision making for allocation of resources and timing of delivery in preterm pregnancies. Furthermore, its applicability in a low-resource referral setting and the share of the burden of HDP for which miniPIERS could be used in regular clinical conditions is assessed.

2 | MATERIALS AND METHODS

Zanzibar is an archipelago, semi-autonomous to the United Republic of Tanzania. Mnazi Mmoja Governmental Hospital (MMH), located in the island's only urban area, serves a population of 1.4 million as a referral hospital, facilitating 30% of all facility deliveries in Zanzibar. The majority of its patients, however, have uncomplicated pregnancies.[13,14] In 2017, the in-hospital maternal mortality ratio was high, at 401/100 000 live births.[13] In a retrospective study by Herklots et al,[13] pre-eclampsia and eclampsia were present in 21.4% and 7.1% of maternal deaths, respectively, with case fatality rates of 3.8% and 3.6%, respectively.

This study was a retrospective cohort study of case files of patients admitted to the maternity ward of MMH from February 1, 2017 to December 31, 2017. Inclusion criteria were: single blood pressure measurement showing HDP after 20 weeks GA and admission before active labor. Exclusion criteria were: active labor on admission, occurrence of adverse outcome within 24 h of admission, unavailability of a predictor variable within 24 h of admission, and incomplete patient files. Project approval was obtained from Zanzibar's Medical Ethical Research Committee (protocol number: ZAMREC/0001/AUGUST/005). Informed consent was waived because the study only concerned an analysis of clinical files with aggregated, anonymous outcomes.

According to the original miniPIERS study,[10] HDP were defined as follows: (1) gestational hypertension, defined as hypertension (systolic >140 mm Hg or diastolic >90 mm Hg) after 20 weeks GA, without significant proteinuria; or (2) pre-eclampsia, defined as hypertension (systolic >140 mm Hg or diastolic >90 mm Hg) and proteinuria more than 2+ after 20 weeks GA; or (3) severe pre-eclampsia, defined as either pre-eclampsia and severe hypertension (systolic >160 mm Hg or diastolic >110 mmHg), or pre-eclampsia and symptoms of organ failure (headache, blurred vision, epigastric pain, chest pain or shortness of breath, nausea or vomiting) after 20 weeks GA; or (4) chronic hypertension (systolic >140 mm Hg or diastolic >90 mm Hg) before 20 weeks GA without significant proteinuria. It was not possible to identify patients with HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome or hyperuricemia, because laboratory parameters were unavailable. Active labor was defined as uterine contractions plus cervical dilatation of more than 3 cm.

Adverse maternal outcome was defined as maternal mortality and morbidity, including organ failure of the nervous, cardiorespiratory, hematological, and renal systems.[10] The miniPIERS predictor variables,[10] systolic blood pressure, GA, parity, urine for protein, headache and/or visual disturbances, chest pain and/or shortness of breath, vaginal bleeding with abdominal pain, were collected from patient file notes for the first 24 h of admission. In the case of multiple measurements, the worst clinical value was used. GA was calculated based on, in order of preference, first-trimester ultrasound, earliest ultrasound, notes regarding GA, last menstrual period, or symphysis fundal height (SFH). To estimate GA from SFH the following formula from the Intergrowth study group was used: GA (weeks) = 6.585838 − 2.7072585 × (SFH0.5) + 1.295291 × (SFH).[16] As vaginal bleeding combined with abdominal pain was rarely noted, this predictor variable was adjusted to vaginal bleeding. In multiple pregnancies, the lowest birthweight was extracted. As a result of the lack of equipment, it was not possible to assess the following outcomes: cortical blindness/retinal detachment, posterior reversible encephalopathy, fraction of inspired oxygen, and infusion of a third parenteral antihypertensive. Hepatic dysfunction was redefined to a serological bilirubin concentration of more than 100 µmol/L, because the International Normalized Ratio test for coagulation was unavailable.

The primary outcome was the predictive performance of miniPIERS by examining measures of discrimination, calibration, and stratification accuracy. The secondary outcome was the applicability of miniPIERS within MMH, defined as the proportion of patients admitted with HDP before the onset of labor and the occurrence of an adverse maternal outcome.

All patients with HDP, not presenting in active labor, were included in this study (cohort A). Because the adverse outcome of blood transfusion for antenatal severe anemia was common, and its relationship with HDP is unclear, a sub-analysis of cohort A was performed in which this outcome was not considered as an exclusion criterion nor as an adverse outcome (cohort B). To see if the model could aid decision-making for preterm pregnancies, a sub-analysis of cohort A was performed for GA below 34 weeks (cohort C). A third sub-analysis was performed, in which the inclusion was restricted to those patients of cohort A presenting with pre-eclampsia on admission only (cohort D).

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The probability of occurrence of any of the predefined adverse outcomes was calculated from the miniPIERS equation.[10] Fisher exact test and Mann–Whitney U test were applied on categorical and continuous variables, respectively. Discrimination was defined as the ability of the model to differentiate between people who did and did not experience one of the adverse outcomes, indicated by the AUROC.[17] The AUROC was classified using the traditional academic point system (0.9–1.0 excellent; 0.8–0.9 good; 0.7–0.8 fair; 0.6–0.7 poor; 0.5–0.6 fail). Calibration was defined as the agreement between the predicted and observed risk per decile of the cohort, indicated by the intercept and calibration slope of the calibration plot.[17] Positive likelihood ratio >10 and negative likelihood ratio <0.1 were considered to be of clinical relevance.[18] Statistical analyses were performed using SPSS version 25 (IBM) and R. A p value below 0.05 was considered to be of statistical significance.

3 | RESULTS

From February 1 to December 31, 2017, 13 395 patient files were assessed retrospectively, out of which 2807 (21%) were identified with any hypertension measurement and 4369 (33%) did not have any blood pressure documented on admission. Over 70% (1969/2807) of patients with HDP were excluded before data collection because they were admitted in active labor (Figure 1). Of the remaining 838 patients, 594 met the inclusion criteria (Figure 2). Less than half of adverse outcomes occurred in the population of interest, since 120/201 (60%) patients were excluded because they experienced one of the adverse outcomes on admission.

Compared with patients without an adverse outcome, patients of cohort A with an adverse outcome were significantly more likely to have a higher systolic blood pressure, higher proteinuria on admission, more symptoms (headache, visual disturbances, vaginal bleeding), to have received antihypertensive drugs, $MgSO_4$ and corticosteroids, to deliver by cesarean section, and to have had an intrauterine fetal death (Table 1). Of all patients in cohort A, 81 (13.6%) experienced an adverse outcome and 3 (0.5%) died, of whom two were <34 weeks pregnant. The most prevalent adverse outcomes were blood transfusion (69, 11.6%), eclampsia (9, 1.5%) and acute renal insufficiency (6, 1.0%) (Table 2). At baseline, cohorts B and C
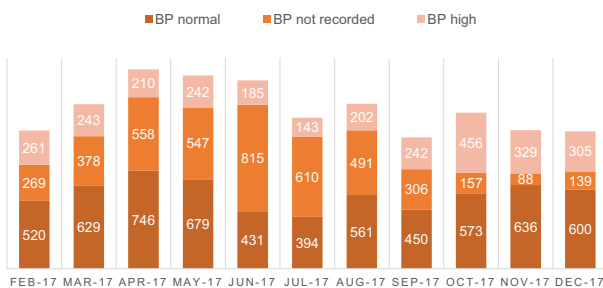
were comparable to cohort A (Appendices S1–S3). Patients in cohort C with an adverse outcome were significantly more likely than patients without an adverse outcome to have higher maternal age, to be multiparous, to have lower GA on admission and at delivery, to have higher diastolic blood pressure, to have severe pre-eclampsia on admission, and to undergo labor induction. In cohort C, adverse outcome was also associated with a significantly higher number of low birth weight infants and neonatal deaths. Baseline results of cohort D (Appendix S3) showed that patients with adverse outcomes had significantly lower GA on admission and at delivery.

The discriminatory ability of miniPIERS was poor for cohorts A, B, and D (Figure 3), indicated by AUROCs of 0.64 (95% CI 0.57–0.71), 0.680 (95% CI 0.60–0.76), and 0.62 (95% CI 0.53–0.72), respectively. The AUROC for cohort C was fair, at 0.72 (95% CI 0.63–0.82). The highest predicted probability for all cohorts was 7.4% (predetermined boundaries 0.7%–29.2%). When using the predicted probability to stratify (Table 3), the number of events decreased with increasing predicted probability. At the cut-off value of more than 2.0% predicted probability, sensitivity and positive predictive values were low for all cohorts. The specificity and negative predictive values for this cut-off value were relatively high, ranging from 0.78% to 0.93% and 0.85% to 0.92%, respectively. As a result of the small group sizes for the other cut-off values, the corresponding results could not be interpreted. The calibration curves (Figure 4; Appendix S4) showed a slope of 0.94 (95% CI 0.51–1.36).

4 | DISCUSSION

Retrospective application of miniPIERS in MMH showed no discriminative ability in our study population. The model showed fair discrimination in the subgroup with HDP before 34 weeks GA (cohort
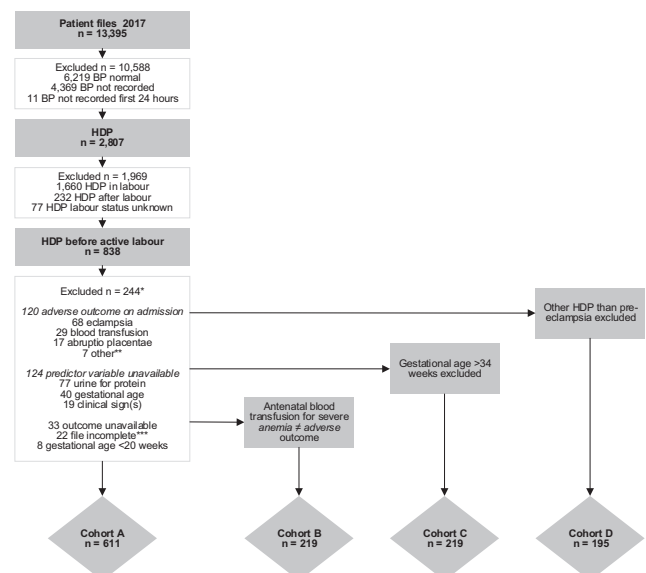

FIGURE 1 Flow-chart miniPIERS Zanzibar part 1

FIGURE 2 Flow-chart miniPIERS Zanzibar part 2

TABLE 1 Baseline characteristics miniPIERS Zanzibar Cohort A (n = 594)[a]

	Without adverse outcome (n = 513)	With adverse outcome (n = 81)	p value[b]	Data available (n)
Demographics				
Age on admission, year	28.0 ± 6.0	29.1 ± 6.0	.158	594
Age on admission <20 year	34 (6.6)	2 (2.5)	.208	594
Age on admission 20–35 year	412 (80.3)	64 (79.0)	.766	594
Age on admission >35 year	67 (13.1)	15 (18.5)	.223	594
Parity	0 (0–2)[c]	1 (0–3)	.186	594
Parity 0	260 (50.7)	35 (43.2)	.233	594
Parity 1–4	209 (40.7)	34 (42.0)	.903	594
Parity >4	44 (8.6)	12 (14.8)	.098	594
Gestational age on admission (weeks)	35.9 (32.7–38.3)	36.4 (31.0–39.1)	.815	594
Multiple pregnancy	11 (2.1)	3 (3.7)	.421	594
Marital status married	507 (99.2)	81 (100.0)	1.000	592
Address urban district	160 (32.3)	27 (33.8)	.798	576
Address rural district	130 (26.2)	19 (23.8)	.682	576
Address mixed district	206 (41.5)	34 (42.5)	.903	576
Clinical measures				
Systolic blood pressure, mm Hg	150 (140–174)	160 (148–190)	<.001	594
Diastolic blood pressure, mm Hg	97 (90–110)	100 (90–117)	.058	593
Worst dipstick proteinuria (+)	0+ (0–2+)	1+ (0–2+)	.005	594
Number of miniPIERS symptoms ≥1	82 (16.0)	31 (38.3)	<.001	594
Headache and/or visual disturbances	78 (15.2)	25 (30.9)	.001	594
Vaginal bleeding	3 (0.6)	6 (7.4)	<.001	594
Chest pain and/or dyspnea	6 (1.2)	0 (0.0)	1.000	594
Severe pre-eclampsia	129 (25.2)	28 (34.6)	.079	593
Mild pre-eclampsia	34 (6.6)	4 (4.9)	.807	593
Other HDP	349 (68.2)	49 (60.5)	.203	593
Antihypertensive drugs (oral or intravenous)	242 (47.2)	57 (70.4)	<.001	594
Prophylactic MgSO$_4$	147 (28.8)	44 (54.3)	<.001	592
Corticosteroids	83 (16.2)	21 (25.9)	.040	594
Labor induction	180 (35.4)	36 (44.4)	.136	590
Pregnancy outcomes				
Admission to delivery interval, day	2.2 ± 6.0	2.4 ± 2.9	<.001	591
GA at delivery, week	36.1 (32.9–38.7)	36.7 (31.6–39.5)	.985	591
Delivery at GA <34 week	166 (32.5)	27 (33.8)	.898	591
Mode of delivery, spontaneous vaginal	347 (68.0)	31 (38.3)	<.001	591
Mode of delivery, instrumental vaginal	2 (0.4)	1 (1.2)	.358	591
Mode of delivery, cesarean section	161 (31.6)	49 (60.5)	<.001	591
Intrauterine fetal death (GA ≥ 20 week and/or birth weight ≥500 g)	37 (7.4)	13 (16.5)	.015	582
Neonatal death	8 (1.8)	3 (5.0)	.135	500
Birthweight, kg	2.9 (2.5–3.3)	2.9 (2.0–3.5)	.742	569

Abbreviations: GA, gestational age; HDP, hypertensive disorders of pregnancy.

[a]Values are given as mean ± SD, median (interquartile range), or number (percentage).

[b]p values calculated using χ^2 test for categorical variables and Mann–Whitney U test for continuous variables.

[c]Interquartile range defined according to Tukey's hinge.

TABLE 2 Adverse outcomes miniPIERS Zanzibar[a]

|	Cohort A (n = 594)	Cohort B (n = 611)	Cohort C (n = 219)	Cohort D (n = 195)
Any adverse outcome	81 (13.6)	54 (8.8)	31 (14.2)	32 (16.4)
Central nervous system				
Eclampsia (≥1 fit)	9 (1.5)	9 (1.5)	4 (1.8)	3 (1.5)
Glasgow coma score <13	2 (0.3)	2 (0.3)	1 (0.5)	1 (0.5)
Stroke or reversible ischemic neurological deficit	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Cardiorespiratory				
Continuous use of vasoactive drugs	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Myocardial ischemia or infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oxygen saturation <90%	2 (0.3)	2 (0.3)	2 (0.9)	1 (0.5)
Respiratory rate >40 or <6/min	1 (0.2)	1 (0.2)	1 (0.5)	0 (0.0)
Intubation (other than for cesarean section)	3 (0.5)	3 (0.5)	1 (0.5)	1 (0.5)
Pulmonary edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematological				
Transfusion of any blood product[b]	69 (11.6)	86 (14.1)	24 (11.0)	26 (13.3)
Main reason for transfusion severe anemia	30 (5.1)	47 (7.7)	7 (3.2)	11 (5.6)
Main reason for transfusion antepartum hemorrhage	2 (0.3)	2 (0.3)	2 (0.9)	2 (1.0)
Main reason for transfusion postpartum hemorrhage	19 (3.2)	21 (3.4)	6 (2.7)	6 (3.1)
Main reason for transfusion unknown	18 (3.0)	18 (2.9)	9 (4.1)	7 (3.6)
Platelets <50 × 10^9/L with no transfusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic				
Hepatic dysfunction (bilirubin >100 µmol/L)	3 (0.5)	3 (0.5)	2 (0.9)	1 (0.5)
Hepatic hematoma or rupture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal				
Acute renal insufficiency (creatinine >150 µmol/L)	6 (1.0)	7 (1.1)	5 (2.3)	4 (2.1)
Dialysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other				
Placental abruption	4 (0.7)	4 (0.7)	2 (0.9)	1 (0.5)
Severe ascites (≥0.5 L)	2 (0.3)	2 (0.3)	1 (0.5)	2 (1.0)
Uterine rupture	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Postpartum psychosis	2 (0.3)	2 (0.3)	1 (0.5)	2 (1.0)
Maternal death	3 (0.5)	3 (0.5)	2 (0.9)	1 (0.5)

[a]Values are given as number (percentage).

[b]The sum of patients who experienced a transfusion of any blood product in cohort B is lower than the subdivisions because two patients were transfused for both severe anemia and postpartum hemorrhage.

C, AUROC 0.72, 95% CI 0.63–0.82). The model was not likely to aid risk stratification because of low sensitivity, positive predictive value, and positive likelihood ratio. The benefits of miniPIERS in this setting were limited, with most patients admitted in active labor and over half of the adverse maternal outcomes occurring before eligibility.

The burden of HDP in MMH was high at 21%, compared with a global rate of 10%.[2,3] As far as can be reconstructed from a retrospective approach, care provided to this patient group was substandard, reflecting an overstretched health system. This included poor documentation and a large amount of missing data with, for example, no

documentation of blood pressure measurement in 32.5% of the cases (4358/13 395). This compares with a retrospective study of Maaløe at al.[15] from October 2014 till January 2016 in MMH, which showed that blood pressure was not recorded in 22%–24% of patient files.

Our population was comparable to the original miniPIERS study in terms of maternal age, parity, GA, and blood pressure at admission. We found an adverse outcome rate of 13.6%, which is lower than that found in the original study (19.3% vs 12.5% within 48 h) despite the fact that the mortality ratio was higher in our cohort (3/594 vs 2/2081).[10] This could be the result of a number of adverse outcomes
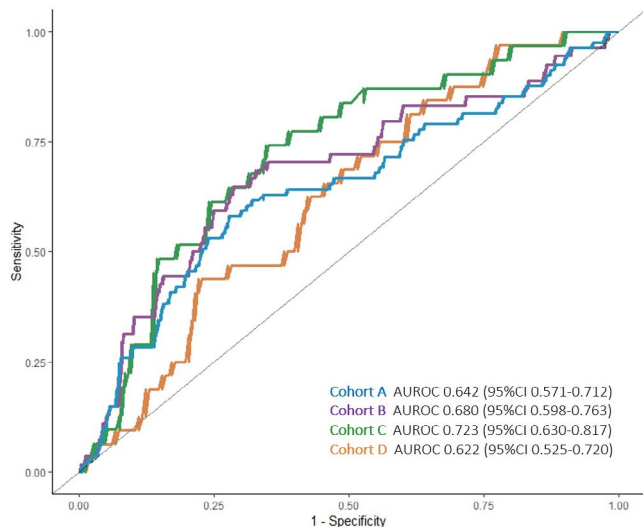
FIGURE 3 Receiver operating characteristics curves miniPIERS Zanzibar

not being included in the analysis. However, this effect is likely to be negligible considering the severity of the outcomes considered. It could also be indicative of delayed patient presentation in our population. The original miniPIERS study does not provide any information on the number of patients presenting with adverse outcome on admission. We found that almost 60% of adverse outcomes are already present on admission. Differences in referral patterns are therefore likely to have a major influence on the overall adverse outcome rate. Similarly to the original miniPIERS study, we found that the most frequent adverse outcome was blood transfusion (11.6% vs 8.4%).[19]

The main interest of the present study is that it is the first external validation attempt in a setting for which miniPIERS has been developed. We faced a dilemma when designing the study given the challenges of

the clinical setting. A prospective approach, although enabling accurate and complete data collection, relies on resources that are most often external and not sustainable in real clinical practice. They are likely to overestimate the range of applicability of the model under real clinical conditions. As an illustration, the number of files with any blood pressure measurement increased from 60% to more than 85% when external research assistants present around the clock were involved in the context of another study in the last 3 months of data collection (Figure 1).

We eventually chose a retrospective approach because, as the original article on the miniPIERS did not provide any information on the applicability of the model, we would contribute more to the subject by giving priority to assessing this aspect. We also acknowledged that the evaluation of the predictive performance of the model might be less accurate and conclusions about performance needed to be drawn with caution. We chose for instance to adapt the inclusion criteria by using only one blood pressure reading and not two with a 4-h interval because clinical decision making is based on that blood pressure measurement in practice. The amount of missing data of predictor variables, leading to selection bias, is another limitation of this approach. For example, GA was solely available by SFH in 224/594 (37%) cases.

By contrast with the original study, we provide an overview of all patients presenting in MMH with HDP. We found that more than half of adverse outcomes were already present at admission, and the majority of patients with HDP presented in labor. Combining poor clinical monitoring and severe conditions at admission means that only a minority of patients with HDP will benefit from miniPIERS.

We do not recommend using miniPIERS for risk stratification in MMH under the current conditions, although its performance could be better in conditions that more closely resemble the conditions in which it was first applied. Future studies are required in a multicenter setting with a higher level of care, but should ideally be conducted as closely as

TABLE 3 Risk stratification for miniPIERS Zanzibar

Predicted probability (%)[a]	Cohort	Event/range, n/n	Sens.	Spec.	PPV	NPV	LR positive[b]	LR negative[b]
0.0%–2.0%	A	66/541	–	–	–	–	0.88	2.50
	B	42/556	–	–	–	–	0.84	2.88
	C	22/186	–	–	–	–	0.81	2.27
	D	22/149	–	–	–	–	0.88	1.41
2.1%–5.0%	A	15/50	0.19	0.93	0.28	0.88	2.71	0.87
	B	12/52	0.22	0.92	0.22	0.92	3.09	0.84
	C	9/31	0.29	0.87	0.27	0.88	2.48	0.80
	D	10/44	0.31	0.78	0.22	0.85	1.50	0.87
5.1%–8.0%	A	0/3	0.00	1.00	0.00	0.86	–	–
	B	0/3	0.00	0.99	0.00	0.91	0.00	–
	C	0/2	0.00	0.99	0.00	0.86	0.00	–
	D	0/2	0.00	0.99	0.00	0.83	0.00	–

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; Sens., sensitivity; Spec., specificity.
[a]Upper limit of predicted probability range used to define a positive test for sensitivity, specificity, positive predictive value and negative predictive value.
[b]Likelihood ratio for each category calculated using the method described by Deeks et al.[18]
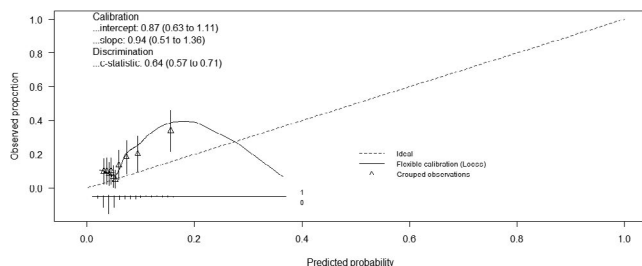
FIGURE 4 Calibration plot Zanzibar cohort A

possible to realistic clinical conditions. The proportion of the population studied for which miniPIERS can be applied in primary, secondary, and tertiary care should also be included to evaluate the contribution of miniPIERS to a sustainable referral system. Finally, the fair predictive performance in preterm pregnancy justifies further investigation.

In conclusion, we assessed the performance of miniPIERS to predict increased risk of adverse outcomes related to HDP in patients admitted to MMH. The benefit of miniPIERS appeared to be limited, although clinical conditions make any validation challenging. Its application for risk stratification in preterm pregnancies should be further investigated.

CONFLICT OF INTEREST

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. We have followed EQUATOR reporting guidelines of the TRIPOD protocol (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis).

AUTHOR CONTRIBUTIONS

BJ, TH, and EM participated in the design of the study. EM and SY performed the data management. EM performed all analyses. All authors (EM, TH, SY, TM, AF, BP, and BJ) contributed to the interpretation of the results. BJ and EM drafted the manuscript; BP, AF, TH, and TM contributed by revising it for important intellectual content. All authors have approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.