**ORIGINAL ARTICLE**

Shock index thresholds to predict adverse outcomes in maternal hemorrhage and sepsis: A prospective cohort study

Hannah L. Nathan | Paul T. Seed | Natasha L. Hezelgrave | Annemarie De Greeff | Elodie Lawley | John Anthony | Wilhelm Steyn | David R. Hall | Lucy C. Chappell | Andrew H. Shennan

Introduction:
Shock index (SI) is a predictor of hemodynamic compromise in obstetric patients. The SI threshold for action is not well understood. We aimed to evaluate SI thresholds as predictors of outcomes in obstetric patients.

Material and methods:
We undertook a prospective cohort study at three South African hospitals of women with postpartum hemorrhage (n = 283) or maternal sepsis (n = 126). The "first" and "worst" SI following diagnosis were recorded. SI was compared with conventional vital signs as predictors of outcomes. The performance of SI <0.9, SI 0.9-1.69 and SI ≥1.7 to predict outcomes (maternal death; Critical Care Unit admission; major procedure; hysterectomy) and hemorrhage-specific outcomes (lowest hemoglobin <70 g/l; blood transfusion ≥4 IU) were evaluated.

Results:
"First" SI was one of two best performing vital signs for every outcome in postpartum hemorrhage and sepsis. In hemorrhage, risk of all outcomes increased with increasing "first" SI; for blood transfusion ≥4 IU odds ratio was 4.24 (95% confidence interval 1.25-14.36) for SI ≥1.7 vs SI 0.9-1.69. In sepsis, risk of all outcomes increased with increasing "worst" SI. Sensitivity, specificity, positive and negative predictive values of "first" SI <0.9 vs SI ≥0.9 for maternal death were 100.0%, 55.2%, 4.6% and 100.0%, respectively, in hemorrhage and 80.0%, 50.4%, 12.3% and 96.7%, respectively, in sepsis.

Conclusions:
The shock index was a consistent predictor of outcomes compared with conventional vital signs in postpartum hemorrhage and sepsis. SI <0.9 performed well as a rule-out test and SI 0.9-1.69 and SI ≥1.7 indicated increased risk of all outcomes in both cohorts. These thresholds may alert to the need for urgent intervention and prevent maternal deaths.

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1 | INTRODUCTION

Approximately 115,000 women die from postpartum hemorrhage (PPH), maternal sepsis and abortion complications (often from hemorrhage or sepsis) annually, contributing to almost half of all maternal deaths. Most deaths are associated with delays in identifying hemodynamic compromise and escalating care and are avoidable. Early identification of compromise using vital sign measurement (commonly blood pressure [BP] and heart rate [HR]) is critical in preventing maternal mortality and morbidity. In low- and middle-income countries, healthcare providers may not have access to devices measuring vital signs or the training to respond appropriately to abnormal vital signs. It is in these environments that 99% of maternal deaths occur. Efforts to improve access to accurate vital sign measurement and training to respond to abnormal vital signs may have a substantial impact on reducing maternal deaths.

The shock index (SI), the ratio of HR to systolic BP, has been shown to be an early predictor of massive transfusion, Intensive Care Unit admission and death in non-obstetric critically ill patients, trauma and sepsis. According to retrospective cohorts of women with PPH, SI has also been shown to be the most consistent predictor of adverse outcomes compared with individual conventional vital signs, including systolic BP and sepsis. SI has also been shown to be the most consistent predictor of adverse outcomes compared with individual conventional vital signs, including systolic BP, trauma and sepsis. For use as an early warning system, thresholds of SI have been proposed (SI < 0.9, SI 0.9-1.69 and SI ≥1.7), based on retrospective cohorts of women with PPH in both well-resourced and low-resourced settings, to indicate increased risk of adverse outcomes. SI has not been evaluated in maternal sepsis or prospectively evaluated in PPH, and the previously proposed SI thresholds have not yet been prospectively validated.

This South African facility-level study aimed to evaluate prospectively whether SI is a consistent predictor of adverse outcomes in both PPH and maternal sepsis and whether the previously determined SI thresholds perform appropriately as predictors of adverse outcomes in both groups of women.

2 | MATERIAL AND METHODS

This prospective cohort study was undertaken between January 2015 and May 2016 at three tertiary maternity units in South Africa (Groote Schuur, Tygerberg and Kimberley Hospitals). Women were eligible if they were diagnosed with either PPH or maternal sepsis (antepartum or postpartum) during their admission, up until discharge from hospital. PPH was defined as an estimated blood loss ≥500 mL for vaginal deliveries and ≥1000 mL for cesarean deliveries, as defined in studies from similar settings. Diagnosis of maternal sepsis was based on clinical features determined by the woman’s healthcare provider and documented in the patient notes.

Existing BP devices were replaced by the Microlife® CRADLE Vital Signs Alert (VSA), a vital signs device that measures BP and heart rate, is suitable for use in low-resource settings and is validated as accurate for use in pregnancy, including preeclampsia and low BP in pregnancy. The device incorporates a traffic light early-warning system triggering a green, yellow or red light according to categories of SI: SI < 0.9, SI 0.9-1.69 and SI ≥1.7, respectively, to alert healthcare providers to abnormalities in vital signs. Anesthetic and recovery areas were allowed access to additional BP devices integrated into existing machines, if requested. Consequently, almost all women had access to the CRADLE VSA and traffic lights triggered by SI. Clinicians used the HR and BP measurements to determine clinical decisions and managed women according to local practice. They were not masked to the traffic light alerts but were not trained to escalate care according to them.

**Key message**

Postpartum hemorrhage and sepsis are the leading causes of maternal deaths. The shock index is a useful predictor of adverse outcomes in postpartum hemorrhage and sepsis. Shock index thresholds may alert to the need for urgent intervention and prevent maternal deaths.

**FIGURE 1** Flow diagram of participants
TABLE 1  Demographic, admission, delivery, perinatal outcomes and hemorrhage/sepsis details for postpartum hemorrhage and maternal sepsis

| Characteristic or outcome | Postpartum hemorrhage (n = 283) | Maternal sepsis (n = 126) |
|---------------------------|----------------------------------|--------------------------|
| Demographic details       |                                  |                          |
| Age at delivery, y        | 29.7 ± 6.2                       | 27.0 ± 6.6               |
| Body mass index, kg/m²     | 30.9 ± 7.9                       | 31.1 ± 9.7               |
| Multiparous               | 225, 79.5%                       | 70, 56.0%               |
| Delivery details          |                                  |                          |
| Gestation at delivery, weeks | 36.3 (32.0-39.0)         | 36.6 (32.9-38.9)         |
| Preterm birth <34 wk      | 97, 34.3%                        | 39, 31.5%                |
| Preterm birth <37 wk      | 155, 54.8%                       | 65, 52.4%                |
| Mode of delivery:         |                                  |                          |
| Cesarean section          | 129, 45.6%                       | 100, 80.0%               |
| Diagnosis details         |                                  |                          |
| Estimated blood loss, mL  | 1100 (800-1500)                  | –                        |
| Time from delivery to diagnosis, minutes | 6 (0-36) | 2586 (1056-4780) |
| Diagnosis made antenatally| NA                               | 13, 10.5%                |
| Intravenous antibiotics given | NA                             | 111, 88.1%              |
| Blood cultures taken      | NA                               | 114, 90.5%               |
| Blood culture result positive | NA                         | 35, 30.7%                |
| Perinatal outcomes        |                                  |                          |
| Stillbirth                | 95, 33.6%                        | 16, 12.7%                |
| Early neonatal death      | 8, 2.8%                          | 3, 2.4%                  |
| Late neonatal death       | 0, 0%                            | 0, 0%                    |

Mean ± standard deviation, median (interquartile range) and n, percentage as shown.
NA, not applicable.
*For postnatal sepsis only.

The “first” and the “worst” sets of BP and HR taken following diagnosis of PPH or sepsis were recorded. The “first” set was defined as those documented immediately after diagnosis and the “worst” set as the set corresponding to the highest SI, documented at any time between diagnosis and discharge (or maternal death). The predefined outcomes included maternal death, maternal Critical Care Unit (CCU) admission, major surgical or invasive procedures and emergency hysterectomy. CCU was defined as a specified Critical Care area providing at least additional monitoring and interventions. Major surgical or invasive procedures were defined as uterine balloon tamponade, artery ligation/embolization/clamping, hemostatic brace suture, emergency laparotomy for hemorrhage, other procedures related to sepsis or emergency hysterectomy. For hemorrhage, additional outcomes included lowest hemoglobin following diagnosis <70 g/L and blood transfusion ≥4 IU. Perinatal complications were recorded but not treated as outcomes because, by definition, diagnosis of PPH and most sepsis diagnoses were made following delivery. We have previously demonstrated that SI is not influenced by regional anesthesia or mode of delivery, so this data was not collected.

Data were extracted from patient notes reviewed by a local researcher. Data quality checks were undertaken on the database by an external researcher. Discrepancies were adjudicated by an obstetrician. Women with missing vital signs were included; women with missing outcomes were included but not analyzed for the outcome for which the data were missing.

2.1 | Statistical analyses

Predefined analysis aimed to determine whether SI was selected as a consistent predictor of adverse outcomes. This was calculated using area under the receiver operating characteristic curve (AUROC) values (95% confidence intervals [CI]) for “first” SI and conventional vital signs [HR, systolic BP, diastolic BP; mean arterial pressure, and pulse pressure] for predicting the predefined outcomes. Mean arterial pressure was defined as (2 × diastolic BP + systolic BP)/3 and pulse pressure was defined as systolic BP – diastolic BP. Predictor equality of AUROCs across the outcomes was tested using unadjusted chi-square analysis.

The ability of the “first” and “worst” SI categories (SI <.9, SI .9-1.69 and SI ≥1.7) to predict the risk of each outcome was evaluated using post-test probabilities for each category, odds ratios of SI .9-1.69 vs SI <.9 and SI ≥1.7 vs SI .9-1.69, and non-parametric trend testing of change in risk across the SI categories.

Post-test probability (with 95% confidence intervals) was defined as the proportion of women with vital signs falling within each category who have the outcome. The 95% CIs were included to allow for generalization from the sample to the population with similar characteristics. Post-test probability was used to evaluate the performance of the three categories (SI <.9, SI .9-1.69, and SI ≥1.7), rather than traditional predictive testing using sensitivity, specificity, positive predictive value and negative predictive testing, which is only appropriate when testing one threshold/two categories. Sensitivity, specificity, and positive predictive value and negative predictive testing were used to evaluate the test performance of the single threshold of SI <.9 as a rule-out test at “first” vital signs measurement following diagnosis for the prediction of the two most severe adverse outcomes (emergency hysterectomy and maternal death). Separate analyses were performed for PPH and maternal sepsis. Women with both diagnoses were included in both groups.

A post-hoc power calculation was performed for two principal outcomes, CCU admission and emergency hysterectomy. The rate of CCU admission could be estimated to within 5.9% and 9.1% of the true value, for PPH and sepsis, respectively, with 95% confidence. The rate of emergency hysterectomy could be estimated to within 3.9% and 6.2% of the true value, for PPH and sepsis, respectively, with 95% confidence. Statistical analysis was performed in the statistical package.
STATA (version 11.2). The conventional significance level was set at $P \leq 0.05$. The study was reported in accordance with STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) guidelines.

**Ethical approval**

The study was approved by the Stellenbosch University Ethics Committee (N14/06068, June 2014), University of Cape Town Ethics Committees (410/2014, July 2014) and the University of the Free State Ethics Committee (230408-011, September 2014). Local ethics committees at two of the three sites (Tygerberg Hospital and Kimberley Hospital) required individual informed written consent to be obtained before the woman was enrolled in the study (or waiver of consent was granted if the woman was unconscious). Institutional-level agreement for the study was given at the third site—Groote Schuur Hospital (ie, individual-level consent was not required).

### 3 RESULTS

A total of 283 women with PPH and 126 women with sepsis were eligible, consented and were included in the analyses (Figure 1). The number of women who declined to take part was not documented. Thirteen women were included in both analyses, having both diagnoses.

Participant characteristics are shown in Table 1. Mean body mass index ± standard deviation was $30.9 \pm 7.9$ for those with PPH and $31.1 \pm 9.7$ for those with maternal sepsis. Cesarean section was more common in women with sepsis: 100 women (80%) with maternal sepsis delivered by cesarean section compared with 129 women (45.6%) with PPH. Our sites had high cesarean section rates in keeping with referral centers (33%-55%), but the high rates in our study population, along with lower gestational age, are in keeping with the adverse obstetric outcomes seen in the study population. In women with sepsis, blood cultures were taken in 114 women (90.5%); of those, 35 women (30.7%) had positive blood culture results.

| SI details | Postpartum hemorrhage ($n = 283$) | Maternal sepsis ($n = 126$) |
|------------|-----------------------------------|------------------------------|
| *First* SI after diagnosis | $0.95 \pm 0.32$ | $0.99 \pm 0.82$ |
| *First* HR after diagnosis | $104 \pm 19$ | $114 \pm 19$ |
| *First* systolic BP after diagnosis | $116 \pm 24$ | $126 \pm 22$ |
| Time from diagnosis to *first* SI, minutes | $15 (0-44)$ | $0 (0-0)$ |
| *First* SI category | | |
| SI < 0.9 | 153, 54.1% | 60, 48.4% |
| SI 0.9-1.69 | 116, 41.0% | 63, 50.8% |
| SI ≥1.7 | 14, 4.9% | 1, 0.8% |
| Worst* SI after diagnosis | $1.12 \pm 0.29$ | $1.12 \pm 0.27$ |
| Worst* HR after diagnosis | $120 \pm 18$ | $130 \pm 20$ |
| Worst* systolic BP after diagnosis | $97 \pm 15$ | $104 \pm 15$ |
| Time from diagnosis to *worst* SI, hours | $4.23 (4.2-16.96)$ | $13.8 (1.73-46.75)$ |
| *Worst* SI category | | |
| SI < 0.9 | 60, 21.2% | 24, 19.4% |
| SI 0.9-1.69 | 206, 72.8% | 94, 75.8% |
| SI ≥1.7 | 17, 6.0% | 6, 4.8% |

Mean ± standard deviation or n, percentage or median (interquartile range) are shown. Abbreviations: SI, shock index; HR, heart rate.

According to AUROC values, SI at *first* vital sign measurement following diagnosis was one of the two best performing vital
TABLE 3  Mean ± standard deviation or n, percentage of adverse clinical outcomes for the postpartum hemorrhage group and the maternal sepsis group

| Outcomes                              | Postpartum hemorrhage (n = 283) | Maternal sepsis (n = 126) |
|---------------------------------------|----------------------------------|--------------------------|
| Maternal death                        | 6, 2.1%                          | 10, 7.9%                 |
| Lowest hemoglobin following diagnosis, g/L | 77 ± 19                          | —                        |
| Lowest hemoglobin <70 g/L following diagnosis| 106, 37.6%                      | —                        |
| Drop in hemoglobin, g/L (n = 247)     | 27 ± 21                          | —                        |
| Drop in hemoglobin ≥2 g/L (n = 247)   | 153, 61.9%                       | —                        |
| Process measures                      |                                  |                          |
| Blood transfusion                     | 198, 70.0%                       | —                        |
| Blood transfusion ≥4 IU, n (% of all women) | 92, 32.5%                      | —                        |
| Number of IU                          | 3.9 ± 2.6                        | —                        |
| Critical Care Unit admission          | 106, 37.5%                       | 61, 48.4%                |
| Procedures                            |                                  |                          |
| Any                                   | 90, 31.8%                        | 30, 23.8%                |
| Major surgical or invasive procedure  | 66, 23.3%                        | 55, 36.5%                |
| Perineal repair                       | 31, 11.0%                        | 3, 2.4%                  |
| Manual removal of placenta            | 14, 4.9%                         | 1, 0.8%                  |
| Uterine balloon tamponade             | 14, 4.9%                         | 2, 1.6%                  |
| Artery ligation/embolization/clamping | 7, 2.5%                         | 3, 2.4%                  |
| Hemostatic brace suturing             | 5, 1.8%                          | 2, 1.6%                  |
| Emergency laparotomy for hemorrhage   | 15, 5.3%                         | 1, 0.8%                  |
| Other procedures related to sepsis     | 1, .4%                           | 10, 7.9%                 |
| Emergency hysterectomy                | 24, 8.5%                         | 10, 7.9%                 |

IU, international units.

signs for every adverse outcome in both hemmorhage and sepsis groups (Table 4). For example, for predicting risk of emergency hysterectomy, SI gave an AUROC of .79 (95% CI; .70-.88) in PPH and .73 (95% CI; .60-.87) in maternal sepsis. SI was selected as the most consistent predictor across the outcomes for both groups of women. Tables 5 and 6 show the frequency and percentage of outcomes across the SI categories, together with the post-test probabilities, odds ratios and the non-parametric trend test, for both groups.

In PPH, statistical testing for trend for every outcome showed a significant increase in risk with higher SI categories at “first” measurement. This was also true for the “worst” SI categories (apart from a nonsignificant trend for maternal death). In sepsis, only one woman had an SI ≥1.7 at “first” vital signs and this woman had no adverse outcomes, limiting the ability to test for trend in this group.

For “worst” vital signs in women with sepsis, statistical testing for trend for every outcome showed a significant increase in risk with increasing SI categories. The small number of septic women with “worst” SI ≥1.7 were associated with very high risks, with one-third (2 of 6) ending in maternal death. Table 7 shows the sensitivity, specificity, positive predictive value and negative predictive value of “first” SI <.9 in PPH and sepsis. There were no maternal deaths, major procedures or emergency hysterectomies in women with “first” SI < .9.

Sensitivity analysis was performed to determine whether a more stringent categorization of sepsis (the administration of intravenous antibiotics) altered the findings. The additional analysis showed similar odds ratios (95% CI) for all the outcomes for both “first” and “worst” SI categories (data not presented). Therefore, the original definition of sepsis was used to maintain power.

4 | DISCUSSION

SI was the most consistent predictor, compared with individual conventional vital signs, of all adverse outcomes in women with PPH and maternal sepsis, two of the leading causes of maternal mortality and morbidity.

Previously determined “abnormal” SI categories (SI .9-1.69 and SI ≥1.7) were significantly associated with a number of severe adverse outcomes in both cohorts of women. Test performance statistics showed the previously determined upper limit of normal (SI < .9) to be a good rule-out test for maternal death and emergency hysterectomy in both cohorts of women.

The SI category at “first” vital signs measurement following PPH diagnosis was predictive of all outcomes, including maternal death and emergency hysterectomy, with a stepwise increase in risk from SI <.9 to SI .9-1.69 to SI ≥1.7. The SI category at “worst” vital signs measurement following maternal sepsis diagnosis was also predictive of all outcomes. As with all vital signs, change over time may be important.

To improve generalizability of the results, multiple centers, limited exclusion criteria and multiple, robust and severe outcomes to assess prediction were used. Sepsis was defined according to clinical features determined by the woman’s healthcare provider. Maternal sepsis has been poorly defined in the literature. Only in 2017, after the completion of this study, did the World Health Organization convene a multidisciplinary international panel of 48 experts to set a definition of maternal sepsis. Maternal sepsis is now defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion or postpartum period. We could not determine whether our inclusion criteria correlate with this new definition; however, sensitivity analysis using an alternative categorization of sepsis showed similar findings.

Our objective was to determine whether SI thresholds could aid decision-making for healthcare providers with limited training and resources. Tertiary centers were chosen to ensure sample size and corresponding outcome rates were high enough for...
meaningful analysis. It would have been considerably more challenging to undertake such a study in community low- and middle-income countries, where the device is likely to show greatest benefit; outcome rates would have been fewer and a much larger sample size would have been required. Although the number of women with SI ≥1.7 was relatively small, severe adverse outcomes were common, unique in comparison with similar maternal health studies.

### TABLE 4

Performance of “first” vital sign parameters to predict adverse clinical outcomes among women with postpartum hemorrhage and maternal sepsis

| Adverse outcomes | Shock index | Heart rate | Systolic BP | Diastolic BP | Pulse pressure | Mean arterial pressure |
|------------------|-------------|------------|-------------|--------------|----------------|------------------------|
| Maternal death   |             |            |             |              |                |                        |
| PPH              | 0.86 (0.73-0.98) | 0.85 (0.76-0.93) | 0.67 (0.41-0.94) | 0.54 (0.19-0.88) | 0.83 (0.70-0.97) | 0.59 (0.26-0.92) |
| Sepsis           | 0.71 (0.55-0.86) | 0.70 (0.54-0.87) | 0.53 (0.33-0.72) | 0.59 (0.33-0.85) | 0.52 (0.28-0.76) | 0.56 (0.33-0.78) |
| Critical Care Unit admission |             |            |             |              |                |                        |
| PPH              | 0.68 (0.62-0.75) | 0.60 (0.53-0.67) | 0.67 (0.60-0.73) | 0.62 (0.56-0.69) | 0.60 (0.53-0.67) | 0.65 (0.58-0.71) |
| Sepsis           | 0.59 (0.48-0.69) | 0.61 (0.51-0.71) | 0.50 (0.39-0.60) | 0.53 (0.42-0.63) | 0.52 (0.41-0.62) | 0.51 (0.41-0.61) |
| Hysterectomy     |             |            |             |              |                |                        |
| PPH              | 0.79 (0.70-0.88) | 0.71 (0.60-0.82) | 0.73 (0.64-0.82) | 0.66 (0.57-0.75) | 0.63 (0.52-0.74) | 0.70 (0.61-0.79) |
| Sepsis           | 0.73 (0.60-0.87) | 0.70 (0.52-0.87) | 0.59 (0.45-0.73) | 0.59 (0.39-0.78) | 0.58 (0.36-0.81) | 0.58 (0.36-0.81) |
| Lowest hemoglobin <70 g/L (PPH) | 0.61 (0.55-0.68) | 0.63 (0.56-0.69) | 0.54 (0.47-0.61) | 0.51 (0.44-0.58) | 0.58 (0.51-0.65) | 0.52 (0.45-0.59) |
| Blood transfusion ≥4 IU (PPH) | 0.65 (0.58-0.72) | 0.65 (0.58-0.71) | 0.58 (0.50-0.65) | 0.52 (0.44-0.59) | 0.59 (0.52-0.67) | 0.54 (0.46-0.61) |
| Major procedure (sepsis) | 0.64 (0.52-0.75) | 0.53 (0.40-0.67) | 0.62 (0.51-0.73) | 0.56 (0.44-0.68) | 0.63 (0.51-0.76) | 0.58 (0.46-0.69) |

AUROC values given as AUROC (95% CI). In bold: highest two AUROC values for each outcome. Results of significance testing for equality of AUROCs using unadjusted chi-square test, with shock index as reference.

### TABLE 5

Frequency and post-test probability of outcomes in women with “first” and “worst” SI <0.9, SI 0.9-1.69, and SI ≥1.7 following hemorrhage diagnosis, odds ratios of SI 0.9-1.69 vs SI <0.9 and SI ≥1.7 vs SI 0.9-1.69 and non-parametric trend test for worsening SI category (SI <0.9 to SI 0.9-1.69 to SI ≥1.7)

| Outcomes                | Maternal death | Lowest hemoglobin <70 g/L | Blood transfusion ≥4 IU (PPH) | Critical Care Unit admission | Hysterectomy |
|-------------------------|----------------|---------------------------|-------------------------------|-------------------------------|-------------|
| **"First" vital signs** |                |                           |                               |                               |             |
| Post-test probability   |                |                           |                               |                               |             |
| SI <0.9 (153)           | 0.00 (0.2-4.4) | 50.32 (25.5-41.0)           | 39.25 (18.8-33.2)             | 39.25 (18.8-33.1)             | 3.20 (0.4-5.6) |
| SI 0.9-1.69 (116)       | 5.4 (1.4-9.8)  | 44.37 (9.1-44.7)            | 43.37 (28.3-46.5)             | 56.48 (38.9-57.7)             | 17.14 (8.8-22.4) |
| SI ≥1.7 (14)            | 1.7 (2.3-33.9) | 12.85 (57.2-98.2)           | 10.71 (41.9-91.6)             | 11.78 (49.2-95.3)             | 4.28 (8.4-58.1) |
| SI 0.9-1.69 vs SI <0.9 OR | 1.3 (0.8-2.1) | 1.7 (1.0-2.9)               | 2.7 (1.6-4.6)                 | 8.59 (2.5-30.1)               |             |
| SI ≥1.7 vs SI 0.9-1.69 OR | 1.7 (2.1-15.8) | 9.8 (2.1-46.0)              | 4.2 (1.3-14.4)                | 3.9 (1.0-14.8)                | 2.3 (0.7-8.3) |
| P                      | 0.006          | 0.004                      | 0.001                         | <0.001                        | <0.001       |
| **"Worst" vital signs** |                |                           |                               |                               |             |
| Post-test probability   |                |                           |                               |                               |             |
| SI <0.9 (60)            | 0.00 (0.6-0.0) | 19.32 (20.6-45.6)           | 17.28 (17.5-41.4)             | 9.15 (7.1-26.6)               | 1.17 (0.8-9.9) |
| SI 0.9-1.69 (206)       | 5.2 (8.5-56.6) | 74.35 (9.1-42.9)            | 63.30 (24.4-37.4)             | 84.40 (3.0-47.8)              | 18.87 (5.3-13.5) |
| SI ≥1.7 (17)            | 1.5 (1.2-8.7)  | 12.76 (9.1-39.1)            | 12.76 (4.0-89.7)              | 13.76 (50.9-39.1)             | 5.29 (10.3-56.0) |
| SI 0.9-1.69 vs SI <0.9 OR | 1.2 (6.2-2.2) | 1.1 (6.2-2.1)               | 3.9 (1.8-8.4)                 | 5.7 (0.7-43.2)                |             |
| SI ≥1.7 vs SI 0.9-1.69 OR | 2.5 (3.2-22.8) | 5.8 (1.8-18.4)              | 5.5 (1.8-16.1)                | 4.7 (1.5-15.0)                | 4.4 (1.4-13.7) |
| P                      | 0.115          | 0.016                      | 0.023                         | <0.001                        | 0.001        |

Post-test probability values are given as n, % (95% confidence interval). Odds ratios given as OR (95% confidence intervals). Values in bold indicate statistical significance. All P-values are based on the non-parametric test for trend.

*Not calculable due to 0%.

Post-test probability values are given as n, % (95% confidence interval). Odds ratios given as OR (95% confidence intervals). Values in bold indicate statistical significance. All P-values are based on the non-parametric test for trend.
The traffic light early-warning system and BP and HR values were visible to healthcare providers (as it was not possible to mask healthcare professionals to the lights and not ethical to withhold the absolute numbers). Healthcare providers could escalate care in response to the traffic lights that were triggered according to SI categories (although SI values were not displayed on the device); however, healthcare providers received no specific training on escalation of care according to the traffic lights. Therefore, outcomes may have improved in response to BP and HR, and to a lesser extent, in response to the traffic lights. As we have found significant associations between the SI categories and adverse outcomes, not only do our results remain valid, but arguably the association would likely have been even stronger if clinicians were masked to the traffic lights.

Our study reinforces the role of SI as a consistent marker of compromise in obstetrics. A 2013 systematic review assessing the association between vital signs and blood loss identified three obstetric studies involving SI. 25 All three studies included only women in early pregnancy and only one was deemed of high methodological quality. 26 In that study, SI performed better than all individual conventional vital signs for predicting ruptured ectopic pregnancy, with an AUROC of .84 (95% CI: .78-.88). 26 Since the systematic

### TABLE 6
Frequency and post-test probability of outcomes in women with “first” and “worst” SI <.9, SI .9-1.69, and SI ≥1.7 following sepsis diagnosis, odds ratios of SI .9-1.69 vs SI <.9 and SI ≥1.7 vs SI .9-1.69 and non-parametric trend test for worsening SI category (SI <.9 to SI .9-1.69 to SI ≥1.7)

| Outcomes        | Maternal death | Critical Care Unit admission | Major procedure | Hysterectomy |
|-----------------|----------------|-----------------------------|----------------|--------------|
| "First" vital signs |                |                             |                |              |
| Post-test probability |              |                             |                |              |
| SI <.9 (60)     | 2 3.3 (0.4-11.5) | 23 38.3 (26.1-51.8)         | 9 15.0 (7.1-26.6) | 2 3.3 (0.4-11.5) |
| SI .9-1.69 (64) | 8 12.5 (5.6-23.2) | 37 57.8 (44.8-70.1)         | 16 25.0 (15.0-37.4) | 8 12.5 (5.6-23.2) |
| SI ≥1.7 (1)     | 0a             | 0a                          | 0a             | 0a           |
| SI ≥1.7 vs SI <.9 OR | 4.14 (0.84-20.36) | 2.20 (1.07-4.52)         | 1.89 (0.76-4.68) | 4.14 (0.84-20.36) |
| SI ≥1.7 vs SI .9-1.69 OR | a             | a                          | a             | a           |
| P               | 0.083          | 0.065                        | 0.226          | 0.083        |
| "Worst" vital signs |                |                             |                |              |
| Post-test probability |              |                             |                |              |
| SI <.9 (24)     | 0a             | 7 29.2 (12.6-51.1)          | 0a             | 0a           |
| SI .9-1.69 (95) | 8 8.4 (3.7-15.9) | 49 51.6 (41.1-62.0)         | 23 24.2 (16.0-34.1) | 8 8.4 (3.7-15.9) |
| SI ≥1.7 (6)     | 2 33.3 (4.3-77.8) | 4 66.7 (22.2-95.7)         | 2 33.3 (4.3-77.8) | 2 33.3 (4.3-77.8) |
| SI ≥1.69 vs SI <.9 OR | a             | 2.59 (0.98-6.81)          | a             | a           |
| SI ≥1.7 vs SI .9-1.69 OR | 5.44 (0.86-34.42) | 1.88 (0.33-1.74)         | 1.57 (0.27-9.11) | 5.44 (0.86-34.42) |
| P               | 0.016          | 0.032                        | 0.008          | 0.016        |

Post-test probability values are given as n, % (95% confidence interval), odds ratios given as OR (95% confidence intervals), values in bold indicate statistical significance. All P-values are based on the non-parametric test for trend. Major procedures included uterine balloon tamponade, artery ligation/embolization/clamping, hemostatic brace suture, emergency laparotomy for hemorrhage, other procedure related to sepsis, emergency hysterectomy.

*Not calculable due to 0%.

### TABLE 7
Test performance statistics for “first” SI <.9 in prediction of adverse outcomes in women with postpartum hemorrhage or maternal sepsis

| Outcomes | PPH Maternal death total N = 6 | Sepsis Maternal death N = 10 | PPH Hysterectomy N = 24 | Sepsis Hysterectomy N = 10 |
|----------|---------------------------------|-------------------------------|-------------------------|----------------------------|
| Sensitivity (%) n/N | 100.0 (54.1-100.0) | 6/6 | 80.0 (44.4-97.5) | 8/10 | 87.5 (67.6-97.3) | 21/24 | 80.0 (44.4-97.5) | 8/10 |
| Specificity (%) n/N | 55.2 (49.2-61.2) | 153/277 | 50.4 (41.0-59.9) | 58/115 | 57.9 (1.69-2.56) | 150/259 | 50.4 (41.0-59.9) | 58/115 |
| PPV (%) n/N | 4.6 (1.7-9.8) | 153/130 | 12.3 (5.5-22.8) | 8/65 | 16.2 (10.3-23.6) | 21/130 | 12.3 (5.5-22.8) | 8/65 |
| NPV (%) n/N | 100.0 (97.6-100.0) | 153/153 | 96.7 (88.5-99.6) | 58/60 | 98.0 (94.4-99.6) | 150/153 | 96.7 (88.5-99.6) | 58/60 |

PPH, postpartum hemorrhage; PPV, positive predictive value; NPV, negative predictive value.
review, two other retrospective obstetric studies have suggested SI to be a reliable marker of deterioration. However, both studies included only women with PPH, with limited statistical analysis and fewer, less meaningful clinical outcomes.5,14,27

Our research team previously performed two retrospective prediction studies to evaluate SI and conventional vital signs as predictors of adverse outcomes in women with PPH (high- and low-income settings) and to develop potential traffic light early-warning system thresholds for the CRADLE VSA.12,13 The utility of SI in maternal settings and to develop potential traffic light early-warning system thresholds for the CRADLE VSA.12,13 The utility of SI in maternal sepsis has not previously been explored. This prospective study has confirmed that SI was one of the two best performing vital signs across the outcomes in PPH and maternal sepsis. The study also validated the previously determined SI thresholds in women with PPH and sepsis. The pathophysiology and clinical courses of these conditions differ and SI varies from minute to minute in each woman. Despite this, and in this study, one-off SI values consistently predicted a variety of severe adverse outcomes in both conditions.

The previously proposed upper limit of normal (SI <.9, green traffic light) performed well as a rule-out test, according to predictive analysis statistics. SI .9-.1.69 and SI ≥1.7 corresponded to stepwise increased risk of multiple outcomes in both cohorts of women. For PPH, the "first" SI following diagnosis was most useful, although both "first" and "worst" had predictive value. For maternal sepsis, the "worst" rather than the "first" SI following diagnosis was most useful. These findings reflect the clinical course of each condition, with complications of hemorrhage evolving more quickly than in sepsis. Complications of sepsis tend to evolve more insidiously and repeated measurements may be more useful in sepsis. The need for an obstetric early warning system is not only relevant for low- and middle-income countries. The latest UK Confidential Enquiries into Maternal Deaths and Morbidity highlights that avoidable maternal deaths and near-misses are often related to delays in recognition of hemodynamic compromise.28 Modified early obstetric warning system charts are recommended by the report and are now commonplace internationally. Despite this, a standardized modified early obstetric warning system does not exist and the evidence for their thresholds is limited.29 They are complicated to use and inappropriate for low-resource settings, where temperature and oxygen saturation is often not routinely measured.

5 | CONCLUSION

SI thresholds evaluated in this study may aid decision-making by healthcare providers caring for women with PPH or maternal sepsis in low-resource settings, allowing for earlier interventions for those at highest risk of adverse outcomes. These thresholds have been incorporated into the CRADLE VSA traffic light early-warning system, together with conventional hypertension thresholds for women with hypertension disorders of pregnancy. A similar study of the performance of the early-warning system in preclampsia was also undertaken.30 By assisting in the prediction for all three conditions, the CRADLE VSA could identify women at greatest risk of the three leading causes of maternal mortality and morbidity worldwide. To confirm the value of SI there is a need for more data from low-income settings where adverse outcomes are more prevalent.

Although recognition of the need for intervention is but one aspect of a functioning health system, it is the gateway to that system. We are undertaking a stepped-wedge randomized control trial to assess whether a maternal mortality and morbidity are reduced in 10 low-income sites, introducing the CRADLE VSA and a simple education package at community-, clinic- and hospital-levels.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

ORCID

Hannah L. Nathan https://orcid.org/0000-0002-4708-8973

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