Table 9: Clinical evidence tables

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Agrawal, Shruti, Maitra, Nandita, Prediction of Adverse Maternal Outcomes in Preeclampsia Using a Risk Prediction Model, Journal of obstetrics and gynaecology of India, 66, 104-11, 2016

Ref Id

803137

Country/ies where the study was carried out

India

Aim of the study

To assess the performance of the fullPIERS model to predict maternal adverse outcomes within 24 hours of</td>
<td>Sample size

N=322

Characteristics
<table>
<tr><th></th><th>With outcome (n = 60)</th><th>Without outcome (n =262)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>24.8 (2.9)</td><td>24.7 (3.9)</td></tr>
<tr><td>Gestational age at entry, weeks (mean, SD)*</td><td>35.47 (3.55)</td><td>34.5 (4.5)</td></tr>
<tr><td>Pre-eclampsia[a] (n ,%)</td><td>60 (100%)</td><td>262 (100%)</td></tr>
<tr><td>Singleton pregnancy (n ,%)</td><td>60 (18.6%)</td><td>262 (81.3%)</td></tr>
<tr><td>Mean (SD) sBP ≥ XY mmHg at entry*</td><td>167.6 (18.8)</td><td>156.6 (15.3)</td></tr>
</table>
</td>
<td>Prognostic tool/test

fullPIERS (Pre-eclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase

Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Sample selection

This study used a prospective cohort of data. The predictor variables were obtained within 24 hours of admission for pre-eclampsia.

Data collection

Data were collected prospectively, no details regarding sampling were reported. Whether the cohort had missing data and methods for handling missing data was not reported.</td>
<td>Prognostic accuracy (sensitivity, specificity)
<table>
<tr><th>Predicted probability (cut-off)</th><th>Total N</th><th>Total N with outcome</th><th>Sensitivity (95% CI)</th><th>Specificity (95%CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>0.00-0.99%</td><td>223</td><td>18</td><td>0.72 (0.47-0.90)</td><td>0.78 (0.72-0.84)</td><td>1.68 (1.17-2.41)</td><td>0.48 (0.22-1.03)</td></tr>
<tr><td>1.0-2.4%</td><td>23</td><td>6</td><td>0.58(0.37-0.78)</td><td>0.84(0.78-0.88)</td><td>3.59 (2.29-5.64)</td><td>0.49 (0.30-0.79)</td></tr>
<tr><td>2.5-4.9%</td><td>17</td><td>7</td><td>0.42 (0.25-0.61)</td><td>0.88 (0.83-0.92)</td><td>3.47 (2.02-5.96)</td><td>0.66 (0.48-0.89)</td></tr>
<tr><td>5.0-9.9%</td><td>15</td><td>5</td><td>0.39 (0.23-0.57)</td><td>0.92 (0.88-0.95)</td><td>4.95 (2.73 - 8.98)</td><td>0.66 (0.51-0.86)</td></tr>
<tr><td>10.0-19.9%</td><td>12</td><td>6</td><td>0.31 (0.18-0.47)</td><td>0.94 (0.90-0.97)</td><td>5.11 (2.62-9.96)</td><td>0.73 (0.59-0.90)</td></tr>
</table>
</td>
<td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Can't tell (how patients were selected was not reported)
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>admission for preeclampsia

Study dates

Not reported

Source of funding

Not reported</td>
<td>
<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Mean (SD) dBP ≥ XY mmHg at entry*</td><td>102.69 (8.1)</td><td>98.02 (9.1)</td></tr>
</table>
*Between group differences were significant for gestational age at entry, mean SBP and mean sBP (p<0.01)
[a]Pre-eclampsia was defined as hypertension (sBP/dBP≥ 140/90 taken twice more than 4 hours apart after 20 weeks of gestational age) in combination with proteinuria (≥ 0.3 g/dl of proteinuria or 2+)

Inclusion criteria

sBP/dBP≥ 140/90 taken twice more than 4 hours apart after 20 weeks of gestational age; ≥ 0.3 g/dl of proteinuria or 2+ after 20 weeks of gestation; non-hypertensive and non-proteinuric HELLP syndrome; one eclamptic seizure without prior hypertension with or without hypertension and proteinuria

Exclusion criteria

Women admitted in spontaneous labour; occurrence of any element of the composite maternal outcomes prior to their meeting the eligibility criteria or before the collection of predictor variables was possible
</td>
<td></td>
<td>Data analysis

Sensitivity, specificity, and likelihood ratios were calculated using MedCalc software.</td>
<td>
<table>
<tr><td>20.0-29.9%</td><td>5</td><td>3</td><td>0.24 (0.13-0.40)</td><td>0.95 (0.91-0.97)</td><td>4.71 (2.25 -9.86)</td><td>0.79 (0.67-0.94)</td></tr>
<tr><td>≥30%</td><td>27</td><td>15</td><td>0.52 (0.38-0.65)</td><td>0.97 (0.94-0.99)</td><td>16.92 (8.19-34.93)</td><td>0.49 (0.38-0.64)</td></tr>
</table>
Data above are reported by converting the risk estimates into dichotomous data, i.e. the LR for the 0-0.99% category treats 0.99% as the cut-off for a positive test. At this cut-off, a positive test result gives a LR of 1.68, and a negative test result gives a LR of 0.48.
Likelihood ratios were also calculated by the NGA using the method of Deeks and Altman 2004 from raw data reported in the article, with 95% CI calculated using https://www.medcalc.org/calc/relative_risk.php:
<table>
<tr><th>Risk category</th><th>Number with outcome</th><th>Number without outcome</th><th>Likelihood ratio</th><th>95% CI</th></tr>
<tr><td>0-0.99%</td><td>18</td><td>205</td><td>(18/60)/(205/262) = 0.38</td><td>0.26 to 0.57</td></tr>
<tr><td>1-2.4%</td><td>6</td><td>17</td><td>(6/60)/(17/262) = 1.54</td><td>0.63 to 3.74</td></tr>
<tr><td>2.5-4.9%</td><td>7</td><td>10</td><td>(7/60)/(10/262) = 3.06</td><td>1.21 to 7.70</td></tr>
<tr><td>5.0-9.9%</td><td>5</td><td>10</td><td>(5/60)/(10/262) = 2.18</td><td>0.77 to 6.15</td></tr>
<tr><td>10-19.9%</td><td>6</td><td>6</td><td>(6/60)/(6/262) = 4.37</td><td>1.46 to 13.07</td></tr>
</table>
</td>
<td>evaluated in a blinded fashion? Unclear (no details regarding sampling have been provided)
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate the rule clearly described? No
B. What are the results?
7 Can the performance of the rule be calculated? Yes
8 How precise was the estimate of the treatment effect? The rule is robust, there was not any attempt to refine the rule with other variables to see whether</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
				<table><tr><td>20-29.9%</td><td>3</td><td>2</td><td>(3/60)/(2/262) = 6.55</td><td>1.12 to 38.34</td></tr><tr><td>≥30%</td><td>15</td><td>12</td><td>(15/60)/(12/262) = 5.45</td><td>2.69 to 11.05</td></tr><tr><td>Total</td><td>60</td><td>262</td><td></td><td></td></tr></table> These data refer to the LR obtained when an individual is given each risk category result, i.e. when an individual is given a risk in the 0-0.99% category, her LR for disease is 0.38 **Model calibration** Not reported **Tool discrimination** Not reported	precision could be improved C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK population) 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** Unclear where sampling was carried out, study was published in India

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Akkermans, J., Payne, B., Dadelszen, P. V., Groen, H., Vries, J. D., Magee, L. A., Mol, B. W., Ganzevoort, W., Predicting complications in pre-eclampsia: External validation of the fullPIERS model using the PETRA trial dataset, European Journal of Obstetrics Gynecology and Reproductive Biology, 179, 58-62, 2014

Ref Id

803144

Country/ies where the study was carried out

The Netherlands

Aim of the study</td><td>Sample size

N=216 (PETRA cohort)

Characteristics

Participant's characteristics (data extracted from Ganzevoort 2005 as Akkermans 2014 did not report data on the HDP outcomes)<table><tr><th></th><th>Control group* (n = 104)</th><th>Treatment group* (n = 110)</th></tr><tr><td>Age, years (median,range)</td><td>30.9 (20-41)</td><td>28.9 (18-41)</td></tr><tr><td>No. with severe pre-eclampsia[a] (n, %)</td><td>43 (41%)</td><td>52 (47%)</td></tr><tr><td>HELLP at entry[b] (n, %)</td><td>27 (26%)</td><td>27 (25%)</td></tr><tr><td>Eclampsia at entry[c] (n,%)</td><td>32 (31%)</td><td>37 (34%)</td></tr><tr><td>Fetal growth restriction[d] (n, %)</td><td>56 (54%)</td><td>67 (61%)</td></tr></table></td><td>Prognostic tool/test

fullPIERS (Pre-eclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase

Outcome(s)

PIERS composite. Out-comes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity. Outcom es included:</td><td>Sample selection

This study used data from the Pre-eclampsia Eclampsia TRial Amsterdam (PETRA), a randomised controlled trial of plasma volume expansion in women with hypertensive disorders of pregnancy between 24 and 34 weeks gestational age. Women were enrolled from 2 different centres in The Netherlands (Department of Obstetrics at the Academic Medical Center [n=118] and the VU</td><td>Prognostic accuracy (sensitivity, specificity)

At 48 h of admission, using a cut-off of 20.1%
Sensitivity (95% CI) = 0.91 (95% CI NR)
Specificity (95% CI)= 0.93 (95% CI NR)
At 7 days of admission, using a cut-off of 20.1%

Sensitivity (95% CI) = 0.90 (95% CI NR)

Specificity (95% CI)= 0.23 (95% CI NR)

Model calibration
<u>Risk stratification table - Prediction of complication within 48 hours of admission</u><table><tr><th>Predicted probability</th><th>Total no of women</th><th>Total no of women with adverse outcomes</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR + (95% CI)</th><th>LR - (95% CI)</th></tr><tr><td>0.00-0.0099</td><td>37 (17%)</td><td>0 (0%)</td><td>-</td><td>-</td><td>0 (0.00 -1.23)</td><td>-</td></tr><tr><td>0.010-0.024</td><td>59 (27%)</td><td>0 (0%)</td><td>-</td><td>-</td><td>0 (0.00-0.76)</td><td>-</td></tr><tr><td>0.025-0.049</td><td>34 (16%)</td><td>1 (3%)</td><td>-</td><td>-</td><td>0.17 (0.02-1.23)</td><td>-</td></tr></table></td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Yes (the author who collected the</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>To provide external validation of the fullPIERS model at 48 h within admission

Study dates

1st April 2000 to 31st May 2003

Source of funding

Dutch National Health Insurance Board</td>
<td>
<table>
<tr><td>Ethnicity: non-white (n, %)</td><td>28 (27%)</td><td>21 (28%)</td></tr>
</table>
[a]Severe pre-eclampsia: dBP ≥110 and proteinuria ≥ 0.3 g per 24h
[b]HELLP: haemolysis, elevated liver enzymes, low platelets, with or without hypertension, and proteinuria.
[c]Eclampsia: generalised convulsions not caused by epilepsy
[d]Fetal growth restriction: estimated fetal weight <10th centile
*N=1 participant missing in each group. Were excluded from the Ganzevoort 2005 because of "unanticipated congenital malformations"
<table>
<tr><th></th><th>Women with adverse outcomes (n=73)</th><th>Women without adverse outcomes (n=143)</th></tr>
<tr><td>Gestational age at inclusion (median, IQR)</td><td>29.3 (27.1-31.3)</td><td>30.3 (27.6-31.4)</td></tr>
<tr><td>Parity ≥1 (n,%)</td><td>18 (25%)</td><td>47 (33%)</td></tr>
</table>
Inclusion criteria

Women were entered into the PETRA dataset if they met at least one of the following: HELLP syndrome; severe pre-eclampsia (dBP ≥110 mmHg and proteinuria ≥0.3g per 24 hours); eclampsia; IUGR (< 10th centile); pregnancy induced
</td>
<td>maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>University Medical Center [n=98]).

Data collection

Data were collected prospectively, although further retrospective data collection was performed to reduce the amount of outstanding parameters in the fullPIERS dataset. The variable oxygen saturation was often irretrievable, in which cases the value of 97% was imputed (this was also done in the internal validation study by von Dadelszen). For missing data, the method of last observation</td>
<td>
<table>
<tr><td>0.050-0.099</td><td>27 (13%)</td><td>1 (4%)</td><td>-</td><td>-</td><td>0.22 (0.03-1.57)</td><td>-</td></tr>
<tr><td>0.010-0.19</td><td>17 (8%)</td><td>1 (6%)</td><td>-</td><td>-</td><td>0.35 (0.04-2.62)</td><td>-</td></tr>
<tr><td>0.20-0.29</td><td>13 (6%)</td><td>3 (23%)</td><td>-</td><td>-</td><td>1.72 (0.50-5.93)</td><td>-</td></tr>
<tr><td>≥0.30</td><td>29 (13%)</td><td>26 (90%)</td><td>-</td><td>-</td><td>49.89 (16.02-154.98)</td><td>-</td></tr>
<tr><td>Total</td><td>216</td><td>32</td><td></td><td></td><td></td><td></td></tr>
</table>
<u>Risk stratification table - Prediction of complication within 7 days of admission</u>
<table>
<tr><th>Predicted probability</th><th>Total no of women</th><th>Total no of women with adverse outcomes</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR + (95% CI)</th><th>LR - (95% CI)</th></tr>
<tr><td>0.00-0.0099</td><td>37 (17%)</td><td>6 (16%)</td><td>-</td><td>-</td><td>0.48 (0.21-1.09)</td><td>-</td></tr>
<tr><td>0.010-0.024</td><td>59 (27%)</td><td>7 (12%)</td><td>-</td><td>-</td><td>0.33 (0.16-0.69)</td><td>-</td></tr>
</table>
</td>
<td>data was not aware of the model parameters)
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate the rule clearly described? Yes
B. What are the results?
7 Can the performance of the rule be calculated? Yes
8 How precise was the estimate of the treatment effect? In the study it is mentioned that "the model was adjusted to account for underlying prevalence of maternal outcomes in this population" (page 61)</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
	hypertension (dBP ≥ 90 mmHg with the absence of proteinuria). **Exclusion criteria** Signs of fetal distress, maternal condition demanding immediate delivery, or previous diagnosis of a lethal fetal congenital abnormality.		carried forward was used. **Data analysis** Calibration was calculated by assessing the slope of the linear predictor resulting from application of the fullPIERS model to the study data. Further assessment was done by adjusting the intercept of the fullPIERS model to reflect the difference in outcome prevalence of the PETRA dataset. Discrimination was calculated using the area under the curve (AUC) ROC. 95% CIs were calculated for combined	<table><tr><td>0.025-0.049</td><td>39 (16%)</td><td>4 (12%)</td><td>-</td><td>-</td><td>0.33 (0.12-0.90)</td><td>-</td></tr><tr><td>0.050-0.099</td><td>27 (13%)</td><td>4 (15%)</td><td>-</td><td>-</td><td>0.43 (0.15-1.19)</td><td>-</td></tr><tr><td>0.010-0.19</td><td>17 (8%)</td><td>6 (35%)</td><td>-</td><td>-</td><td>1.35 (0.52-3.50)</td><td>-</td></tr><tr><td>0.20-0.29</td><td>13 (6%)</td><td>8 (62%)</td><td>-</td><td>-</td><td>3.97 (1.35-11.67)</td><td>-</td></tr><tr><td>≥0.30</td><td>29 (13%)</td><td>27 (93%)</td><td>-</td><td>-</td><td>33.53 (8.22-136.76)</td><td>-</td></tr><tr><td>**Total**</td><td>216</td><td>62</td><td></td><td></td><td></td><td></td></tr></table> **Tool discrimination** **AUC ROC (95% CI) 48 hours of admission=** 0.97 (0.94 to 0.99) **AUC ROC (95% CI) 7 days of admission=** 0.80 (0.72 to 0.87) **Calibration slope (95% CI) =** 1.69 (1.10-2.28)* **Calibration slope (95% CI) after adjustment for differences between PETRA and fullPIERS population =** 1.67 (109-226) *assumed typographical error in paper, CI reported as 110 to 228	C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK population), although 27% of women did not present with pre-eclampsia 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** PETRA dataset - 73% of participants presented with pre-eclampsia

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>adverse maternal outcomes within 48h and within 7 days after inclusion, with 24h intervals.</td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Almeida, Silvana T., Katz, Leila, Coutinho, Isabela, Amorim, Melania M. R., Validation of fullPIERS model for prediction of adverse outcomes among women with severe pre-eclampsia, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 138, 142-147, 2017

Ref Id

803158</td><td>Sample size

N=325 (non pre-existing cohort)

Characteristics
<table><tr><th></th><th>With outcome

(n =55)</th><th>Without outcome

(n =270)</th></tr><tr><td>Age, years (mean, SD)</td><td>25.4 (6.5)</td><td>25.1 (6.8)</td></tr><tr><td>Ethnicity: white</td><td>14 (25.5)</td><td>68 (25.2)</td></tr><tr><td>Gestational age (mean, SD)</td><td>33.6 (4.8)</td><td>36.1 (3.4)</td></tr><tr><td>Parity (median IQR)</td><td>1 (1-2)</td><td>1 (1-2)</td></tr></table></td><td>Prognostic tool/test

fullPIERS (Pre-eclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase

Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td><td>Sample selection

This study used data from women admitted to a teaching hospital in Brazil. Sample size calculations were performed using OpenEpi, and it was assessed that for predicting a 7 day complication rate of 10%, the total number of women that would be required would be of 283.</td><td>Prognostic accuracy (sensitivity, specificity)

Sensitivity (95% CI)= 60% (46.8%- 71.80%)
Specificity (95% CI)= 65.1% (59.3% - 70.6%)

Risk stratification table
<table><tr><th>Predicted probability</th><th>With outcome</th><th>Without outcome</th></tr><tr><td>>1.7%</td><td>33 (26%)</td><td>94 (74%)</td></tr><tr><td><1.7%</td><td>22 (11%)</td><td>176 (89%)</td></tr></table>
Model calibration

Not reported

Tool discrimination

AUC ROC (95% CI)= 0.72 (95% CI 0.67 - 0.77)</td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome</td></tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Brazil **Aim of the study** To assess the performance of the fullPIERS model to predict maternal adverse outcomes within 48 hours of admission among women with severe pre-eclampsia from Brazil **Study dates** January - December 2014 **Source of funding** Not reported	<table><tr><td>Severe pre-eclampsia[a]</td><td>55 (100%)</td><td>270 (100%)</td></tr><tr><td>Mean (SD) sBP, mmHg</td><td>167.6 (20.5)</td><td>161.4 (18)</td></tr><tr><td>Mean (SD) dBP, mmHg</td><td>110.1 (11.9)</td><td>106.6 (11.6)</td></tr></table> [a]increased BP (threshold not reported) from the 20th weeks of pregnancy with proteinuria, maternal organ dysfunction and/or uteroplacental insufficiency **Inclusion criteria** Women admitted with severe pre-eclampsia (increased BP from the 20th weeks of pregnancy with proteinuria, maternal organ dysfunction and/or uteroplacental insufficiency). **Exclusion criteria** Women with chronic hypertension; diabetes; collagenosis; complications related with cardiology, haematology, or pulmonary; and women with sickle cell anaemia.		**Data collection** Data was applied retrospectively to all patients using the fullPIERS online tool. **Data analysis** Discrimination was calculated using the area under the curve (AUC) ROC. Sensitivity, specificity and likelihood ratios were calculated using the software Medcalc.		evaluated in a blinded fashion? Can't tell (no details regarding sampling have been reported) 5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes 6 Are the statistical methods used to construct and validate the rule clearly described? Yes B. What are the results? 7 Can the performance of the rule be calculated? Yes 8 How precise was the estimate of the treatment effect? The rule is robust (there were not any attempts to refine the rule to see whether precision could be improved)

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
					C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Can't tell (data was obtained from a middle income setting)) 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** Data obtained from a low/middle income setting

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Chan, Patricia, Brown, Mark, Simpson, Judy M., Davis, Gregory, Proteinuria in pre-eclampsia: how much matters?, BJOG : an international journal of obstetrics and gynaecology, 112, 280-5, 2005

Ref Id

775773

Country/ies where the study was carried out

Australia

Aim of the study

To assess whether in women with proteinuric pre-eclampsia, a specific spot urine/creatinine ratio at the time of antenatal diagnosis exists to</td><td>Sample size

N=321 (non pre-existing dataset)

Characteristics

<table><tr><th></th><th>Total cohort (n=321)</th></tr><tr><td>Age (mean, SD)</td><td>30 (5)</td></tr><tr><td>sBP at entry (mean mmHg, SD)</td><td>115 (11)</td></tr><tr><td>Gestational age</td><td>Not reported</td></tr><tr><td>Pre-eclampsia[a] (n, %)</td><td>321 (100)</td></tr><tr><td>dBP at entry (mean mmHg, SD)</td><td>70 (8)</td></tr><tr><td>Nulliparity (n, %)</td><td>233 (73)</td></tr></table>[a]ISHHP research definition

Inclusion criteria</td><td>Prognostic tool/test

Spot urine PRCR and maternal age at diagnosis

Outcome(s)

Adverse maternal outcomes: any new episode of severe hypertension (≥170/110); renal insufficiency; liver disease; cerebral irritation and thrombocytopenia. Adverse fetal outcomes: perinatal mortality and/or SGA.</td><td>Sample selection

Women with pre-eclampsia (ISSHP definition) who were admitted to the hospital since the year 1987 were entered into the study

Data collection

Data regarding demographic details, laboratory data, time of referral, and delivery were entered into a database between the years 1998 and 2001

Data analysis</td><td>Prognostic accuracy (sensitivity, specificity)

Maternal adverse outcomes
<table><tr><th>Total number of women with outcome</th><th>Test</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95%CI)</th><th>LR- (95% CI)</th></tr><tr><td>108</td><td>Spot urine PCR> 500 and maternal age > 35 years</td><td>10.2 (5.4-17.9)</td><td>100 (97.8-100)</td><td>-</td><td>0.9 (0.55-0.71)</td></tr></table>Perinatal adverse outcomes
<table><tr><th>Total number of infants with outcome</th><th>Test</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95%CI)</th><th>LR- (95% CI)</th></tr><tr><td>60</td><td>GA< 34 weeks and sBP < 115 mmHg*</td><td>48.33 (35.39-61.48)</td><td>39.08 (33.17-45.31)</td><td>0.79 (0.60-1.04)</td><td>1.32 (1.02-1.70)</td></tr></table>*PCR reading was a statistically significant predictor but did not add much information to the discriminatory power of the model</td><td>Limitations

<u>Limitations assessed with the QUADAS-2 checklist</u>
<u>Domain 1. Patient selection</u>
A. Risk of bias
Was a consecutive or random sample of patients enrolled? yes
Was a case-control design avoided? yes
Did the study avoid inappropriate exclusions? yes
Could the selection of patients have introduced bias? low
B. Concerns regarding applicability
Is there a concern that the included patients do not match the review question? low</td></tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
predict adverse outcomes in women and babies within 24 hours of admission **Study dates** 1998 to 2001 **Source of funding** Not reported	Women with pre-eclampsia (ISSHP research definition) with spot protein creatinine results available **Exclusion criteria** Women with superimposed pre-eclampsia		Area under the curve AUC ROC, sensitivity and specificity were calculated (no details were provided as to how this was done). Likelihood ratios were calculated as sensitivity/ (specificity-1)	**Model calibration** Not reported **Tool discrimination** AUC ROC (95% CI) for adverse maternal outcomes = 0.67(0.55-0.71) AUC ROC (95% CI) for adverse fetal outcomes= 0.72	<u>Domain 2. Index test(s)</u> A. Risk of bias Were the index test results interpreted without knowledge of the results of the reference standard? yes If a threshold was used, was it pre-specified? no (data-driven) **Could the conduct or interpretation of the index test have introduced bias? low** B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? no <u>Domain 3. Reference standard</u> A. Risk of bias Is the reference standard likely to correctly classify the

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
					target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? low** B. Concerns regarding applicability **Is there concern that the target condition as defined by the reference standard does not match the review question? low** Domain 4. Flow and timing Was there an appropriate interval between index test(s) and reference standard? yes

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Did all patients received a reference standard? yes
Did patients receive the same reference standard? yes
Were all patients included in the analysis? yes
Could the patient flow have introduced bias? low

Indirectness

No indirectness

Other information</td></tr>
<tr><td>Full citation

Laskin, Samara, Payne, Beth, Hutcheon, Jennifer A., Qu, Ziguang, Douglas, M. Joanne, Ford, Jason, Lee, Tang, Magee, Laura A., von Dadelszen, Peter, The role of platelet counts in</td><td>Sample size

N=1405 (from the PIERS cohort)

Characteristics

<table><tr><th></th><th>Abnormal coagulation (n=105)</th><th>Normal coagulation (n=1300)</th></tr></table></td><td>Prognostic tool/test

Platelets ≤ 100 x 10^9/L
Platelets ≤ 150 x 10^9/L
Abnormal coagulation (INR> 1.06 and serum fibrinogen < 3.54 g/L)</td><td>Sample selection

Women in the PIERS dataset meeting inclusion criteria were selected to participate in the study.</td><td>Prognostic accuracy (sensitivity, specificity)

Sensitivity and specificity of platelet count and abnormal coagulation for predicting adverse maternal outcomes
<table><tr><th>Test</th><th>Total N with adverse outcome</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr></table></td><td><u>Limitations assessed with the QUADAS-2 checklist</u>

<u>Domain 1. Patient selection</u>
A. Risk of bias
Was a consecutive or</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>the assessment of inpatient women with preeclampsia, Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC, 33, 900-8, 2011

Ref Id

776230

Country/ies where the study was carried out

Canada, Australia, new Zealand and UK

Aim of the study

To assess the relationship between platelet count and adverse outcomes in pregnant women with pre-eclamspia within 48 hours of admission

Study dates</td>
<td>
<table>
<tr><td>Maternal range (median, IQR)</td><td>30 (26 to 34)</td><td>32 (28 to 36)</td></tr>
<tr><td>GA at eligibility in weeks (median, IQR)</td><td>32.7 (30.3 to 36.7)</td><td>36.4 (33.4 to 38.4)</td></tr>
<tr><td>Multiple pregnancy (n, %)</td><td>10 (9.5)</td><td>142 (10.9)</td></tr>
<tr><td>Parity ≥1</td><td>30 (28.6)</td><td>354 (27.2)</td></tr>
<tr><td>Hypertension and proteinuria[a]</td><td>76 (72.4)</td><td>841 (64.7)</td></tr>
<tr><td>Hypertension and hyperuricaemia[b]</td><td>11 (10.5)</td><td>212 (16.3)</td></tr>
<tr><td>HELLP with hypertension and proteinuria[c]</td><td>7 (6.7)</td><td>39 (3)</td></tr>
<tr><td>Superimposed pre-eclampsia[d]</td><td>11 (10.5)</td><td>208 (16)</td></tr>
</table>
</td>
<td>Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Data collection

The data used in this study were extracted from the PIERS dataset. it was prospectively collected and it covers women who were admitted to tertiary obstetric centres. Data were collected between September 2003 and January 2010. The list of adverse maternal outcomes was developed by Delphi consensus

Data analysis

The diagnostic value of the different thresholds was assessed by calculating sensitivity and</td>
<td>
<table>
<tr><td>Platelet <100 x 10^9/L</td><td>152</td><td>15.8 (10.6 to 22.8)</td><td>92.2 (90.5 to 93.6)</td><td>2 (1.3-3.1)</td><td>0.9 (0.9-1)</td></tr>
<tr><td>Abnormal coagulation</td><td>105</td><td>15.1 (10 to 22.1)</td><td>93.5 (91.9 to 94.7)</td><td>2.17 (1.32-3.56)</td><td>0.91 (0.84-0.98)</td></tr>
</table>
Model calibration

Not reported

Tool discrimination

Not reported
</td>
<td>random sample of patients enrolled? yes
Was a case-control design avoided? yes
Did the study avoid inappropriate exclusions? yes
Could the selection of patients have introduced bias? low
B. Concerns regarding applicability
Is there a concern that the included patients do not match the review question? low

<u>Domain 2. Index test(s)</u>
A. Risk of bias
Were the index test results interpreted without knowledge of the results of the reference standard? unclear(no details were provided)
If a threshold was used, was</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Sep 2003 - Jan 2010 **Source of funding** Canadian Institutes for Health Research: CIHR, UNDP, UNFPA, WHO, World Bank Speical Programme of Research, Development and Research Training in Human Reproduction	<table><tr><td>sBP, mmHg (median, iQR)</td><td>161 (150 to 180)</td><td>162 (151 to 178)</td></tr><tr><td>dBP,mmHg (median, IQR)</td><td>103 (100 to 110)</td><td>102 (98 to 110)</td></tr></table> [a]sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) and proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) [b]sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) and hyperuricaemia (upper limit greater than normal for non-pregnant women) [c]Definition not reported [d]rapidly increasing requirements for antihypertensive drugs, sBP> 170 mmHg or dBP> 120 mmHg, new proteinuria or new hyperuricaemia **Inclusion criteria** Women with either a)sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) and either proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or hyperuricaemia (upper limit greater than normal for non-pregnant women), or b) HELLP syndrome, or c) superimposed PE (rapidly increasing requirements for antihypertensive drugs, sBP> 170 mmHg or dBP> 120 mmHg, new proteinuria or new hyperuricaemia) Women with recorded values for INR and fibrinogen and a platelet count within 12 hours of their relevant platelet count.		specificity (no further details were provided)		it pre-specified? not pre-specified **Could the conduct or interpretation of the index test have introduced bias? unclear** B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? no <u>Domain 3. Reference standard</u> A. Risk of bias Is the reference standard likely to correctly classify the target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? unclear(no details were provided)

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
	Exclusion criteria Women admitted in labour or those who had any of the maternal outcomes prior to data collection				**Could the reference standard, its conduct, or its interpretation have introduced bias? unclear** B. Concerns regarding applicability **Is there concern that the target condition as defined by the reference standard does not match the review question? low** Domain 4. Flow and timing Was there an appropriate interval between index test(s) and reference standard? yes Did all patients received a reference standard? yes Did patients receive the same reference standard? yes Were all patients included in the analysis? yes

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Could the patient flow have introduced bias? low

Indirectness

No indirectness

Other information</td></tr>
<tr><td>Full citation

Livingston, J. R., Payne, B., Brown, M., Roberts, J. M., Cote, A. M., Magee, L. A., von Dadelszen, P., Uric Acid as a predictor of adverse maternal and perinatal outcomes in women hospitalized with preeclampsia, Journal of Obstetrics & Gynaecology Canada: JOGC, 36, 870-7, 2014

Ref Id</td><td>Sample size

N= 1487

Characteristics
<table><tr><th></th><th>Full cohort (n=1487)</th></tr><tr><td>Age at expected day of delivery (median, IQR)</td><td>31 (26 to 35)</td></tr><tr><td>Gestational age at entry (median weeks, IQR)</td><td>35 (33 to 38)</td></tr><tr><td>Parity ≥1 (N,%)</td><td>390 (26)</td></tr></table></td><td>Prognostic tool/test

Uric acid (highest level recorded within 24 h of enrolment)

Outcome(s)

PIERS composite outcome. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity Perinatal outcome comprised perinat</td><td>Sample selection

PIERS cohort of women (only women with pre-eclampsia were included)

Data collection

Serum uric acid concentration was measured within 24 hours of enrolment. Local laboratories were</td><td>Prognostic accuracy (sensitivity, specificity)

Predictors by outcome for hyperuricemia (uric acid >345 µmol/L)<table><tr><th>Outcome type</th><th>Total outcomes</th><th>Time since admission</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr><tr><td>All adverse maternal</td><td>-</td><td>48h</td><td>0.80 (0.70-0.87)</td><td>0.28 (0.25-0.30)</td></tr><tr><td></td><td>-</td><td>7 d</td><td>0.82 (0.76-0.88)</td><td>0.28 (0.26-0.31)</td></tr><tr><td></td><td>199</td><td>Any time</td><td>0.83 (0.77-0.88)</td><td>0.29 (0.26-0.31)</td></tr></table></td><td>Limitations

<u>Limitations assessed with the QUADAS-2 checklist</u>
<u>Domain 1. Patient selection</u>
A. Risk of bias
Was a consecutive or random sample of patients enrolled? yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>658299

Country/ies where the study was carried out

Canada, UK, Australia and New Zealand

Aim of the study

To analyse data from an existing cohort of women with pre-eclampsia and assess whether uric acid is a good predictor of adverse and perinatal outcomes within 48 hours and 7 days of admission

Study dates

September 2003 to December 2011

Source of funding

Canadian Institutes of Health Research; UNDP; UNFPA; WHO; World Bank Special</td>
<td>
<table>
<tr><td>Median sBP (IQR), mmHg</td><td>160 (150-175)</td></tr>
<tr><td>Median dBP (IQR), mmHg</td><td>100 (95-110)</td></tr>
<tr><td>Preeclampsia[a] (N,%)</td><td>1487 (100)</td></tr>
</table>
[a]Preeclampsia was defined as hypertension (sBP/dBP ≥ 140/90 mmHg on 2 recordings or more, more than 4 hours apart) with proteinuria (≥ 0.3 g/day by 24 hour urine excretion, or ≥ 30mg/mmol by spot urine:creatinine ratio)
Demographic data of the subset of women included in the analyses was not available

Inclusion criteria

Not reported

Exclusion criteria

Women who developed any of the outcomes before the clinical predictors were measured; women admitted in spontaneous labour</td>
<td>al or infant mortality, admission to NICU for greater than 48 hours, or both.</td>
<td>responsible for measurement of serum acid.

Data analysis

AUC ROC was calculated using univariate logistic regression using STATA. AUC ROC of 0.7 was determined as the minimum value for a discriminative test.
The sensitivity and specificity of hyperuricemia and hyperuricemia corrected for GA was assessed to assess the relationship with neonatal and maternal outcomes.</td>
<td>
<table>
<tr><td>Adverse maternal (non-renal)</td><td>-</td><td>48 h</td><td>0.79 (0.70-0.87)</td><td>0.28 (0.25-0.30)</td></tr>
<tr><td></td><td>-</td><td>7 d</td><td>0.82 (0.75-0.87)</td><td>0.28 (0.26-0.31)</td></tr>
<tr><td></td><td>196</td><td>Any time</td><td>0.83 (0.77-0.88)</td><td>0.29 (0.26-0.31)</td></tr>
<tr><td>Perinatal</td><td>420</td><td>Any time</td><td>0.78 (0.073-0.82)</td><td>0.29 (0.27-0.32)</td></tr>
</table>
Predictors by outcome for hyperuricemia corrected for gestational age (defined as 1 SD above the mean value for GA)
<table>
<tr><th>Outcome type</th><th>Total outcomes</th><th>Time since admission</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>All adverse maternal</td><td>-</td><td>48h</td><td>0.86 (0.77-0.92)</td><td>0.21 (0.19-0.24)</td></tr>
<tr><td></td><td>-</td><td>7 d</td><td>0.86 (0.80-0.91)</td><td>0.22 (0.20-0.24)</td></tr>
<tr><td></td><td>199</td><td>Any time</td><td>0.86 (0.80-0.90)</td><td>0.22 (0.20-0.24)</td></tr>
<tr><td>Adverse maternal (non-renal)</td><td>-</td><td>48 h</td><td>0.86 (0.77-0.92)</td><td>0.21 (0.19-0.24)</td></tr>
</table>
</td>
<td>Could the selection of patients have introduced bias? low
B. Concerns regarding applicability
Is there a concern that the included patients do not match the review question? low

<u>Domain 2. Index test(s)</u>
A. Risk of bias
Were the index test results interpreted without knowledge of the results of the reference standard? uncle ar
If a threshold was used, was it pre-specified? thresholds have not been used
Could the conduct or interpretation of the index test have introduced bias? low</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Programme of Research, Development & Research Training in Human Reproduction; Preeclampsia Foundation; International Federation of Obstetricians and Gynaecologists; Michael Smith Foundation for Heath Research; Child and Family Research Institute				<table><tr><td></td><td>-</td><td>7 d</td><td>0.86 (0.80-0.91)</td><td>0.22 (0.20-0.24)</td></tr><tr><td></td><td>196</td><td>Any time</td><td>0.86 (0.80-0.90)</td><td>0.22 (0.20-0.24)</td></tr><tr><td>Perinatal</td><td>420</td><td>Any time</td><td>0.92 (0.90-0.95)</td><td>0.26 (0.24-0.29)</td></tr></table> **Model calibration** Not applicable	B. Concerns regarding applicability **Is there concern that the index test, its conduct, or interpretation differ from the review question? low** <u>Domain 3. Reference standard</u> A. Risk of bias Is the reference standard likely to correctly classify the target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? no** B. Concerns regarding applicability

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
					Is there concern that the target condition as defined by the reference standard does not match the review question? low <u>Domain 4. Flow and timing</u> Was there an appropriate interval between index test(s) and reference standard? yes Did all patients received a reference standard? yes Did patients receive the same reference standard? yes Were all patients included in the analysis? yes **Could the patient flow have introduced bias? low** **Indirectness** No indirectness

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Payne, B. A., Hutcheon, J. A., Ansermino, J. M., Hall, D. R., Bhutta, Z. A., Bhutta, S. Z., Biryabarema, C., Grobman, W. A., Groen, H., Haniff, F., Li, J., Magee, L. A., Merialdi, M., Nakimuli, A., Qu, Z., Sikandar, R., Sass, N., Sawchuck, D., Steyn, D. W., Widmer, M., Zhou, J., von Dadelszen, P., Walley, K., Joseph, K. S., Mirembe, F., Noovao, A., Qureshi, R., Duan, T., van Papendorp, E., Ssegirinya, M., Sewagaba, M., Byenkya, R. M., Namulema, B., Namiiro, J., Nakayiza, R. M., Akao, G., Nankabirwa, I.,</td>
<td>Sample size

N= 1300 (PIERS cohort)

Characteristics
<table><tr><th></th><th>Total cohort (n=1300)</th></tr><tr><td>Maternal range (mean, SD)</td><td>31.7 (6)</td></tr><tr><td>GA at eligibility in weeks (median, IQR)</td><td>37 (34.1-38.9)</td></tr><tr><td>Parity ≥1 (n, %)</td><td>403 (31)</td></tr><tr><td>Pre-eclampsia[a] (n, %)</td><td>1020 (78.5)</td></tr><tr><td>Other HDP[b] (n, %)</td><td>280 (21.5)</td></tr><tr><td>sBP, mmHg (median, IQR)</td><td>166 (155-180)</td></tr><tr><td>dBP,mmHg (median, IQR)</td><td>104 (98-110)</td></tr></table></td>
<td>Prognostic tool/test

miniPIERS model 25% predicted probability. Factors included in the model are: gestational age at admission, previous deliveries before 20 weeks gestation, presence/absence of chest pain/dyspnoea, presence/absence of headache and/or visual changes, presence/absence vaginal bleeding with abdominal pain, sBP (mmHg), SpO2 (optional).

Outcome(s)

PIERS composite. Out-comes included: maternal mortality or one or more</td>
<td>Sample selection

Data collected after the 1 March 2008 in the PIERS dataset meeting inclusion criteria were selected to participate in the study. Prior to this date, the PIERS dataset was not collecting data regarding abdominal pain, vaginal bleeding or any headache.

Data collection

The data used in this study were extracted from the PIERS</td>
<td>Prognostic accuracy (sensitivity, specificity)

Not reported for the external validation model

Model calibration

Not reported

Tool discrimination

Complete cohort
AUC ROC (95% CI) = 0.71 (0.65-0.76)
Complete cohort - including only women who were admitted ≤34+6wk GA
AUC ROC (95% CI) = 0.72 (0.63-0.82)
Complete cohort - include all but transfusion as an adverse outcome
AUC ROC (95% CI) = 0.75 (0.73-0.78)
Women with pre-eclampsia only
AUC ROC (95% CI) = 0.72 (0.64-0.79)</td>
<td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded</td></tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Nakazibwe, R., Noorjahan, A., Azeem, F., Menzies, J., Pipkin, F. B., Cote, A. M., Douglas, M. J., Gruslin, A., Kyle, P., Lee, T., Loughna, P., Mahajan, S., Millman, A., Moore, M. P., Moutquin, J. M., Ouellet, A., Smith, G., Walker, J., Walters, B., Lee, S., Russell, J., Brown, M., Davis, G., Robson, S., de Swiet, M., Lindheimer, M., Roberts, J., Shaw, D., Donnay, F., 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 Medicine,	[a]sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) and either proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or hyperuricaemia (upper limit greater than normal for non-pregnant women) [b]Other HPD duch as estational hypertension, chronic hypertension, partial HELLP. **Inclusion criteria** Women with either a)suspected or confirmed pre-eclampsia after 20 weeks of gestational age defined as BP ≥ 140/90 (at least 1 component; measured 2 times at least between 4 and 24 hours apart) and either proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or hyperuricaemia (upper limit greater than normal for non-pregnant women); b) HELLP syndrome, even in the absence of hypertension or proteinuria; c) superimposed pre-eclampsia. Women with other hypertensive disorders of pregnancy, such as gestational hypertension, chronic hypertension, partial HELLP. **Exclusion criteria** Women who were admitted in labour or who had developed any of the adverse outcomes prior eligibility or collection of predictor variables. Women with positive HIV/AIDS status with CD4 count < 250 cells/ml or AIDS-defining illness.	serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity	dataset. it was prospectively collected and it covers women who were admitted to tertiary obstetric centres in the UK, Australia and New Zealand. **Data analysis** Discrimination was calculated using the area under the curve (AUC) ROC. Owing to the underlying difference in adverse outcomes between the miniPIERS and fullPIERS dataset (6.5% in the fullPIERS versus 12.5% in the miniPIERS), the model intercept was adjusted prior the estimation of the		fashion? Unclear 5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes 6 Are the statistical methods used to construct and validate the rule clearly described? Yes B. What are the results? 7 Can the performance of the rule be calculated? No 8 How precise was the estimate of the treatment effect? In the study it is mentioned that "the model intercept was adjusted before estimating predictive performance" (page 4) C. Will the results help locally? Are the results

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
11, e1001589, 2014 **Ref Id** 776498 **Country/ies where the study was carried out** Canada **Aim of the study** To provide external validation of the miniPIERS clinical prediction tool within 48 hours of admission **Study dates** July 2008- March 2012 **Source of funding** "Bill & Mellinda Gates Foundation; UNDP/UNFPA/WHO/World Bank Special Programme of Research; Development and Research Training			predictive performance. Sensitivity analyses were carried out in various subsets of the study data to assess the generalis-ability of the miniPIERS prognostic tool.		applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (high income settting population), although 21.5% of women did not present with pre-eclampsia 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** 21.5% of the population did not present with pre-eclampsia **Other information**

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>in Human Reproduction; Canadian Institutes of Health Research; Preeclampsia Foundation; the Rockefeller Foundation; United States Agency for International Development; the International Federation of Gynecology and Obstetric; and the Child and Family Research Institute" (page 1)</td><td></td><td></td><td></td><td></td><td>Conflicts of interest: PVD id a paid consultant of Alere International; JMA is the founder of Lions Gate Technologies and is focused on commercializin g a device for measuring pulse oximeter; JMA holds <5% equity in the company. ZAM is a member of the Educational Board of PLOS medicine.</td></tr>
<tr><td>Full citation

Payne, B. A., Hutcheon, J. A., Dunsmuir, D., Cloete, G., Dumont, G., Hall, D., Lim, J., Magee, L. A., Sikandar, R., Qureshi, R., van Papendorp, E., Mark Ansermino, J., von Dadelszen, P., Assessing the Incremental Value of Blood Oxygen</td><td>Sample size

N= 852

Characteristics
<table><tr><th></th><th>Pakistan cohort (n=617)</th><th>SA cohort (n=235)</th></tr><tr><td>Maternal age (median, IQR)</td><td>29 (26-33)</td><td>27 (23-33)</td></tr></table></td><td>Prognostic tool/test

miniPIERS model and oxygen saturation, 25% predicted probability

Outcome(s)

PIERS composite (within 48 hours of admission=. Outc omes included: maternal mortality</td><td>Sample selection

Women meeting inclusion criteria were recruited from participating centres in Pakistan and South Africa.

Data collection</td><td>Prognostic accuracy (sensitivity, specificity)
<table><tr><th>Predicted probability (cut off)</th><th>Sensitivity (95% CI)</th><th>Specificity (95%CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr><tr><td>15%</td><td>68.1 (58.8-76.1)</td><td>77.9 (74.7-80.8)</td><td>3.1 (2.6-3.7)</td><td>0.4 (0.4-0.69</td></tr><tr><td>25%</td><td>49.6 (40.3-58.8)</td><td>91.5 (89.2-93.4)</td><td>5.9 (4.3-7.9)</td><td>0.6 (0.5-0.7)</td></tr></table></td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Saturation (SpO2) in the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) Risk Prediction Model, Journal of Obstetrics and Gynaecology Canada, 37, 16-24, 2015

Ref Id

803790

Country/ies where the study was carried out

Canada

Aim of the study

To examine the incremental value of blood oxygen saturation as a predictor in the miniPIERS clinical prediction model within 48 hours of admission

Study dates

January 2011-March 2012 (recruitment in Pakistan); November 2012 -</td>
<td>
<table>
<tr><td>GA at delivery (median, IQR)</td><td>37.2 (35.4-38.2)</td><td>34.6 (30-37.9)</td></tr>
<tr><td>Multiple pregnancy (n,%)</td><td>13 (2.1)</td><td>1 (0.4)</td></tr>
<tr><td>Parity ≥1</td><td>350 (51.9)</td><td>126 (53.6)</td></tr>
<tr><td>Pre-eclampsia[a] (n,%)</td><td>343 (55.6)</td><td>173 (73.6)</td></tr>
<tr><td>Other HDP (n,%)</td><td>274 (44.4)</td><td>62 (26.4)</td></tr>
<tr><td>sBP (median, IQR), mmHg</td><td>150 (140-160)</td><td>146 (140-160)</td></tr>
<tr><td>dBP (median, IQR), mmHg</td><td>100 (90-110)</td><td>69 (90-101)</td></tr>
</table>
[a]sBP/dBP ≥140/90 with proteinuria ≥2+ on a dipstick test

Inclusion criteria

Women with new (onset after 20 weeks gestation) or chronic hypertension (sBP/dBP ≥140/90) on at least 2 occasions between 4 and 24 h apart after 20 weeks gestation with or without proteinuria (≥2+ on a dipstick test) or other conditions.
</td>
<td>or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Data were collected prospectively during inpatient stays, except for Pakistan, where it was collected from medical records. POM application was used for data collection.

Data analysis

The miniPIERS equation was used as the linear predictor variable. A 25% predicted probability was used to define thise at high risk, based on the optimal threshold identified. AUC ROC was used to discriminate the predicted ability of oxygen saturation to</td>
<td>
<table>
<tr><td>35%</td><td>39.5 (30.8-48.9)</td><td>96.3 (94.6-97.5)</td><td>10.7 (7.0-16.5)</td><td>0.6 (0.5-0.7)</td></tr>
</table>
Data above are reported by converting the risk estimates into dichotomous data, i.e. the LR for the 15% category treats 15% as the cut-off for a positive test. At this cut-off, a positive test result gives a LR of 3.1, and a negative test result gives a LR of 0.4.
Likelihood ratios were also calculated by the NGA using the method of Deeks and Altman 2004 from raw data reported in the article, with 95% CI calculated using https://www.medcalc.org/calc/relative_risk.php:
<table>
<tr><th>Risk category</th><th>Number with outcome</th><th>Number without outcome</th><th>Likelihood ratio</th><th>95% CI</th></tr>
<tr><td><25%</td><td>80</td><td>705</td><td>(80/119)/(705/733) = 0.70</td><td>0.61 to 0.79</td></tr>
<tr><td>≥25%</td><td>39</td><td>28</td><td>(39/119)/(28/733) = 8.58</td><td>5.50 to 13.39</td></tr>
<tr><td>Total</td><td>119</td><td>733</td><td></td><td></td></tr>
</table>
These data refer to the LR obtained when an individual is given each risk category result, i.e. when an individual is given a risk in the ≥25% category, her LR for disease is 8.58

Model calibration

Not reported

Tool discrimination

AUC ROC (95% CI)
Oxygen saturation alone 0.72 (0.68-0.77)
Oxygen saturation adjusted 0.81 (0.76-0.85)
AUC ROC (95% CI) - Sensitivity analyses -using non cardiorespiratory outcomes
</td>
<td>which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Uncle ar (no details regarding sampling have been provided)
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate the rule clearly described? Yes
B. What are the results?
7 Can the performance of the rule be</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
December 2013 (recruitment in South Africa) **Source of funding** Grand Challenge Canada; University of British Columbia PRE-EMPT initiative; Bill & Melinda Gates Foundation.	**Exclusion criteria** Not reported		differentiate women at risk of developing adverse outcomes. The association between oxygen saturation and the composite maternal outcome was done using logistic regression.	0.69 (0.63-0.74) - unadjusted 0.75 (0.69-0.81) - adjusted using miniPIERS outcomes	calculated? No (TP,FP,TN,FN or total % of women with AE at each predicted probability have not been reported) 8 How precise was the estimate of the treatment effect? The rule was recalibrated by fitting to 2 variables C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? No, the study was conducted in a low/middle income setting 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>the management of the patient or the information you can give to him/her? Yes

Indirectness

39.4% of the population did not present with PE

Other information

PVD is a consultant of Alere International (for work not related to the manuscript); JMA and GD are co-founders of LGT medical and hold <5% of equity for the company.</td></tr>
<tr><td>Full citation

Thangaratinam, S., Allotey, J., Marlin, N., Dodds, J., Cheong-See, F., von Dadelszen, P.,</td><td>Sample size

For the validation component: N=634 in the PIERS dataset and N=216 in the PETRA dataset.</td><td>Prognostic tool/test

Prediction of complications in early-onset pre-eclampsia (PREP)</td><td>Sample selection

For the validation component, this study used data</td><td>Prognostic accuracy (sensitivity, specificity)

Risk stratification table, PIERS cohort*
<table><tr><th>48 hours</th><th>7 days</th></tr></table></td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ganzevoort, W., Akkermans, J., Kerry, S., Mol, B. W., Moons, K. G. M., Riley, R. D., Khan, K. S., Prediction of complications in early-onset pre-eclampsia (PREP): Development and external multinational validation of prognostic models, BMC Medicine, 15, 68, 2017

Ref Id

776782

Country/ies where the study was carried out

UK

Aim of the study

To provide external validation of the PREP model within 48 hours and 7 days of admission

Study dates</td>
<td>Characteristics
<table>
<tr><th></th><th>PIERS (n=634)</th><th>PETRA (n=216)</th></tr>
<tr><td>Age, years (median, range)</td><td>31.2 (6.3)</td><td>30 (5)</td></tr>
<tr><td>Gestational age at diagnosis (mean, SD)</td><td>30.2 (3)</td><td>29.4 (2.6)*</td></tr>
<tr><td>New-onset PE (n,%)</td><td>51.9 (82)</td><td>96 (44)*,d</td></tr>
<tr><td>Superimposed PE (n,%)</td><td>95 (15)</td><td>-</td></tr>
<tr><td>HELLP (n,%)</td><td>22 (3)</td><td>54 (25)*,e</td></tr>
<tr><td>Eclampsia (n,%)</td><td>-</td><td>5 (2.3)*,f</td></tr>
<tr><td>Fetal growth restriction/pregnancy induced hypertension (n,%)</td><td>-</td><td>125 (58)*,g</td></tr>
</table>
*Some women matched with more than 1 diagnostic criteria
[a]sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 w GA) with either proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or</td>
<td>Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>from 2 datasets: PIERS (Pre-eclampsia integrated estimate of risk) and PETRA (pre-eclampsia trial Amsterdam)

Data collection

Data were collected retrospectively. Missing predictor values were dealt with by using the ICE package in Stata with five imputations.

Data analysis

Calibration was assessed using calibration plots and estimating the calibration slope. Discrimination was assessed with the c-statistic from</td>
<td>
<table>
<tr><td>5/59</td><td>11/59</td></tr>
<tr><td>8/70</td><td>27/70</td></tr>
<tr><td>12/123</td><td>74/123</td></tr>
<tr><td>47/87</td><td>75/87</td></tr>
</table>
*Calculated by the NGA using the observed survival probability and predicted survival probability reported in the study

Model calibration

Observed and expected probability of survival using the PREP-S model at different time points in the PIERS cohort
<table>
<tr><th>Risk stratification</th><th>No of women</th><th>Time point</th><th>Observed (O)</th><th>Expected (E)</th><th>O:E ratio</th></tr>
<tr><td>≤15th</td><td>59</td><td>48 hours</td><td>0.91</td><td>0.95</td><td>0.96</td></tr>
<tr><td></td><td></td><td>1 week</td><td>0.81</td><td>0.79</td><td>1.0</td></tr>
<tr><td>>15th-50th</td><td>70</td><td>48 hours</td><td>0.88</td><td>0.89</td><td>1.0</td></tr>
<tr><td></td><td></td><td>1 week</td><td>0.62</td><td>0.60</td><td>1.0</td></tr>
<tr><td>>50th-85th</td><td>123</td><td>48 hours</td><td>0.90</td><td>0.70</td><td>1.3</td></tr>
<tr><td></td><td></td><td>1 week</td><td>0.40</td><td>0.23</td><td>1.7</td></tr>
</table>
</td>
<td>prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Can't tell
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes, although a reduced version was developed since not all the predictor variables were</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Not reported

Source of funding

National Institute for Health Research - Health Technology Assessment programme</td>
<td>hyperuricaemia (upper limit greater than normal for non-pregnant women)
[b]rapidly increasing requirements for antihypertensive drugs, sBP> 170 mmHg or dBP> 120 mmHg, new proteinuria or new hyperuricaemia
[c]Definition not reported
[d]dBP ≥110 mmHg in combination with proteinuria (≥0.3 g/24h)
[e]platelet count <100x10^9/L and AST ≥ 70U/L and/or LDH ≥ 600U/L
[f]convulsions in pregnancy in the absence of epilepsy
[g]abdominal circumference<5th percentile for GA or estimated fetal weight<10th percentile for GA and dBP≥90 mmHg

Inclusion criteria

PIERS cohort: Women with either a)suspected or confirmed pre-eclampsia after 20 weeks of gestational age defined as BP ≥ 140/90 (at least 1 component; measured 2 at least 4 hours apart) and either proteinuria or hyperuricaemia; b) HELLP syndrome, even in the absence of hypertension or proteinuria; c) superimposed pre-eclampsia.
PETRA cohort: HELLP syndrome; fetal growth restriction and pregnancy induced hypertension; severe pre-eclampsia or eclampsia, singleton pregnancies.

Exclusion criteria

Women in whom the outcome took place before the assessment of predictors; women in whom there was insufficient time to obtain the informed consent</td>
<td></td>
<td>the PREP-L model.
The ratio of observed and predicted probability of outcomes was assessed at 48 hours, 1 week and overall.
For missing data, the ICE package in STATA was used.
The study reported the external validation of 2 prediction models: PREP-S and PREP-L. The PREP-S is a survival model that predicts the time to adverse outcomes before 34 weeks of gestational age, whereas the PREP-L is a model to predict the overall risk of maternal complications by discharge only. For</td>
<td>
<table>
<tr><td>>85th</td><td>87</td><td>48 hours</td><td>0.46</td><td>0.28</td><td>1.6</td></tr>
<tr><td></td><td></td><td>1 week</td><td>0.14</td><td>0.02</td><td>7.0</td></tr>
</table>
Comparison of predicted versus observed risk of outcome for reduced PREP-L model (data obtained from Thangaratinam S, Allotey J, Marlin N, Mol BW, Von Dadelszen P, Ganzevoort W, et al. Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study. Health Technol Assess 2017;21 (18).)
<table>
<tr><th>Risk stratification</th><th>PIERS cohort
observed/predicted (%)</th><th>PETRA cohort
observed/predicted (%)</th></tr>
<tr><td>≤10th</td><td>0/0</td><td>0/0</td></tr>
<tr><td>10-20th</td><td>0/3 (0%)</td><td>0/0</td></tr>
<tr><td>20-30th</td><td>6/20 (30%)</td><td>2/4 (50%)</td></tr>
<tr><td>30-40th</td><td>8/24 (33%)</td><td>1/1 (100%)</td></tr>
<tr><td>40-50th</td><td>16/33 (48%)</td><td>4/11 (36%)</td></tr>
<tr><td>50-60th</td><td>21/34 (62%)</td><td>8/13 (62%)</td></tr>
<tr><td>60-70th</td><td>19/38 (50%)</td><td>18/22 (82%)</td></tr>
<tr><td>70-80th</td><td>42/58 (72%)</td><td>25/30 (83%)</td></tr>
<tr><td>80-90th</td><td>59/72 (82%)</td><td>70/74 (95%)</td></tr>
</table>
</td>
<td>available in the PREP and PETRA datasets
6 Are the statistical methods used to construct and validate the rule clearly described? Yes
B. What are the results?
7 Can the performance of the rule be calculated? No
8 How precise was the estimate of the treatment effect? The rule was simplified because not all the predictor variables were available from the PREP and PETRA datasets
C. Will the results help locally? Are the results applicable to the scenario?
9 Would the prediction rule be reliable and the results interpretable if used for your</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
			validating the PREP-S, only data from the PIERS was used as the PETRA dataset did not have time to event outcomes. Since not all the predictors from the PREP model were available in the PETRA and PIERS dataset, a slightly reduced model was used to externally validate the tool (rPREP). To develop this, coefficients were re-estimated and then adjusted for optimism. The reduced version of the PREP-S did not have serum urea and deep tendon reflex and the reduced version of	**90-100th** 147/155 (95%) 52/56 (93%) **Tool discrimination** **<u>PREP-S model performance</u>** **PIERS cohort** *C-statistic (95% CI)* At 48 hours: 0.75 (0.69 to 0.81) At 1 week: 0.72 (0.68 to 0.76) Overall: 0.71 (0.67 to 0.75) *Calibration slope (95% CI)* At 48 hours: 0.80 (0.62 to 0.99) At 1 week: 0.75 (0.61 to 0.89) Overall: 0.67 (0.56 to 0.79) **<u>PREP- L model performance</u>** **PIERS cohort** *C-statistic (95% CI)* = 0.81 (0.77-0.85) *Calibration slope (95% CI)*= 0.93 (0.72 - 1.13) **PETRA cohort** *AUC (95% CI)*= 0.75 (0.64-0.86) *Calibration slope (95% CI)* = 0.90 (0.48 - 1.32)	patient? Yes (the populations from which the data was obtained were high income settings) 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** The model was modified for the validation, as not all predictor variables were included in the validation datasets. 27% of women in the PETRA dataset did not present with pre-eclampsia No indirectness in the PIERS cohort

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>PREP-L did not have serum urea.</td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Thangaratinam, S., Koopmans, C. M., Iyengar, S., Zamora, J., Ismail, K. M. K., Mol, B. W. J., Khan, K. S., Accuracy of liver function tests for predicting adverse maternal and fetal outcomes in women with preeclampsia: A systematic review, Acta Obstetricia et Gynecologica Scandinavica, 90, 574-585, 2011

Ref Id

804009

Country/ies where the study was carried out

UK

Aim of the study

To assess the accuracy of liver</td><td>Sample size

Median sample size was 230 (range 64 - 737)

Characteristics

There were 13 included studies, assessing maternal and fetal outcomes

Inclusion criteria

Test accuracy studies; including women with pre-eclampsia in which liver function tests (AST, ALT, LDH, GGT, ALP) were carried out, reporting composite maternal or fetal outcomes.

Exclusion criteria

Case reports</td><td>Prognostic tool/test

Liver function tests (AST,ALT,LDH,GGT,ALP)

Outcome(s)

Adverse maternal outcomes
Maternal complications
Adverse fetal outcomes</td><td>Sample selection

A prospective protocol was carried out, MEDLINE, EMBASE, and the Cochrane Library were searched for relevant citations. Corresponding authors were contacted to retrieve relevant data. Language restrictions were not applied

Data collection

The electronic searches were screened and the studies likely to meet the predefined criteria were</td><td>Prognostic accuracy (sensitivity, specificity)

Adverse maternal outcome
<table>
<tr><th>Study</th><th>Liver test</th><th>Cut-off</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>Martin 1999</td><td>AST</td><td>150</td><td>0.70 (0.63-0.77)</td><td>0.48 (0.43-0.53)</td><td>1.4 (1.2 - 1.5)</td><td>0.62 (0.48-0.8)</td></tr>
<tr><td>Martin 1999</td><td>LDH</td><td>1400</td><td>0.72 (0.65-0.79)</td><td>0.49 (0.44-0.54)</td><td>1.4 (1.2-1.6)</td><td>0.57 (0.44-0.74)</td></tr>
<tr><td>Martin 1999</td><td>ALT</td><td>100</td><td>0.66 (0.59-0.73)</td><td>0.47 (0.42-0.52)</td><td>1.2 (1.1-1.4)</td><td>0.72 (0.57-0.91)</td></tr>
<tr><td>Girling 1997</td><td>AST/ALT/Bil/GGT</td><td>30/32/14/41</td><td>0.93 (0.52-1)</td><td>0.57 (0.37-0.76)</td><td>2.2 (1.4-3.5)</td><td>0.12 (0.01-1.7)</td></tr>
<tr><td>Menzies 2007</td><td>ALT/AST</td><td>40/55</td><td>0.33 (0.22-0.45)</td><td>0.80 (0.77-0.84)</td><td>1.7 (1.2-2.4)</td><td>0.83 (0.71-0.99)</td></tr>
</table></td><td>Limitations

Systematic review assessed using AMSTAR checklist. Total score: 11/16

Indirectness

No indirectness

Other information

Only studies reporting on composite adverse maternal outcomes have been extracted</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>function tests in women with pre-eclampsia for the prediction of maternal or fetal complications

Study dates

Not reported

Source of funding

"No specific funding"</td>
<td></td>
<td></td>
<td>selected by 2 independent reviewers; final exclusion and inclusion was done by the reviewers; the studies meeting the inclusion criteria were selected and information regarding study characteristics, quality, and accuracy data were extracted.

Data analysis

A 2x2 table was constructed for each of the studies identified</td>
<td>
<table>
<tr><td>Menzies 2007</td><td>LDH</td><td>600</td><td>0.62 (0.49-0.74)</td><td>0.60 (0.56-0.64)</td><td>1.6(1.3-1.9)</td><td>0.63 (0.46-0.86)</td></tr>
</table>
Adverse fetal outcome
<table>
<tr><th>Study</th><th>Liver test</th><th>Cut-off</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>Girling 1997</td><td>AST/ALT/Bi/GGT</td><td>30/32/14/41</td><td>0.86 (0.23-1)</td><td>0.5 (0.32-0.68)</td><td>1 (0.99-3)</td><td>0.27 (0.02-3.8)</td></tr>
</table>
Model calibration

Not reported

Tool discrimination

Not reported
</td>
<td></td>
</tr>
<tr>
<td>Full citation

Ukah, U. Vivian, Hutcheon, Jennifer A., Payne, Beth, Haslam, Matthew D., Vatish, Manu, Ansermino, J. Mark, Brown,</td>
<td>Sample size

17 studies were included in total, although for the purpose of this review, 2 studies have been included (those including women with suspected or confirmed pre-eclampsia and reporting on maternal adverse outcomes)</td>
<td>Prognostic tool/test

Placental growth factor

Outcome(s)</td>
<td>Sample selection

A electronic search was performed in MEDLINE, Embase, CINAHL until January 2017.</td>
<td>Prognostic accuracy (sensitivity, specificity)

Composite maternal outcomes
<table>
<tr><th>Author, year</th><th>Test/cut-off for sFlt-1/PLGF ratio</th><th>Total N and outcome (%)</th><th>Sensitivity (95%CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
</table>
</td>
<td>Limitations

AMSTAR overall quality score: 13/16

Indirectness

No indirectness</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Helen, Magee, Laura A., von Dadelszen, Peter, Placental Growth Factor as a Prognostic Tool in Women With Hypertensive Disorders of Pregnancy: A Systematic Review, Hypertension (Dallas, Tex. : 1979), 70, 1228-1237, 2017

Ref Id

804045

Country/ies where the study was carried out

Canada

Aim of the study

To systematically review the evidence examining the ability of the placental growth factor (both independently and combined with other factors) to predict maternal and fetal complications</td>
<td>Characteristics
<table>
<tr><th>Type of PE</th><th>Maternal characteristics</th><th>Outcomes</th></tr>
<tr><td colspan="3">Leaños-Miranda 2013
Prospective cohort, Mexico</td></tr>
<tr><td>PE</td><td>GA at presentation: 32
Mean age: 28.3
Primigravida: 43.5%</td><td>Composite maternal outcome
Composite fetal/ neonatal outcomes</td></tr>
<tr><td colspan="3">Palomaki 2015
Prospective cohort, USA</td></tr>
<tr><td>Suspected preterm PE (GA ≤34 W)</td><td>Mean GA:30</td><td>Composite maternal outcomes</td></tr>
</table>
Inclusion criteria

Studies in which PlGF was used either as an independent or combined marker with women with hypertensive disorders of pregnancy*. Studies should perform at least one predictive performance measure or sufficient data for this to be calculated

Exclusion criteria

Not reported</td>
<td>PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Google scholar and grey literature sources were also searched. Titles and abstracts were screened by 2 reviewers.

Data collection

Study details were extracted and, as part of the predictive performance measures, study quality was assessed with QUIPS (Quality in Prognostic Studies Checklist).

Data analysis

2x2 tables were constructed for each of the outcomes reported, and LRs were used for interpreting</td>
<td>
<table>
<tr><td>Leaños-Miranda 2013</td><td>Serum sFlt-PlGF ratio ≥ 871</td><td>501 (9.5)</td><td>52.1 (37.4-66.5)</td><td>77.9 (73.8-81.6)</td><td>2.36 (1.71-3.26)</td><td>0.61 (0.46 - 0.83)</td></tr>
<tr><td>Palomaki 2015</td><td>sFlt-1/PlGF ratio>85</td><td>237 (8.9)</td><td>61.9 (38.7-81.0)</td><td>69.4 (62.8-75.4)</td><td>2.0 (1.4-3.0)</td><td>0.5 (0.3-1.0)</td></tr>
</table>
Model calibration

Not reported

Tool discrimination

Not reported</td>
<td>Other information

*Please note that for the purpose of this review, only studies including women with PE (with confirmed and suspected) have been included</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>resulting from hypertensive disorder of pregnancy

Study dates

Studies published before 30th of January 2017

Source of funding

Canadian Institutes of Health Research (CIHR)</td><td></td><td></td><td>the usefulness of a given test.</td><td></td><td></td></tr>
<tr><td>Full citation

Ukah, U. V., Payne, B., Lee, T., Magee, L. A., Von Dadelszen, P., External Validation of the fullPIERS Model for Predicting Adverse Maternal Outcomes in Pregnancy Hypertension in Low- and Middle-Income Countries, Hypertension, 69, 705-711, 2017</td><td>Sample size

N=757 (miniPIERS cohort)

Characteristics

<table><tr><td></td><td>miniPIERS cohort (n=757)</td></tr><tr><td>Age, years (median, IQR)</td><td>28 (24-33)</td></tr><tr><td>No. with pre-eclampsia[a] n (%)</td><td>568 (75.03%)</td></tr></table></td><td>Prognostic tool/test

fullPIERS (Preeclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase

Outcome(s)</td><td>Sample selection

This study used data from the miniPIERS cohort, a multi-country prospective study for developing a tool to predict adverse outcomes during pregnancy in low and middle income countries.</td><td>Prognostic accuracy (sensitivity, specificity)

With a cut-off of 30%
Sensitivity 78 (95% CI NR)
Specificity 0.66 (95% CI NR)

Model calibration

Risk stratification of women with and without adverse outcomes and risk stratification at varying predicted probability within 48 hours
<table><tr><th>Predicted probability</th><th>Total no of women</th><th>Total no of observed adverse outcomes</th><th>LR +(95% CI)</th></tr></table></td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? Yes
2 The population from which the rule was derived included an</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ref Id

804075

Country/ies where the study was carried out

Canada

Aim of the study

To provide external validation of the fullPIERS model within 48 hours of admission with data from low and middle income countries

Study dates

July 2008 to March 2012

Source of funding

Canadian Institutes of Health Research (CIHR)</td>
<td>
<table>
<tr><td>Other HDP (type not specified) n (%)</td><td>189 (24.97%)</td></tr>
<tr><td>Gestational age at eligibility, weeks (median, IQR)</td><td>36.6 (33.1-38.1)</td></tr>
<tr><td>Multiple pregnancy n (%)</td><td>18 (2.4%)</td></tr>
<tr><td>Parity N (%)</td><td>406 (53.6%)</td></tr>
<tr><td>sBP ≥ XY mmHg at entry (median, IQR)</td><td>160 (150 - 170)</td></tr>
<tr><td>dBP ≥ XY mmHg at entry (median, IQR)</td><td>100 (100-110)</td></tr>
</table>
[a] severe pre-eclampsia: BP≥ 140/90 (at least one component, twice, measured more than 4 hours apart at or after 20 weeks GA) without significant proteinuria

Inclusion criteria

Women with any hypertensive disorder of pregnancy.

Exclusion criteria

Having experienced any adverse outcome (i.e. hepatic dysfunction, hepatic hematoma or rupture, stroke, cortical blindness.) before</td>
<td>PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>Women from Fiji, Uganda, South Africa, Brazil and Pakistan were enrolled.

Data collection

Data was collected prospectively and entered into a standardised form. The variable oxygen saturation was often irretrievable, in which cases the value of 97% was imputed (this was also done in the internal validation study by von Dadelszen). Only women with complete predictor data were included. Sensitivity analyses were conducted to ensure that there were not</td>
<td>
<table>
<tr><td>0-0.99%</td><td>30 (4%)</td><td>2 (6.7%)</td><td>-</td></tr>
<tr><td>1.0-2.4%</td><td>107 (14.1%)</td><td>3 (2.8%)</td><td>0.17 (0.06-0.53)</td></tr>
<tr><td>2.5-4.9%</td><td>140(18.5%)</td><td>12 (8.6%)</td><td>0.56 (0.32-0.97)</td></tr>
<tr><td>5.0-9.9%</td><td>178 (23.5%)</td><td>8 (4.5%)</td><td>0.28 (0.14-0.55)</td></tr>
<tr><td>10.0-29.9%</td><td>204(26.9%)</td><td>35 (32.1%)</td><td>1.23 (0.91-1.67)</td></tr>
<tr><td>≥0.30</td><td>98 (12.1%)</td><td>49 (50%)</td><td>5.9 (4.23-8.35)</td></tr>
</table>
Tool discrimination

Calibration slope = 0.67 (95% CI nor reported)
AUC ROC (95% CI)= 0.77 (0.72 - 0.82)</td>
<td>appropriate spectrum of patients? Yes
3 Was the rule validated in a different group of patients? Yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? Yes (the author who collected the data was not aware of the model parameters)
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? Yes
6 Are the statistical methods used to construct and validate the rule clearly described? Yes
B. What are the results?
7 Can the performance of</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
	hospital admission or having been admitted in spontaneous labour.		any bias because of missing data. **Data analysis** Discrimination was calculated using the area under the AUC ROC. Calibration was assessed by estimating the slope in a calibration plot of predicted versus observed outcomes.		the rule be calculated? Yes 8 How precise was the estimate of the treatment effect? The authors of the study did not try to refine/simplify the tool C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? No (study was developed in low and middle income countries, a different setting than the UK) 10 Is the rule acceptable in your case? Can´t tell 11 Would the results of the rule modify your decision about the management of

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>the patient or the information you can give to him/her? Can´t tell

Indirectness

Sample obtained from low and middle income settings (Fiji, Uganda, South Africa, Brazil)
No conflicts of interest have been declared

Other information</td></tr>
<tr><td>Full citation

Ukah, U. V., Payne, B., Hutcheon, J. A., Ansermino, J. M., Ganzevoort, W., Thangaratinam, S., Magee, L. A., von Dadelszen, P., Assessment of the fullPIERS Risk Prediction Model in Women With Early-Onset Preeclampsia,</td><td>Sample size

N=1388 (n=218 in the BCW cohort; N=216 in the PETRA cohort; and N= 954 in the PREP cohort)

Characteristics
<table><tr><th></th><th>BCW cohort (n=218)</th><th>PETRA cohort (N=216)</th><th>PREP cohort (n=954)</th></tr></table></td><td>Prognostic tool/test

fullPIERS (Pre-eclampsia Integrated Estimate of Risk). Factors included in the model: gestational age, respiratory pulse oximetry, platelets, creatinine, hepatic aspartate transaminase</td><td>Sample selection

The data from this study was obtained from 3 pre-existing cohorts: BCW cohort; PETRA cohort; PREP cohort.
Sample size calculations were performed by</td><td>Prognostic accuracy (sensitivity, specificity)

<u>PETRA, PREP and BCW cohorts combined</u>
<table><tr><th>Time since admission</th><th>Total N with outcomes</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr><tr><td>48 hours</td><td>101</td><td>0.57 (95% CI NR)</td><td>0.94 (95% CI NR)</td></tr><tr><td>7 days</td><td>179</td><td>0.68 (95% CI NR)</td><td>0.70 (95% CI NR)</td></tr></table></td><td>Limitations

The quality of this study was assessed using the CASP tool for clinical prediction rule (CPR).
A. Are the results valid?
1 Is the CPR clearly defined? yes</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Hypertension, 71, 659-665, 2018

Ref Id

867315

Country/ies where the study was carried out

Canada

Aim of the study

To externally validate the fullPIERS model within 48 hours and 7 days of admission using data from 3 pre-existing cohorts of women

Study dates

Data was collected at different time points depending on the cohort. All data was collected between the years 2000 and 2014

Source of funding</td>
<td>
<table>
<tr><td>Maternal age at estimated day of delivery (median, IQR)</td><td>35 (30-39)</td><td>30 (27-34)</td><td>30 (26-35)</td></tr>
<tr><td>No. with severe pre-eclampsia [a] n (%)</td><td>191 (87.6%)</td><td>123 (56.9%)</td><td>940 (98.5%)</td></tr>
<tr><td>HELLP syndrome [b] n (%)</td><td>27 (12.4%)</td><td>93 (43%)</td><td>10 (1%)</td></tr>
<tr><td>Multiple pregnancy</td><td>40 (18.4%)</td><td>-</td><td>84 (8.8%)</td></tr>
<tr><td>Gestational age at eligibility (median weeks, IQR)</td><td>31 (28.4-32.7)</td><td>30 (27.4-31.4)</td><td>31.4 (28.7-32.7)</td></tr>
<tr><td>Median sBP (IQR), mmHg</td><td>161 (150-173)</td><td>160 (145-170)</td><td>155 (145-169)</td></tr>
<tr><td>Median dBP</td><td>100 (94-106)</td><td>105 (95-110)</td><td>99 (32-105)</td></tr>
</table>
</td>
<td>Outcome(s)

PIERS composite. Outcomes included: maternal mortality or one or more serious central nervous system, cardiorespiratory, renal, haematological, or hepatic morbidity</td>
<td>simulations studies. It was concluded that validation studies should at minimum have 100 events to have 80% power at the 5% significance level.

Data collection

Data from the PETRA and PREP were collected prospectively whereas data from the BCW were collected retrospectively. Data collection took between 3 and 4 years in the 3 cohorts and was obtained between the years 2000 and 2014. The variable oxygen saturation was often irretrievable, in which cases</td>
<td><u>Sensitivity analyses (prognostic accuracy after exclusion of the PETRA cohort)</u>
<table>
<tr><th>Time since admission</th><th>Total N with outcomes</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>48 hours</td><td>69</td><td>0.68 (95% CI NR)</td><td>0.72 (95% CI NR)</td></tr>
<tr><td>7 days</td><td>117</td><td>0.59 (95% CI NR)</td><td>0.74 (95% CI NR)</td></tr>
</table>
Model calibration

<u>Risk stratification table within 48 hours</u>
<table>
<tr><th>Predicted probability</th><th>Total no of women</th><th>Total no of women with adverse outcomes (%)*</th><th>LR (95% CI)</th></tr>
<tr><td>0.00-0.0099</td><td>594 (30.5%)</td><td>14 (1.7%)</td><td>-</td></tr>
<tr><td>0.010-0.024</td><td>409 (33.1%)</td><td>17 (2.8%)</td><td>0.55 (0.36-0.86)</td></tr>
<tr><td>0.025-0.049</td><td>158 (19.1%)</td><td>8 (4.5%)</td><td>0.68 (0.34-1.34)</td></tr>
<tr><td>0.050-0.099</td><td>91 (7.8%)</td><td>6 (13.7%)</td><td>0.90 (0.40-2.01)</td></tr>
<tr><td>0.010-0.29</td><td>68 (5.1%)</td><td>12 (15.6%)</td><td>2.73 (1.51-4.92)</td></tr>
</table>
</td>
<td>2 The population from which the rule was derived included an appropriate spectrum of patients? yes
3 Was the rule validated in a different group of patients? yes
4 Were the predictor variables and the outcome evaluated in a blinded fashion? unclear BCW and PREP cohort; yes for PETRA dataset
5 Were the predictor variables and the outcome evaluated in the whole sample selected initially? yes
6 Are the statistical methods used to construct and validate the rule clearly described? yes
B. What are the results?</td>
</tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
Canadian Institutes of Health Research	(IQR), mmHg [a,b]See inclusion criteria **Inclusion criteria** BCW and the PREP study included only women with pre-eclampsia (a) sBP/dBP ≥140/90 mmHg (at least 1 component, measured ≥ 4h apart, after 20 with a) proteinuria (≥0.3g per day by 24h collection or ≥ 30mg mmol as measured by protein:creatinine ratio) or hyperuricaemia, or b) HELLP syndrome, or c) superimposed PE (rapidly increasing requirements for antihypertensive drugs, sBP> 170 mmHg or dBP> 120 mmHg, new proteinuria or new hyperuricaemia). The PETRA study included women with severe pre-eclampsia (defined as dBP ≥110 mmHg), HELLP syndrome, gestational hypertension, and fetal growth restriction. All cohorts included women before 34 weeks of gestation. **Exclusion criteria** Not reported		the value of 97% was imputed (this procedure is in line with the validation study developed by von Dadelszen). **Data analysis** Data from the 3 cohorts was merged into a single dataset. Discrimination was calculated using the area under the curve (AUC) ROC. Calibration was calculate d by assessing the slope of the linear predictor. Sensitivity analyses excluding the PETRA cohort were undertaken to account for differences in the study design and	≥0.30 | 68 (4.4%) | 44 (54.5%) | 23.4 (14.83-36.79) * percentages reported are as stated in the published report, not calculated by the NGA **Tool discrimination** **<u>AUC within 48 hours of admission (individual datasets)</u>** **BCW (N= 218)** AUC ROC (95% CI) =0.72 (0.59-0.86) Calibration slope (95% CI) = 0.31 (0.21-0.41) **PETRA (N=216)** AUC ROC (95% CI)= 0.97 (0.94-0.99) Calibration slope (95% CI) = 1.69 (1.39-1.99) **PREP (N=695)** AUC ROC (95% CI) = 0.73 (0.64-0.81) Calibration slope (95% CI) = 0.74 (0.63-0.86) **Combined dataset** Calibration slope (95% CI) = 0.68 (0.86-0.79) **<u>AUC ROC combined dataset</u>** **AUC ROC within 48 h of admission** AUC ROC (95% CI) 0.80 (0.75 - 0.86) **AUC ROC within 7 days of admission** AUC ROC (95% CI) 0.74 (0.70-0.79) **<u>Sensitivity analyses (prognostic accuracy after exclusion of the PETRA cohort)</u>** **Within 48 h of admission** AUC ROC (95% CI) 0.74 (0.67-0.81) **Within 7 days of admission** AUC ROC (95% CI) 0.70 (0.65-0.75)	7 Can the performance of the rule be calculated? yes 8 How precise was the estimate of the treatment effect? In the study it is mentioned that "recalibration of the model was also performed to account for differences between the development and validation cohort" (page 3) C. Will the results help locally? Are the results applicable to the scenario? 9 Would the prediction rule be reliable and the results interpretable if used for your patient? Yes (UK, Canada and Dutch population) 10 Is the rule acceptable in your case? Yes 11 Would the results of the rule modify your

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results	Comments
			definitions for PE in the PETRA cohort as compared to the BCW and PREP.		decision about the management of the patient or the information you can give to him/her? Yes **Indirectness** BCW cohort: 12.4% of women did not present with PE PETRA cohort: 43% of women did not present with PE PREP cohort: 1% of women did not present with PE **Other information** Note overlap with PETRA dataset (Thangaratinam 2017)
Full citation Waugh, Jason, Hooper, Richard, Lamb, Edmund, Robson, Stephen, Shennan, Andrew,	**Sample size** N=959 **Characteristics**	**Prognostic tool/test** Tests done in the urine sample:	**Sample selection** Women were identified through different	**Prognostic accuracy (sensitivity, specificity)** **Prognostic accuracy of the four index tests and the two 24-hour urine samples assessments to predict severe pre-eclampsia at pre-defined thresholds**	**Limitations** **Limitations assessed with the QUADAS-2 checklist**

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Milne, Fiona, Price, Christopher, Thangaratinam, Shakila, Berdunov, Vladislav, Bingham, Jenn, Spot protein-creatinine ratio and spot albumin-creatinine ratio in the assessment of pre-eclampsia: a diagnostic accuracy study with decision-analytic model-based economic evaluation and acceptability analysis, Health technology assessment (Winchester, England), 21, 1-90, 2017

Ref Id

776890

Country/ies where the study was carried out

UK

Aim of the study

To assess the ability of spot</td>
<td>
<table>
<tr><th></th><th>Women included in main analysis (n =959)</th></tr>
<tr><td>Age, years (median, IQR)</td><td>30 (26-34)</td></tr>
<tr><td>Gestational age (median)</td><td>37</td></tr>
<tr><td>Origin: UK (n, %)</td><td>706 (74)</td></tr>
<tr><td>Origin: Africa (n, %)</td><td>59 (6)</td></tr>
<tr><td>Origin: Europe (n, %)</td><td>88 (9)</td></tr>
<tr><td>Origin: other (n, %)</td><td>106 (11)</td></tr>
<tr><td>With severe PE[a]</td><td>417 (43)</td></tr>
<tr><td>Without severe PE</td><td>542(57)</td></tr>
<tr><td>sBP mmHg (median, IQR)</td><td>145 (140-152)</td></tr>
<tr><td>dBP mmHg (median, IQR)</td><td>94 (90-100)</td></tr>
</table>
[a]sBP/dBP ≥160/110 after 20 weeks' gestation and significant proteinuria (≥ 300 from 24 hour urine collection using the central lab BZC assay)
</td>
<td>

"(1) sPCR test (conducted at the local laboratory),
(2) sPCR test (conducted at the local laboratory using the benzethonium chloride (BZC) assay),
(3) sPCR test (conducted at the central laboratory using the pyrogallol red (PGR) assay),
(4) sACR test (conducted at the central laboratory using an automated chemistry analyser)" (page 24, para 6)

Outcome(s)

Adverse maternal and fetal
</td>
<td>hospital settings, across 37 UK trusts, including maternity units, delivery suites or the outpatient setting.Those with confirmed hypertension and trace of proteinuria were detected through antenatal care and invited to participate in the study by the midwife. The revised sample calculations estimated that the recruitment target should be of 1790 women. This figure was based on the prevalence of severe pre-eclampsia of the first 500 participants recruited, and under the assumption that 14%</td>
<td>
<table>
<tr><th></th><th>Threshold (mg/mmol)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>Recruitment sample</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>sPCR (local lab)</td><td>30</td><td>85 (80-90)</td><td>40 (37-44)</td><td>1.43 (1.31-1.55)</td><td>0.36 (0.23-0.45)</td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>30</td><td>84 (78-89)</td><td>43 (40-47)</td><td>1.48 (1.35-1.61)</td><td>0.37 (0.25-0.50)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>30</td><td>85 (80-90)</td><td>39 (35-42)</td><td>1.39 (1.28-1.51)</td><td>0.38 (0.24-0.51)</td></tr>
<tr><td>sACR (central lab)</td><td>2</td><td>97 (93-99)</td><td>16 (14-19)</td><td>1.15 (1.11-1.20)</td><td>0.19 (0.04-0.35)</td></tr>
<tr><td>24-h sample</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>30</td><td>83 (77-88)</td><td>44 (41-48)</td><td>1.49 (1.36-1.63)</td><td>0.38 (0.25-0.50)</td></tr>
</table>
</td>
<td>Domain 1. Patient selection
A. Risk of bias
Was a consecutive or random sample of patients enrolled? yes
Was a case-control design avoided? yes
Did the study avoid inappropriate exclusions? yes
Could the selection of patients have introduced bias? no
B. Concerns regarding applicability
Is there a concern that the included patients do not match the review question? no

Domain 2. Index test(s)
A. Risk of bias
Were the index test results interpreted without knowledge of the results of</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>protein:creatinine ratio (sPCR) and spot albumin-creatinine ratio (sACR) in predicting severe pre-eclampsia as compared to 24 hour urine collection

Study dates

Feb 2013 - Nov 2015

Source of funding</td>
<td>Inclusion criteria

Pregnant women, of 16 years old and older, who were ≥20 weeks pregnant, with confirmed gestational hypertension (sBP/dBP ≥140/90) and with 1 trace or more of proteinuria.

Exclusion criteria

Women with pre-gestational diabetes or chronic hypertension and women with pre-existing renal disease (proteinuria before 20 weeks gestation)</td>
<td>outcomes (composite identified by Delphi survey of clinicians)</td>
<td>would have some missing data.

Data collection

Three different urine samples were taken from the study participants:

1. Urine sample for POC test.
2. Urine sample for 24 hours: women were given instructions as to when start and finish the collection
3. Urine sample immediately before birth

The laboratory was blinded to</td>
<td>
<table>
<tr><td>sPCR (using the PGR assay)</td><td>30</td><td>84 (78-89)</td><td>39 (3643)</td><td>1.38 (1.26-1.50)</td><td>0.41 (0.27-0.55)</td></tr>
<tr><td>POC-proteinuria dipstick test</td><td>1+</td><td>92 (88-96)</td><td>13 (11-16)</td><td>1.06 (1.01-1.12)</td><td>0.58 (0.28-0.89)</td></tr>
</table>
Prognostic accuracy of the four index tests and the two 24-hour urine samples assessments to predict adverse perinatal outcomes at pre-defined thresholds
<table>
<tr><th></th><th>Threshold (mg/mmol)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>LR+ (95% CI)</th><th>LR- (95% CI)</th></tr>
<tr><td>Recruitment sample</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>sPCR (local lab)</td><td>30</td><td>69 (56-80)</td><td>35 (32-39)</td><td>1.07 (0.89-1.26)</td><td>0.87 (0.53-1.20)</td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>30</td><td>77 (65-87)</td><td>39 (36-42)</td><td>1.26 (1.08-1.45)</td><td>0.58 (0.31-0.85)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>30</td><td>79 (67-88)</td><td>35 (32-38)</td><td>1.21 (1.04-1.38)</td><td>0.60 (0.31-0.90)</td></tr>
</table>
</td>
<td>the reference standard? yes
If a threshold was used, was it pre-specified? yes
Could the conduct or interpretation of the index test have introduced bias? no
B. Concerns regarding applicability
Is there concern that the index test, its conduct, or interpretation differ from the review question? no

<u>Domain 3. Reference standard</u>
A. Risk of bias
Is the reference standard likely to correctly classify the target condition? yes
Were the reference standard results interpreted without knowledge of the results of</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>clinical info and POC

Data analysis

ROC curves were plotted with different cut-offs using sPCR and sACR as index tests and the NICE definition of severe pre-eclampsia as the reference standard. AUC ROC curve, sensitivity and specificity LR+, LR- were summarised using pre-established cut-off points (30 mg/mmol for sPCR and 2ng/mml for sACR).</td>
<td>
<table>
<tr><td>sACR (central lab)</td><td>2</td><td>94 (84-98)</td><td>14 (12-16)</td><td>1.09 (1.01-1.16)</td><td>0.46 (0.02-0.91)</td></tr>
<tr><td>24-h sample</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>30</td><td>68 (55-79)</td><td>39 (36-42)</td><td>1.11 (0.91-1.31)</td><td>0.83 (0.52-1.13)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>30</td><td>71 (58-82)</td><td>35 (32-38)</td><td>1.09 (0.91-1.27)</td><td>0.83 (0.50-1.16</td></tr>
</table>
Model calibration

Not applicable

Tool discrimination

AUC ROC of the four index tests and the two 24-hour urine samples assessments to predict severe PE
<table>
<tr><td></td><td>AUC ROC

(95% CI)</td></tr>
<tr><td>Recruitment sample</td><td></td></tr>
<tr><td>sPCR (local lab)</td><td>0.70 (0.66 - 0.74)</td></tr>
</table>
</td>
<td>the index test? yes
Could the reference standard, its conduct, or its interpretation have introduced bias? no
B. Concerns regarding applicability
Is there concern that the target condition as defined by the reference standard does not match the review question? no

<u>Domain 4. Flow and timing</u>
Was there an appropriate interval between index test(s) and reference standard? yes
Did all patients received a reference standard? yes
Did patients receive the same reference standard? yes</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Number of participants and participant's characteristics</th><th>Prognostic tool</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>sPCR (using the BZC assay)</td><td>0.72 (0.68 - 0.76)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>0.71 (0.67-0.75)</td></tr>
<tr><td>sACR (central lab)</td><td>0.72 (0.68-0.76)</td></tr>
<tr><td>24-h sample</td><td></td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>0.74 (0.70-0.78)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>0.73 (0.69 - 0.77)</td></tr>
</table>
AUC ROC of the four index tests and the two 24-hour urine samples assessments to predict adverse perinatal outcome
<table>
<tr><td></td><td>AUC ROC (95% CI)</td></tr>
<tr><td>Recruitment sample</td><td></td></tr>
<tr><td>sPCR (local lab)</td><td>0.59 (0.51-0.67)</td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>0.64 (0.56-0.71)</td></tr>
<tr><td>sPCR (using the PGR assay)</td><td>0.63 (0.56-0.70)</td></tr>
<tr><td>sACR (central lab)</td><td>0.63 (0.56-0.71)</td></tr>
<tr><td>24-h sample</td><td></td></tr>
<tr><td>sPCR (using the BZC assay)</td><td>0.60 (0.52-0.68)</td></tr>
</table>
</td><td>Were all patients included in the analysis? yes
Could the patient flow have introduced bias? no

Indirectness

No indirectness

Other information</td></tr>
</table>

Study details	Number of participants and participant's characteristics	Prognostic tool	Methods	Outcomes and results		Comments
				sPCR (using the PGR assay)	0.60 (0.52-0.68)	