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Review article

Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review

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ABSTRACT

Background: The hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality and morbidity. The ability to predict these complications using simple tests could aid in management and improve outcomes. We aimed to systematically review studies that reported on potential predictors of adverse maternal outcomes among women with a hypertensive disorder of pregnancy.

Methods: We searched MEDLINE, Embase and CINAHL (inception – December 2016) for studies of predictors of severe maternal complications among women with a hypertensive disorder of pregnancy. Studies were selected in a two-stage process by two independent reviewers, excluding those reporting only on adverse fetal outcomes. We extracted data on study and test(s) characteristics and outcomes. Accuracy of prediction was assessed using sensitivity, specificity, likelihood ratios and area under the receiver operating curve (AUROC). Strong evidence of prediction was taken to be a positive likelihood ratio > 10 or a negative likelihood ratio < 0.1, and for multivariable models, an AUROC ≥0.70. Bivariate random effects models were used to summarise performance when possible.

Results: Of 32 studies included, 28 presented only model development and four examined external validation. Tests included symptoms and signs, laboratory tests and biomarkers. No single test was a strong independent predictor of outcome. The most promising prediction was with multivariable models, especially when oxygen saturation, or chest pain/dyspnea were included.

Conclusion: Future studies should investigate combinations of tests in multivariable models (rather than single predictors) to improve identification of women at high risk of adverse outcomes in the setting of the hypertensive disorders of pregnancy.

1. Introduction

The hypertensive disorders of pregnancy (HDPs) complicate about 3–10% of pregnancies [1–3]. They are one of the major contributors to maternal and fetal mortality and morbidity globally, with approximately 30,000 maternal and 500,000 perinatal deaths attributed to the HDPs annually [2,4]. Maternal complications include eclampsia, stroke, and damage to the hepatic and renal organs [2,5]. Predicting the onset of these complications could aid in timely interventions such as increased surveillance, treatment of symptoms, transfer to higher care facility and delivery when necessary, which could reduce morbidity and mortality from the HDPs [6,7].

Maternal risk factors used as criteria for severity classification by some international clinical practice guidelines do not accurately identify women at high risk of developing maternal complications [8–11]. While many studies have reported associations between certain biomarkers and adverse outcomes [12–15], only a few studies have examined the accuracy of these tests in predicting adverse maternal outcomes; in other words, the accuracy of discriminating women who do experience serious morbidities versus those who do not at the individual level. The tests reported in these studies range from single markers to multiple markers combined in prediction models. Prediction models are increasingly used in clinical practice since they have the advantage of combining various factors to potentially provide more

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accurate predictions [16]. Regardless of the prediction method used, there is a need for the results from these studies be summarised and compared to determine if they give meaningful and accurate information to assist clinicians in the management of the HDPs.

Several systematic reviews have assessed the predictive ability of individual variables such as uric acid, maternal symptoms, and liver function tests for maternal and fetal complications resulting specifically from pre-eclampsia [17–20]. To our knowledge, there have been no reviews assessing predictors for maternal complications resulting from all types of HDPs. This broader disease definition is important, as other HDPs still contribute substantially to the burden of the disease [2,10,21]. In addition, these reviews were conducted between 2006 and 2011 and since then the definition for HDPs, particularly pre-eclampsia, has evolved [3]. Furthermore, the studies included in these reviews solely assessed potential univariable predictors, thus the need to also review potential predictors combined in multivariable models. Therefore, we aimed to systematically review studies reporting the predictive ability, for both single and combined markers, of adverse maternal outcomes in women with HDPs.

2. Methods

2.1. Protocol and registration

A protocol for this review has been registered on PROSPERO (registration number: CRD42017054328).

2.2. Eligibility criteria

The population of interest was women with a HDP: pre-eclampsia, gestational hypertension, or chronic (pre-existing) hypertension, as defined by the study (with study definitions documented). The predictors of interest were any tests measured to predict adverse maternal outcomes from HDP. The adverse maternal outcomes considered were severe complications from the HDPs which had been agreed upon in a Delphi Consensus in the PIERS (Pre-eclampsia Integrated Estimates of RiSks study) (https://pre-empt.cfri.ca/monitoring/fullpiers) [7]; in addition, postpartum haemorrhage (PPH) and disseminated intravascular coagulation (DIC) were considered as these outcomes have been subsequently reported to be strongly linked with HDPs [21]. Detailed inclusion and exclusion criteria and full list of outcomes of interest are shown in Appendix S1.

2.3. Search and selection strategy

We searched MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO), and EBM Reviews (Ovid) Library databases from their inception to December 2016. We also searched Google Scholar and grey literature sources (such as University of British Columbia cIRcle, government websites, etc.) for other potential articles. Web of Science was used for citation tracking of review and eligible articles and the reference lists of studies selected for inclusion were scanned to capture any articles that were not identified through the electronic search. The search terms included both subject headings terms and key words related to the HDPs, with methodological filters to identify prognostic test studies for maternal complications (Appendix S2).

All retrieved articles were screened independently for eligibility by two reviewers (UVU and DAD), first by title and abstract and then, by reviewing the full articles. Final selections were compared and any conflicts resolved by discussion and/or by a third reviewer (BP).

The predictive measures used were sensitivity, specificity, likelihood ratios (LRs), and area under the receiver operating characteristic curve (AUROC). Studies that reported none of these predictive measures were included only if adequate data were provided to calculate these measures. We excluded studies reporting both maternal and fetal outcomes as a combined outcome except in cases where the test prediction performance for the maternal outcomes could be separated. We also excluded studies that included any of the HDPs as one of the outcomes.

2.4. Data extraction and assessment of study quality

For each eligible study, information on population characteristics, tests used as predictors, measures and accuracy of prediction were extracted by one reviewer (UVU) and reviewed by another (DAD). Methodological quality assessment of the included studies was carried out using the QUIPS (Quality in Prognostic Studies) tools [22], which have been validated and also used in similar studies [23]. The relevant study aspects that were scrutinized included methods of sampling and recruitment, adequate description of tests and outcomes, complete follow-up or handling of missing data explained, and sample size. In total, there were eight questions considered and one point was awarded for each assessment question that was met. In addition, studies reporting multivariable prediction models were assessed for internal and external validation. We considered studies with a total score of ≥ 7 as having a low risk of bias, 4–6 as medium risk of bias, and < 4 as high risk of bias.

2.5. Data synthesis

We constructed 2×2 tables for each included study cross-classifying test results and the occurrence of adverse maternal outcomes. Measures of predictive performance were sensitivity, specificity, LRs, predictive values, and AUROC. These measures were either retrieved directly from the studies or calculated from constructed from raw data and 2×2 tables. LRs were used to provide interpretations for clinical usefulness as a measure that is independent of disease prevalence; for positive LRs (LR+), an LR of 5–10 and > 10 were interpreted as having moderate and strong evidence to 'rule in' the disease respectively while for negative LRs (LR-), an LR of 0.1–0.2 and < 0.1 were interpreted as having moderate and strong evidence to 'rule out' the disease respectively [24]. An AUROC ≥ 0.70 was also considered to reflect good discriminatory ability for multivariable models [25]. Wherever possible, *meta*-analyses were conducted for similar tests predicting similar outcomes and having 3 or more 2×2 tables. Meta-analyses were performed using a bivariate *meta*-regression model, which uses a random effects approach, to calculate pooled estimates of the likelihood ratios [26–28].

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

3. Results

3.1. Literature search and identification results

Fig. 1 summarizes article identification and selection. Of 2137 articles retrieved, we included 32 primary articles. Important exclusions presented an outcome that either included but were not restricted to women with a HDP (N = 6), presented combined maternal and fetal outcomes (N = 12), or studies for which a $2 * 2$ table could not be constructed in order to calculate the diagnostic tests characteristics of interest (N = 3) (see Appendix S3 for excluded references).

3.2. Characteristics of included studies

Characteristics of the included studies are presented in Appendix S4. In brief, included articles were published between 1988 and 2017. Eleven were multicentre and 21 from single centres. Most studies (30/32) were cohort in design, usually prospective (24/30); one was a randomized trial and another was a case-control study. The countries where data were collected included Australia (N = 8), the United Kingdom (N = 8), Canada (N = 7), New Zealand (N = 7), USA (N = 7),

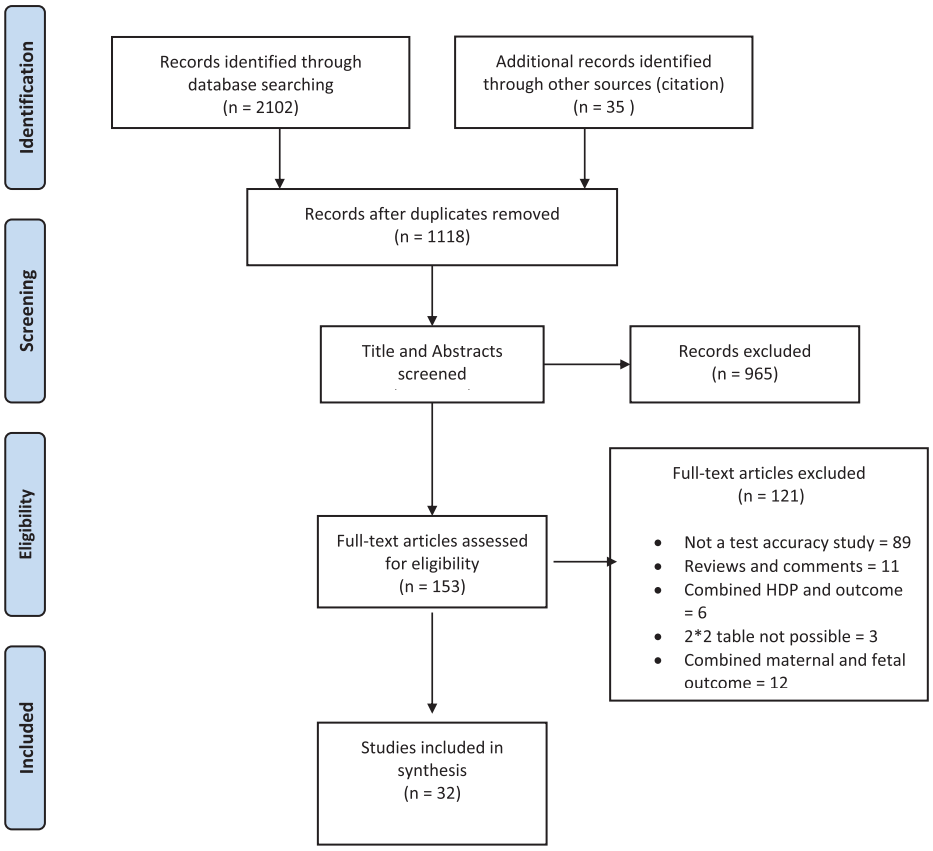

Fig. 1. PRISMA flow diagram showing study selection process.

South 4652010-753745Africa (N = 5), India (N = 3), The Netherlands (N = 2), Pakistan (N = 2), and one each of Iran, Spain, Tunisia, Turkey, Uganda, Mexico and Brazil.

In total, the number of independent women in the included studies was 9360, with a mean or median gestational age at admission or recruitment ranging from 23 weeks to 36 weeks. The mean maternal age ranged from 23 to 35 years old, and 13% to 89% were nulliparous.

All included studies were published in English except for one study that was in French. Four studies presented external validation of a study.

3.3. Definition of HDPs

Four studies included women diagnosed with chronic hypertension; four studies also included gestational hypertension while the remaining studies reported solely on women with pre-eclampsia (including HELLP syndrome) or/and superimposed pre-eclampsia. Chronic hypertension was defined as high blood pressure (≥140/90 mmHg) before pregnancy or at < 20 weeks gestation, and gestational hypertension as high blood pressure at ≥20 weeks gestation across all the studies; however, the definition of pre-eclampsia varied by the reference guideline used: the International Society for the Study of Hypertension in Pregnancy (ISSHP) (N = 9) [29], American Congress of Obstetricians and Gynecologists (ACOG) (N = 8) [30], National Institute for Health and Clinical Excellence (NICE) (N = 1) [9], Society of Obstetricians and Gynaecologists of Canada (SOGC) (N = 13) [3], or National High Blood Pressure Education Program (NHBPEP) (N = 1) [31] guidelines.. Some studies also specifically mentioned the severity of the HDP such as severe pre-eclampsia, [32–38] early-onset pre-eclampsia [33,38], or mild chronic hypertension [33] (Appendix Table S4).

3.4. Quality of studies

The quality of the included studies is summarised in Fig. 2 and Appendix S5. The studies scored well with respect to adequacy of population selection description, appropriateness of the patient spectrum/representativeness, and adequacy of test and outcome descriptions. However, of the 32 studies, only 14 mentioned complete follow up or explained withdrawals, 11 reported on handling of missing data, six reported sample size calculations, and two of five multivariable model studies reported both internal and external validation; all four external validation studies were classified as having a medium to high risk of bias. As a result, only eight studies were ranked as being at low risk of bias, 22 at medium risk, and two at high risk.

3.5. Predictors, outcomes and data synthesis

The predictors reported in the studies included demographics and pregnancy characteristics (e.g., gestational age), maternal signs and symptoms of pre-eclampsia [including oxygen saturation (SpO_2)], urinary protein excretion, laboratory abnormalities associated with pre-eclampsia, and/or biomarkers (Table 1).

The prevalence of adverse maternal outcomes ranged from 1.1% to 34.2%. Nine studies reported on single outcomes, most commonly eclampsia (N = 6), and placental abruption (N = 6). Most studies (23/32) reported on composite outcomes; these usually included the common single outcomes as well as thrombocytopenia, PPH, ascites and hepatic rupture.

The 32 studies resulted in 74 2 × 2 tables. Table 1 presents the sensitivities, specificities, likelihood ratios, and AUROCs for the predictor variables. We were unable to perform *meta*-analysis on the majority of predictors evaluated. The only predictor meeting our *a priori* criteria for *meta*-analysis, specifically having 3 published reports of effect using a similar outcome type, was the sFlt1/PlGF ratio for the prediction of composite maternal outcomes.

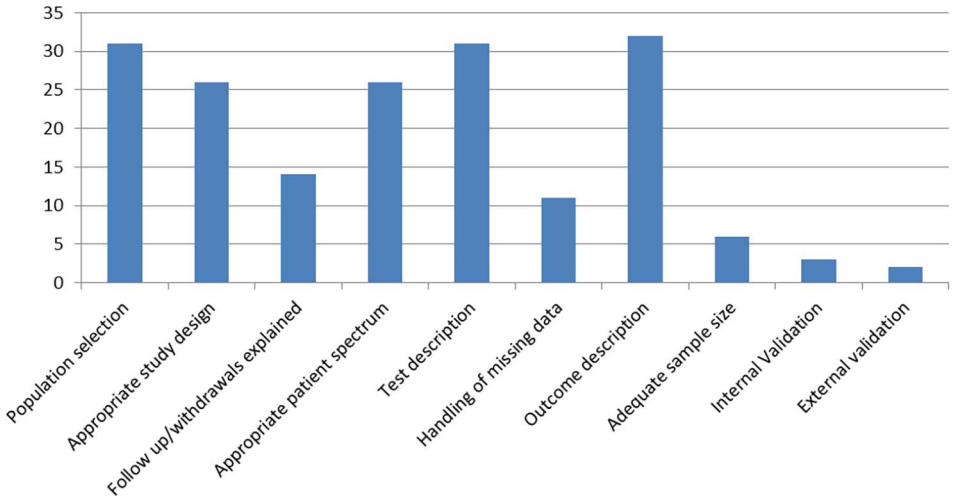

Fig. 2. Quality assessment of the included studies.

3.6. Univariable predictors

3.6.1. Signs and symptoms

In the univariable analyses, the maternal symptoms [39–42] evaluated were: headache (N = 3 studies), visual disturbance (N = 3), nausea or vomiting (N = 2), right upper quadrant pain or epigastric pain (N = 2), chest pain or dyspnoea (N = 2), abdominal pain and vaginal bleeding (N = 1), and hyperreflexia (defined as "vivid" deep tendon reflexes) or "non-specific viral symptoms" (not defined) (N = 1 study each). The signs evaluated were oxygen saturation (N = 1), and BP [N = 3] [33,35,40].

Only non-specific viral symptoms had moderate LR + for ruling in composite adverse maternal outcomes [39] while headache, visual symptoms and hyperreflexia each had moderate LRs (-) for ruling out eclampsia (LRs between 0.1 and 0.2) [40]. Non-specific viral symptoms and oxygen saturation of < 93% also had reported AUROCs of ≥0.7 suggesting good discriminatory ability for the prediction of composite adverse maternal outcomes. The usefulness of each of these symptoms was demonstrated in only one study.

3.6.2. Blood pressure

One of the signs evaluated was blood pressure, which was assessed in three studies [33,35,40] as systolic (N = 2), diastolic (N = 1), or mean arterial pressure (MAP, N = 1). The outcomes being predicted in these studies were eclampsia and placental abruption, for women with either pre-eclampsia or mild chronic hypertension. The cut-off for SBP evaluated were > 140 and ≥160 mmHg [33,40] while the cut-off for DBP was > 90 mmHg [33]; MAP was assessed at > 105 mmHg [35]. Although significant associations (p-values < 0.05) between blood pressure and adverse outcomes were presented in these studies, none of them showed a clinically useful measure for blood pressure as a prognostic test for adverse maternal outcomes.

3.6.3. Proteinuria

Proteinuria was assessed in six studies [36,37,40,43–45], using measurements of 24 h urinary protein excretion (N = 5), spot protein/creatinine ratio (N = 1), spot albumin/creatinine ratio (N = 1) and/or urinary dipstick testing (N = 3).

Only the study by Bouzari et al. [43] reported a moderate LR- for ruling out placental abruption using 24-h urine proteinuria, at a cut-off of 1750 mg [LR- of 0.1 (95% CI: 0.0–0.6)] with an AUROC of 0.78. No other study reported a clinically useful measure for ruling in or out adverse maternal outcomes using proteinuria testing.

3.6.4. Laboratory tests

The laboratory tests assessed were: platelet count (N = 4 studies) [35,39,46,47], serum creatinine (N = 1) [40], serum uric acid (N = 3) [40,48,49], international normalized ratio (INR, N = 1) [32], aspartate transaminase (AST, N = 4) [32,39,40,50], alanine transaminase (ALT, N = 2) [32,39], lactate dehydrogenase (LDH, N = 2) [32,39], serum albumin [32] and total bilirubin [32] (N = 1 each).

None of the laboratory tests had a useful LR+ to rule in adverse maternal outcomes. Only serum uric acid had a moderate LR- for ruling out eclampsia in one study (LR- of 0.1 (95% CIs: 0–0.9) [49]. However, AST, ALT, and LDH were reported to have good discriminatory abilities, with AUROCs of > 0.70 for prediction of adverse maternal outcome in the study by Kozic et al. [32]

3.6.5. Biomarkers

Placental growth factor (PlGF) only (N = 1 study) [51], soluble fms-like tyrosine kinase-1 (sFlt1) to PlGF ratio (N = 4) [52–55], and Neutrophil Gelatinase-Associated Lipocalin (NGAL, N = 1) [34] were evaluated as predictors. The study on PlGF alone was reporting on the prediction of PPH while the studies on sFlt1:PlGF ratio and NGAL were evaluating the prediction of composite adverse maternal outcomes. None of these biomarkers were reported to have clinically useful measures to either rule in or rule out adverse maternal outcomes. The *meta*-analysis for the sFlt1: PlGF ratio for predicting composite outcomes demonstrated poor pooled LRs:- LR + 1.7 (95% CIs: 1.2–2.0)] and LR- of 0.6 (95% CIs: 0.5–0.8) (tau^2 for heterogeneity = 0).

3.7. Multivariable predictors

Six studies evaluated a combination of multiple variables to predict a composite of adverse maternal outcomes [6,42,56–58]. Four of these multivariable studies were part of the PIERS studies: the fullPIERS model [7], miniPIERS model [6], extended miniPIERS model with SpO_2 [56], and a combined cardiorespiratory symptom model by Millman et al. [42] for the prediction of the PIERS composite outcome; the outcomes in the two other studies by Chan et al. [57] and Girling et al. [58] also included some components of the PIERS outcomes such as renal failure, thrombocytopenia, liver disease and pulmonary oedema. The miniPIERS model [6], and extended miniPIERS model with SpO_2 [56],were the only multivariable models that included women with all HDPs, while the others were for women with (super-imposed) pre-eclampsia. The most commonly used predictors in these models were chest pain and dyspnoea (N = 4 models), oxygen saturation and gestational age (N = 3), and AST (N = 2). Three of the multivariable models (fullPIERS model [7], miniPIERS model [6], and extended miniPIERS model with SpO_2 [56]) reported moderate to high LR + for ruling in adverse maternal outcomes (LR + of 5 and above) and four of them (models by Millman, fullPIERS model [7], miniPIERS model [6],

Table 1
Accuracy of tests in the prediction of adverse maternal outcomes in women with HDP, $N = 32$ studies.

UNIVARIABLE TESTS, N = 24 studies								
Author, Year	Test / cut-off	Outcome	Total (outcome rate %)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	AUROC (95% CI)
Signs and/or symptoms								
Aziz et al. 2011	Headache	Composite	74 (27%)	30.0 (11.9–54.3)	46.3 (32.6–60.4)	0.6 (0.3–1.1)	1.5 (1.0–2.3)	0.40 (0.20–0.50)
Ben Salem et al. 2003	Headache	Eclampsia	120 (34.2%)	97.6 (85.6–99.9)	26.6 (17.6–37.9)	1.3 (1.2–1.5)	0.1 (0–0.7)	–
Yen et al. 2011	Headache	PIERS Composite	2020 (7.1%)	–	–	–	–	0.535 (0.47–0.58)
Aziz et al. 2011	Vomiting	Composite	74 (27%)	10.0 (1.2–31.7)	77.9 (64.4–88.0)	0.5 (0.1–1.8)	1.2 (0.9–1.4)	0.40 (0.30–0.50)
Yen et al. 2011	Nausea/vomiting	PIERS Composite	2020 (7.1%)	–	–	–	–	0.54 (0.48–0.60)
Ben Salem et al. 2003	Visual symptoms	Eclampsia	120 (34.2%)	85.4 (70.1–93.9)	65.8 (54.2–75.9)	2.5 (1.8–3.5)	0.2 (0.1–0.5)	–
Yen et al. 2011	Visual symptoms	PIERS Composite	2020 (7.1%)	–	–	–	–	0.50 (0.45–0.56)
Yen et al. 2011	Abdominal pain or vaginal bleeding	PIERS Composite	2020 (7.1%)	–	–	–	–	0.57 (0.47–0.67)
Aziz et al. 2011	Epigastric pain	Composite	74 (27%)	10.0 (1.2–31.7)	70.4 (56.4–82.0)	0.3 (0.1–1.3)	1.3 (1.0–1.6)	0.4 (0.3–0.5)
Yen et al. 2011	RUQ or epigastric pain	PIERS Composite	2020 (7.1%)	–	–	–	–	0.605 (0.545–0.664)
Millman et al. 2011	Chest pain and/or dyspnoea	PIERS Composite	1534 (6.1%)	–	–	–	–	0.59 (0.52–0.65)
Millman et al. 2011	Chest pain and/or dyspnoea	Non-respiratory PIERS Composite	1534 (4.4%)	–	–	–	–	0.53 (0.45–0.60)
Yen et al. 2011	Chest pain or dyspnoea	PIERS Composite	2020 (7.1%)	–	–	–	–	0.58 (0.52–0.64)
Millman et al. 2011	$SpO_2 < 93\%$	PIERS Composite	1534 (6.1%)	–	–	–	–	0.71 (0.65–0.77)
Millman et al. 2011	$SpO_2 < 93\%$	Non-respiratory PIERS Composite	1534 (4.4%)					0.64 (0.57–0.71)
Aziz et al. 2011	Non-specific viral symptoms	Composite	74 (27%)	65.0 (40.8–84.6)	87.0 (75.1–94.6)	5.0 (2.3–10.7)	0.4 (0.2–0.7)	0.80 (0.60–0.90)
Ben Salem et al. 2003	Vivid deep tendon reflexes	Eclampsia	120 (34.2%)	97.6 (85.6–99.9)	46.8 (35.6–58.3)	1.8 (1.5–2.3)	0.1 (0.0–0.4)	–
Blood pressure (BP)								
Ben Salem et al. 2003	sBP ≥160 mmHg	Eclampsia	120 (34.2%)	92.7 (79.0–98.1)	24.1 (15.4–35.2)	1.2 (1.0–1.4)	0.3 (0.1–1.0)	–
Ankumah et al. 2014	sBP and/or dBP > 140/90 mmHg	Placental abruption	759 (1.4%)	36.4 (12.4–68.4)	62.8 (59.2–66.3)	1.0 (0.4–2.1)	1.0 (0.6–1.9)	–
Witlin et al. 1999	MAP > 105 mmHg	Eclampsia	445 (9.0%)	92.5 (78.5–98.0)	3.2 (1.8–5.6)	1.0 (0.9–1.0)	2.3 (0.9–8.0)	–
Witlin et al. 1999	MAP > 105 mmHg	Placental abruption	445 (7.2%)	87.5 (70.1–95.9)	2.2 (1.1–4.2)	0.9 (0.8–1.0)	5.7 (1.9–17.8)	–
Proteinuria								
Ben Salem et al. 2003	Dipstick > 3+	Eclampsia	120 (34.2%)	85.3 (70.1–93.9)	53.2 (41.7–64.4)	1.8 (1.4–2.4)	0.3 (0.1–0.6)	–
Ben Salem et al. 2003	24 h urine > 3 g/d	Eclampsia	120 (34.2%)	36.6 (22.6–53.1)	91.1 (82.0–96.1)	4.1 (1.8–9.3)	0.7 (0.6–0.9)	–
Bouzari et al. 2014	24 h urine > 1.75 g/d	Placental abruption	289 (5.9%)	94.1 (69.2–99.7)	63.7 (57.5–69.3)	2.6 (2.1–3.1)	0.1 (0.0–0.6)	0.777
Gangaram et al. 2009[†]	Spot urine ACR ≥300 mg/g	Composite	155 (2.6%)	0	55.0 (46.7–63.0)	–	1.8 (1.8–1.8)	
Hall et al. 2002	24 h urine increased by ≥2 g	Placental abruption	74 (13.5%)	30.0 (8.1–64.6)	59.4 (46.4–71.2)	0.7 (0.3–2.0)	1.2 (0.8–1.8)	–
Hall et al. 2002	24 h urine increased by ≥2 g	Ascites	74 (10.8%)	62.5 (25.9–89.8)	63.6 50.8–74.9)	1.7 (0.9–3.2)	0.6 (0.2–1.5)	–
Hall et al. 2002	24 h urine increased by ≥2 g	Pulmonary edema[†]	74 (1.4%)	0 (0–94.5%)	60.3 (48.1–71.3)	–	1.7 (1.6–1.7)	
Hall et al. 2002	24 h urine increased by ≥2 g	Eclampsia[†]	74 (1.4%)	100 (5.5–100)	61.6 (49.5–72.6)	2.6 (1.9–3.5)	–	
Payne et al. 2011	Dipstick	PIERS Composite	2002 (5.3%)	–	–	–	–	0.55 (0.49–0.61)
Payne et al. 2011	Spot urine PRCR	PIERS Composite	2002 (5.3%)	–	–	–	–	0.48 (0.42–0.55)
Payne et al. 2011	24hr urine	PIERS Composite	2002 (5.3%)	–	–	–	–	0.55 (0.47–0.63)
Schiff et al. 1996	24 h urine increased by ≥2 g	Placental abruption	2002 (5.3%)	40 (7.3–83.0)	63.9 (50.6–75.5)	1.1 (0.4–3.4)	0.9 (0.5–2.0)	–
Laboratory tests								
Aziz et al. 2011 2011	Platelets ≤ 100 × 10^5/L	Composite	74 (27%)	70.0 (45.7–88.1)	20.4 (10.6–33.5)	0.9 (0.6–1.2)	1.5 (0.6–3.4)	0.40 (0.30–0.60)
Laskin et al. 2011	Platelets ≤ 100 × 10^9/L	PIERS Composite	1405 (10.8%)	15.8 (10.6–22.8)	92.2 (90.5–93.6)	2.0 (1.3–3.1)	0.9 (0.9–1.0)	–
Witlin et al. 1999	Platelets < 60,000/mm^3	Placental abruption	445 (7.2%)	37.5 (21.7–56.3)	85.0 (81.1–88.2)	2.5 (1.5–4.1)	0.7 (0.6–1.0)	–
Yucesoy et al. 2005	Platelets < 50,000/mm^3	Eclampsia	44 (29.5%)	38.5 (15.1–67.7)	64.5 (45.4–80.2)	1.1 (0.5–2.5)	1.0 (0.6–1.5)	–
Yucesoy et al. 2005	Platelets < 50,000/mm^3	Placenta abruption	44 (11.4%)	40.0 (7.3–83.0)	64.1 (47.1–78.3)	1.1 (0.4–3.5)	0.9 (0.4–2.0)	–
Yucesoy et al. 2005	Platelets < 50,000/mm^3	Disseminated intravascular coagulation	44 (18.2%)	75.0 (35.6–95.5)	72.2 (54.6–85.2)	2.7 (1.4–5.2)	0.3 (0.1–1.2)	–
Yucesoy et al. 2005	Platelets < 50,000/mm^3	Acute renal failure	44 (15.9%)	71.4 (30.3–94.9)	70.3 (52.8–83.6)	2.4 (1.2–4.8)	0.4 (0.1–1.3)	–
Yucesoy et al. 2005	Platelets < 50,000/mm^3	Maternal mortality	44 (9.1%)	25.0 (1.3–78.1)	62.5 (1.3–76.8)	0.7 (0.1–3.8)	1.2 (0.6–2.2)	–
Kozic et al. 2011	INR	PIERS Composite	2008 (5.1%)	–	–	–	–	0.65 (0.58–0.71)
Ben Salem et al. 2003	Creatinine > 100 μmol/L	Eclampsia	120 (34.2%)	39.0 (24.6–55.5)	81.0 (70.3–88.6)	2.1 (1.1–3.7)	0.8 (0.6–1.0)	–

(*continued on next page*)

Table 1 (*continued*)

UNIVARIABLE TESTS, N = 24 studies								
Author, Year	Test / cut-off	Outcome	Total (outcome rate %)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	AUROC (95% CI)
Ben Salem et al. 2003	Uric acid ≥350 μmol/L	Eclampsia	120 (34.2%)	82.9 (67.4–92.3)	65.8 (54.2–92.3)	2.4 (1.7–3.4)	0.3 (0.1–0.5)	–
Livingston et al. 2014	Uric acid > 345 μmol/L	PIERS Composite	1487 (13.3%)	80.2 (70.8–87.6)	28.2 (25.9–30.7)	1.1 (1.0–1.2)	0.7 (0.5–1.0)	0.62 (0.56–0.69)
Yassaee et al. 2003[†]	Uric acid ≥6 mg/dL	Maternal mortality[†]	103 (8.7%)	100 (62.9–100)	53.2 (42.6–63.4)	2.1 (1.7–2.7)	0	–
Yassaee et al. 2003[†]	Uric acid ≥6 mg/dL	Eclampsia	103 (12.6%)	92.3 (62.1–99.6)	54.4 (43.6–64.9)	2.0 (1.5–2.7)	0.1 (0–0.9)	–
Aziz et al. 2011	ALT ≥70 IU/L	Composite	74 (27%)	55.0 (31.5–76.9)	25.9 (15.0–39.7)	0.7 (0.5–1.1)	1.7 (0.9–3.4)	0.4 (0.3–0.5)
Kozic et al. 2011	ALT	PIERS Composite	2008 (5.1%)	–	–	–	–	0.73 (0.67–0.79)
Aziz et al. 2011	AST ≥70 IU/L	Composite	74 (27%)	60.0 (36.1–80.9)	42.6 (29.2–56.8)	1.1 (0.7–1.6)	0.9 (0.5–1.8)	0.50 (0.40–0.60)
Ben Salem et al. 2003	AST > 30 IU/L	Eclampsia	120 (34.2%)	63.4 (46.9–77.4)	70.9 (59.4–80.3)	2.2 (1.4–3.3)	0.5 (0.4–0.8)	–
Kozic et al. 2011	AST	PIERS Composite	2008 (5.1%)	–	–	–	–	0.73 (0.67–0.79)
Romero et al. 1988	AST 2SD above mean	Pulmonary edema	275 (1.1%)	66.7 (12.5–98.2)	79.4 (74.0–84.0)	3.2 (1.4–7.5)	0.4 (0.1–2.1)	–
Romero et al. 1988	AST 2SD above mean	Eclampsia	275 (2.5%)	71.4 (30.3–94.9)	80.2 (74.8–84.7)	3.6 (2.1–6.1)	0.4 (0.1–1.2)	–
Aziz et al. 2011	LDH ≥600 IU/L	Composite	74 (27%)	75.0 (50.9–91.3)	55.6 (41.4–61.9)	1.7 (1.1–2.5)	0.5 (0.2–1.0)	0.7 (0.6–0.8)
Kozic et al. 2011	LDH	PIERS Composite	2008 (5.1%)	–	–	–	–	0.74 (0.68–0.81)
Kozic et al. 2011	Serum albumin	PIERS Composite	2008 (5.1%)	–	–	–	–	0.63 (0.57–0.69)
Kozic et al. 2011	Total bilirubin	PIERS Composite	2008 (5.1%)	–	–	–	–	0.68 (0 61–0.74)
Biomarkers								
Ghosh et al. 2012	Serum PlGF < 122 pg/mL	Postpartum hemorrhage (PPH)	766 (8.7%)	73.1 (60.7–82.9)	76.7 (73.3–79.7)	3.14 (2.57–3.82)	0.35 (0.24–0.52)	–
Leaños-Miranda et al. 2013	Serum sFlt-1/PlGF ratio ≥871	Composite	501 (9.6%)	52.1 (37.4–66.5)	77.9 (73.8–81.6)	2.36 (1.71–3.26)	0.61 (0.46–0.83)	–
Palomaki et al. 2015	Serum Flt-1/PlGF ratio > 85	Composite	237 (8.9%)	61.9 (38.7–81.0)	69.4 (62.8–75.4)	2.0 (1.4–3.0)	0.5 (0.3–1.0)	–
Rana et al. 2013[†]	Serum Flt-1/PlGF ratio ≥85	Composite	97 (8.2%)	100 (59.7–100)	51.7 (40.9–62.3)	2.1 (1.7–2.6)	∞	–
Saleh et al. 2016[†]	Serum Flt-1/PlGF ratio ≥85	Composite	62 (9.7%)	100 (51.7–100)	10.7 (4.4–22.6)	1.1 (1.0–1.2)	–	–
Scazzochio et al. 2013	Maternal NGAL > 100 ng/mL	Composite	67 (17.9%)	41.7 (16.5–71.4)	65.5 (51.3–77.4)	1.2 (0.6–2.6)	0.9 (0.5–1.5)	–
MULTIVARIABLE TESTS, N = 6 studies								
Chan et al.[†] 2005	Spot urine PRCR > 500 and maternal age > 35 years	Composite	321 (34%)	10.2 (5.4–17.9)	100 (97.8–100)	–	0.9 (0.8–1.0)	0.67 (0.55–0.71)
Girling et al. 1997[†]	AST 30 U/L ALT 32 U/L Bilirubin 14 U/L GGT 41 U/L	Composite	35 (20%)	100 (56.1–100)	57.1 (37.4–75.0)	2.3 (1.5–3.6)	–	–
Millman et al. 2011	Chest pain and/or dyspnoea and SpO_2	PIERS Composite	1534 (6.1%)	–	–	–	–	0.73 (0.67–0.78)
Payne et al. 2014	miniPIERS model[ǂ] 25% predicted probability	PIERS Composite	2081 (12.5%)	41.4 (35.4–47.6)	91.9 (90.5–93.1)	5.1 (4.1–6.3)	0.6 (0.6–0.7)	0.79 (0.74–0.80)
Payne et al. 2015	miniPIERS model[ǂ] and SpO_2, 25% predicted probability	PIERS Composite	852 (17.3%)	49.6 (40.3–58.8)	91.5 (89.2–93.4)	5.9 (4.3–7.9)	0.6 (0.5–0.7)	0.81 (0.76–0.86)
von Dadelszen et al. 2011	GA, chest pain or dyspnea, SpO_2, platelet count, creatinine and AST; 30% predicted probability	PIERS Composite	2023 (5%)	44.9 (34.5–55.3)	98.4 (97.6–98.9)	26.5 (17.4–40.2)	0.6 (0.5–0.7)	0.88 (0.84–0.92)
EXTERNAL VALIDATION STUDIES, N = 4 studies								
Agrawal et al. 2015	30% predicted probability	PIERS composite	322 (18.3%)	25.0 (15.1–38.1)	95.4 (91.9–97.5)	17.5 (8.52–36.1)	0.8 (0.7–0.9)	–
Akkermans et al. 2014	30% predicted probability	PIERS composite	216 (14.8%)	81.3 (63.0–92.1)	98.4 (94.9–99.6)	49.8 (16.0–155.0)	0.2 (0.1–0.4)	0.97 (0.94–0.99)
Hadley et al. 2016[*]	–	PIERS composite	503 (12.3%)	–	–	–	–	0.68 (0.60–0.76
Ukah et al. 2015	30% predicted probability	PIERS composite	757 (14.0%)	45.0 (0.36–0.55)	92.4 (84.9–99.9)	5.9 (4.2–8.4)	0.2 (0.1–0.5)	0.77 (0.72–0.82)

ACR (albumin:creatinine ratio); AUROC (Area under the receiver operating characteristic curve); dBP (diastolic blood pressure); GA (gestational age); INR (international normalized ratio); LR+ (Positive likelihood ratio); LR- (Negative likelihood ratio); MAP (mean arterial pressure); NGAL (neutrophil gelatinase-associated lipocalin); PIERS (pre-eclampsia integrated estimate of risk); PRCR (protein:creatinine ratio); RUQ (Right upper quadrant pain); sBP (systolic blood pressure); SD (standard deviation); SpO_2 (oxygen saturation).

[†] Contains some zero cells.

* Abstract only.

[ǂ] MiniPIERS includes parity, gestational age, chest pain/dyspnea, headache or visual symptoms, vaginal bleeding with abdominal pain; sBP, and dipstick proteinuria.

extended miniPIERS model with SpO_2) reported AUROCs of ≥0.7; all of these were predicting PIERS adverse outcomes. The model with the highest AUROC was reported in the study by von Dadelszen et al. [7] (AUROC 0·88 (95% CI 0·84–0·92) and also had the highest LR + of 26.5 to strongly rule in composite adverse maternal outcomes. The multivariable model, called the fullPIERS model, included six variables: gestational age of disease onset, platelet count, serum creatinine, AST, chest pain or dyspnea and SpO_2. For details of the model variable coefficients, please see Appendix S6.

3.8. External validation

Four studies on external validation were included [38,59–61]. All assessed the fullPIERS model by von Dadelszen et al. [7] AUROCs were > 0.7 (N = 2 studies) [38,60] and 0.68 (95% CI 0·60–0·76) in the study by Hadley; AUROC was not reported in the study by Agrawal et al. Likelihood ratios were reported in only two studies and these studies reported moderate LRs (+) for ruling in adverse outcomes [38,59]. Although all four studies were assessing the validity of the fullPIERS model, there were substantial differences between the fullPIERS and external validation populations, such as disease spectrum, setting, and management (Table S4b). Due to these case-mix differences, we refrained from pooling the results of these studies.

4. Discussion

4.1. Main findings

Our systematic review included 32 studies of women with HDPs that explored the ability of various tests to predict adverse maternal outcomes. There was substantial heterogeneity in the characteristics of the populations included in these studies and the outcomes used. This heterogeneity likely contributed to the inconsistent results found for the predictive performance of the evaluated tests. Overall, the univariable predictors that had moderate performance as a rule in test were "non-specific viral symptoms" and 24hr urinary protein, and as rule-out tests were headache, visual symptoms, hyperreflexia, and serum uric acid. Non-specific viral symptoms, oxygen saturation < 93%, AST, ALT, and LDH were the only univariable tests that had good discrimination with a reported AUROC of ≥0.7. However, these tests were either assessed in only one study (e.g. hyperreflexia and "non-specific viral symptoms") or were evaluated in multiple studies but performed poorly in them. As such, individual tests were interpreted as lacking strong evidence of clinical usefulness. In addition, the definition of non-specific viral symptoms was not clearly stated in the study [39].

In our review, oxygen saturation showed the most promise as a prognostic test for the hypertensive mother in univariable and especially in multivariable models. Other tests to consider when combining variables in multivariable models include headache, visual symptoms, AST, chest pain or dyspnea and gestational age, based on their inclusion in well performing multivariable models, which had also been internally validated. However, the performance of the multivariable models may have been due to the presence of other possible good predictors in the models driving the effect (Appendix S6), thus, some of these tests (e.g. AST) may require further investigations as possible predictors for adverse maternal outcomes of HDPs [64].

The best performing multivariable model included gestational age, chest pain or dyspnoea, oxygen saturation, platelet count, creatinine and AST as predictors of composite maternal outcomes in women with pre-eclampsia and superimposed pre-eclampsia [7]. This model was externally assessed in four studies that were included in this review. Although three of these validation studies showed a good discriminatory performance (AUROC > 0.7), two of these studies were underpowered. In addition, there were case-mix differences between the studies and the development study which could have affected the model performance.

4.2. Comparison with literature and guidelines

Except for one study on predicting eclampsia, our findings are similar to the study by Thangaratinam et al. [17] which reported that proteinuria was a poor predictor of maternal complications in pre-eclampsia based on the pooled positive and negative LRs in their study. Another review by Moris et al. [20] concluded that there was insufficient evidence to recommend proteinuria as a prognostic test for the prognosis of adverse maternal outcomes in pre-eclampsia. Proteinuria is also not recommended as a test for the prediction of adverse maternal outcomes for women with HDPs by ACOG, AOM, and SOGC guidelines; however, the NICE guideline calls for large high quality prospective studies to determine the best methods of measurement and threshold for predicting adverse outcomes [9].

In a systematic review of maternal symptoms as predictors of adverse outcomes [19], epigastric pain and visual disturbance were reported to be the most useful predictors based on their AUROCs; however, this was not the case in our review for epigastric pain. Also, contrary to the findings in the review by Koopmans et al. [62] and Thangaratinam et al. [63] uric acid did not show any clinical usefulness in the prediction of maternal outcomes in our review except for eclampsia. Noteworthy is the difference between the inclusion criteria and outcomes of interest between these reviews and ours. In the reviews, HELLP syndrome was considered as an adverse outcome and was one of their most common outcomes; however, for our review, HELLP syndrome was one of our inclusion criteria for HDP because it has been recognised as part of the spectrum of pre-eclampsia rather than an outcome [30]. Therefore, it is possible that the performances of epigastric pain and uric acid in these reviews were related to women with HELLP rather than predictive of adverse maternal outcomes that measure end-organ failure.

A review by Thangaratinam et al. [8] reported that liver enzyme tests (AST, ALT and LDH) were moderate predictors of combined maternal and fetal complications in women with pre-eclampsia. Although, AST, ALT and LDH did not have any strong clinical utility in univariable analyses based on LRs, their AUROCs in the individual studies suggested good discrimination and may therefore be considered for further investigation. This is also in line with the NICE guideline which recommends that more studies for kidney and liver function, and coagulation for the prediction of adverse outcomes are needed [9].

4.3. Strengths and limitations

Our review is the first to review potential predictors of maternal complications among women with all types of HDPs. Including all HDPs improve the clinical applicability because it includes a broader population of women at risk and not all women initially present with pre-eclampsia at admission. We were able to systematically identify and collate the performance of possible predictors using updated definitions for HDPs and with no restrictions on language or year of publication. We ran our search terms again in July 2017 to ensure that we covered any recent eligible publications. Our review also included the use of multivariable models which have not been assessed in any previous review.

The majority of the included studies in this review were deemed to be of low or moderate quality. Many of the studies were underpowered and some of the multivariable models were not externally validated; thus the results from these studies may not be applicable in a different setting or population. However, we did not exclude these studies because we were interested in reviewing any tests with potential maternal prognostic value for HDPs and also due to sparse literature in the study area. The only articles not included were ones that did not meet the inclusion criteria for severe maternal outcomes; for example, we excluded a new prognostic study by Allotey et al. [65] which included preterm delivery are one of their composite maternal outcomes as we did thought that this qualified more as a perinatal than a maternal

outcome. The methodological issues in the included studies and the heterogeneity in population characteristics affect our ability to draw any strong conclusions in our review. The limited numbers of studies evaluating similar tests and outcomes also made it impossible to synthesize most of the predictors using *meta*-analyses.

5. Conclusion

Prediction of adverse maternal outcomes from the HDPs is key to optimal management, including timing of delivery and planning the most appropriate place of care [4,15]. Overall, the multivariable models performed better than the univariable tests. However, sufficiently-powered external validation studies using a similar population as the development studies are still required for most of these models. Our review highlights the need for better quality studies in prediction and supports the use of a combination of predictors for better chances of prediction of adverse maternal outcomes.

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Disclosures

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.preghy.2017.11.006.

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