Predicting adverse maternal outcomes in pre-eclampsia: the fullPIERS (Pre-eclampsia Integrated Estimate of RiSk) model – development and validation

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ABSTRACT

BACKGROUND

Pre-eclampsia is a leading cause of maternal deaths. These deaths primarily result from eclampsia, uncontrolled hypertension and/or systemic inflammation. The fullPIERS (Pre-eclampsia Integrated Estimate of RiSk) model was developed and validated for women with pre-eclampsia to identify their risk of life-ending, -altering, or -threatening complications within 48h of hospital admission with pre-eclampsia.

METHODS

We assessed the vulnerable organ systems of 2023 women with pre-eclampsia admitted to tertiary centres. The outcome of interest was maternal mortality or other serious complications of pre-eclampsia. Routinely reported and informative variables were included in stepwise backward elimination regression model to predict the adverse maternal outcome. Performance was assessed using area under the curve (AUC) statistics. Standard bootstrapping techniques were used to assess potential overfitting and performance was also assessed in 3 other relevant populations of women with a hypertensive disorder of pregnancy (HDP).

FINDINGS

Predictors of adverse maternal outcome included gestational age, chest pain/dyspnoea, oxygen saturation (SpO2), platelet count, creatinine, and aspartate transaminase. The fullPIERS model AUC was 0.88 [95%CI: 0.84, 0.92]. There was no significant overfitting. fullPIERS performed well (AUC >0.7) up to 7d after eligibility, and for the other HDP cohorts admitted to various levels and places of care.

INTERPRETATION

The fullPIERS model identifies women at increased risk of adverse outcomes up to 7d before complications arise and can thereby modify direct patient care (e.g., timing of delivery, place of care), improve the design of clinical trials, and inform biomedical investigations related to pre-eclampsia.

INTRODUCTION

Pre-eclampsia is more than proteinuric gestational hypertension alone, is a state of exaggerated systemic inflammation, and remains a leading direct cause of maternal morbidity and mortality worldwide (1). Reducing the burden of illness associated with pre-eclampsia (2) will address, in part, the aims of Millennium Development Goal 5 (3;4). In high income countries, this excess maternal morbidity and mortality relates to both uncontrolled hypertension and the pulmonary and hepatic consequences of systemic inflammation (5;6).

The only cure for pre-eclampsia is delivery. For pre-eclampsia arising remote from term, supportive and temporising measures ("expectant management") are used to improve perinatal outcomes. However, the magnitude of the maternal risks associated with expectant management is unclear (1). The perinatal benefits of expectant management near term are even less clear (1). Concerns around maternal risk have caused experts to hesitate in recommending expectant management either remote from, or near to, term (1). At term, maternal benefits derive from a policy of effecting delivery (7).

The best method of risk assessment in pre-eclampsia pregnancies being managed expectantly or during induction of labour remains unclear (8). Currently, assessment is directed by expert opinion-based guidelines that perform poorly when operationalised (9). A validated tool that allows real-time maternal risk stratification is needed to guide care (e.g., expectant management both remote from term or during an induction of labour). Previous modelling was unsuccessful in predicting adverse outcomes occurring at any time after admission with pre-eclampsia (10). However, being able to predict adverse maternal outcomes within a time frame that would inform and guide clinical care (e.g., 48 hours - 7 days) would optimise both the management of women admitted with pre-eclampsia and resource utilisation.

Standardising antenatal and postnatal assessment and surveillance of pre-eclampsia with protocols that recognise the systemic inflammatory model of pre-eclampsia (1) has been associated with reduced maternal morbidity (11). Using this standardised approach, we have developed and validated a pre-eclampsia outcome prediction model, the fullPIERS (Pre-eclampsia Integrated Estimate of RiSk) model. fullPIERS is designed for use in well-resourced settings.

METHODS

fullPIERS was developed and internally validated in a prospective, multicentre study of women who fulfilled a research definition of pre-eclampsia, and who were admitted to participating academic tertiary obstetric centres in Canada, New Zealand, Australia, and the United Kingdom (Appendix). All centres had a general policy of expectant management remote from term to maximise temporal exposure of the cohort to the natural history of the condition.

PIERS was conducted as either a continuous quality improvement (n=4 sites) or a consented research (n=4 sites initially, eventually only one) project depending on local ethics committee requirements. Inpatient women with either suspected or confirmed pre-eclampsia received care that included predetermined guidelines for initial assessment and ongoing surveillance (for details see (11;12)).

Women were included if admitted with pre-eclampsia, or having developed pre-eclampsia following admission. Pre-eclampsia was defined as: i) blood pressure (BP) ≥140/90mmHg (at least one component, twice, ≥4 hours apart, after 20 weeks) and either proteinuria (of ≥2+ by dipstick, ≥0.3g/d by 24 hour collection, or ≥30mg/mmol by urinary protein:creatinine ratio) or hyperuricaemia (greater than local upper limit of local non-pregnancy normal range) (5), ii) HELLP syndrome even in the absence of hypertension or proteinuria (13), or iii) superimposed pre-

eclampsia (rapidly increasing requirements for antihypertensives, systolic BP (sBP) >170mmHg or diastolic BP (dBP) >120mmHg, new proteinuria, or new hyperuricaemia). This definition, although differing from many international definitions (14) reflects both the variable and multisystem nature of pre-eclampsia at presentation and the spectrum of women seen in clinical practice (15). Women were excluded if either admitted in spontaneous labour or having achieved any component of the maternal outcome prior to either fulfilling eligibility criteria or collection of predictor data.

The candidate maternal and fetal predictor variables chosen were those that were predictive, available, measurable, frequent, and reliable (Table 1) (20). Symptoms, although difficult to quantify, were included for face validity due to their use to classify severe disease (12;14), and potential predictive performance in pre-eclampsia (16). While some of the candidate predictors were associated with components of the outcome (e.g. the predictor of creatinine and the outcome component of renal insufficiency or failure) they were retained for consideration in the model because we were interested in predicting the development of adverse events *in the future* based on information available *at the time of admission*. As our study criteria specifically excluded women who had achieved any component of the outcome, all women included in the modelling had the potential to remain free of adverse outcomes.

The components of the combined adverse maternal outcome (Table 3) were: maternal mortality or one/more serious central nervous system, cardiorespiratory, hepatic, renal, or haematological morbidities. This outcome was developed by iterative Delphi consensus (17;18). A single case of Bell's palsy and two cases of severe ascites were included as the onset and resolution were temporally related to the clinical course of the pre-eclampsia.

Data quality and missing data

Customised case report forms and database were utilised by all participating sites. Data were collected from the patient medical record(s) and predictor variables were collected within 48 hours of eligibility. If absent, the 'last observation carried forward' method was used by which any preceding observation performed within two weeks of admission was considered current unless replaced by a more recent value. While not universally supported (19), this is consistent with clinical practice as clinicians do not re-evaluate what they believe has not changed, and is conservative in underestimating the effect of any given variable in modelling. For example, 24 hour urine proteinuria of 0.6g/d measured 4 days previously could be carried forward to the day of delivery for the purpose of the analyses.

Lead-time bias: We selected either the date/time of admission with pre-eclampsia or the post-admission development of pre-eclampsia (which ever was later) to standardise for the level of clinical concern justifying admission and the concurrent presence of pre-eclampsia.

Missing values and misclassification: We undertook abstractor training, checked the data collection methods, monitored data logic, and performed random re-abstraction of charts (randomly in 102 (5%) cases and for all adverse maternal or perinatal outcomes were suspected or confirmed). Cases of uncertainty (n=13 [1.0%]) were resolved by iterative discussion between PvD, LAM, BP, and the relevant site investigator.

One highly informative variable, oxygen saturation by pulse oximetry (SpO_2), was prone to missing data before all participating centres achieved regular pulse oximetry. Missing pulse oximetry data points were assigned a value, 97%, to lie within the normal range (95-100%), assuming that non-use of oximetry was associated with better clinical state, and biasing analyses to underestimate the impact of falling SpO_2 to identify increasing maternal risk (20).

Study size

In response to a falling incidence of adverse outcomes observed in all centres, and previously reported in one site (11), an early decision was made to assess the model iteratively once 200 women were entered into the database, and monthly thereafter, so that non-informative variables (p>0.2) could be abandoned. Study size was based on the following calculation:

N = (n x15)/I = 1731women (21-23)

where N is the sample size, n = number of informative, non-convergent variables to be considered in the model (= 15), and I = incidence of the combined adverse outcome (0.13 at any time after eligibility).

Quantitative variables

For lactate dehydrogenase (LDH), values were corrected to the midpoint of the relevant laboratory's normal range to standardise across sites. For women who developed de novo postpartum pre-eclampsia, gestational age was defined as the gestational age at delivery.

Statistical methods

Only candidate predictor variables available for ≥80% of the women were included in modelling, as, routine use is a prerequisite for day-to-day clinical utility. Consequently, we considered 54 independent variables collected over the first 48 hours to predict the combined adverse maternal outcome occurring within the first 48 hours after eligibility (Table 1). The 'worst value' (e.g., highest sBP or lowest platelet count) measured prior to outcome occurrence or completion of the 48 hour time period, whichever was first, was used. A 48 hour time period was chosen because it would improve perinatal outcomes by giving time for steroid administration remote from term and it would inform decisions about the place of delivery/in utero transfer from level 1 and 2 units.

The relationship between each predictor variable and the combined adverse maternal outcome was assessed by univariable logistic regression. Continuous variables were modelled using quadratic terms, and categorised based on risk thresholds to evaluate the potential for non-linearity. Variables associated with the outcome (p<0.1) were included in the initial multivariable regression model along with variables deemed important, a priori, on clinical grounds. To avoid colinearity, the correlation between variables was assessed and the more clinically relevant variable of a pair of highly correlated variables included. Clinical expectations regarding possible interactions were specifically examined.

Stepwise backward elimination was used to build the parsimonious final model. The AUC of the receiver-operating characteristics curve (ROC) was calculated using standard methods (24). The final model was internally validated using Efron's enhanced bootstrap method (details available [www.piers.cfri.ca]) (22;25;26). Such a bootstrap validation is recommended over alternative validation approaches (e.g., splitting data into training and test datasets) because it maximises statistical efficiency and directly validates the final model (22).

Performance was assessed using calibration ability, stratification capacity, and classification accuracy (27).

Model performance in related clinical contexts

In addition, we prospectively assessed the predictive ability of fullPIERS in a broader range of women with pregnancy hypertension. First, women admitted with pre-eclampsia to five level I/II obstetric centres in British Columbia (n=4) and Western Australia (n=1). Second, women admitted to BC Women's with either pre-existing or gestational hypertension (17). Third, women with pre-eclampsia admitted to three academic centres in low and middle income countries (Fiji, South Africa, and Uganda).

RESULTS

From 1 September 2003 - 31 January 2010, data for 2023 women (2221 fetuses) were entered into the fullPIERS database from eight international sites (Table 2). There were 261 (12.9 %) combined adverse maternal outcomes at any time following eligibility. Compared with the women who did not develop adverse outcomes, the women who developed adverse outcomes were of lower gestational age at eligibility, and less likely to be either parous, to smoke during the pregnancy, or to be eligible on the basis of hyperuricaemia. They were more likely to develop HELLP syndrome, and to receive both antihypertensives and/or antenatal corticosteroids (for either fetal lung maturation or HELLP). Maternal blood pressure indices, dipstick proteinuria, and AST were higher in women who developed adverse outcomes, while platelet counts were lower. The eligibility-to-delivery interval did not vary between groups, except among women eligible at <34wk. Such women who developed outcomes had briefer eligibility-to-delivery intervals. Women who developed adverse outcomes were more likely to receive $MgSO_4$ during their clinical course (62% vs 30%) and to deliver babies earlier and of lower birth weight. Perinatal and infant mortality did not differ significantly between groups.

The median eligibility-to-outcome interval was 4 days (Table 3). These adverse outcomes occurred antenatally in 6.0% of women, intrapartum in 3.4%, and postnatally in 3.5%. The most common outcomes reached were pulmonary oedema (63 (3%)) or blood product transfusion (85 (4%)).

Having excluded some historically important variables after univariable modelling, we modelled using variables with possible explanatory power (Table 4; full list of tested variables and univariable relations with the combined adverse outcome available [www.piers.cfri.ca]).

Developed with data from 1935 women during the first 48 hours after eligibility, fullPIERS, predicts adverse maternal outcomes within 48 hours of eligibility (AUC ROC 0.88 [95% CI 0.84, 0.92])

(Figure 1). The final fullPIERS equation was: $\text{logit}(pi) = 2.68 + -5.41 \times 10^{-2}$ (gestational age (eligibility)) $+ 1.23$ (chest pain/dyspnoea) $+ -2.71 \times 10^{-2}$ (creatinine) $+ 2.07 \times 10^{-1}$ (platelets) $+ 4.00 \times 10^{-5}$ (platelets^2) $+ 1.01 \times 10^{-2}$ (AST) $+ -3.05 \times 10^{-6}$ (AST^2) $+ 2.50 \times 10^{-4}$ (creatinine x platelet) $+ -6.99 \times 10^{-5}$ (platelet x AST) $+ -2.56 \times 10^{-3}$ (platelet x SpO$_2$). On-line fullPIERS propability calculator available (www.piers.cfri.ca). After 200 cycles of bootstrapping the average optimism was 0.02 [95% CI -0.03, 0.06,] suggesting minimal overfitting.

fullPIERS successfully stratified the population into clinically relevant risk categories (Table 5), with a large percentage (65%) of women classified into a low risk group (predicted probability of <0.025), and 4% of women into the highest risk group (predicted probability ≥0.30). The majority (60%) of women with a predicted probability ≥0.30 had an adverse outcome. Conversely, the adverse outcome only occurred in 1.1% ((11+3)/(671+586)) of women with a predicted probability of <0.025, and in only 0.4% of women with a predicted probability <0.01 (negative predictive value:, 99.6%).

The classification accuracy of fullPIERS was good. For example, using a predicted probability of 0.05 as a threshold, fullPIERS identified >75% of women who subsequently had events as being 'high risk,' while only 16% of the population was incorrectly identified as being 'high risk.' In practice, the predicted probability would best be used as a continuous value, "probability of an adverse outcome," to customise management.

 fullPIERS also performed well predicting adverse maternal outcome from 2 to 7 days following eligibility (i.e., AUC ROC >0.7; Figure 2).

These AUC and risk stratification findings were replicated for women admitted with pre-eclampsia prior to 34^{+0} weeks (AUC ROC 0.85 [95% CI 0.79, 0.92]) and for primigravid women admitted with

pre-eclampsia defined solely as proteinuric gestational hypertension (AUC ROC 0.87 [95% CI 0.82, 0.93]) (tables available [www.piers.cfri.ca]).

Preliminary assessments of fullPIERS in a broader range of women with pregnancy hypertension confirmed its performance (i.e., AUC ROC >0.7). The AUC ROC for fullPIERS was 0.77 [95% CI 0.45, 1.00], 0.85 [95% CI 0.65, 1.00], and 0.80 [95% CI 0.66, 0.94] for women admitted to level I/II centres with pre-eclampsia (n=6 outcomes/139 women), one tertiary centre (level III) with a non-pre-eclampsia HDP (n=4/224), and LMIC centres with pre-eclampsia (n=17/145), respectively.

DISCUSSION

Key results

We carried out a prospective, international study to develop and validate a maternal outcome prediction model for women admitted to tertiary units with pre-eclampsia. Among women admitted to hospital with pre-eclampsia, fullPIERS predicted adverse maternal outcomes occurring within the first 48 hour following eligibility [AUC ROC 0.88]. The model included the following predictors: gestational age at eligibility, chest pain/dyspnoea, SpO_2, platelet count, serum creatinine, and AST. PIERS modelling identified SpO_2, a clinical variable that has not been included traditionally in lists of adverse features. All components of the model fulfilled the requirement for clinical face validity, in view of the particular risks of pre-eclampsia (5), especially remote from term (1). fullPIERS attained similar stratification capacity, calibration ability, and classification accuracy as established cardiovascular, adult critical care, and neonatal critical care scores (28-30). fullPIERS should assist decisions around delivery, especially at gestational ages when expectant management has important perinatal advantages (1).

Limitations

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There are several limitations to this study.

First, to attain generalizability, our population included women who fulfilled a broad definition of pre-eclampsia, including women without significant proteinuria. Restricting the analysis to the tightest possible research definition (primigravid women with proteinuric hypertension) did not meaningfully change the AUC ROC.

Second, while components of our combined adverse maternal outcome are not of equal value, all components were assessed and validated by iterative Delphi consensus (17;18) and are independently worthy of avoidance.

Third, the study was performed solely in high income country tertiary obstetric units and in women fulfilling our research definition of pre-eclampsia. We have begun to address these limitations through initial assessments of the predictive ability of fullPIERS across the HDP spectrum and are developing and validating a specific, symptom- and sign-based, version of PIERS (miniPIERS) for use in rural and remote settings in high, middle, and low income countries..

A fourth limitation was the relatively small sample size, especially when considering the low rate of adverse maternal outcomes. This may be particularly important with uncommon outcomes such as eclampsia, as headache and/or visual symptoms did not contribute independently to fullPIERS. Therefore, our bootstrap validation was only able to confirm the predictive ability of fullPIERS for the occurrence of the combined maternal outcome. Since internal validation methods such as the bootstrap have limitations (31), we have commenced a process of external validation of fullPIERS through new data sets.

The fifth limitation is that fullPIERS is limited to maternal surveillance and does not address the acknowledged excess perinatal risks associated with pre-eclampsia (1).

Interpretation

fullPIERS accurately predicted adverse maternal outcomes for up to 48 hours, a clinically useful time period that permits steroid administration, transfer, or induction. Also, fullPIERS maintained good performance (AUC ROC >0.8), beyond 3 days post-eligibility, and maintained reasonable performance (AUC ROC >0.7) up to 7 days post-eligibility. Remote from term, measurable perinatal gains accrue at weekly intervals (32). However, like Ganzevoort et al (10), we were unable to predict adverse maternal outcomes at any time following admission to hospital with pre-eclampsia. This was anticipated, as deteriorating maternal and/or fetal status directs clinical decision making, especially remote from term.

In the PIERS cohort, gestational age on admission for pre-eclampsia was significantly lower, and independently predictive, in women destined to develop complications. Disease onset <32 weeks is associated with a 20-fold increase in maternal mortality risk (1).

Many traditional clinical variables of importance were not included in the final model either because they were collected in <80% of cases (e.g., 24 hour urine), they lacked univariable association with the combined adverse outcome (9), or they were displaced within the multivariable modelling (e.g., blood pressure, 'heavy' proteinuria, uric acid, ALT, and LDH) by variables with greater independent explanatory power. Our findings support the view that once significant proteinuria has been identified, serum creatinine can be used for monitoring renal function and risk in women with pre-eclampsia (33).

For face validity, we did examine whether or not blood pressure could be forced into fullPIERS. Blood pressure did not independently predict adverse maternal outcomes in the multivariable model, perhaps as it is the sole element of the maternal syndrome amenable to intervention. Effective antihypertensive agents exist for severe and non-severe pregnancy hypertension (1). During the first 48 hours after eligibility, women who proceeded to develop adverse outcomes had blood pressure

indices 3-10mmHg higher than those women with uncomplicated courses. We do not advocate that blood pressure measurement in women with suspected or confirmed pre-eclampsia be abandoned. Severe systolic ($\geq$160 mmHg) and diastolic hypertension ($\geq$ 110mmHg) convey significant maternal risks and should be brought into the non-severe or normotensive range (1).

Our results suggest that only one of AST or ALT need to be measured, and that the measurement of LDH is redundant in these women. Other tests that could reasonably be abandoned in light of these data are urea and routine coagulation studies.

Why were 24 hour collections performed in fewer than 50% of these women? Pragmatically, we believe that clinicians faced with a hypertensive woman with proteinuria on dipstick analysis at term will decide to advise delivery rather than accept the delay inherent in a 24 hour collection; a decision supported by both the HYPITAT trial (7), and the inaccuracy of 24 hour urine collections for proteinuria estimation in pregnancy (33). We suggest that dipstick proteinuria, despite its inherent flaws, be used to screen and identify women at risk (1;33).

The low rate of $MgSO_4$ administration to women who developed adverse outcomes (62%) in these academic tertiary centres was surprising; these women all developed significant personal complications of pre-eclampsia. While the results of the randomised controlled trials of $MgSO_4$ as eclampsia prophylaxis are compelling (34), for women with 'mild' pre-eclampsia there remains apparent uncertainty about when, and with whom, to start $MgSO_4$ (12).

Generalisability

How do we suggest that these findings be used to direct care?

First, we believe that these data will help clinicians gain a fuller sense of disease evolution. This may be what underlay the reduced incidence of adverse maternal outcomes associated with the single site introduction of the PIERS assessment and surveillance guidelines (11).

Second, we propose that gestational age, maternal symptoms, pulse oximetry, serum creatinine, platelet count, and AST be used to stratify maternal risk during the assessment and surveillance of women admitted with pre-eclampsia using the fullPIERS equation (available on-line at www.piers.cfri.ca). The derived fullPIERS probability has similar performance characteristics as established cardiovascular and critical care models. (28-30).

Third, it appears reasonable to abandon redundant tests. For example, the testing of AST, ALT, and LDH might be replaced by AST alone without losing important information and with reduced laboratory costs.

An important impact of fullPIERS may be to identify women at lowest risk of adverse outcomes, who can be offered expectant management either remote from term for perinatal benefit or at or near term during induction of labour (7).

By grouping women according to the risk of adverse maternal outcomes, fullPIERS should also contribute to our understanding of the pathophysiology of pre-eclampsia. Analogous to the use of POP-Q in pelvic floor prolapse (35), fullPIERS may, over time, aid in describing the heterogeneous populations in the pre-eclampsia literature, and enhance the development of new treatments and interventions.

Although the model-making process is not finished (36), we hope that the planned external validation (through prospective data collection and using extant international databases) and implementation of fullPIERS will help to reduce the risk of the life-ending, life-altering (e.g., stroke), and life-threatening (e.g., eclampsia) complications that make pre-eclampsia so important.

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References

(1) Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010 June 30.

(2) Langer A, Villar J, Tell K, Kim T, Kennedy S. Reducing eclampsia-related deaths--a call to action. Lancet 2008 March 1;371(9614):705-6.

(3) Hill K, Thomas K, AbouZahr C, Walker N, Say L, Inoue M et al. Estimates of maternal mortality worldwide between 1990 and 2005: an assessment of available data. Lancet 2007 October 13;370(9595):1311-9.

(4) Horton R. What will it take to stop maternal deaths? Lancet 2009 October 24;374(9699):1400-2.

(5) Lewis, G. and Drife, J. O. Why women die; 2000-2002. Report on confidential enquiries into maternal deaths in the United Kingdom. London: RCOG; 2004.

(6) Martin JN, Jr., Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol 2005 February;105(2):246-54.

(7) Koopmans C, van den Berg P, Mol BW, Groen H, Willekes C, Kwee A et al. Pregnancy-induced hypertension and preeclampsia after 36 weeks: induction of labour versus expectant monitoring. The HYPITAT trial [abstract]. Hypertens Pregnancy 2008;27:421.

(8) Thangaratinam S, Coomarasamy A, Sharp S, O'Mahony F, O'Brien S, Ismail KM et al. Tests for predicting complications of pre-eclampsia: a protocol for systematic reviews. BMC Pregnancy Childbirth 2008;8(1):38.

(9) Menzies J, Magee LA, Li J, Lam J, Richardson K, Douglas JM et al. The Canadian Hypertension Society and National High Blood Pressure Education Program criteria for 'severe' pre-eclampsia do not uniformly predict adverse outcomes. Hypertens Pregnancy 2007;26(4):447-62.

(10) Ganzevoort W, Rep A, de Vries JI, Bonsel GJ, Wolf H. Prediction of maternal complications and adverse infant outcome at admission for temporizing management of early-onset severe hypertensive disorders of pregnancy. Am J Obstet Gynecol 2006 August;195(2):495-503.

(11) Menzies J, Magee LA, Li J, Yin R, Lam E, Stuart H et al. Instituting surveillance guidelines and adverse outcomes in preeclampsia: a single site study. Obstet Gynecol 2006;110(1):121-7.

(12) Magee LA, Helewa ME, Moutquin JM, von Dadelszen P, Cardew S, Cote AM et al. SOGC guidelines; diagnosis, evaluation and management of the hypertensive disorders of pregnancy. J Obstet Gynaecol Can 2008;30(3 (Suppl)):S1-S48.

(13) Audibert F, Friedman SA, Frangieh AY, Sibai BM. Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Am J Obstet Gynecol 1996 August;175(2):460-4.

(14) Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust N Z J Obstet Gynaecol 2000 May;40(2):139-55.

(15)   Homer CS, Brown MA, Mangos G, Davis GK. Non-proteinuric pre-eclampsia: a novel risk

         indicator in women with gestational hypertension. J Hypertens 2008 February;26(2):295-302.

(16)   Stoger S, Walters B. Diagnostic value of clinical history in pre-eclampsia [abstract].

         Hypertens Pregnancy 2008;21 (Suppl 1):48.

(17)   Milholland AV, Wheeler SG, Heieck JJ. Medical assessment by a Delphi group opinion

         technic. N Engl J Med 1973 June 14;288(24):1272-5.

(18)   Pill J. The Delphi method: substance, context, a critique and an annotated bibliography.

         Socio-Economic Planning Science 1971;5:57-71.

(19)   Molenberghs G. Editorial: what to do with missing data? J Roy Stat Soc Ser A 2007;170:861-

         3.

(20)   Williams AJ. ABC of oxygen: assessing and interpreting arterial blood gases and acid-base

         balance. BMJ 1998 October 31;317(7167):1213-6.

(21)   Altman DG, Lyman GH. Methodological challenges in the evaluation of prognostic factors

         in breast cancer. Breast Cancer Res Treat 1998;52(1-3):289-303.

(22)   Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing

         models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med

         1996 February 28;15(4):361-87.

(23)   Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and

         methodological standards. N Engl J Med 1985 September 26;313(13):793-9.

(24) Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982 April;143(1):29-36.

(25) Efron B, Tibsherani R. An introduction to the bootstrap. New York: Chapman and Hall; 1993.

(26) Harrell FE, Jr. Regression modeling strategies. New York: Springer Science & Business, Inc; 2001.

(27) Janes H, Pepe MS, Gu W. Assessing the value of risk predictions by using risk stratification tables. Ann Intern Med 2008 November 18;149(10):751-60.

(28) Knuiman MW, Vu HT. Prediction of coronary heart disease mortality in Busselton, Western Australia: an evaluation of the Framingham, national health epidemiologic follow up study, and WHO ERICA risk scores. J Epidemiol Community Health 1997 October;51(5):515-9.

(29) Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. J Pediatr 2001 January;138(1):92-100.

(30) Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med 2006 May;34(5):1297-310.

(31) Young GA, Daniels HE. Bootstrap bias. Biometrika 2010;77(1):179-85.

(32) von Dadelszen P, Magee LA, Lee SK, Stewart SD, Simone C, Koren G et al. Activated protein C in normal human pregnancy and pregnancies complicated by severe preeclampsia: a therapeutic opportunity? Crit Care Med 2002 August;30(8):1883-92.

(33)   Lindheimer MD, Kanter D. Interpreting abnormal proteinuria in pregnancy: the need for a
       more pathophysiological approach. Obstet Gynecol 2010 February;115(2 Pt 1):365-75.

(34)   Duley L, Gulmezoglu AM, Henderson-Smart DJ. Magnesium sulphate and other
       anticonvulsants for women with pre-eclampsia. Cochrane Database Syst Rev
       2003;CD000025.

(35)   Novara G, Artibani W. Surgery for pelvic organ prolapse: current status and future
       perspectives. Curr Opin Urol 2005 July;15(4):256-62.

(36)   Leushuis E, van der Steeg JW, Steures P, Bossuyt PM, Eijkemans MJ, van der Veen F et al.
       Prediction models in reproductive medicine: a critical appraisal. Hum Reprod Update 2009
       September;15(5):537-52.

(37)   Lessoway VA, Schulzer M, Wittmann BK, Gagnon FA, Wilson RD. Ultrasound fetal
       biometry charts for a North American Caucasian population. J Clin Ultrasound 1998
       November;26(9):433-53.

(38)   Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic
       weight standard. Radiology 1991 October;181(1):129-33.

(39)   Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M et al. A new and
       improved population-based Canadian reference for birth weight for gestational age.
       Pediatrics 2001 August;108(2):E35.

(40)   Bellomo R, Kellum JA, Ronco C. Defining and classifying acute renal failure: from advocacy
       to consensus and validation of the RIFLE criteria. Intensive Care Med 2007
       March;33(3):409-13.

Table 1 Variables considered in the PIERS modelling

Variable	
Demographics	Past obstetric history
Maternal age at EDD (yr)	Gestational hypertension (y/n)
Number of fetuses	Gestational proteinuria (y/n)
Gestational age at onset (wk)	GDM (prior preg) (y/n)
Gestational age at delivery (wk)	GDM (this preg) (y/n)
Weight – on admission (kg)	
Body mass index (kg/m2)	Past medical history
Gravidity (n)	Hypertension (y/n)
Parity (n)	Renal disease (y/n)
Smoking in this pregnancy (y/n)	Diabetes mellitus (y/n)
Symptoms	Cardiorespiratory signs
Severe nausea and vomiting (y/n)	dBP on eligibility (mmHg)
Frontal headache (y/n)	sBP on eligibility (mmHg)
Visual disturbance (y/n)	MAP on eligibility (mmHg)
RUQ/epigastric pain (y/n)	SpO2 (%)/SpO2 (filled) * (%)
Chest pain/dyspnoea (y/n)	
≥1 symptom (y/n)	
Haematological tests	Renal signs and tests
Total leukocyte count (x 10^9/L)	Dipstick (categorical) †
Platelet count (x 10^9/L)	Dipstick (continuous) ‡
MPV (fL)	24h urine protein (g/d)

MPV/plt ratio	Pr:Cr ratio (mg/mM)
INR	Creatinine (mmol/L)
APTT (sec)	Uric acid (mmol/L)
Fibrinogen (µmol/L)	
Hepatic tests	Fetal assessment tests
ST (U/L)	FHR (normal/suspicious/pathological) **
ALT (U/L)	EFW (%ile category) ¶
LDH as a ratio of the local normal range midpoint (U/L)	AC (%ile category) ¶
Bilirubin (µmol/L)	UA EDF
Albumin (g/L)	
Random glucose (mmol/L)	

* missing data filled assuming 97% (described in the Methods); [†] classified as 0, trace, 1+, 2+, 3+, 4+; [‡] classified as 0, 0.5, 1, 2, 3, 4; [¶] classified as <1.0%, 1.0-2.4%, 2.5-4.9%, 5.0-9.9%, 10.0-49.9%, 50.0-89.9%, 90.0-94.9%, 95.0-97.4%, 97.5-98.9%, ≥99.0% using BC Women's Hospital published data (37); ** using Royal College of Obstetricians and Gynaecologists definitions (http://www.rcog.org.uk/resources/public/pdf/efm_guideline_final_2may2001.pdf).

AC abdominal circumference; AFI amniotic fluid index; ALT alanine transaminase; APTT activated partial thromboplastin time; AST aspartate transamninase; BPP biophysical profile; DAP deepest amniotic fluid pocket; dBP diastolic blood pressure; EDD expected date of delivery; EFW estimated fetal weight (Hadlock (38)); FHR fetal heart rate; GDM gestational diabetes mellitus; INR international normalised ratio; LDH lactate dehydrongenase; MAP mean arterial pressure; MPV

mean platelet volume; preg pregnancy; RUQ rught upper quadrant; SpO$_2$ oxygen saturation (pulse oximetry); sBP systolic blood pressure; UA EDF umbilical artery Doppler end diastolic flow

Table 2 Characteristics of women in the PIERS study (median [interquartile range] and number (%))

Characteristic	Women with adverse outcomes (N=261)	Women without adverse outcomes (N=1762)	p value
Demographics (within 48h of eligibility)			
Maternal age at EDD (years)	31 [27, 35]	31 [27, 36]	0.68
Gestational age at eligibility (weeks)	33.9 [30.0, 36.6]	36.3 [33.4, 38.3]	8.2E-20
Gestational age at eligibility <34 weeks	133 (51.0%)	503 (28.5%)	3.3E-12
Multiple pregnancy	36 (13.8%)	156 (8.9%)	0.02
Parity ≥ 1	72 (27.6%)	509 (28.9%)	0.71
Smoking in this pregnancy	26 (10.0%)	223 (12.7%)	0.26
Pre-eclampsia description			
Hypertension and proteinuria	178 (68.2%)	1164 (66.1%)	0.53
Hypertension and hyperuricaemia	21 (8.0%)	303 (17.2%)	8.9E-05
HELLP without hypertension or proteinuria	23 (8.8%)	29 (1.6%)	8.0E-08
Superimposed pre-eclampsia	39 (14.9%)	266 (15.1%)	1.0
Clinical (within 48h of eligibility)			
Peak blood pressure (mmHg)			
Mean arterial pressure	123 [116, 133]	120 [113, 129]	5.2E-05
Systolic BP	170 [155, 181]	160 [150, 175]	1.7E-06
Diastolic BP	104 [98, 112]	101 [97, 110]	0.02
Worst dipstick proteinuria (+)	3 [1, 4]	2 [trace, 3]	6.7E-11

Lowest platelets (x 10^9/L)	170 [121, 230]	194 [153, 243]	2.8E-06
Highest aspartate transaminase (U/L)	31 [22, 51]	26 [20, 36]	4.5E-07
Interventions			
Corticosteroid administration	114 (43.7%)	436 (24.7%)	5.8E-10
Antihypertensive medications administered	214 (82.0%)	1167 (66.2%)	6.9E-08
MgSO4 administered	161 (61.7%)	529 (30.0%)	4.7E-22
Pregnancy outcomes			
Admission-to-delivery interval (all cases) (d)	2 [1, 6]	2 [1, 5]	0.14
Admission-to-delivery interval (<34+0 wks) (d)	4 [1, 9]	5 [2, 16]	0.01
Gestational age at delivery (wk)	34.7 [30.7, 37.0]	37.0 [34.6, 38.7]	8.2E-20
Birth weight (g)	1938 [1189, 2750]	2685 [1935, 3300]	4.5E-18
Birth weight <3rd percentile*	22 (8.4%)	143 (8.1%)	0.90
Intrauterine fetal death ($\geq 20_{+0}$ wk and/or ≥ 500g)	4 (1.5%)	16 (0.9%)	0.31
Neonatal death (before 28d)	5 (1.9%)	15 (0.9%)	0.17
Infant death prior to hospital discharge or 6wk	7 (2.7%)	19 (1.1%)	0.07

dBP diastolic blood pressure; **EDD** expected date of delivery; **HELLP** haemolysis, elevated liver enzymes, low platelets; **sBP** systolic blood pressure. * Data from Kramer *et al* (39).

Table 3 Adverse maternal outcomes (definitions available [www.piers.cfri.ca])

One or more of maternal morbidity or mortality:	within 48h	within 7d	any time
TOTAL	106 (5.2%)	203 (10.0%)	261 (12.9%)
Maternal death	0	0	0
Central nervous system			
Eclampsia (≥1)	6	10	11
Glasgow coma score <13	1	1	3
Stroke or reversible ischaemic neurological deficit	0	0	1
Transient ischaemic attack	0	1	1
Cortical blindness or retinal detachment	0	0	0
Posterior reversible encephalopathy	0	0	0
Cardiorespiratory			
Positive inotropic support	0	0	3
Infusion of a 3rd parenteral antihypertensive	0	1	3
Myocardial ischaemia/infarction	1	1	1
SpO_2 <90%	11	30	41
≥50% FiO_2 for >1hr	12	21	32
Intubation (other than for Caesarean section)	1	4	6
Pulmonary oedema	22	52	63
Haematological			
Transfusion of any blood product	28	63	85
Platelets <50 x 10^9/L with no transfusion	22	36	40
Hepatic			

Dysfunction	9	11	12
Haematoma/rupture	0	0	0
Renal			
Acute renal insufficiency (creatinine > 150µmol/L; no pre-existing renal disease) (40)	3	4	6
Acute renal failure (creatinine>200µmol/L; pre-existing renal disease) (40)	4	4	4
Dialysis	0	0	1
Placental outcomes			
Placental abruption	15	24	34
Other adverse events			
Severe ascites	1	2	2
Bell's palsy	0	1	1

Table 4 Univariable analyses of candidate predictor variables with p<0.1 and collected in >80% of cases

Variable	N (%)	OR [95% CI]	P value	AUC ROC [95% CI]
Demographics				
Maternal age at EDD (yr)	2020 (99.9)	0.99 [0.96, 1.02]	0.57	0.51 [0.46, 0.57]
Number of fetuses (n)	2020 (99.9)	0.86 [0.43, 1.70]	0.66	0.51 [0.45, 0.57]
Gravidity (n)	2020 (99.9)	0.894 [0.81, 0.99]	0.03	0.56 [0.50, 0.61]
Weight at eligibility (kg)	1784 (88.2)	0.99 [0.97, 0.998]	0.03	0.59 [0.53, 0.65]
BMI (kg/m^2)	1647 (81.4)	0.99 [0.95, 1.02]	0.45	0.55 [0.49, 0.61]
Height (cm)	1763 (87.2)	0.99 [0.97, 1.02]	0.62	0.52 [0.46, 0.58]
Past medical history				
Hypertension (y/n)	2015 (99.6)	0.57 [0.29, 1.11]	0.10	0.53 [0.48, 0.58]
Symptoms				
Severe nausea and vomiting (y/n)	2020 (99.9)	2.14 [1.22, 3.73]	0.008	0.54 [0.48, 0.60]
RUQ/epigastric pain (y/n)	2020 (99.9)	2.92 [1.94, 4.39]	2.7E-07	0.61 [0.55, 0.66]
Headache (y/n)	2020 (99.9)	1.23 [0.83, 1.83]	0.30	0.53 [0.47, 0.58]
Visual disturbance (y/n)	2020 (99.9)	0.99 [0.60, 1.63]	0.96	0.50 [0.45, 0.56]
Chest pain/dyspnoea (y/n)	2020 (99.9)	6.13 [3.56, 10.54]	5.6E-11	0.58 [0.52, 0.66]
Number of symptoms (n)	2020 (99.9)	1.49 [1.26, 1.76]	3.2E-06	0.62 [0.57, 0.68]
Cardiovascular signs				
dBP on eligibility (mmHg)	2020 (99.9)	1.04 [1.02, 1.05]	8.6E-05	0.63 [0.57, 0.68]

sBP on eligibility mmHg)	2020 (99.9)	1.03 [1.02, 1.04]	1.1E-08	0.65 [0.59, 0.70]
MAP on eligibility (mmHg)	2019 (99.8)	1.04 [1.03, 1.06]	4.6E-08	0.65 [0. 60, 0.71]
Respiratory				
SpO$_2$ (filled) (%) *	2020 (99.9)	0.63 [0.58, 0.70]	4.8E-22	0.72 [0.67, 0.78]
Renal				
Dipstick (continuous) †	1949 (96.3)	1.43 [1.24, 1.66]	1.6E-06	0.65 [0.59, 0.71]
Creatinine (µmol/L)	2000 (98.9)	1.02 [1.02, 1.03]	4.2E-09	0.63 [0.57, 0.69]
Uric acid (mmol/L)	2008 (99.3)	1.004 [1.00, 1.01]	1.1E-04	0.59 [0.53, 0.65]
Haematological				
Platelet count (x 10^9/L)	2015 (99.6)	0.99 [0.98, 0.99]	4.9E-17	0.69 [0.63, 0.75]
Mean platelet volume (fL)	1953 (96.5)	1.00 [0.88, 1.13]	0.939	0.51 [0.46, 0.57]
MPV x 10^6/platelet count ratio	1952 (96.5)	45.46 [1.63, 1269]	2.9E-25	0.66 [0.59, 0.72]
International normalised ratio (INR)	1758 (86.9)	2710 [143, 51381]	1.3E-07	0.64 [0.58, 0.70]
Activated partial thromboplastin time (sec)	1759 (87.0)	1.04 [1.02, 1.07]	1.7E-04	0.64 [0.58, 0.70]
Hepatic				
Aspartate transaminase (U/L)	1947 (96.2)	1.005 [1.00, 1.01]	1.6E-14	0.73 [0.67, 0.79]
Alanine transaminase (U/L)	2011 (99.4)	1.005 [1.00, 1.01]	7.9E-16	0.72 [0.66, 0.78]
Lactate dehydrogenase (U/L)	1623 (80.2)	1.63 [1.43, 1.86]	2.0E-13	0.75 [0.68, 0.81]
Bilirubin (µmol/L)	1911 (94.5)	1.15 [1.11, 1.18]	8.7E-17	0.67 [0.60, 0.73]
Albumin (g/L)	1749 (86.5)	0.92 [0.88, 0.96]	7.8E-05	0.62 [0.56, 0.68]

Fetal assessment tests				
FHR	1829 (90.4)	2.15 [1.47, 3.14]	6.9E-05	0.58 [0.51, 0.64]
EFW (%ile category)	1665 (82.3)	0.99 [0.98, 0.99]	5.9E-05	0.61 [0.55, 0.68]
AC (%ile category)	1665 (82.3)	0.99[0.98, 0.99]	5.8E-05	0.61 [0.55, 0.68]

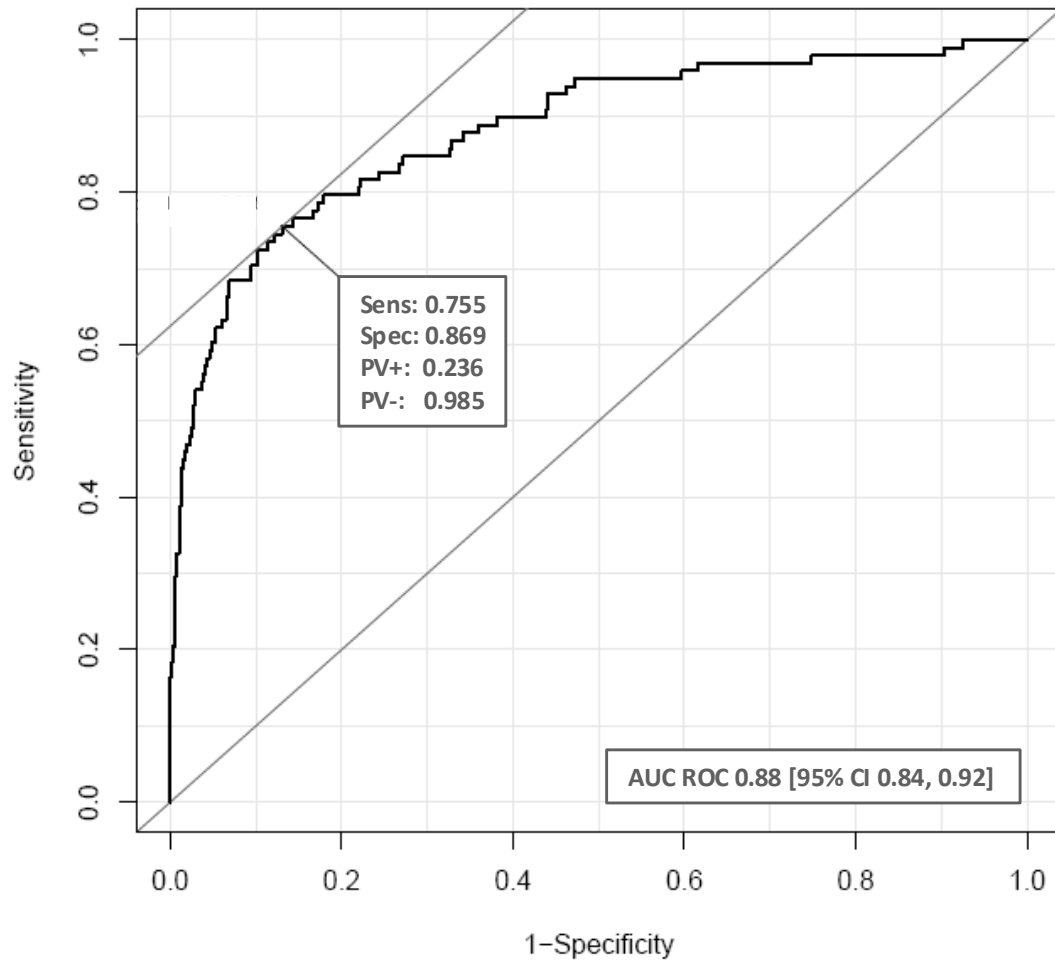* missing data filled assuming 97% (described in the Methods); † classified as 0, 0.5, 1, 2, 3, 4.

%ile percentile; **AC** abdominal circumference; **BMI** body mass index; **dBP** diastolic blood pressure;

MAP mean arterial pressure; **MPV** mean platelet volume; **RUQ** right upper quadrant; **SpO$_2$** oxygen

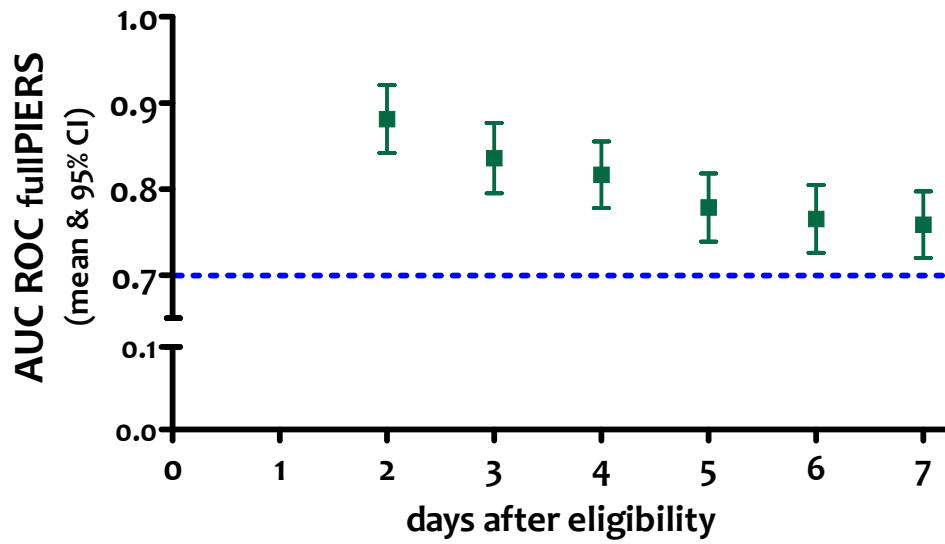saturation (pulse oximetry); **sBP** systolic blood pressure

Table 5 Risk stratification table assessing the value of the fullPIERS model in risk prediction

Predicted probability of adverse maternal outcome within 48 hours	Number of women (%)	Number of women with outcome (%)	Number of women without outcome (%)	True positive rate*	False positive rate*
0.00 – 0.0099	671 (34.7%)	3 (0.4%)	668 (99.6%)		
0.01 – 0.024	586 (30.3%)	11 (1.9%)	575 (98.1%)	0.969	0.636
0.025 – 0.049	314 (16.2%)	9 (2.9%)	305 (97.1%)	0.857	0.323
0.050 - 0.099	160 (8.3%)	8 (5.0%)	152 (95.0%)	0.765	0.157
0.10 - 0.19	98 (5.1%)	14 (14.3%)	84 (85.7%)	0.684	0.073
0.20 - 0.29	32 (1.65%)	9 (28.13%)	23 (71.88%)	0.541	0.029
≥0.30	74 (3.82%)	44 (59.46%)	30 (40.54%)	0.449	0.016
Total	**1935**	**98**	**1837**		

Figure 1 Performance of the fullPIERS model developed with data from first 48h after eligibility.
Combined adverse maternal outcome predicted within 48h of eligibility using only data collected
prior to the outcome (an on-line tool to calculate fullPIERS probabilities is available at
www.piers.cfri.ca).

AUC ROC area under the curve of the receiver operator characteristic; **PV-** negative predictive
value; **PV+** positive predictive value; **Sens** sensitivity; **Spec** specificity

Figure 2 fullPIERS areas under the receiver-operator curves (AUCs; error bars: 95% confidence intervals) from 2 – 7 days after PIERS study eligibility.