Effectiveness and safety of 1 vs 4 h blood pressure profile with clinical and laboratory assessment for the exclusion of gestational hypertension and pre-eclampsia: a retrospective study in a university affiliated maternity hospital

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ABSTRACT
Objective: We asked whether 60 compared with 240 min observation is sufficiently informative and safe for pregnancy day assessment (PDAC) of suspected pre-eclampsia (PE).

Design: A retrospective study of 209 pregnant women (475 PDAC assessments, 6 months) with routinely collected blood pressure (BP), symptom and laboratory information. We proposed a 60 min screening algorithm comprising: absence of symptoms, normal laboratory parameters and ≤1 high-BP reading (systolic blood pressure, SBP 140 mm Hg or higher or diastolic blood pressure, DBP 90 mm Hg or higher). We also evaluated two less inclusive screening algorithms. We determined short-term outcomes (within 4 h): severe hypertension, proteinuric hypertension and pregnancy-induced hypertension, as well as long-term outcome: PE-related diagnoses up to the early puerperium.

We assessed performance of alternate screening algorithms performance using 2×2 tables.

Results: 1 in 3 women met all screen negative criteria at 1 h. Their risk of hypertension requiring treatment in the next 3 h was 1.8% and of failing to diagnose proteinuric hypertensive PE at 4 h was 5.1%. If BP triggers were 5 mm Hg lower, 1 in 6 women would be screen-negative of whom 1.1% subsequently develops treatment-requiring hypertension and 4.5% demonstrate short-term proteinuric hypertension. We present sensitivity, specificity, negative and positive likelihood ratios for alternate screening algorithms.

Conclusions: We endorse further research into the safest screening test where women are considered for discharge after 60 min. Safety, patient and staff satisfaction should be assessed prospectively. Any screening test should be used in conjunction with good clinical care to minimise maternal and perinatal hazards of PE.

BACKGROUND
Pre-eclampsia (PE) is an important cause of maternal and perinatal mortality and morbidity.¹ Late onset PE is not well predicted by early prediction algorithms,² and so detection and management of late onset PE forms the basis of the traditional increase in late pregnancy surveillance. Since the 1990s Pregnancy Day Assessment Clinics (PDAC) have become increasingly common, preferred by women

Strengths and limitations of this study
- We present novel data from a contemporary, cohort of pregnant women attending Pregnancy Day Assessment Clinic (PDAC), raising the question of whether shorter than traditional observation times safely allow exclusion of pre-eclampsia and clinically significant hypertension.
- Our results suggest that up to 1 in 3 women could be considered for discharge at 60 min compared with the standard 210 to 240 min provided strict screen negative criteria are met.
- The retrospective and uncontrolled nature of this study limits inferences which can be drawn but it sets the scene for future prospective research in quality and safety in the PDAC setting.
- We did not examine the consequences of failing to diagnose 1.8% cases of severe hypertension or 5.1% cases of proteinuric hypertensive pre-eclampsia which become evident between 60 and 240 min.
- Future research is particularly needed about patient and staff satisfaction and cost-effectiveness of current routine care compared with shorter observation periods with or without home-based blood pressure monitoring and/or new point of care tests targeted at assessing placental health.

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and possibly offering healthcare savings when compared with inpatient management. The USA definition of pregnancy-induced hypertension (PIH) and PE requires hypertension measured at least 4 h apart and a recent Australasian guideline requires hypertension to be present ‘on repeated readings over several hours.’ These definitions are ‘rule-in,’ rather than ‘rule-out’ for PIH and PE but have influenced the common practice to use a 4 h (240 min) blood pressure profile in PDAC to identify and manage gestational hypertension and PE. A single study based on 120 min profiles has been reported, but the optimal observation duration to reliably exclude PIH or PE has not been determined. A shorter duration of assessment would have clear patient satisfaction and cost benefits.

We decided to assess whether information available during the first 60 min of observation could accurately and safely rule out women who would be diagnosed with PIH or PE or who have hypertension to a degree usually requiring medication, based on a longer 240 min observation period. We also assessed the screening effectiveness for identifying women who developed PIH or PE at any stage up to the inpatient postnatal stay if they had had a PDAC visit within 1 week of birth. Test characteristics of a 60 min ‘screening test’ derived from the current retrospective analysis can inform prospective studies to determine the safety of shorter duration of blood pressure monitoring for ‘screen negative’ women.

**METHODS**

**Participants, setting and procedures**

This study comprised retrospective records of all women with a generic privacy consent statement (indicating consent to involvement in hospital audit) who attended a tertiary maternity hospital PDAC over a 6-month period in 2014. Participants were referred by medical or midwifery practitioners for indications including hypertension in antenatal clinic, symptoms or high-risk pregnancy. Care always included serial, manual blood pressure measurements every 30 min by PDAC midwives using anaeroid sphygmomanometers. Blood pressure was measured by registered midwives using an appropriate sized cuff with women in seated position consistent with Society for Obstetric Medicine of Australia and New Zealand (SOMANZ) recommendations. The sphygmomanometers are regularly calibrated against a mercury sphygmomanometer, as per SOMANZ recommendations. In addition to routinely collected demographic and clinical data, we retrospectively calculated Pre-eclampsia Integrated Estimate of Risk Scores (PIERS) as a method of describing the sample risk profile. PIERS calculations estimate the risk of maternal mortality and severe morbidity, including eclampsia, hepatic rupture, cerebrovascular accident and other specified organ dysfunction within 48 h of admission. The risk equation was developed from eight international perinatal tertiary centres with further validation studies in progress and is accessible as a web-based calculator (http://www.piers.cfri.ca). These calculations are not part of clinical care.

**Screening algorithms**

Component criteria for screen negativity were as follows: Screen-negative blood pressure (BP) was defined as ≤1 episode of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg after admission to PDAC. We specifically searched the medical record for screen-positive symptoms or signs, defined as: oedema, headache, visual disturbance, abdominal pain, bruising or hyper-reflexia. Screen-negative laboratory tests were defined by local reference ranges when not otherwise specified. Specifically, we considered the following as screen negative: urinary protein: creatinine ratio <0.03 mg/mmol, platelet count ≥150×109/L (local reference range), alanine transaminase (ALT)<41 u/L and γ glutamate transaminase (GGT)<60 u/L (local reference range), serum creatinine<90 µmol/L and non-elevated serum uric acid. In the absence of a standard reference range, but recognising that uric acid changes with pregnancy duration, and that elevated levels may reflect systematic oxidative stress both during and outside of pregnancy, we defined screen-negative uric acid levels as that below gestational age (weeks)/100 in mmol/L.

Three screening algorithms were investigated:

1. Any predefined symptom or sign together with one or more abnormal blood pressure reading within 0–60 min.
2. Any abnormal laboratory finding together with one or more abnormal blood pressure within 0 to 60 min.
3. Two or more abnormal blood pressure readings within 0 to 60 min or criteria met for algorithm 1 or 2.

**Outcomes**

The outcomes of interest were:

1. Severe hypertension, defined as DBP of 110 mm Hg or higher or SBP of >150 mm Hg.
2. Proteinuric hypertension, recommended by SOMANZ and the International Society for the Study of Hypertension in Pregnancy (ISSHP) as a method to identify a relatively homogeneous group of women with PE. This outcome was defined as 2 or more blood pressure readings of ≥140/90 during a 240 min observation period with proteinuria excretion of 300 mg or more per 24 h or a protein: creatinine ratio of 0.03 mg/mmol, or greater.
3. Clinically significant hypertension, defined as 2 or more blood pressure readings of ≥140/90 during a 240 min observation period, with or without proteinuria or other organ dysfunction, consistent with PIH or PE.
4. Any diagnosis of PE, eclampsia or PIH at discharge from the postnatal wards.

Two medical students (TAC, YH) entered screening and outcome component data and final diagnosis from
the medical record into a web-based database system (Survey Monkey) which was then transferred to a spreadsheet. The data entry form is available as a see online supplementary file 1. Screen positivity and presence or absence of short-term outcomes were calculated from components using mathematical ‘IF’ statements in MS Excel by another clinician researcher (EAM). The nature of the spreadsheet meant that the link between calculated screening algorithms and calculated outcomes was somewhat obscured but no specific blinding method was employed.

Statistical methods
We constructed two by two tables of observed screen and outcome positive and negative instances to estimate screening test characteristics with 95% CIs around the positive and negative likelihood ratios. We classified likelihood ratios as poor (2.1 to 5.0 for positive, 0.5 to 0.2 for negative), good (5.1 to 10.0 for positive, 0.19 to 0.1 for negative) or excellent (>10.0 or <0.1) for clinical utility.

Sample size
Given the absence of previous data on which power calculation could reliably be inferred, we assessed 6 months of clinical activity which included 209 women and 475 PDAC admission episodes.

RESULTS
We reviewed auditable records for 475 visits and 209 women between 19 February and 22 October 2014. Obstetric and demographic data shown in table 1 demonstrate many recognised risk factors for PE including nulliparity, previous PE, high-body mass index and pre-pregnancy hypertension. The PIERS risks indicate they were nevertheless at low short-term risk of severe adverse events related to PE. The STARD flow diagram (figure 1) indicates that 92.2% of PDAC attendance records (relating to 92.5% of eligible pregnant women) were available for audit.

The median number of visits per woman was 1, the IQR 1–2 visits, with one woman each attending 12, 13 or 14 times during a pregnancy.

Not all women completed 30 minutely blood pressure measurements for the planned 240 min observation period (see online supplementary file 2). Ninety-five per cent of assessable PDAC visits had more than 60 min of observation. The median observation time was between 210 and 240 min. Thirty-two (6.7%) PDAC attendances led to inpatient admission and 92.3% were discharged for outpatient follow up.

Blood pressure patterns
After a maximum of 240 min observation, 324 of 475 visits (68.2%) met the definition of clinically important hypertension, that is, 2 or more readings of 140/90 or higher. Of these, 118 (24.8%) visits met the blood pressure and proteinuria requirements for PE and 206 (43.4%) visits met criteria for non-proteinuric hypertension with or without other evidence of organ dysfunction. Fifty-three (11.3%) visits recorded very high-systolic pressure (greater than 150 mm Hg) or very high-diastolic pressure (110 mm Hg or greater).

Figure 2 shows that the incidence of severe hypertension (defined as blood pressure greater than 150 mm Hg systolic or equal or greater than 110 mm Hg diastolic) was lower in the last ¾ compared with the first ¼ of the 240 min observation period. Blood pressure trends were lower in the last 180 min compared with the first 60 min of the 240 min observation period: mean SBP 4.8 mm Hg lower (95% CI 2.9 to 6.9 mm Hg, paired t test, p<0.001) and mean DBP 3.2 mm Hg lower (95% CI 2.7 mm Hg to 3.7 mm Hg lower, paired t test p<0.001).

| Participant characteristic (N=209) | Median (IQR) or N (%) |
|-----------------------------------|-----------------------|
| Age (years)                       | 31.8 (28.4, 35.7)     |
| Nulliparous                       | 118 (56.5%)           |
| Maternal body mass index (pre-pregnancy or early pregnancy) (kg/m²) | 27.4 (23.7, 33.3)     |
| Body mass index (BMI) category 18.5–24.9 kg/m² (“normal”) | 74 (35.5%)           |
| Early pregnancy systolic blood pressure (mm Hg) | 120 (110, 125)       |
| Early pregnancy systolic hypertension ≥140 mm Hg | 4 (2%)               |
| Early pregnancy diastolic blood pressure (mm Hg) | 70 (65, 80)          |
| Early pregnancy diastolic hypertension ≥90 mm Hg | 3 (1.5%)             |
| Pre-pregnancy hypertension        | 12 (5.7%)             |
| Past history of pre-eclampsia     | 26 (28.6%)*           |
| Low dose aspirin treatment        | 28 (13.4%)            |
| Cigarette smoking                 | 10 (4.8%)             |
| Gestational age (GA) at first PDAC visit (weeks) | 36.3 (32.6, 38.3) |
| PIERS’ risk at PDAC visit         | 0.6% (0.3 to 1.3%)    |
| Time between first PDAC visit and delivery (days) | 15 (6, 37)           |

*91 parous women.

PDAC, Pregnancy Day Assessment Clinic; PIERS, Pre-eclampsia Integrated Estimate of Risk Scores.
Symptoms, signs and laboratory investigations other than BP

The number of visits (% incidence) with symptoms or signs were: headache 102 (21.5%), oedema 64 (13.5%), visual disturbance 34 (7.2%), abdominal pain 18 (3.8%), hyper-reflexia 9 (1.9%), nausea 2 (0.4%). Bruising, vomiting or dyspnoea were not recorded as symptoms in this medical record review.

Of 425 cardiotocographs (CTGs) performed, 2 (0.5%) demonstrated prolonged decelerations. Nine (2.1%) CTGs with variable and 1 (0.2%) CTG with early decelerations were reported.

The proportion of visits missing laboratory data were as follows: Urine protein:creatinine ratio 1.3%, Platelets 0.8%, Urea 1.5%, Creatinine 1.1%, Urate 1.5%, ALT 0.8%, GGT 1.1%. For the purposes of this study, visits with any missing absent laboratory information were assumed to be ‘normal’. Screen-positive laboratory investigations were: 44 (9.3%) instances of thrombocytopenia (<150×10⁹/L), 9 instances (1.9%) of renal impairment (creatinine >90 µmol/L), 35 instances (7.4%) of elevated ALT, 8 instances (1.7%) of elevated GGT and 163 instances (35%) of proteinuria (spot protein to creatinine ratio of 0.03 mg/mmol or more).

Screen positivity at 60 min for the prediction of short-term (240 min observation period) and long-term (until early postpartum period) PE and related conditions

Table 2 shows test characteristics of three alternative screening algorithms (defined in Methods) for three short-term outcomes—severe hypertension, proteinuric hypertension and PIH during 240 min observation. Raw data and calculations relating to table 2 can be found in see online supplementary files 3–5. Figure 1 is a flow diagram where the index test under investigation is screening algorithm 3 and the reference standard (outcome) is proteinuric hypertension after maximum of 240 min observation, that is, depicting information in table 2, 8th (second last) data row.

If the screen-positive blood pressure triggers are made more stringent, 135 mm Hg instead of 140 mm Hg systolic and 85 mm Hg instead of 90 mm Hg diastolic, the screen positivity rate rises from 67.4% to 81.5% with minor reductions in false-negative rates: 4.5% compared with 5.1% for proteinuric hypertension and 1.1% compared with 1.8% for very high-blood pressure diagnosed within 240 min.

Table 3 shows test characteristics of the same three screening algorithms for longer term, ‘whole pregnancy’ occurrence of PE and related complications including...
PIH and eclampsia for 163 women where birth occurred within 1 week of PDAC assessment. The related raw data and calculations are available in see online supplementary 6.

Symptoms alone were neither sensitive nor specific for short-term diagnosis of PIH when defined as persisting hypertension of 140/90 on two or more occasions within 240 min. Presence of symptoms gave a sensitivity 35.2% and specificity 78.7% for meeting BP criteria for PIH. Similarly, laboratory anomalies did not predict PIH within 240 min very well: sensitivity 57.1% and specificity 43.7% (see online supplementary file 3).

The most inclusive screening test at 60 min was algorithm 3 (see Methods), which included all women with ≥2 screen-positive hypertensive BP readings (≥140 mm Hg systolic or ≥90 mm Hg diastolic) or with 1 screen-positive BP and one or more symptoms or laboratory anomalies. This screening algorithm was positive in about 2 of 3 PDAC visits (67.4%). Compared with the other screening algorithms, this screening method had the lowest false-positive rates. The false-positive rates in the short term (up to 240 min) with this screening algorithm were 5.1% for proteinuric hypertension and 1.8% for severe hypertension (see table 2). The specificity was lower for algorithm 3 compared with algorithms 1 and 2.

The screen-positive criteria for algorithm 2 overlap to a large degree with diagnostic criteria for PE as per the homogenous research definition of proteinuric hypertension endorsed by SOMANZ.5 Compared with diagnostic criteria for proteinuric hypertension, screening criteria in algorithm 2 limits the duration of observed BP to 60 min but is more inclusive of laboratory anomalies including, but not limited to, proteinuria. In view of this overlap, it is not surprising that algorithm 2 is the most specific of the 3 alternate algorithms for the diagnosis of PE. In contrast algorithm 2 showed higher false-negative rates compared with other algorithms, particularly in predicting severe hypertension (43.4%) reflecting the observation that severe hypertension can occur in the absence of laboratory abnormalities or symptoms.

Algorithm 3 was even more inclusive for the 163 women whose visits preceded birth by 1 week or shorter interval. The screen-positive rate in this group was 77.9% (see table 3). The false-positive rates in the longer term (up to inpatient postnatal observations) for any hypertensive disease including PIH, PE and eclampsia was 16.4%.

DISCUSSION

This retrospective audit confirms clinicians’ impressions that normal BP readings in the first 60 min when a pregnant woman is referred to PDAC often predict subsequent normal BP, even though this referral population is at moderately high risk for PE: 38.9% of PDAC visits demonstrated hypertension and proteinuria of degrees which could be consistent with PE. Not unexpectedly, attempts to predict hypertension which rely on maternal symptoms, hyper-reflexia, proteinuria or laboratory anomalies are neither sensitive nor specific for the detection of PE and related disorders where BP measurement is central to these diagnoses. Our data show that ceasing observations at 60 min for the 1 in 3 women where strict screen-negative criteria are met (algorithm 3) is associated with a low risk (1.8%) of subsequent severe hypertension in the following 3 h. The risk of under-diagnosing hypertension which requires medication is low on the day of PDAC assessment. The chance of mis-diagnosing PE with a 60 min compared with 240 min observation period is also fairly low (5.1%). If BP trigger points are made more stringent at 135 mm Hg systolic and 85 mm Hg diastolic, fewer women (1 in 6) meet screen-negative criteria, but their risks of subsequent severe hypertension (1.1%) or missed PE (4.5%) are also slightly lower. Serial PDAC assessments and prudent birth timing are still required to minimise clinical hazards associated with under-diagnosis of severe hypertension or PE.

The strengths of the current study include a moderate sample size, addressing a common and serious pregnancy complication with current practice in a low perinatal mortality setting. A larger, 6-year retrospective study of 560 women presenting to an English PDAC reflects patient demographics and fetal medicine practices of 14 to 20 years earlier than the current study.5 The current study has a high prevalence of the outcome of interest, clinically significant hypertension and a range of data which are routinely available to clinicians
Screening performance of various 60 min observation algorithms for the prediction of short-term outcomes within 240 min observation

| Short-term outcome | False-negative rate (%)(95% CI) | Specificity(%) | Positive LR† | Negative LR† |
|--------------------|----------------------------------|---------------|--------------|--------------|
| 1 or more high BP and symptoms | 23.8 | 79.0 | 0.8 (0.65 to 0.99) | 0.8 (0.71 to 0.97) |
| Severe hypertension | 56.6 | 76.2 | 0.7 (0.51 to 1.00) | 0.6 (0.45 to 0.69) |
| P (1.15 to 2.53) | 0.8 | 62.3 | 79.8 | 0.8 (0.71 to 0.97) |
| PE | 34.7 | 79.8 | 1.7 (1.15 to 2.53) | 0.8 (0.71 to 0.97) |
| PIH | 33.3 | 96.7 | 1.0 (1.00 to 2.23) | 0.07 (0.03 to 0.15) |
| 1 or more high BP and symptoms | 23.8 | 79.0 | 0.7 (0.51 to 1.00) | 0.6 (0.45 to 0.69) |
| Severe hypertension | 56.6 | 76.2 | 0.7 (0.51 to 1.00) | 0.6 (0.45 to 0.69) |
| P (1.15 to 2.53) | 0.8 | 62.3 | 79.8 | 0.8 (0.71 to 0.97) |
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| PIH | 33.3 | 96.7 | 1.0 (1.00 to 2.23) | 0.07 (0.03 to 0.15) |

**Criteria for screen positivity at 60 min**

- 1 or more high BP and symptoms
- Severe hypertension
- P (1.15 to 2.53)
- PE
- PIH

**Screen positive rate (%)(95% CI)**

- 23.8 - 56.6
- 41.5 - 96.7
- 67.4

**Sensitivity(%)**

- 37.7 - 94.9

**Specificity(%)**

- 79.0 - 82.1

**Positive LR†**

- 0.8 (0.65 to 0.99)

**Negative LR†**

- 0.8 (0.71 to 0.97)

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The current study has some weaknesses. The retrospective nature of it likely introduces biases of missing information, especially records of symptoms and hyperreflexia. It is plausible that once hypertension is identified, staff more diligently enquire about and record symptoms which could indicate PE. Conversely, staff may be understandably less likely to enquire about or record ‘pre-eclampsia’ symptoms if BP measurements are within the normal range. Researchers recording predictors were not systematically blinded to outcomes. Missing symptoms or laboratory data were counted as screen negative which may have introduced biases. Generalisability may be limited by the fact that this is a single centre, not multicentre, uncontrolled study and that women were referred to the pregnancy day assessment clinic at clinician discretion rather than by predefined criteria. We are not able to comment on detailed perinatal outcomes other than the absence of perinatal death in this cohort. A prospective study could better address short and long-term paediatric outcomes including sequelae of late preterm and early term birth when the majority of infants were born.

Similar to the current study, PIERS scoring uses routinely collected clinical and laboratory data in women presenting with PE. However, the purpose of PIERS scoring is to calculate the probability of severe maternal morbidity associated with PE in order to escalate care. This contrasts with the current study’s aims of determining if shorter observations are safe and effective for exclusion of PE and management of mild forms of PE and PIH. Standardised graphic records of clinical observations assist clinicians in recognising clinical deterioration. Future research could address whether such records assist clinicians to make safe decisions about fitness for discharge too.

One of several questions which require future research is whether laboratory and cardiotocographic assessment can be realistically completed within 60 min prior to considering discharge from PDAC. A prospective audit should address feasibility of a 60 min timeframe.

The main clinical implication is that screen negativity does not equate with zero risk of either PE or further escalation of hypertension. Previous studies found that...
transient or ‘white coat’ hypertension progresses to PE in 5% to 10% of cases,26 29 30 slightly higher than the 5% rate of short-term progression seen in our study. Screen negativity thus does not obviate the need for appropriately vigilant clinical follow-up and prudent birth planning. Future research could address other possible risk mitigating interventions for women considered for discharge at 60 min such as further risk stratification by point of care placental growth factor level12 42 5 and/or by employing home BP monitoring. At term gestation, induction of labour may be more sensible than ongoing surveillance.

CONCLUSIONS

We endorse further research into the safest appearing screening test where women are considered for discharge with appropriate follow-up after 60 min if no symptoms, reassuring laboratory tests and 1 or fewer high-BP readings (SBP either 135 or 140 mm Hg or higher or DBP 85 or 90 mm Hg or higher). Safety, patient and staff satisfaction should be assessed prospectively.

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Table 3  Screening performance of various 60 min observation algorithms for the prediction of pre-eclampsia or related complications (including PIH and eclampsia) where childbirth occurred within 1 week of PDAC attendance

| Criteria for screen positivity at 60 min | Screen positive rate (%) | Sensitivity (%) | Specificity (%) | Positive LR* (95% CI) | Negative LR* (95% CI) | False-negative rate (%) |
|----------------------------------------|--------------------------|----------------|----------------|------------------------|------------------------|------------------------|
| 1 or more high BP and symptoms         | 31.3                     | 32.3           | 92.9           | 5.1 E (1.3 to 19.7)     | 0.7 P (0.6 to 0.8)      | 67.7                   |
| 1 or more high BP and abnormal lab Ix  | 54.6                     | 59.3           | 73.1           | 1.8 P (1.1 to 3.2)      | 0.6 P (0.5 to 0.8)      | 40.7                   |
| 2 or more high BP, or 1 high BP with either symptoms, lab Ix abnormal or both | 77.9                     | 83.7           | 50.0           | 1.7 P (1.1 to 2.4)      | 0.3 P (0.2 to 0.5)      | 16.4                   |

*Grading of clinical utility of likelihood ratios as per Mahutte and Duleba:15 E excellent, G good, P poor.

BP, blood pressure; lab Ix, laboratory investigations; negative LR, negative likelihood ratio=(1-sensitivity)/specificity; PDAC, Pregnancy Day Assessment Clinic; PIH, pregnancy-induced hypertension; positive LR, positive likelihood ratio=sensitivity/(1−specificity).
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