Proposed clinical management of pregnancies after combined screening for preeclampsia at 35-37 weeks' gestation

Anca M. Panaitescu,[1] David Wright,[2] Anna Militello,[1] Ranjit Akolekar,[1,3] Kypros H. Nicolaides.[1]

1. Harris Birthright Research Centre for Fetal Medicine, King's College, London, UK.
2. Institute of Health Research, University of Exeter, Exeter, UK.
3. Department of Fetal Medicine, Medway Maritime Hospital, Gillingham, UK

Third trimester screening for preeclampsia

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Correspondence
Professor KH Nicolaides,
Fetal Medicine Research Institute,
King's College Hospital,
16-20 Windsor Walk,
Denmark Hill, London SE58BB
Telephone: +442032998256
Fax: +442077339534
email: kypros@fetalmedicine.com

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ABSTRACT

Objective: To estimate the patient-specific risk of preeclampsia (PE) at 35-37 weeks' gestation by a combination of maternal characteristics and medical history with multiple of the median (MoM) values of mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), serum placental growth factor (PLGF) and serum soluble fms-like tyrosine kinase-1 (sFLT-1) and stratify women into high-, intermediate- and low-risk management groups.

Methods: This was a prospective observational study in women attending for a third-trimester ultrasound scan at 35-37 weeks as part of routine pregnancy care. Patient-specific risks of delivery with PE at <4 weeks from assessment and PE at <42 weeks' gestation were calculated using the competing risks model to combine the *prior* risk from maternal characteristics and medical history with MoM values of MAP, UTPI, PLGF and sFLT-1. On the basis of these risks the population was stratified into high-,

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intermediate- and low-risk groups. Different risk cut-offs were used to vary the proportion of the population stratified into each risk category and the performance of screening for delivery with PE at <40 and ≥40 weeks' gestation was estimated.

Results: The study population of 3,703 singleton pregnancies included 38 (1.0%) with PE at <40 weeks' gestation and 22 (0.6%) with PE at ≥40 weeks. Using a risk cut-off for PE at <4 weeks of 1 in 50 to define the high-risk group and a risk cut-off of <1 in 100 for PE at <42 weeks' gestation to define the low-risk group, the proportion of the population stratified into high-, intermediate- and low-risk was about 12.7%, 28.8% and 58.5%, respectively. The high-risk group contained 92% of pregnancies with PE at <40 weeks' gestation and 73% of those with PE at ≥40 weeks. The intermediate-risk group contained a further 27% of women with PE at ≥40 weeks. In the low-risk group, none of the women developed PE at <40 or >40 weeks' gestation.

Conclusion: The study presents risk stratification of PE by the combined test at 35-37 weeks aiming to identify a high-risk group in need of intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation, an intermediate-risk group in need of reassessment at 40 weeks' gestation and a low-risk group which can be reassured that they are unlikely to develop PE.

Introduction

In the traditional approach to prenatal care, screening and diagnosis of preeclampsia (PE) is based on the demonstration of elevated blood pressure and proteinuria during a routine clinical visit in the late second- or third-trimester of pregnancy. In a proposed new pyramid of pregnancy care, the timing and content of clinical visits should be defined by the patient-specific risk of developing PE.[1] The objectives of screening for PE are firstly, to reduce the prevalence of the disease through pharmacological intervention in the high-risk group identified in the first-trimester of pregnancy [2,3] and secondly, to minimize adverse perinatal events for those that develop PE by determining the appropriate time and place for delivery.[4] The second objective can be potentially achieved through risk stratification in the second and / or third-trimester of pregnancy.

Screening for term-PE by a combination of maternal factors with multiples of the median (MoM) values of mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), serum placental growth factor (PLGF) and serum soluble fms-like tyrosine kinase-1 (sFLT-1) at 35-37 weeks' gestation predicted about 85% of affected pregnancies, at false positive rate of 10% and this performance is superior to that achieved by screening at 11-13, 19-24 or 30-34 weeks with respective detection rates of 47%, 46% and 66%.[5-9]

The objective of this study is to estimate the patient-specific risk of PE at 35-37 weeks' gestation by a combination of maternal characteristics and medical history with MAP, UTPI, PLGF and sFLT-1 and stratify women into high-, intermediate- and low-risk management groups. The high-risk group would require intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation, the intermediate-risk group would require reassessment at 40 weeks and the low-risk could be reassured that they are unlikely to develop PE.

Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for a third-trimester routine hospital visit at 35-37 weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK between February and December 2014. In this visit we first, recorded maternal demographic characteristics and medical history, second, carried out an ultrasound examination for fetal anatomy and growth, third, measured the left and right UTPI by transabdominal color Doppler ultrasound and calculated the mean value of the two arteries,[10] fourth, measured the MAP by validated automated devices and a standardized protocol[11] and fifth, measured serum concentration of PLGF and sFLT-1 by an automated biochemical analyzer within 10 minutes of blood sampling (Cobas e411 system, Roche Diagnostics, Penzberg, Germany). Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.[12,13]

The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee. The inclusion criteria for this study were singleton pregnancies delivering non-malformed live birth or stillbirth at $\geq$35 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities. The study population is the same as in our previous report,[6] but included pregnancies with measurements of all four biomarkers at 35^{+0}-36^{+6} weeks.

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy associated hypertension were examined to determine if the condition was PE, as defined by the International Society for the Study of Hypertension in Pregnancy.[14]

In order to focus clinical resources effectively, we investigated a policy whereby pregnancies assessed for PE at 35-37 weeks are stratified into three groups (Figure 1). A group at high-risk for delivery with PE within 4 weeks of assessment (PE <4 weeks), would require intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation; this group should be ideally small and contain a large proportion of pregnancies with PE at <40 weeks' gestation. Conversely, the low-risk group, that would have no further assessment, should be large and contain very few pregnancies that develop PE at <40 or ≥40 weeks' gestation. The intermediate-risk group, would ideally contain very few pregnancies with PE at <40 weeks' gestation and a large proportion of pregnancies that deliver with PE ≥40 weeks; this group would require reassessment at 40 weeks' gestation.

Statistical analysis

Patient-specific risks of delivery with PE at <4 weeks from assessment and PE at <42 weeks' gestation were calculated using the competing risks model to combine the *prior* risk for PE from maternal characteristics and medical history with MoM values of MAP, UTPI, PLGF and sFLT-1.[5,15-18] Pregnancies were allocated to the high-risk group if their risk for PE at <4 weeks was above a specific high-risk threshold and they were allocated to the low-risk group if their risk for PE at <42 weeks' gestation was below a specified low-risk threshold. Otherwise, they were allocated to the intermediate-risk group. Performance was assessed in terms of the distribution of pregnancy outcomes by risk group.

The statistical software package R was used for data analyses.[19]

Results

The study population of 3,703 singleton pregnancies included 38 (1.0%) with PE at <40 weeks' gestation and 22 (0.6%) with PE at ≥40 weeks; maternal and pregnancy characteristics are summarized in Table 1. The performance of screening for delivery with PE at ≥40 weeks' gestation is poorer than that of screening for delivery with PE at <40 weeks (Figure 2); the area under the receiver operating characteristic curve for PE at <40 weeks was 0.953, 95% CI 0.913-0.993 and for PE at ≥40 weeks was 0.887, 95% CI 0.840-0.933. This is the consequence of lower deviation from normal for each biomarker with increasing interval between assessment and delivery with PE.[6]

The allocation of pregnancies to high-, intermediate- and low-risk groups according to the estimated risk for PE at <4 weeks and PE at <42 weeks' gestation is given in Table 2.

At risk cut-off for PE at <4 weeks of 1 in 10, 4.0% of pregnancies were allocated to the high-risk group and these contained 73.7% of pregnancies with PE at <40 weeks' gestation and 18.2% of pregnancies with PE at ≥40 weeks' gestation. The proportion of

the population classified as high-risk varied according to the risk cut-off for PE at <4 weeks from 1.1% for cut-off of 1 in 3 to 12.7% for cut-off of 1 in 50 and the positive predictive value for PE at <40 weeks' gestation ranged from 28.6% (12/42) to 7.4% (35/472).

At a risk of <1 in 100 for PE at <42 weeks' gestation, 58.5% of pregnancies were allocated to the low-risk group; in this group there were no cases of PE at <40 or ≥40 weeks' gestation and therefore, the negative predictive value for PE was 100%.

At a risk cut-off of 1 in 50 for PE at <4 weeks and risk cut-off of 1 in 100 for PE at <42 weeks' gestation, 28.8% of pregnancies were allocated to the intermediate-risk group and these contained 7.9% of pregnancies with PE at <40 weeks' gestation and 27.3% of pregnancies with PE at ≥40 weeks' gestation. Consequently, for these particular risk cut-offs, 41.5% of pregnancies were allocated to the high- or intermediate-risk group and the combination of these groups contained all 22 of pregnancies with PE at ≥40 weeks' gestation.

Discussion

Main findings

The study has demonstrated an approach for stratification of the population into three management groups based on the estimated risk for PE at <4 weeks from assessment and PE at <42 weeks' gestation by a combination of maternal factors, MAP, UTPI, PLGF and sFLT-1 at 35-37 weeks' gestation. A high-risk group would require intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation, an intermediate-risk group, together with those pregnancies in the high-risk group that had not yet delivered, would require reassessment at 40 weeks' gestation to decide the best time and method of delivery and a low-risk group would be managed expectantly.

The proportion of the population stratified into high- intermediate- and low-risk groups and the proportion of each strata delivering with PE at <40 and ≥40 weeks' gestation would inevitably depend on the risk cut-offs used for defining the groups. At estimated risk cut-off of 1 in 50 for PE at <4 weeks to define the high-risk group and risk of <1 in 100 for PE at <42 weeks' gestation to define the low-risk group, 12.7%, 28.8% and 58.5% of pregnancies were allocated to the high-, intermediate- and low-risk groups, respectively. The high-risk group contained 92.1% of pregnancies with PE at <40 weeks' gestation and the combined high- and intermediate-risk groups contained all pregnancies with PE at ≥40 weeks' gestation. In the low-risk group there were no cases of PE at <40 or ≥40 weeks' gestation.

Strengths and limitations

The strengths of this late third-trimester screening study for PE are first, examination of pregnant women attending for routine assessment of fetal growth and wellbeing, second, recording of data on maternal characteristics and medical history to define the *prior* risk, third, use of a specific methodology and appropriately trained doctors to measure MAP and UTPI, fourth, use of automated machines to provide accurate measurement within 40 minutes of sampling of maternal serum concentration of PLGF and sFLT-1, fifth, expression of the values of the biomarkers as MoMs after adjustment for factors that

affect the measurements, and sixth, use of Bayes theorem to combine the *prior* risk from maternal factors with biomarkers to estimate patient-specific risks and stratify women into high-, intermediate- and low-risk management groups.

A limitation of the study is that fitting of the risk model [6] and development and assessment of risk stratification were on the same data, which induces a degree of optimistic bias into the results. However, our risk model [6] is a parsimonious one with just two parameters for the mean log MoM value for each of the markers and a pooled estimate of an assumed common covariance matrix and this limits the degree of bias induced. Nevertheless, prospective evaluation using an independent test data set is needed to validate the results.

Comparison with previous studies

In a previous study at 35-37 weeks' gestation we presented the results on the performance of screening in a routine population by maternal factors and MAP, UTPI, PLGF and sFLT-1.[6] This study investigated a policy whereby pregnancies assessed for PE at 35-37 weeks are stratified into risk groups for subsequent pregnancy management. A previous study reported on a policy whereby pregnancies assessed for PE at 30-34 weeks are stratified into risk groups for subsequent pregnancy management.[20]

Clinical implications of the study

The performance of screening for term-PE by a combination of maternal factors with biomarkers at 12, 22 or 32 weeks' gestation is relatively poor compared to screening at 36 weeks [5-9] and we have therefore proposed that all women, irrespective of whether they had prior screening or not, should have assessment of risk at 35-37 weeks.[6]

This study provides the framework for stratification of risk for PE based on screening at 35-37 weeks. In all pregnancies, the routine ultrasound examination carried out at 35-37 weeks would have already identified any possible impairment of fetal growth and in such case the decision on timing of delivery would be based on fetal heart rate patterns and / or Doppler findings in the umbilical artery, middle cerebral artery and ductus venosus. The group classified as being at high-risk for PE can be monitored by measurement of blood pressure and urinalysis at least on a weekly basis and the women can be advised to report any of the symptoms associated with severe PE, such as visual disturbance and epigastric pain. The intermediate-risk group, require reassessment at 40 weeks' gestation but these women would also be advised to report any symptoms associated with severe PE. The low-risk group can be reassured that development of PE is very unlikely and in the absence of any abnormal ultrasound findings or other obstetric indications the pregnancies can be managed expectantly awaiting for spontaneous onset of labor.

The cut-offs in risks to define the proportion of the population stratified into each of the three management groups and the protocols for such management will inevitably vary according to local preferences and health economic considerations. Future studies will examine whether the implementation of such protocols could improve perinatal outcome.

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Figure legends

Figure 1. Stratification of pregnancies into high-, intermediate- and low-risk management groups based on the estimated risk for preeclampsia at 35-37 weeks' gestation. The high-risk group would require intensive monitoring from the time of the initial assessment and up to 40 weeks' gestation, the intermediate-risk group would require reassessment at 40 weeks' gestation and the low-risk group would be managed expectantly.

Figure 2. Receiver operating characteristic curves for prediction of delivery with preeclampsia at <40 weeks' gestation (red curve) and at ≥40 weeks (blue curve) by combined screening at 35-37 weeks' gestation.

Table 1. Maternal and pregnancy characteristics of the study population.

Maternal characteristics	Preeclampsia		
	None (n=3,643)	<40 w (n=38)	≥40 w (n=22)
Age, median (IQR)	31.7 (26.8-35.3)	33.4 (27.7-36.4)	34.1 (30.5-36.0)
Weight, median (IQR)	78.7 (70.6-89.3)	83.0 (74.4-98.7)	86.1 (81.3-98.3)
Height, median (IQR)	1.64 (1.60-1.69)	1.65 (1.62-1.71)	1.64 (1.61-1.72)
Racial origin			
Caucasian, n (%)	2,709 (74.4)	26 (68.4)	19 (86.4)
Afro-Caribbean, n (%)	615 (16.9)	7 (18.4)	2 (9.1)
South Asian, n (%)	132 (3.6)	2 (5.3)	1 (4.5)
East Asian, n (%)	76 (2.1)	0	0
Mixed, n (%)	111 (3.0)	3 (7.9)	0
Method of conception			
Spontaneous, n (%)	3,538 (97.1)	35 (92.1)	20 (90.9)
Assisted conception, n (%)	105 (2.9)	3 (7.9)	2 (9.1)
Cigarette smoking, n (%)	352 (9.7)	2 (5.3)	1 (4.5)
Chronic hypertension, n (%)	44 (1.2)	2 (5.3)	1 (4.5)
SLE / APS, n (%)	11 (0.3)	0	0
Diabetes mellitus, n (%)	43 (1.2)	2 (5.3)	0
Parity			
Nulliparous, n (%)	1,797 (49.3)	26 (68.4)	19 (86.4)
Parous no previous PE, n (%)	1,773 (48.7)	7 (18.4)	2 (9.1)
Parous previous PE, n (%)	73 (2.0)	5 (13.2)	1 (4.5)
Inter-pregnancy interval, median (IQR)[¥]	3.1 (2.1-5.0)	4.9 (2.3-10.9)	2.9

[¥] Inter-pregnancy interval reported for parous women

Table 2. Proportion of the population stratified into high- intermediate- and low-risk groups based on the risk for preeclampsia (PE) at <4 weeks from assessment (PE <4w) and PE at <42 weeks' gestation (PE <42GW) by a combination of maternal factors, MAP, UTPI, PLGF and sFLT-1 at 35-37 weeks' gestation.

Risk cut-off for PE	Strata		PE with delivery at:	
	Type	Size (n=3,703)	≤40 weeks (n=38)	>40 weeks (n=22)
1 in 3 for PE <4w and 1 in 50 for PE <42 GW	High	42 (1.1; 0.8, 1.5)	12 (31.6; 17.5, 48.7)	1 (4.5; 0.1, 22.8)
	Intermediate	980 (26.5; 25, 27.9)	25 (65.8; 48.6, 80.4)	20 (90.9; 70.8, 98.9)
	Low	2681 (72.4; 70.9, 73.8)	1 (2.6; 0.1, 13.8)	1 (4.5; 0.1, 22.8)
1 in 3 for PE <4w and 1 in 100 for PE <42 GW	High	42 (1.1; 0.8, 1.5)	12 (31.6; 17.5, 48.7)	1 (4.5; 0.1, 22.8)
	Intermediate	1496 (40.4; 38.8, 42.0)	26 (68.4; 51.3, 82.5)	21 (95.5; 77.2, 99.9)
	Low	2165 (58.5; 56.9, 60.1)	0 (0; 0, 9.3)	0 (0; 0, 15.4)
1 in 10 for PE <4w and 1 in 50 for PE <42 GW	High	148 (4.0; 3.4, 4.7)	28 (73.7; 56.9, 86.6)	4 (18.2; 5.2, 40.3)
	Intermediate	874 (23.6; 22.2, 25.0)	9 (23.7; 11.4, 40.2)	17 (77.3; 54.6, 92.2)
	Low	2681 (72.4; 70.9, 73.8)	1 (2.6; 0.1, 13.8)	1 (4.5; 0.1, 22.8)
1 in 10 for PE <4w and 1 in 100 for PE <42 GW	High	148 (4.0; 3.4, 4.7)	28 (73.7; 56.9, 86.6)	4 (18.2; 5.2, 40.3)
	Intermediate	1390 (37.5; 36.0, 39.1)	10 (26.3; 13.4, 43.1)	18 (81.8; 59.7, 94.8)
	Low	2165 (58.5; 56.9, 60.1)	0 (0; 0, 9.3)	0 (0; 0, 15.4)
1 in 20 for PE <4w and 1 in 50 for PE <42 GW	High	250 (6.8; 6.0, 7.6)	32 (84.2; 68.7, 94)	10 (45.5; 24.4, 67.8)
	Intermediate	772 (20.8; 19.5, 22.2)	5 (13.2; 4.4, 28.1)	11 (50.0; 28.2, 71.8)
	Low	2681 (72.4; 70.9, 73.8)	1 (2.6; 0.1, 13.8)	1 (4.5; 0.1, 22.8)
1 in 20 for PE <4w and 1 in 100 for PE <42 GW	High	250 (6.8; 6.0, 7.6)	32 (84.2; 68.7, 94.0)	10 (45.5; 24.4, 67.8)
	Intermediate	1288 (34.8; 33.2, 36.3)	6 (15.8; 6.0, 31.3)	12 (54.5; 32.2, 75.6)
	Low	2165 (58.5; 56.9, 60.1)	0 (0; 0, 9.3)	0 (0; 0, 15.4)
1 in 25 for PE <4w and 1 in 50 for PE <42 GW	High	292 (7.9; 7.0, 8.8)	33 (86.8; 71.9, 95.6)	10 (45.5; 24.4, 67.8)
	Intermediate	730 (19.7; 18.4, 21.0)	4 (10.5; 2.9, 24.8)	11 (50.0; 28.2, 71.8)
	Low	2681 (72.4; 70.9, 73.8)	1 (2.6; 0.1, 13.8)	1 (4.5; 0.1, 22.8)
1 in 25 for PE <4w and 1 in 100 for PE <42 GW	High	292 (7.9; 7.0, 8.8)	33 (86.8; 71.9, 95.6)	10 (45.5; 24.4, 67.8)
	Intermediate	1246 (33.6; 32.1, 35.2)	5 (13.2; 4.4, 28.1)	12 (54.5; 32.2, 75.6)
	Low	2165 (58.5; 56.9, 60.1)	0 (0; 0, 9.3)	0 (0; 0, 15.4)
1 in 50 for PE <4w and 1 in 50 for PE <42 GW	High	472 (12.7; 11.7, 13.9)	35 (92.1; 78.6, 98.3)	16 (72.7; 49.8, 89.3)
	Intermediate	550 (14.9; 13.7, 16.0)	2 (5.3; 0.6, 17.7)	5 (22.7; 7.8, 45.4)
	Low	2681 (72.4; 70.9, 73.8)	1 (2.6; 0.1, 13.8)	1 (4.5; 0.1, 22.8)
1 in 50 for PE <4w and 1 in 100 for PE <42 GW	High	472 (12.7; 11.7, 13.9)	35 (92.1; 78.6, 98.3)	16 (72.7; 49.8, 89.3)
	Intermediate	1066 (28.8; 27.3, 30.3)	3 (7.9; 1.7, 21.4)	6 (27.3; 10.7, 50.2)
	Low	2165 (58.5; 56.9, 60.1)	0 (0; 0, 9.3)	0 (0; 0, 15.4)

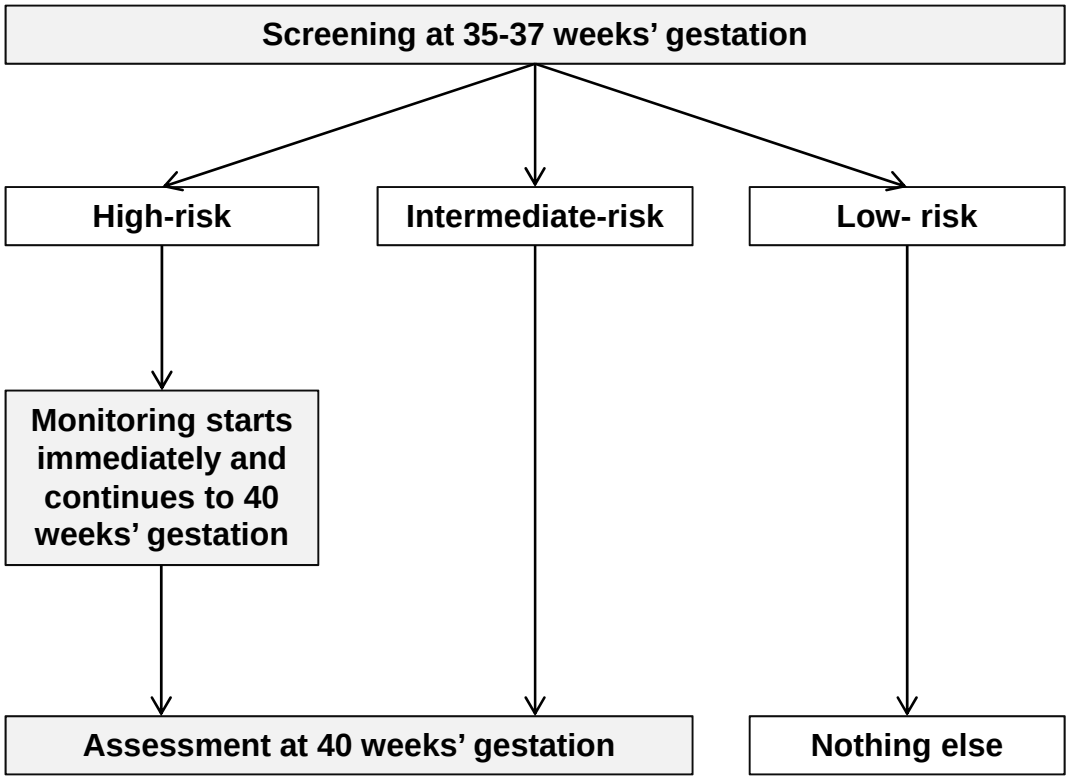

Figure 1

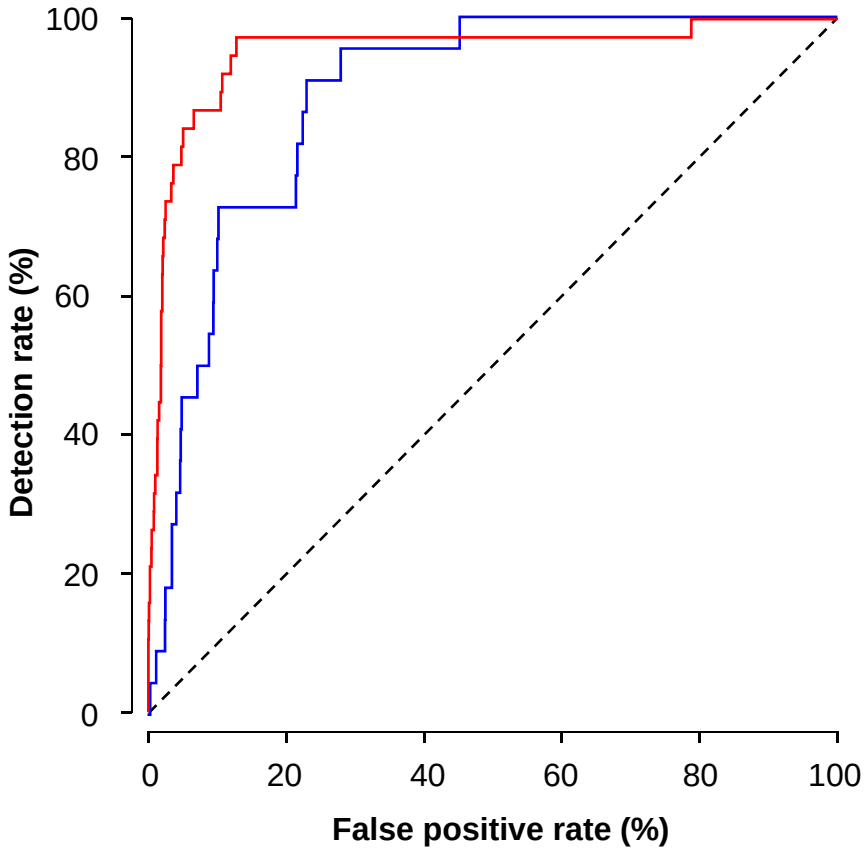

Figure 2