New prognostic prediction tool for suspected early-onset pre-eclampsia: model development and performance evaluation.

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Abstract

Objectives (1) To develop a risk score for early-onset pre-eclampsia leading to delivery within one week from repeated marker determinations on pregnancies with an sFlt-1/PlGF ratio above 38, and (2) to compare it (i) with sFlt-1/PlGF ratio model and (ii) with the sFlt-1/PlGF ratio 655 cut-off. Design Retrospective cohort study. Setting Oviedo, Spain. Sample 522 blood samples from 363 singleton pregnancies with clinical suspicion of pre-eclampsia between 27 and 34 weeks of gestation. Methods NT-proBNP, sFlt-1 and PlGF were combined using linear mixed models with random intercept based on 213 samples from 123 pregnancies with an sFlt-1/PlGF ratio above 38. Main outcome measures Early-onset pre-eclampsia diagnosis leading to delivery within one week from assessment. Results None of the 253 pregnancies with an sFlt-1/PlGF ratio of 38 or below developed early-onset pre-eclampsia. The prognostic prediction tool included sFlt-1 MoM, NT-proBNP and gestational age at time (GA) of repeated measurements. The area under the ROC curve (AUC) for early-onset pre-eclampsia diagnosis leading to delivery within one week was 88.247 (95% CI 0.822-0.934) for the prediction tool and 82.639 (95% CI 0.752-0.892) for the sFlt-1/PlGF + GA model (P=0.04). At an sFlt-1/PlGF ratio 655 cut-off the detection ratio was 31.9% (19.1-47.1) with false positive rate of 4.2% (1.7-8.5). With the same false positive rate, the detection rate with the prognostic prediction tool was 53.2% (38.1-67.9) (P=0.03). Conclusions A prediction tool derived from NT-proBNP, sFlt-1 MoM and gestational age linear mixed model provided clinically useful prediction of early-onset pre-eclampsia prognosis when clinically suspected.

TWEETABLE ABSTRACT

NT-proBNP and sFlt-1 MoM improves prediction of short-term delivery due to early-onset pre-eclampsia, when sFlt-1/PlGF ratio above 38.

INTRODUCTION

Pre-eclampsia is a pregnancy-related disorder and is a leading cause of maternal and perinatal complications (1). Early-onset pre-eclampsia is a rare and severe subtype of pre-eclampsia (0.2-0.5% of pregnancies) that presents before 34 weeks of gestation (2).

The main biochemical achievement in predicting pre-eclampsia has been defining a cut-off point for the soluble FMS-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio of 38 or below to rule-out pre-eclampsia in one week with a negative predictive value of 99.3%, in the PROGNOSIS study (3). On the other hand, the sFlt-1/PlGF ratio rises in cases of other pathologies (4) and has an elevated false positive

rate, such as 21.7% in the PROGNOSIS study and 32.5% in our previous study (5). Therefore, no treatment can be indicated to test positive pregnancies.

Apart from placental dysfunction, women with pre-eclampsia experience cardiovascular abnormalities such as increased blood pressure and peripheral vascular resistance, vasoconstriction or reduced plasma volume (6). The heart responds by producing N-terminal pro-B-type natriuretic peptide (NT-proBNP), which shows higher concentrations in women presenting with severe pre-eclampsia and may predict cardiovascular complications (7-9). Additionally, NT-proBNP levels do not change during pregnancy in healthy women (10), and their transplacental transfer seems negligible (11).

There is a considerable rate of repeated consultations when pre-eclampsia is clinically suspected. In our previous study (12), 42.6% of women with an sFlt-1/PlGF ratio above 38 had repeated measurements, even though only one determination per gestational week was permitted.

In this study, we focus on early-onset pre-eclampsia and only consider samples obtained between 27 and 34 weeks of gestation, with repeated testing permitted. The aim of the study is two-fold: to develop an online prognostic prediction tool to predict delivery due to early-onset pre-eclampsia within seven days of determination, in pregnancies with an sFlt-1/PlGF ratio above 38 and to compare it (i) with sFlt-1/PlGF ratio model and (ii) with the sFlt-1/PlGF ratio 655 cut-off. When constructing the prognostic prediction tool, we assessed the addition of NT-proBNP and the adequacy of using sFlt-1/PlGF ratio raw values or whether these two markers should be gestational age adjusted and considered individually.

MATERIAL AND METHODS

Study design

A retrospective cohort study was carried out in women with clinical suspicion of pre-eclampsia. A total of 381 pregnant women were enrolled at Hospital Universitario Central de Asturias (HUCA) between January 2015 and November 2018. The inclusion criteria were: high blood pressure, proteinuria, worsening of pre-existing hypertension or proteinuria, abnormal uterine artery Doppler scan, headache not responding to analgesics, visual symptoms and/or severe edema. An abnormal uterine artery Doppler scan was defined as a pulsatility index above the 95^{th} percentile for the Spanish population.

Of all pregnant women enrolled, 17 twin pregnancies and one pregnancy with incomplete data were excluded.

We adopted a repeated measures design instead of using baseline measurements only as the former allows risk to be continually reassessed at each gestational week if clinical suspicion of pre-eclampsia persisted. 152 samples were excluded to ensure a minimum interval between subsequent determinations of seven days. The final number was 363 women and 522 samples (Figure 1).

We considered samples with an sFlt-1/PlGF ratio of 38 or below as at low risk of pre-eclampsia leading to delivery within one week (309 samples from 253 pregnancies) and developed the predictive models with samples with an sFlt-1/PlGF ratio above 38 (213 samples from 123 pregnancies). Twelve pregnancies initially had an sFlt-1/PlGF ratio of 38 or below but subsequently rose above 38 and only one pregnancy did the opposite.

As the severity of pre-eclampsia can vary greatly, the evaluated endpoint was diagnosis of early-onset pre-eclampsia leading to delivery within one week from the measurement. The majority of deliveries with pre-eclampsia were induced deliveries. The clinical staff members making the decision to expedite delivery were blinded to the marker results. Women who had manifested pre-eclampsia were not excluded, as this would reduce the external validity of the study.

The laboratory staff members were blinded to subjects' clinical information. The study was approved by the Independent Ethics Committee of Asturias. Written informed consent was obtained from each woman.

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Analytical assay

Blood samples were centrifuged at 1,200 g for 10 min. The sFlt-1, PlGF and NT-proBNP concentrations were determined using an electrochemiluminescence immunoassay (Elecsys PlGF, sFlt-1 and NT-proBNP) on the Cobas e601 automated immunoanalyser (Roche Diagnostics, Germany) with a turnaround time of 18 min. The measuring ranges were 3-10,000 pg/ml for PlGF, 10-85,000 pg/ml for sFlt-1 and 5-35,000 ng/ml for NT-proBNP, with corresponding Limits of Quantification of 10 pg/ml, 15 pg/ml and 5 ng/ml, respectively. The inter-assay coefficients of variation, determined with PreciControl Multimarker 1 and 2 for PlGF and sFlt-1 and with PreciControl Cardiac 1 and 2 (Roche Diagnostics, Germany) for NT-proBNP, ranged from 1.5% to 4.5% throughout the study. No specific interferences have been reported for any of the assays used.

Diagnostic criteria

Pre-eclampsia was diagnosed according to the American College of Obstetricians and Gynecologists (ACOG) definition (13). Hypertension was defined as blood pressure [?] 140/90 mmHg on two separate occasions ([?] 24 hours apart). The proteinuria definition used was either [?] 300 mg of protein per 24-hour urine collection or a protein/creatinine ratio [?] 30 mg/mmol. Note that 2+ protein or greater in dipstick urinalysis and [?] 30 mg of protein/dl in a spot urine sample were not considered suitable markers of proteinuria. In the absence of proteinuria, preeclampsia was defined as new onset of hypertension with the new onset of any of the following: thrombocytopenia ($<$ 100,000/μl), kidney failure (creatinine concentration $>$ 1.1 mg/dl), impaired liver function, pulmonary edema or cerebral or visual symptoms.

Final outcomes were reviewed by an independent obstetrician and assessed at time of delivery. To be considered early-onset pre-eclampsia, the onset had to occur before 34 weeks of pregnancy (2).

Intrauterine growth restriction is defined as an estimated fetal weight below the 10th percentile due to a pathological process that inhibits normal growth potential. This pathological process must be demonstrated after 22 weeks of gestation by oligohydramnios (amniotic fluid index below the 10th percentile) or a Doppler ultrasound of the umbilical artery with a pulsatility index above the 95th percentile.

Predictive model

Linear mixed models' construction

Since multiple marker measurements were taken within each subject at different time points, the usual regression model is inappropriate as it assumes independence among observations (14). Therefore, we analyzed the data using linear mixed models that offer personal risk estimation, introducing a random component to the prediction.

We did not include patient data (maternal age, weight, comorbidities, etc.) in the model. The Wald chi-squared test was used to decide the inclusion of covariates in the model applying a backwards elimination process with $p < 0.05$. The gestational age at measurement was retained to control potential confounding effects.

The open source, freely available R statistical software (R version 3.1.1) (15) was used to conduct all the statistical analyses. Linear mixed model construction and paired area under the curve (AUC) comparison were performed using the *lmer* (16) and the *pROC*(17) R add-on packages, respectively.

Comparisons between groups were performed using the Mann-Whitney U test for quantitative variables and Pearson's chi-squared test and McNemar's test for unpaired and paired proportions, respectively.

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RESULTS

Of the 309 samples from 253 pregnancies with an sFlt-1/PlGF ratio of 38 or below, none delivered with early-onset pre-eclampsia in the subsequent week and none of the pregnancies developed early-onset pre-eclampsia. Conversely, 42.3% (52 of 123) of pregnancies with an sFlt-1/PlGF ratio above 38 delivered with early-onset pre-eclampsia. However, only 22.1% (47 of 213 samples from 123 pregnancies) were diagnosed with early-onset pre-eclampsia leading to delivery within one week. Note that five pregnancies that delivered with early-onset pre-eclampsia did not have any blood test during the last week of pregnancy. Table S1 (supporting information) shows the epidemiological and clinical characteristics of the population and samples, respectively, by study group. NT-proBNP did not vary significantly during the considered gestational weeks in pregnancies that did not develop pre-eclampsia (Pearson correlation= -0.092 p= 0.149) (see Figure S2). In contrast, sFlt-1, PlGF and sFlt-1/PlGF ratio changed with gestational age. Equations describing sFlt-1, PlGF and sFlt-1/PlGF ratio medians per gestational week are described in supporting information (see Table S2).

As the assessed endpoint is a subrogated marker of severity, we compared this endpoint with the definition of severe pre-eclampsia in our sample (13). We found that 97.9% (46/47) of pregnancies with early-onset pre-eclampsia leading to delivery within one week were cases of severe pre-eclampsia. However, the assessed endpoint was observed in only 48.9% (46/94) cases of severe pre-eclampsia. Therefore, we conclude that the assessment of early-onset pre-eclampsia leading to delivery within one week is a more restrictive criterion of severe pre-eclampsia than the ACOG definition of severe pre-eclampsia.

When assessing individual marker prediction performances, we observed a significantly lower estimate of the AUC of the model based on gestational age and PlGF MoM than the AUC obtained with the model that includes gestational age and sFlt-1 MoM ($p< 0.001$) (Figure 2).

Model development

We developed two types of linear mixed model. One type including the raw marker values and another considering the gestational age-corrected markers. Marker values were logarithmized to overcome the skewness in the data.

Addition of NT-proBNP to sFlt-1/PlGF ratio

We compared the prediction ability of the raw value marker models from the respective ROC curves (Figure 3, left panel). The estimate of the AUC of the model that includes gestational age, sFlt-1/PlGF ratio and NT-proBNP was significantly greater (DeLong test, p= 0.013) than the estimate of the AUC of the model without NT-proBNP.

Use of sFlt-1/PlGF ratio

PlGF MoM was excluded from the MoM transformed marker model during its construction due to low prediction ability. We did not consider including sFlt-1/PlGF ratio MoM in the models as the inclusion of PlGF MoM was non-informative.

The estimate of the AUC of the model that combines gestational age, sFlt-1 MoM and NT-proBNP was significantly greater (p= 0.031) than the estimate of the AUC of the model without NT-proBNP (Figure 3, right panel). Therefore, the selected model for the prognostic prediction tool included gestational age, sFlt-1 MoM and NT-proBNP. Description and predictions of the selected model for each possible value are summarized in Table S3 and Figure S1 (supporting information), respectively.

There were no significant differences between the AUC of the raw value marker model that combines gestational age, sFlt-1/PlGF ratio and NT-proBNP and the gestational age-adjusted model that includes gestational age and sFlt-1 MoM and NT-proBNP (p= 0.648).

Subgroup analysis

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Prediction ability of the model that combines gestational age and sFlt-1 MoM and NT-proBNP did not differ from the model without NT-proBNP in pregnancies with intrauterine growth restriction (p= 0.200) or chronic hypertension (p= 0.361).

Model performance

The area under the AUC for early-onset pre-eclampsia diagnosis leading to delivery within one week was 0.882 (95% CI 0.822-0.934) for the model that combines gestational age, sFlt-1 MoM and NT-proBNP and 0.826 (95% CI 0.752-0.892) for the model that combines sFlt-1/PlGF ratio raw values and gestational age model (P = 0.044).

At a 5% false positive rate cut-off level the model that combines gestational age, sFlt-1 MoM and NT-proBNP reached a detection rate of 59.6%, which was significantly greater (p= 0.001) than the model without NT-proBNP (31.9%). At this cut-off level, the model with NT-proBNP resulted positive in 16.9% of the sample and the likelihood ratio of a positive test was 12.4 (95% CI: 6.0-25.3). In other words, the odds of a developing the event is increased twelvefold when the prognostic prediction tool result is positive.

At the sFlt-1/PlGF ratio 655 cut-off the detection ratio was 31.9% (19.1-47.1) with false positive rate of 4.2% (1.7-8.5), predicting early-onset pre-eclampsia diagnosis leading to delivery within one week. With the same false positive rate, the detection rate with the prognostic prediction tool was 53.2% (38.1-67.9) (P=0.03).

Globally, if we compare the application of the criteria based on the sFlt-1/PlGF ratio cut-off value of 38 with the application of the prognostic assessment tool (to pregnancies with an sFlt-1/PlGF ratio above 38), the latter reduced the false positive rate from 34.9% to 1.7% increasing positive predictive value from 22.1% to 77.8%, at the expense of including 33.9% inconclusive valid results (Table 1).

DISCUSSION

Main findings

Combination of NT-proBNP and sFlt-1 MoM improves prediction of short-term delivery due to early-onset pre-eclampsia between those pregnancies with an sFlt-1/PlGF ratio above 38, compared to higher sFlt-1/PlGF ratio raw value cut-offs. We have built a prognostic prediction calculator that is freely available at http://sbpsoftware.com/peprogntool.

Repeated sFlt-1/PlGF ratio of 38 or below adequately rule out early-onset pre-eclampsia leading to delivery within one week.

When sFlt-1/PlGF ratio is above 38, the addition of NT-proBNP has proven superior to the use of sFlt-1/PlGF ratio as a single marker. Gestational age-adjusted PlGF predictive ability is suboptimal and inferior than gestational age-adjusted sFtl-1. Therefore, after selecting at risk pregnancies using an sFlt-1/PlGF ratio cut-off of 38, repeated determinations of sFlt-1/PlGF ratio and predictions based solely on this marker cannot be recommended.

Strengths and limitations

The only current validated use of sFlt-1/PlGF ratio in pre-eclampsia prognosis is the first measurement for each pregnancy (PROGNOSIS study). Subsequent measurements in the same woman are of unknown value.

This prognostic prediction tool, after proper external validation, will only be able to identify a portion of high-risk pregnancies between those with an sFlt-1/PlGF ratio above 38 (detection rate= 59.6%). However, it is the first step towards the reduction of the sFlt-1/PlGF ratio 38 cut-off criteria false positive rate. It has also been shown as superior to the use of a higher sFlt-1/PlGF ratio cut-off level, considering repeated determinations.

Despite MoM transformation of sFlt-1 not yet being usual practice, it should be considered when assessing pre-eclampsia prognosis prediction. sFlt-1 also depends on maternal weight. However, as multiple testing

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was allowed, markers should be adjusted for maternal weight at determination, which varies substantially during pregnancy. Unfortunately, this information was not available in the present study.

Despite the study duration (nearly four years), sample size may have reduced the accuracy of predictions; on the other hand, it has been sufficient to prove the superiority of adding NT-proBNP to the model and showed the risks of using sFlt-1/PlGF ratio raw values after selecting pregnancies with an sFlt-1/PlGF ratio above 38.

We did not consider maternal characteristics to assess the prior risk. One possible alternative approach would have been to combine the information obtained from first trimester pre-eclampsia screening to assess pregnancy's prior risk particularly when first trimester pre-eclampsia screening since the inclusion of PlGF has shown adequate test performances predicting early-onset pre-eclampsia (18-19). Despite the ASPRE study not showing the preventive role of low dose aspirin intake from 16 weeks of pregnancy in early-onset pre-eclampsia (20), future studies may offer further information of prior risk adjustment.

Interpretation

The purpose of prolonging pregnancy duration in patients with clinical suspicion of early-onset preeclampsia is the reduction of newborn morbidity by decreasing the number of preterm deliveries and their severity. This potential benefit is counterbalanced by potential life-threatening maternal complications. Despite published randomized clinical trials (21-23), the potential benefit of prolonging pregnancy duration is still unclear. Currently, the decision of inducing delivery depends on clinical signs and fetal well-being markers, which may be insufficient to prevent severe complications. The emergence of proangiogenic and antiangiogenic markers may be a valuable opportunity to select pregnancies that can be prolonged without major risks and to standardize the decision-making in preeclampsia management. An improvement in this patient selection is proposed in the present study.

A study by Verlohren et al. (24) identified the cut-off value of 655 for the sFlt-1/PlGF ratio that was associated with early-onset preeclampsia leading to imminent delivery (within 48h). A posterior publication (25) did not confirm the clinical relevance of the previous described cut-off value. When applying the sFlt-1/PlGF ratio cut-off of 655 to study population for predicting early-onset pre-eclampsia diagnosis leading to delivery within one week, the developed prognostic prediction tool showed superior test performance.

CONCLUSIONS

The aim of this prognostic assessment tool is the identification of high-risk pregnancies among those with an sFlt-1/PlGF ratio above 38. This prognostic assessment tool includes NT-proBNP, which is a cardiac damage marker that has been identified as a pre-eclampsia prognosis predictor using a study design that allows repeated measurements. In this context, we do not recommend assessing pregnancy prognosis solely using sFlt-1/PlGF ratio raw values as there seems to be better alternatives.

Clinical implications

The advantage of using the sFlt-1/PlGF ratio cut-off of 38 is the ease of interpretation if negative. Then ambulatory management and repeated pre-eclampsia markers assessment in more than one week if suspicion persists seems a safe approach, as no event has been observed in these groups (309 assessments). On the other hand, pregnancies with an sFlt-1/PlGF ratio above 38 require a more complex assessment and 16.9% (36/213) of assessments obtained a positive result with the prognostic assessment tool. The prognostic assessment tool reached a positive predictive value of 77.8%, which compared with the positive predictive value of the sFlt-1/PlGF ratio cut-off of 38 (22.1%) indicates its value as a confirmatory test. However, in approximately 85% of occasions, the prognostic assessment tool resulted negative and no position can be recommended for these pregnancies as 10.7% of them (19/177) delivered due to early-onset pre-eclampsia within one week. Once externally validated, this prognostic prediction tool may allow induced delivery indication and planning of adequate maternal and neonatal care in test positive pregnancies.

As proangiogenic and antiangiogenic markers vary with gestational age in healthy pregnancies, the predictive

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ability of those markers should benefit from MoM transformation (26). Besides, the ratio between markers with unequal discriminatory power is likely to be misleading, suboptimal and unnecessary (27-28). Moreover, we did not observe any obvious advantage in using raw sFlt-1/PlGF ratio values when above 38.

Costs of NT-proBNP inclusion can be balanced with the withdrawal of repeated PlGF determinations in pregnancies with clinical suspicion of early-onset pre-eclampsia and a previous sFlt-1/PlGF ratio above 38.

PlGF-based tests are also used to assist ruling out a diagnosis of pre-eclampsia in women presenting with suspected pre-eclampsia. PlGF levels above 100 pg/mL have been described as suggestive of patients without placental dysfunction who are unlikely to progress to delivery within 14 days from testing (29). The application of a PlGF cut-off value of 100 pg/mL to our study would omit 4.26% (2 out of 47) of pregnancies with early-onset pre-eclampsia leading to delivery within seven days of testing. Cut-off values above 150 pg/mL showed similar results to an sFlt-1/PlGF ratio cut-off of 38.

Research implications

Although there is need of acute and specific markers, usual study designs that only consider one test per pregnancy may not identify them. For instance, Verlohren et al. (30) assessed the role of NT-proBNP for predicting pre-eclampsia using regression analysis and their results were not conclusive. Conversely, in the present study NT-proBNP has been identified as an early-onset pre-eclampsia prognostic predictor. Maternal cardiac biophysical parameters have also been reported as predictors of severe forms of pre-eclampsia (31). Therefore, future studies designed to address early-onset pre-eclampsia prognosis and management should consider NT-proBNP inclusion and the use of study designs that allow repeated measurements.

Pregnancies with intrauterine growth restriction or chronic hypertension may require specific or adjusted prognosis assessment that was not possible in this study.

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Disclosure of interests

The authors have declared that no potential conflicts of interest exist.

Contribution to authorship

All authors approved the final version of the manuscript. ES was the first and main author of the manuscript, contributed to the planning of the study and acquisition, analysis, interpretation of data, software development and the writing of the article. PL_1 and PL_2 contributed to acquisition of data and revised the article critically. AIE contributed to the acquisition, interpretation of data and revised the article critically. EM contributed to acquisition of data and revised the article critically. CB designed the study and contributed to planning, analysis and revised the article critically. FVA contributed to the planning of the study, analysis and interpretation of data and the writing of the article.

Details of ethics approval

The local ethics committee (Comité de Ética de la Investigación del Principado de Asturias) approved the study (date of approval 29.06.2018, diary number 175/18).

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TABLE/FIGURE CAPTION LIST

Table 1: Comparison of binary test performance of the sFlt-1/PlGF ratio cut-off of 38 criteria and its combination with the prognostic prediction tool using all the included population, independently from sFlt-1/PlGF ratio value. Pregnancies with an sFlt-1/PlGF ratio of 38 or below have been considered as negative for the prognostic prediction tool. 95% CI: 95% confidence interval. DR: detection rate. FPR: false positive rate. PPV: positive predictive value. NPV: negative predictive value. PLR: positive likelihood ratio.

Figure 1: Inclusion-exclusion flow-chart.

Figure 2: Receiver operating characteristics (ROC) curve for median risk predictions of early-onset pre-eclampsia leading to delivery within one week in 123 women (213 samples) with suspected early-onset pre-eclampsia and an sFlt-1/PlGF ratio above 38, using a linear mixed model based on individual markers and gestational age (GA). Significant differences between AUC estimates of the sFlt-1 MoM model (solid line) and the PlGF MoM model (dashed line) were observed, referred to as A p-value ($p< 0.001$). While no differences were observed between the NT-proBNP (dotted line) and sFlt-1 MoM models, referred to as B p-value.

Figure 3: Receiver operating characteristics (ROC) curve for median risk predictions of early-onset pre-

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eclampsia leading to delivery within one week in 123 women (213 samples) with suspected early-onset pre-eclampsia and an sFlt-1/PlGF ratio above 38. The curves show the predictive performance of generalized linear mixed (GLM) models that combine gestational age (GA), and sFlt-1/PlGF ratio (left panel) and GA and sFlt-1 MoM (right panel) with NT-proBNP (solid line) and without NT-proBNP (dashed line). Vertical dashed red line indicates 5% false positive rate. Addition of NT-proBNP to both models significantly increases their predictive ability.

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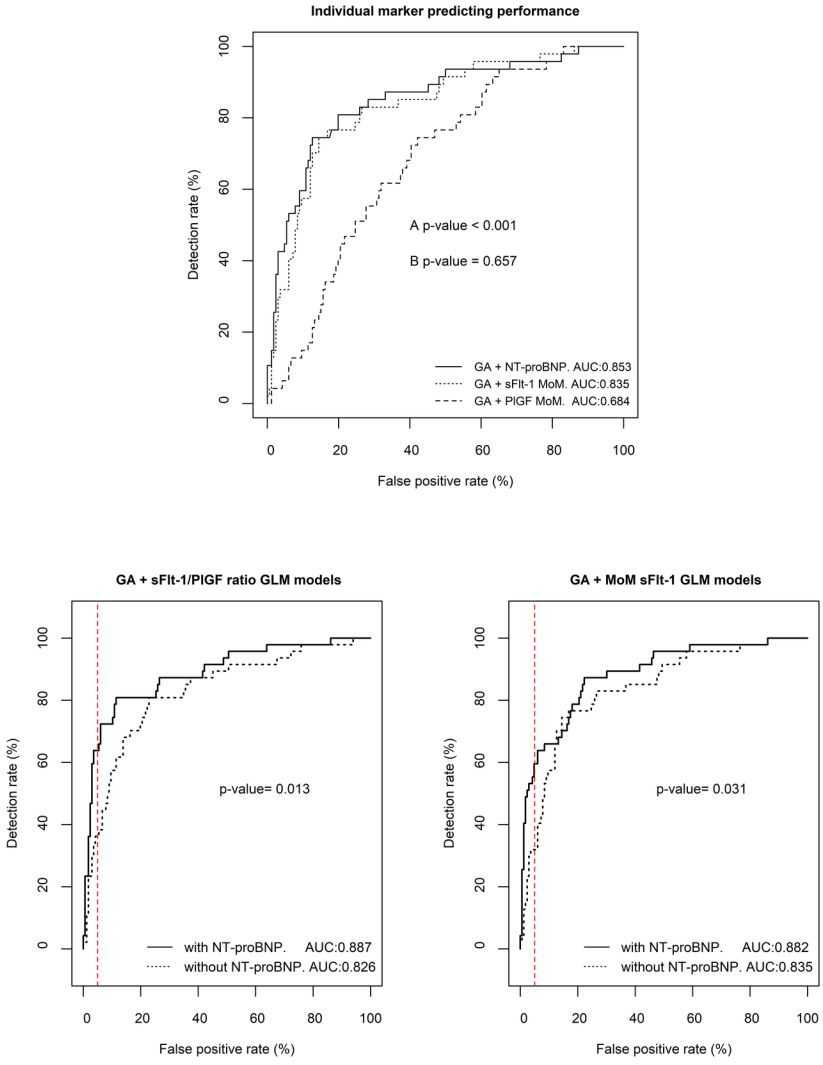

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