Added prognostic value of longitudinal changes of angiogenic factors in early-onset severe preeclampsia: analysis of maternal outcomes.

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Abstract

Background: Maternal levels of angiogenic factors are promising prognostic parameters in patients with suspected preeclampsia, but in women with confirmed preeclampsia this performance has been less explored. Objective: To assess in women with early-onset severe preeclampsia whether longitudinal changes in angiogenic factors improve the prediction of adverse outcome. Study design: A cohort was created of consecutive women admitted for early-onset severe preeclampsia with no indication for immediate delivery. Levels of placental growth factor [PlGF], soluble fms-like tyrosine kinase [sFlt-1] and sFlt-1/PlGF ratio were measured at admission and before delivery; and average daily change was calculated. The association of longitudinal changes of angiogenic factors with maternal complications and with the time interval to delivery was evaluated by logistic and Cox regression. Results: Sixty-three women were analyzed, of which 23 (36.5%) had a complication. Longitudinal changes of sFlt-1 were more pronounce in complicated pregnancies (median: 1079.5 vs. 343.7 pg/mL/day; p=0.04). On the multivariate analysis, the baseline model (clinical risk score and sFlt-1 at admission) explained a 6.6% of the uncertainty for complication (R2-Naegelkerke). The addition of sFlt-1 longitudinal changes improved this performance to 23.2% (p=0.004). The median time from admission to delivery was 3 days (95% confidence interval: 1.9-4.05) in those in the highest quartile of sFlt-1 longitudinal changes vs. 10 days (95% confidence interval: 8.1-11.9) in the remaining women (Log-rank test p<0.001). Conclusions: Longitudinal changes in sFlt-1 maternal levels from admission for confirmed early-onset severe preeclampsia add to baseline characteristics in the prediction of maternal complications.

INTRODUCTION

Preeclampsia (PE) is a severe multisystem condition characterized by hypertension and end-organ dysfunction. It complicates 2-8% of pregnancies (1) and is a leading cause of maternal and neonatal morbidity and mortality (2,3).

We can distinguish two entities in terms of pathophysiology, in one hand late-onset PE (developed after 34 weeks' gestation) and in the other hand early-onset PE that is thought to be more related to placental insufficiency (4–6), which confers higher maternal and neonatal risks (3,7,8).

Expectant management improves neonatal outcome in selected cases of early-onset PE (9,10). Thus, clinical decisions are determined by a trade-off between reducing the risks of maternal complications by timely delivery and minimizing the risks of prematurity by expectant management. Therefore, a reliable prediction of maternal complications is essential in selecting women for expectant management. So far, even when multi-parametric risk-scoring is used, such prediction capacity is still moderate (11,12).

Maternal levels of angiogenic factors at admission for suspected PE have emerged as prognostic predictors,

including placental growth factor [PlGF], soluble fms-like tyrosine kinase 1 [sFlt-1] and the sFlt-1/PlGF ratio. These factors have showed a good capacity in ruling out maternal complications and a moderate capacity in predicting its occurrence (13,14). In addition, they may predict the interval to delivery in suspected PE (15). It has been also suggested that longitudinal changes of the angiogenic factors levels may provide additional prediction capacity for the occurrence of complications in suspected PE (16). The performance of this capacity in women with confirmed PE has been less explored. Sequential angiogenic factors differences has been compared retrospectively between early and late-onset PE (17) or described prospectively in women admitted with mixed hypertensive disorders (18). However, the clinical value of the angiogenic factors longitudinal changes has not been specifically investigated in early-onset cases already meeting severity criteria, which is the clinical presentation with the greatest risk of maternal and fetal complications (19).

The objective of this study is to test in early-onset severe PE whether the longitudinal changes in maternal anigiogenic factors levels improve the prediction capacity of adverse outcome and time interval to delivery.

MATERIALS AND METHODS

Population

Between March 2017 and April 2019 a prospective cohort was created of consecutive singleton pregnancies with early-onset severe PE who were admitted to the Departments of Maternal-Fetal Medicine at BCNatal (Barcelona, Spain), comprising two referral university hospitals (Hospital Clínic and Hospital Sant Joan de Déu). Additional inclusion criteria were the absence of maternal complications at admission (as detailed below) and the absence of fetal indication for imminent delivery. The study protocol was approved by the Ethics Committee (HCB/2017/0077) and participants provided their written informed consent.

Definitions

PE was defined by the presence of de novo hypertension (systolic blood pressure (BP) > 140 mmHg and/or diastolic BP> 90 mmHg measured on two occasions at least 4 hours apart) after 20 weeks of gestation accompanied by proteinuria (> 300 mg/24h or a urine protein/creatinine ratio > 0.3 mg/mmol)(20). Early-onset cases were considered when admission occurred before 34 weeks of gestation. Gestational age was calculated according to the crown-rump length at first-trimester ultrasound scan (21). Severe features were defined according the American College of Obstetricians and Gynecologists as: systolic BP> 160 mmHg or diastolic BP > 110 mmHg on two occasions at least 4 hours apart, thrombocytopenia (<100x10^9/L platelets), impaired liver function (blood concentrations of liver enzymes to twice normal and/or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses), renal insufficiency (serum creatinine concentration greater than 1.1 mg/dl in absence of other renal disease), pulmonary edema or new-onset cerebral or visual disturbances (22).

At admission, the risk for complications was estimated according to the Prediction of complications in Early-onset-Preeclampsia (PREP-L) score (12,23), which includes maternal age, gestational age, preexisting medical conditions, protein-to-creatinine ratio, serum urea concentration, platelet count, systolic blood pressure, need for antihypertensive treatment or magnesium sulphate.

Maternal complications were defined as: (i) HELLP syndrome (lactate dehydrogenase [LDH] >600 IU/L, AST to twice normal values and platelet count <100x10^9/L); (ii) Central nervous system dysfunction (eclampsia, Glasgow Coma Score <13 (24), stroke, reversible ischemic neurological deficit or cortical blindness); (iii) hepatic dysfunction (INR >1.2 in the absence of disseminated intravascular coagulation, MELD score> 10 (25,26) or hepatic hematoma or rupture); (iv) renal dysfunction (dialysis, serum creatinine concentration greater than 150 μmol/L or urine output <0.5 ml/kg/h during 12 hours, according to renal insufficiency by RIFLE criteria (27); or need for treatment with furosemide to maintain urine output >0.5ml/kg/h for 3 hours); (v) respiratory dysfunction (pulmonary edema, requirement of invasive or non-invasive mechanical ventilation, oxygen requirement greater than 50% concentration for longer than 1 hour or severe breathing difficulty [no criteria of pulmonary edema but presence of dyspnea, crackles in pulmonary auscultation and

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SaO_2<90%]); and/or (vi) cardiovascular dysfunction (need for inotropic support, left ventricle failure or myocardial infarction); (vii) critical hypertension (requirement for three or more different antihypertensive treatments to control BP).

Fetal growth restriction (FGR) was defined according to the Delphi consensus for early-onset form (28).

Management

At admission, all women underwent a physical and biochemical examination according to standard recommendations. Maternal BP was monitored continuously and laboratory tests were assessed at least once daily. Magnesium sulfate for seizure prophylaxis and corticosteroid therapy for fetal lung maturity were administered to all women. Antihypertensive treatment was administered when BP was persistently 160/110 mmHg or higher. Fetal assessment was performed by cardiotocograhy every day and Doppler at least twice a week.

Indications for delivery were uncontrollable BP, maternal complications (defined above), placental abruption or non-reassuring cardiotocographic reading (29). Beyond 26 weeks, indications for delivery also included persistent (>6 hours apart) ductus venosus (DV) Doppler with reversed diastolic flow; and beyond 30 weeks persistent (>6 hours apart) umbilical artery (UA) Doppler with reversed end-diastolic flow or DV pulsatility index above the 95^{th} centile for gestational age (30). Elective delivery was performed beyond 34 weeks after completion of pulmonary maturation. Clinicians and researchers were unaware of the angiogenic factor levels as they were measured after delivery on stored samples.

Samples collection and angiogenic factors measurement

At admission and before delivery (within 12 hours), a 5 ml peripheral maternal blood sample was obtained. Serum was separated by centrifugation at 2000 g for 10 min at room temperature, and samples were immediately stored at -80^{o}C until assayed at an independent laboratory.

Maternal serum concentrations of sFlt-1 and PlGF were determined by the fully automated Elecsys assays for sFlt-1 and PlGF on an electrochemiluminescence immunoassay platform (Cobas analyzers, Roche Diagnostics). In all the kits, the intra-assay precision was <4% for both assays and the inter-assay precision was 2.3-5.6% and 2.4-4.6% for sFlt-1 and PlGF assays respectively.

Longitudinal changes were quantified by calculating delta values: (level at delivery - levels at admission)/days from admission to delivery.

Sample size and statistical analysis

From a previous cohort of women with severe early PE (31) we estimated the interval from admission to delivery to be 12 days in non-complicated and 5 days in complicated pregnancies. Assuming this difference between women in the highest quartile of angiogenic delta values and those in the 1^{st}-3^{rd} quartiles, for an alpha-risk of 5% and a power of 80%, 56 women would be needed (log-rank test)(32).

Variables were checked for normal distribution by Kolmogorov-Smirnov test. Paired comparisons of the angiogenic values between admission and delivery were performed by non-parametric Wilcoxon sign test. Comparisons between uncomplicated and complicated pregnancies were performed by Student-T (assuming unequal variances), Mann-Whitney U, Pearson Chi-squared and Fisher-F, as appropriate.

The likelihood of maternal complications was modelled by logistic regression (with robust estimation of the standard errors). Levels of angiogenic factors were log-transformed. The predictive performance was determined by receiver–operating characteristic (ROC) curve analysis.

The interval from admission to delivery was graphed by Kaplan-Meier procedure and tested for differences in the survival time by the angiogenic delta values quartile using Log Rank (Mantel-Cox) test. The interval to delivery was modelled by multivariate Cox regression checking for the assumptions of proportionality and log-linear relationship.

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Statistical analyses and graph constructions were performed using STATA 13.0 (StataCorp LT, Texas, USA) and R 3.1.2 (The R Foundation for Statistical Computing) [package "pROC"].

RESULTS

During the study period 86 women were admitted for early-onset severe PE. 68 of them had no maternal complications at admission and no fetal indication for imminent delivery. Blood samples for angiogenic factors measurement were not collected from 4 of these patients due to a breach of the study protocol. In one additional case, blood sample was not obtained at delivery. Thus, a total of 63 women were available for analysis with both at-admission and at-delivery measurements. Out of them, 23 patients (36.5%) had a complication. Table 1 shows the baseline characteristics by the presence of complications and supplementary table 1 details the maternal complications. The median time interval between admission and delivery was 9 days (ranging from 2 to 24). It was shorter in complicated pregnancies [7 (2-22)] vs [10 (2-24)] in those without complications.

Supplementary table 2 shows the levels of the angiogenic factors at admission and at delivery, with the delta values (expressing average daily change). Of note, all the evaluated angiogenic factors significantly differed between admission and delivery. Table 2 and supplementary figure 1 depict the angiogenic factors levels in uncomplicated and complicated pregnancies. Only the sFlt-1 delta values were significantly different between those without and with complication (median values: 343.7 vs. 1079.5 pg/mL/day; p=0.04). Expressed as relative changes from the admission values, this corresponds to 2.6% vs. 8.2% daily increase. Supplementary figure 2 shows the individual and averaged changes of sFlt-1 by the occurrence of complications.

On the multivariate analysis, the baseline model (PREP-L risk score and sFlt-1 at admission) explained 6.6% of the uncertainty of complications occurrence (R^2 Naegelkerke). The addition of sFlt-1 delta values significantly improved this performance (R^2 Naegelkerke of 23.2%; p=0.004). Table 3 shows the logistic regression model which includes all three predictors. While the area under the curve of the baseline model was 0.6 (95%CI 0.46-0.75), it increased to 0.75 (95% CI 0.62-0.87) when the sFlt-1 delta was added. For a 20%, 30% and 40% of false-positive rates, detection rates were better for the model including sFlt-1 delta: 57.1% vs. 33.3%; 66.7% vs. 38.1%; and 76.2% vs. 47.6%, respectively. Figure 1 shows both ROC curves.

Figure 2 shows the Kaplan-Meier graph of the time interval to delivery: the median time was 3 days (95%CI 1.96-4.05) in those in the highest quartile of delta sFlt-1 values vs. 10 (95%CI 8.1-11.9) in those in the 1^{st}-3^{rd} quartiles [Log Rank (Mantel-Cox) p<0.001].

Table 3 shows the Cox regression modelling of the time interval from admission to delivery. Of note, to meet the proportional hazards assumption, log-transformed sFlt-1 delta values had to be categorized in quartiles and entered in the model as binary (highest quartile vs. those the 1^{st}-3^{rd} quartile): hazard ratio of 3.15 (95%CI 1.67-5.86; p<0.001).

DISCUSSION

Our findings demonstrate that the longitudinal changes in sFlt-1 levels from admission for early-onset severe PE improve the prediction of maternal complications and the interval to delivery over baseline clinical and analytical parameters.

Several previous studies have showed the ability of angiogenic factors when cross-sectionally measured at admission for suspected PE in stratifying the risk of adverse outcome, and demonstrated that abnormal values were associated with a shorter duration to delivery (14,15,33). The angiogenic factors changes during pregnancy are also well known (34–36). In light of this evidence, it is reasonable to assume that the change of the angiogenic factors levels over time may add further predicting capacity for adverse outcome. Indeed, Zeisler et al (37) found that in patients with suspected PE there was a greater longitudinal increase in the sFlt-1/PlGF ratio in women who developed PE and adverse maternal outcome than in those who did not develop it. Additionally, Schoofs et al (16) suggested that repeated measurements of the sFlt-1/PlGF ratio seem to be superior in predicting PE and its complications to a single measurement.

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All this evidence, however, come from studies in women with suspected PE and whether these findings apply to women with diagnosed PE was unclear, especially in early-onset severe PE. A retrospective study including 34 patients with diagnosed PE demonstrated that early-onset cases had a higher daily increase in sFlt-1 (11% vs. 3%) and sFlt-1/PlGF ratio (23% vs. 8%) compared to late-onset PE (17). More recently, Baltajian et al (18) reported in a prospective cohort of 99 women with suspected PE (53 of them confirmed) admitted before 37 weeks that daily changes of sFlt-1 and sFlt-1/PlGF ratio were significantly higher in women ending up having a maternal or fetal adverse outcome. This study could be criticized because many of the described complications like FGR and transaminitis were likely already present at admission. Thus, rather than assessing the role of the angiogenic factors longitudinal changes in predicting complications, this study may have addressed the association of these changes with features of severe PE. Our results strengthen the findings from previous studies and demonstrate the clinical value of the angiogenic factors longitudinal changes even in confirmed early-onset severe PE.

Interestingly, we found sFlt-1 more strongly associated with maternal complications than PlGF. Consistently with our findings, the series by Baltajian et al (18), that included women admitted for PE suspicion, found that the median daily increase of sFlt-1 was 6 times higher in women with adverse outcome, while no significant difference were found in daily decrease of PlGF between women with and without adverse outcome. In PE, maternal sFlt-1 levels drop after delivery to $< 1\%$ of its pre-delivery value while PlGF drops to 30% (36), suggesting that sFlt-1 is almost uniquely produced by the placenta while PlGF have other sources. Indeed, PlGF is expressed in a variety of organs , tissues and cells (38). As the stressed endothelium produces PlGF (39), this may be a compensatory mechanism to keep minimum levels of circulating PlGF. Thus, one may speculate that being more closely correlated with placental disease, sFlt-1 is a better marker of PE severity than PlGF. The increased sFlt-1 values may trigger the endothelial dysfunction that leads to PE complications (40).

Most guidelines recommend expectant management in selected cases of PE until 34 weeks (41), based on the evidence that the risk of serious complications is low when appropriate care is provided and on the derived neonatal benefits (9,10,42). However, the selection of cases at especially high-risk for maternal complications is clinically challenging. All guidelines recommend a similar set of severity criteria (41), that were established from experts opinion without a good evidence on their individual performance in predicting complications. In addition, except for the Canadian guideline (43), gestational age at diagnosis was not included as a severity criteria, while there is good evidence on its independent contribution in predicting maternal morbidity (44). A step forward was made by the PRE-EMPT consortium developing and validating a scoring tool for risk-stratification of women admitted with PE (the PIERS score), with good capacity and predictive performance (11). However, this model included women with any onset PE, and not specifically those with early-onset. More recently, the PREP-L model was specifically derived for early-onset PE. Compared to the PIERS model, which had an AUC between 0.7-0.8 at one week after admission, the PREP-L model showed discrimination of 0.82 for a longer period until postnatal discharge from hospital (12). Our study shows that the addition of sFlt-1 delta values may increase the prediction of maternal complications achieved by PREP-L and sFlt-1 at admission. If confirmed, our results would enable the use of longitudinal changes in angiogenic factors as a stratifying tool to stablish time of delivery.

Our series has some unique features. It is a prospective cohort of women admitted for confirmed early-onset severe PE. The angiogenic factors were longitudinally measured and evaluated for the prediction of incident complications. In addition, managing clinicians were blinded to these measurements. We also acknowledge some limitations. First, the relatively small sample size which does not allow the evaluation of individual complications. However, this sample size has to be regarded in the context of the very low incidence of early-onset PE (˜0.5%), which is even lower if we consider severe cases without complications at admission (7). Thus, 63 cases correspond to a base population of more than 15,000 deliveries. Second, we only measured the angiogenic factors at two time points, and, therefore, other non-linear trends could not be explored. In particular, whether the rise in sFlt-1 precedes the onset of the complication could not be assessed in our study. Finally, our findings do not necessarily mean that modifying the clinical management according to longitudinal changes in sFlt-1 would improve the maternal outcomes.

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CONCLUSION

In summary, our study suggests that longitudinal changes in maternal sFlt-1 levels from admission for confirmed PE add to baseline characteristics in predicting maternal complications and interval to delivery. Further studies are needed to evaluate the evolution of angiogenic factors levels at fixed time points after admission and to address the impact of incorporating this parameter in the clinical management of early-onset PE on maternal and fetal outcomes.

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DISCLOSURE OF INTERESTS

The authors report no conflict of interest.

CONTRIBUTION TO AUTHORSHIP

AP, EM, and FF: study design. AP, LFB, EM, and SH: patient recruitment. LFB, LB, and AG: data collection. AP and FF: data analysis. AP, LFB, EM, LB, AG, LY, FC, SH, and FF: drafting the manuscript and critical revision. All the authors have seen and approved the final version of the article.

DETAILS OF ETHICS APPROVAL

This study was approved on 22 March 2017 by the Institutional Ethics Committee of Hospital Clinic de Barcelona (Reference number: HCB/2017/0077).

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Table 1. Baseline characteristics by the subsequent occurrence of complications

	uncomplicated preeclampsia (n=40)	complicated preeclampsia (n=23)
Demographic characteristics	Demographic characteristics	Demographic characteristics
Maternal age (years) (Mean[SD])	32.6 (5.6)	35.3 (6.1)
Non-Hispanic white (n[%])	18 (45)	8 (34.8)
Smoking (n[%])	5 (12.5)	2(8.7)
Obesity (BMI >30) (n[%])	6 (15)	2 (8.7)
Nulliparity (n[%])	28 (70)	14(60.9)
Preeclampsia history (n[%])	3 (7.5)	4(17.4)
FGR history (n[%])	3 (7.5)	0
Chronic hypertension (n[%])	6 (15)	3 (13)
Renal disease (n[%])	2 (5)	1 (4.3)
Diabetes (n[%])	2 (5)	0
Maternal characteristics at admission	Maternal characteristics at admission	Maternal characteristics at admissio
GA at admission (weeks) (Mean[SD])	30.3 (2.9)	29.7 (2.8)
Systolic blood pressure (mmHg) (Mean[SD])	168 (16)	167(15)
Diastolic blood pressure (mmHg) (Mean[SD])	104 (8.5)	101 (7.8)
Proteinuria (mg/24h) (Median[IQR])	1375 (3107)	2564 (4791)
Platelet count (x10^9 L) (Mean[SD])	216 (78.6)	172 (64.2)
Creatinine (µmol/L) (Mean[SD])	61.2 (14.3)	64.8 (21.1)
Aspartate transaminase IU/L, (Median[IQR])	22 (31)	26 (25)
Oxygen saturation (%)(Median[IQR])	98.5(2)	97.5(2)
PREP-L risk score (Mean[SD])	73.4 (18.6)	80.3 (10)
Perinatal characteristics		
GA at delivery (weeks) (Mean[SD])	31.7 (2.5)	31.1 (2.3)
Birthweight (g) (Mean[SD])	1252 (458)	1286(437)
FGR (n[%])	34 (85)	18 (78.3)
Cesarean section (n[%])	34 (85)	22 (95.7)
5-min Apgar<7 (n[%])$^+$	5 (13.2)	4(17.4)
Acidosis at birth (n[%])$^+$	2(5.3)	0
NICU admission (n[%])$^+$	30 (78.9)	21 (91.3)
Perinatal death (n[%])	4 (10)	2(8.7)

FGR: fetal growth restriction; GA: gestational age; NCIU: neonatal intensive care unit

*Non-parametric test (Fisher-F or Mann-Whitney-U); + Stillbirths excluded

Table 2. Angiogenic factors levels (median, interquartile range)

		uncomplicated preeclampsia (n=40)	**complicated preeclampsia** (n=23)
At admission	PlGF(pg/mL)	37(52.1)	35.4(70.5)
	sFlt-1 (pg/mL)	13453(9372)	13120(9843)
	sFlt-1/PlGF ratio	416.4(459.7)	412.9(435.9)
At delivery	PlGF(pg/mL)	27.1(45.4)	42(29.5)
	sFlt-1 (pg/mL)	16227(9773)	23094(20501)

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		uncomplicated preeclampsia (n=40)	**complicated preeclampsia** (n=23)
Delta values	sFlt-1/PlGF ratio	705.7(782)	674.8(834.5)
	PlGF(pg/mL)*day^{-1}	-1(4.2)	-1.4(7.9)
	sFlt-1 (pg/mL)*day^{-1}	343.7(1431.2)	1079.5(3880.3)
	sFlt-1/PlGF ratio*day^{-1}	24.2(77.2)	19.1(72.4)

***** Mann-Whitney U test

Table 3. Logistic regression of the association to maternal complications and Cox regression of the time interval from admission to delivery (days)

		Coefficient	SE	p	OR/HR	95% CI Lower	95% CI Upper
Logistic regression	sFlt-1 at admission (log-transformed)	-0.49	0.56	0.385	0.61	0.21	1.84
	PREP_L risk score (%)	0.06	0.02	0.012	1.06	1.01	1.12
	Delta sFlt-1 value (log-transformed)	4.28	1.56	0.006	72.14	3.37	1544
Cox regression	sFlt-1 at admission (log-transformed)	0.17	0.29	0.546	1.19	0.68	2.09
	PREP_L risk score (%)	0.03	0.01	0.004	1.03	1.01	1.05
	Delta sFlt-1 value (log-transformed)	1.15	0.32	<0.001	3.15	1.67	5.86

SE: Standard Error; OR: Odds Ratio; HR: Hazard Ratio

Figure 1. Prediction performance (receiver–operating characteristic curves) for maternal complications of the baseline model including PREP-L and sFlt-1 at admission (dashed line) vs. the model where delta sFlt-1 value is added (dotted line).

Figure 2. Kaplan-Meier graph of the time interval from admission to delivery (days) of women with delta sFlt-1 values in the highest quartile (dashed line) vs. those the 1st-3rd quartile (solid line).

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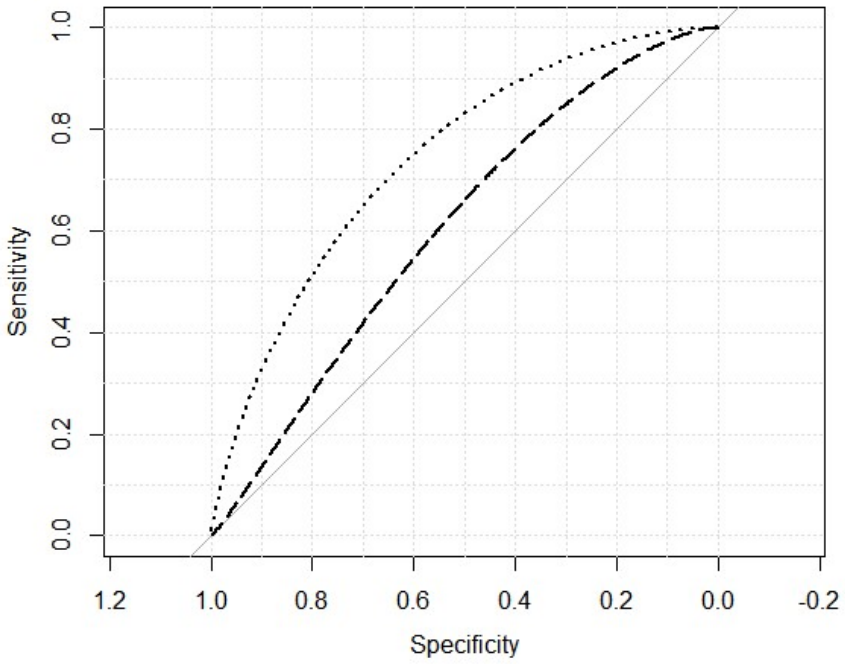

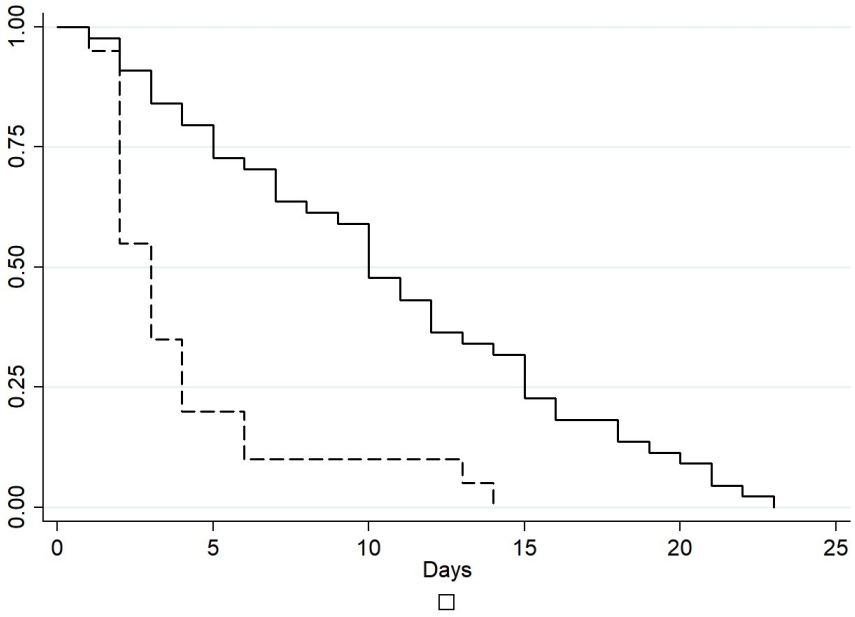

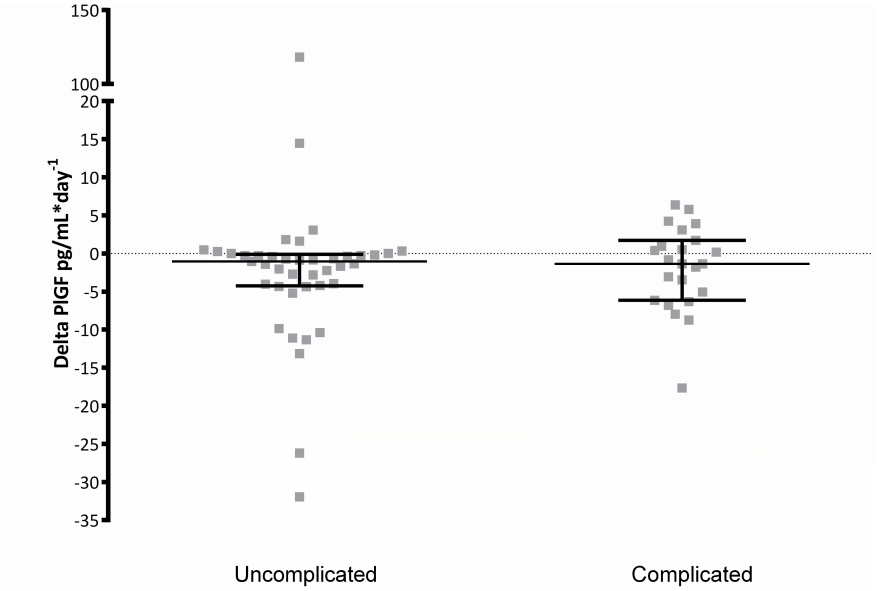

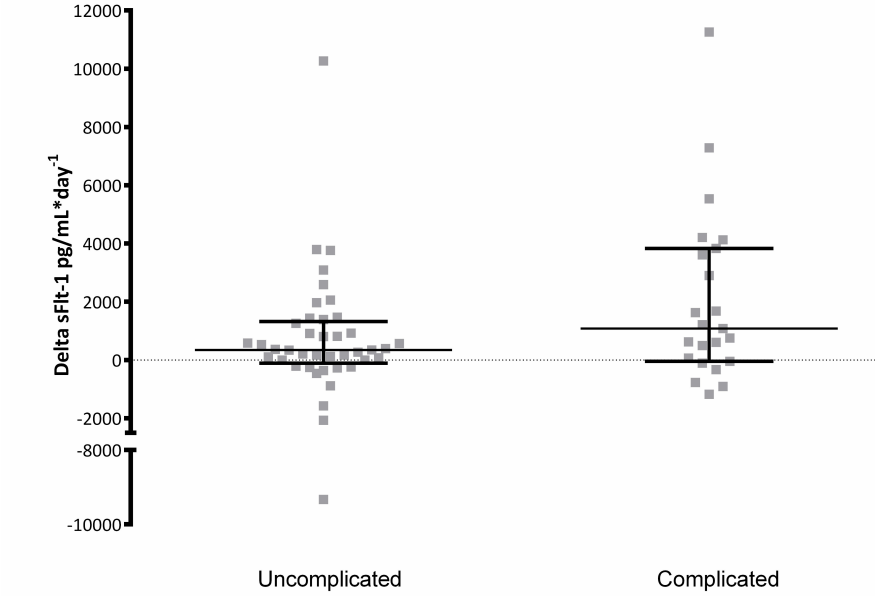

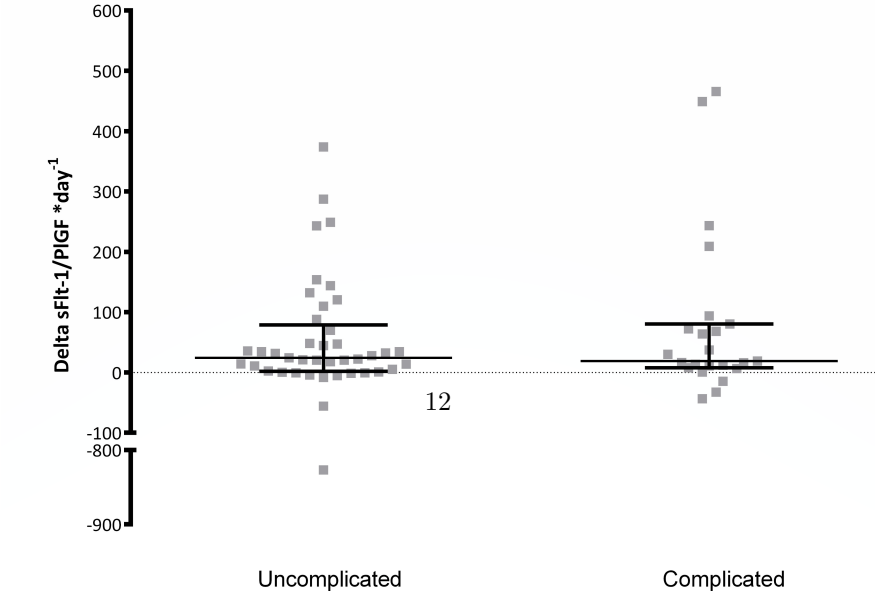

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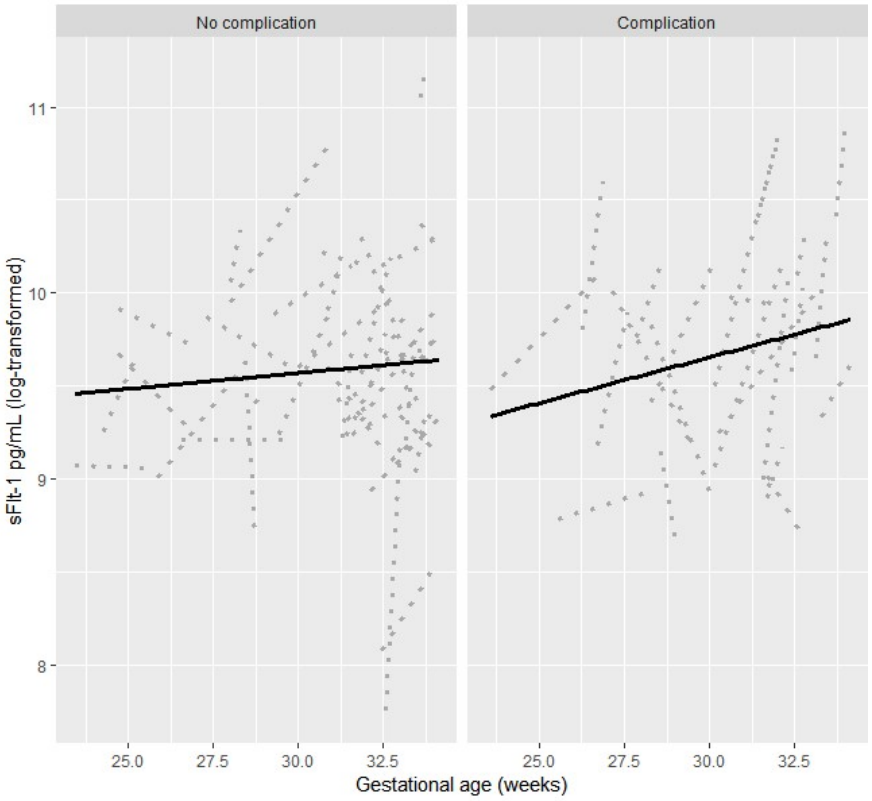

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