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Prediction of organ complications in women with a confirmed diagnosis of preeclampsia by glycocalyx degradation products

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ABSTRACT

Objectives: Elevated plasma concentrations of glycocalyx degradation products have been associated with organ dysfunction in preeclampsia. We hypothesized that the glycocalyx degradation products syndecan-1, hyaluronic acid, and thrombomodulin, could predict subsequent organ dysfunction in women diagnosed with preeclampsia.
Study design: This was a prospective, observational cohort study.
Main outcome measures: Women were enrolled at the time of diagnosis, provided no organ dysfunction was present. The primary outcome was a composite of complications based on the core outcome set for preeclampsia research (BJOG 2020). Exposures were plasma concentrations of syndecan-1, hyaluronic acid and thrombomodulin. Receiver operating characteristic curves were constructed for the composite and for single outcomes with ≥ 10 events. Predictive performance was quantified as the area under the curve (AUC) with a 95% confidence interval (CI).
Results: None of the glycocalyx degradation products predicted the composite outcome. For single outcomes, syndecan-1 was associated with elevated liver enzymes (AUC of 0.64; 95% CI 0.52–0.76). Hyaluronic acid predicted thrombocytopenia (AUC 0.67; 95% CI 0.52–0.83) and elevated liver enzymes (AUC 0.69; 95% CI 0.57–0.82).
Combining the markers in multivariable analyses showed similar results as univariable analyses. When combined with sFlt-1, none of the glycocalyx degradation products improved the predictive performance compared to sFlt-1 alone.
Conclusion: In women with a confirmed diagnosis of preeclampsia, plasma concentrations of syndecan-1, hyaluronic acid, and thrombomodulin demonstrated limited predictive ability for the subsequent composite outcome of organ dysfunction. Hyaluronic acid was the most promising marker for the single outcomes thrombocytopenia and elevated liver enzymes.

1. Introduction

Preeclampsia is defined as hypertension and maternal organ dysfunction occurring after 20 weeks of gestation and affects 3–5% of all pregnant women, with an estimated 42,000 maternal deaths worldwide annually.[1] The pathophysiology of preeclampsia remains poorly understood, and it is likely that multiple mechanisms lead to its wide spectrum of clinical manifestations. Among many proposed

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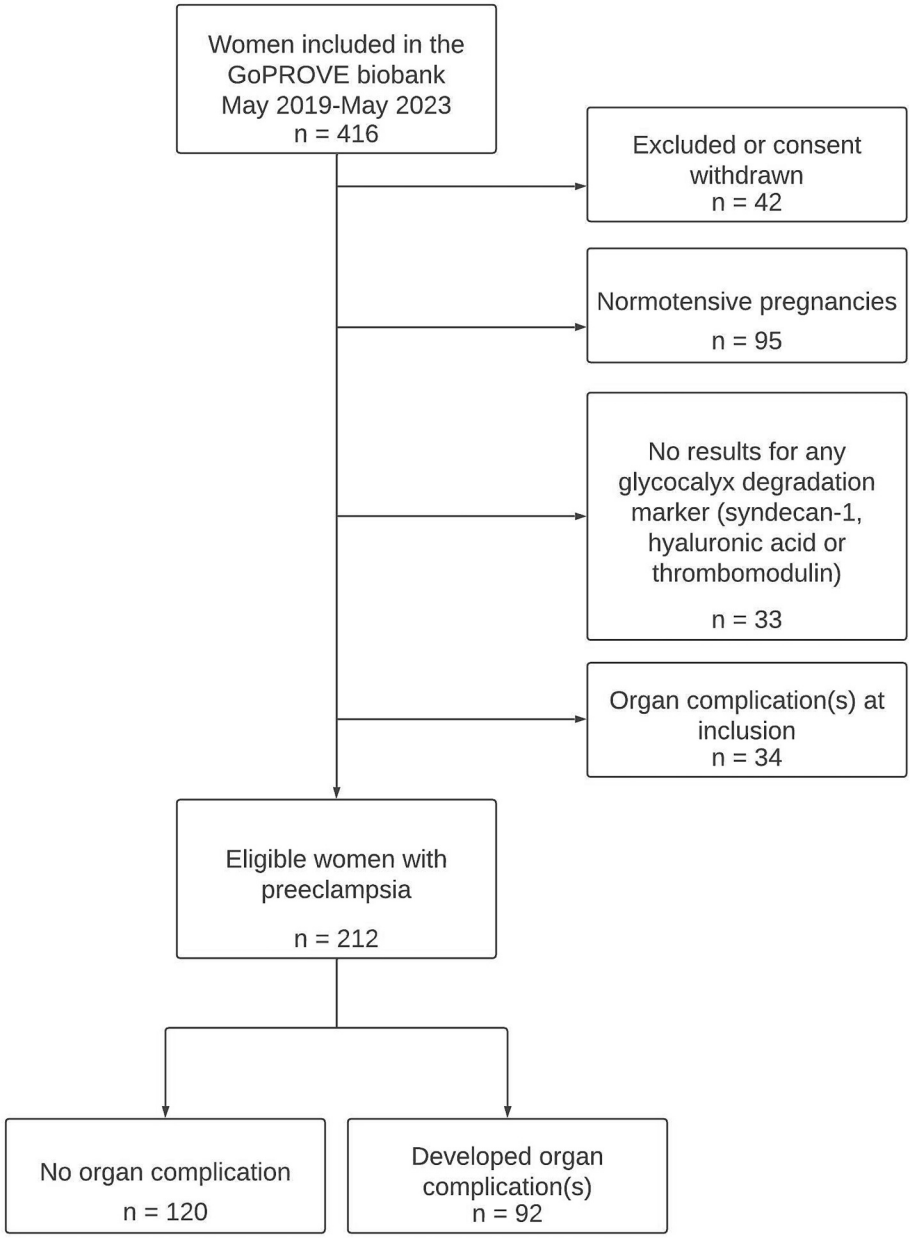

Fig. 1. Flow chart of the study population.

mechanisms, placental malfunction that results in the excessive release of soluble fms-like tyrosine kinase (sFlt-1) causing maternal endothelial dysfunction, is a widely recognized central pathway.[2,3].

The healthy endothelium is covered by the endothelial glycocalyx, which plays a crucial role in regulating capillary permeability, vessel tone, and coagulation. In diseases that cause multiorgan failure, the glycocalyx is shed, and degradation products can be detected in the circulation.[4–6] Circulating concentrations of glycocalyx degradation products, including syndecan-1, hyaluronic acid, and thrombomodulin, have been previously investigated in preeclampsia.[7–10] Syndecan-1 exhibits a complex association with preeclampsia, with conflicting results across studies as to whether plasma concentrations are decreased, similar, or increased in preeclampsia compared with unaffected pregnancies.[7] On the other hand, plasma concentrations of hyaluronic acid and thrombomodulin have repeatedly been reported increased at diagnosis in women with preeclampsia compared with normotensive controls.[8–10] However, the predictive value of these glycocalyx degradation products for determining the risk of subsequent maternal organ dysfunctions upon diagnosis of preeclampsia has not been evaluated. Therefore, we set out to investigate whether plasma concentrations of syndecan-1, hyaluronic acid, and thrombomodulin, alone or in combination, could predict organ dysfunction in women with a confirmed diagnosis of preeclampsia.

2. Methods

Ethical approval was obtained on December 28, 2018, by the Regional Ethics Committee of Gothenburg (Dnr 955–18) with amendments approved on April 4, 2023, by Ethix, the Swedish Ethical Review Authority (Dnr 2023–02271-02–391236). The study was conducted in accordance with the Helsinki Declaration. Written and oral informed consent was obtained from all participants before the start of the study.

2.1. Population

This was a prospective, observational cohort study based on the

Table 1
Maternal and fetal characteristics at enrollment and birth in women with preeclampsia, stratified by the presence or absence of the composite outcome.

Maternal or fetal characteristics	All women (n = 212)	The composite outcome Yes (n = 92)	No (n = 120)
Age (years)	31 (4.9)	31 (4.6)	31 (5.1)
Nulliparous	184 (79.3%)	80 (87.0%)	91 (75.8%)
Body mass index (kg/m^2)	26.8 (5.6)	26.6 (6.1)	27.0 (5.3)
Gestational diabetes	7 (3.3%)	2 (2.2%)	5 (4.2%)
Chronic hypertension	11 (5.2%)	4 (4.3%)	7 (5.8%)
Smoking at any time during pregnancy	9 (≤4.2%)	2 (2.2%)	7 (≤5.8%)
At inclusion			
Gestational age at blood sampling (weeks + days)	37 + 2 (34 + 0–38 + 6)	37 + 5 (34 + 5–39 + 1)	36 + 4 (32 + 3–38 + 5)
Systolic blood pressure (mmHg)	144 (13)	144 (12)	144 (14)
Missing	1 (n = 211)	1 (n = 91)	0
Diastolic blood pressure (mmHg)	90 (10)	90 (8)	90 (11)
Missing	1 (n = 211)	1 (n = 91)	0
Hemoglobin (g/dL)	12.0 (1.0)	12.0 (1.0)	12.1 (1.0)
Platelet count (x10^9)	211 (60)	196 (60)	221 (58)
Creatinine (μmol/L)	57 (13)	60 (11)	54 (13)
Alanine aminotransferase (μkat/L)	0.29 (0.22)	0.31 (0.24)	0.27 (0.19)
Duration of antihypertensive treatment before birth (days)	5 (2–13)	4 (2–10)	6 (2–20)
At birth			
Gestation at birth (weeks + days)	37 + 4 (34 + 6–39 + 0)	38 + 0 (35 + 5–39 + 2)	37 + 1 (34 + 4–38 + 6)
Birth before 37 + 0 weeks gestational age	86 (40.6%)	31 (33.7%)	55 (45.8%)
Days from diagnosis of preeclampsia to birth	4 (2–9)	4 (2–8)	5 (2–10)
Liveborn	210 (99.1%)	91 (98.9%)	119 (99.2%)
Birthweight (g)	2692 (952)	2834 (907)	2584 (975)
Vaginal birth	111 (52.4%)	54 (58.7%)	57 (47.5%)
Cesarean section	101 (47.6%)	38 (41.3%)	63 (52.5%)

Numeric variables are presented as mean (standard deviation), or median (interquartile range) as appropriate. Categorical variables are presented as counts and percentages.

Gothenburg Preeclampsia Obstetric Adverse Events Database and Biobank study (GoPROVE).[11] Women with a confirmed diagnosis of preeclampsia were recruited between May 2019 and May 2023 at Sahlgrenska University Hospital Östra, Gothenburg, Sweden. Preeclampsia was defined as new-onset hypertension (>140/90 mmHg on two occasions at least 15 min apart) after 20 gestational weeks and excessive proteinuria, defined as a urine albumin/creatinine ratio > 8 g/μmol, or protein/creatinine > 30 mg/mmol, or ≥ 2 + protein on a urine dipstick after 20 gestational weeks. Superimposed preeclampsia on chronic hypertension was defined as de novo excessive proteinuria after 20 gestational weeks in a woman with chronic hypertension. Exclusion criteria included preexisting cardiac disease, neurologic disease, renal disease, or any complication included in the composite outcome (defined under Outcomes) present at the time of blood sampling at inclusion. A flow chart of the study population is presented in Fig. 1.

2.2. Exposures

Exposures were plasma concentrations of syndecan-1 (ng/mL), hyaluronic acid (ng/mL), and thrombomodulin (ng/mL) at GoPROVE inclusion. Serum concentrations of sFlt-1 (pg/mL) obtained from a previous work by our group (submitted manuscript) were included to construct multivariable models alongside the glycocalyx degradation products.

2.3. Outcomes

The primary outcome was a composite of preeclampsia-associated maternal organ dysfunctions and complications as recommended by a core set of outcomes for preeclampsia research developed through a Delphi process.[12] These included maternal mortality, eclampsia, stroke, cortical blindness, retinal detachment, pulmonary oedema, acute kidney injury, liver capsule hematoma or rupture, placental abruption, postpartum hemorrhage, raised liver enzymes, low platelets, admission to intensive care unit required, and intubation and mechanical ventilation (except for general anesthesia for cesarean section). While these outcomes were selected for inclusion in the core outcome set for preeclampsia research, their individual definitions (e.g. the threshold for thrombocytopenia) were not established within the Delphi process, and definitions used in this study are listed in Table S1. The secondary outcomes were single-organ dysfunctions (all part of the core set of outcomes) with ≥ 10 recorded events (hereafter single outcomes). Dates of diagnosis and organ dysfunctions were retrieved from medical charts. All data were checked for accuracy.

2.4. Sample collection

Venipuncture was performed at inclusion by research staff or midwives, and blood was collected in ethylenediaminetetraacetic acid (EDTA) and serum test tubes. All samples were centrifuged at 2000 g within 24 h before being aliquoted and stored at − 80℃ in the hospital integrated biobank at Biobank Väst.

2.5. Biomarker analysis

Analyses of syndecan-1 and thrombomodulin were performed with ELLA (Biotechne, Minneapolis, USA), an automated enzyme linked immunosorbent assay (ELISA) platform, using open cartridges. The working concentrations of capture and detection antibodies were validated according to the manufacturer's instructions. Standard curves for syndecan-1 and thrombomodulin were produced using defined concentrations diluted from a working solution. A control sample with a known concentration was analyzed on each cartridge. Samples were diluted with a sample diluent buffer 1:10. Hyaluronic acid was analyzed with the R&D Quantikine ELISA kit according to the manufacturer's instructions. If beyond the standard curve, the samples were diluted 1:25 and rerun. All samples, standards, and controls were analyzed in duplicate. sFlt-1 was analyzed by the commercial laboratory iLab Medical AB, Gothenburg, Sweden, using the automated platform Delfia Xpress 1–2-3 and assays (Revvity Inc, Wallac Oy, Turku, Finland).

2.6. Statistics

Descriptive data were presented as mean and standard deviation or median and interquartile range, as appropriate, for numeric variables and as counts and percentages for categorical variables. Biomarker concentrations were log-transformed prior to analysis to account for the positively skewed distribution of data. Biomarkers that varied with gestational age were adjusted for gestational age at sampling using linear regression on the log-transformed values and were reported as multiples of the median, calculated by exponentiating the residual from the regression model. Missing data were limited (<5% for any individual biomarker, <10% overall). Therefore, no imputation was employed, and analyses were conducted on an available-case basis, utilising all data available for each analysis.

Predictive accuracy was assessed with receiver operating characteristic curves (ROC) for syndecan-1, hyaluronic acid, thrombomodulin,

Table 2
Levels of baseline glycocalyx degradation products and angiogenic marker sFlt-1 in women with preeclampsia, stratified by the presence or absence of the composite outcome.

Biomarker	Preeclampsia (n = 212)	The composite outcome	
		Yes (n = 92)	No (n = 120)
Syndecan-1 (ng/mL)	25 (16–40)	27 (17–44)	24 (14–39)
Missing	*2 (n = 210)*	*1 (n = 91)*	*1 (n = 119)*
Hyaluronic acid (ng/mL)	92.0 (47.8–176.0)	92.8 (49.7–193.4)	84.4 (44.1–169.4)
Missing	*7 (n = 205)*	*3 (n = 89)*	*4 (n = 116)*
Thrombomodulin (ng/mL)	4.08 (3.17–5.22)	3.95 (3.06–5.32)	4.11 (3.31–5.11)
Missing	*3 (n = 209)*	*1 (n = 91)*	*2 (n = 118)*
sFlt-1 (pg/mL)	4313 (3084–5993)	4563 (3415–6027)	4140 (2802–5936)
Missing	*5 (n = 207)*	*4 (n = 88)*	*1 (n = 119)*
GA-adjusted sFlt-1 (MoM)	−0.05 (−0.31–0.31)	0.12 (−0.23–0.38)	−0.02 (−0.37–0.26)
GA-adjusted Syndecan-1 (MoM)	0.05 (−0.45–0.47)	0.06 (−0.51–0.53)	−0.04 (−0.46–0.42)

Values are presented as median (interquartile range). GA: gestational age; ng, nanograms; mL, milliliters;MoM: multiples of median; pg, picograms; sFlt-1: soluble FMS-like tyrosine kinase.

Table 3
Frequency of single outcomes.

Maternal adverse event	n	% of women	% of events
All maternal adverse events	121	43.4%	100%
Postpartum hemorrhage	55	25.9%	45.5%
Elevated liver enzymes	25	11.8%	20.7%
Acute kidney injury	18	8.5%	14.9%
Low platelet count	17	8.0%	14.0%
Placental abruption	4	1.9%	3.3%
Eclampsia	≤3	≤1.4%	≤2.5%
Pulmonary edema	≤3	≤1.4%	≤2.5%
Admission to ICU	0	0.0%	0.0%
Cerebrovascular accident	0	0.0%	0.0%
Cortical blindness	0	0.0%	0.0%
Hepatic rupture	0	0.0%	0.0%
Maternal death	0	0.0%	0.0%
Respiratory failure	0	0.0%	0.0%
Retinal detachment	0	0.0%	0.0%
Median time (IQR) to first event was 1 (1–4) day.Median number (IQR) of complications per affected woman was 1 (1–1)			

ICU: intensive care unit; IQR: interquartile range.

and sFlt-1, with area under the curve (AUC) and 95% confidence intervals (CI). Univariable analyses were conducted for each biomarker individually. Multivariable analyses were conducted using logistic regression to assess pairwise combinations of biomarkers. Analyses were performed for the composite outcome and for single outcomes with ≥ 10 events in the study population. Statistical analyses were performed using IBM SPSS Statistics for Mac or Windows, Version 28.0 (IBM Corp., Armonk, NY).

3. Results

Of 416 women enrolled in the GoPROVE biobank between May 2019 and May 2023, 245 women had a confirmed diagnosis of preeclampsia without any components of the composite outcome at the time of inclusion. Due to missing biomarker data, 33 women were excluded, resulting in a final cohort of 212 participants included in the analysis (Fig. 1). Of these women, 92 developed one or more organ dysfunctions (the composite outcome) amounting to a total of 121 single outcomes.

Background characteristics of the included women are presented in Table 1. The mean (SD) age was 31 (4.9) years, the mean body mass index was 26.8 (5.6) kg/m^2, and the mean blood pressure was 144/90 (13/10) mmHg. Most women were nulliparous (n = 184, 79.3%). Most women delivered at term, but the median gestational age was 8 days longer at inclusion and 6 days longer at birth among women who developed the composite outcome.

Plasma and serum concentrations of glycocalyx degradation products and sFlt-1 at inclusion are presented in Table 2. The frequencies of single outcomes are provided in Table 3. The most common single outcome was postpartum hemorrhage (n = 55), followed by elevated liver enzymes (n = 25), acute kidney injury (n = 18), thrombocytopenia (n = 17), and placental abruption (n = 4). There were fewer than three cases of eclampsia and pulmonary edema. There were no cases of admission to the intensive care unit, cerebrovascular accident, cortical blindness, hepatic rupture, maternal death, respiratory failure, or retinal detachment. The median (interquartile range) time from inclusion to the first recorded organ dysfunction was 1 (1–4) day(s).

3.1. Univariable analysis

Syndecan-1, hyaluronic acid, and thrombomodulin showed no association with the composite outcome (Fig. 2), with AUCs of 0.52 (95% CI 0.44–0.60), 0.54 (0.46–0.62), and 0.49 (0.41–0.57), respectively.

For single outcomes, syndecan-1 concentrations were associated with elevated liver enzymes, with an AUC of 0.64 (95% CI 0.52–0.76). Hyaluronic acid predicted thrombocytopenia (AUC 0.67; 95% CI 0.52–0.83) and elevated liver enzymes (AUC 0.69; 95% CI 0.57–0.82). All other univariable tests of glycocalyx degradation products for single outcomes were non-significant (Fig. 3).

3.2. Multivariable analysis

In multivariable analyses evaluating pairwise combinations of syndecan-1, hyaluronic acid, and thrombomodulin, no associations were observed with the composite outcome (Fig. 4). For single outcomes, the combination of syndecan-1 and hyaluronic acid concentrations was associated with thrombocytopenia (AUC 0.67; 95% CI 0.51–0.84) and elevated liver enzymes (AUC 0.70; 95% CI 0.58–0.82). The combination of syndecan-1 and thrombomodulin concentrations was associated with elevated liver enzymes (AUC 0.66; 95% CI 0.54–0.78). The combination of hyaluronic acid and thrombomodulin concentrations was associated with thrombocytopenia (AUC 0.67; 95% CI 0.50–0.84) and elevated liver enzymes (AUC 0.71; 95% CI 0.59–0.82) (Fig. 4).

When combined with sFlt-1, none of the glycocalyx degradation products improved the predictive performance of sFlt-1 alone on neither the composite outcome nor any single outcome (Fig. 5).

4. Discussion

Plasma concentrations of the glycocalyx degradation products syndecan-1, hyaluronic acid, and thrombomodulin showed generally poor performance for the prediction of maternal organ dysfunction in women with a confirmed diagnosis of preeclampsia. However, for the single outcomes thrombocytopenia and elevated liver enzymes, hyaluronic acid showed moderate predictive performance. Multivariable analyses adding sFlt-1 did not improve the predictive performance compared with sFlt-1 alone.

To the best of our knowledge, this is the first study to investigate the predictive performance of glycocalyx degradation products on organ dysfunction in women with a confirmed diagnosis of preeclampsia. A few studies have assessed plasma concentrations of glycocalyx degradation products in women with preeclampsia with organ dysfunction already present. In a previous study, our group did not find any significant difference in median plasma concentrations of syndecan-1 and hyaluronic acid between groups of women with preeclampsia with or without multiple organ complications. However, we found increased plasma concentrations of thrombomodulin in women with multiple organ complications.[13] Edvinsson et al. compared women with

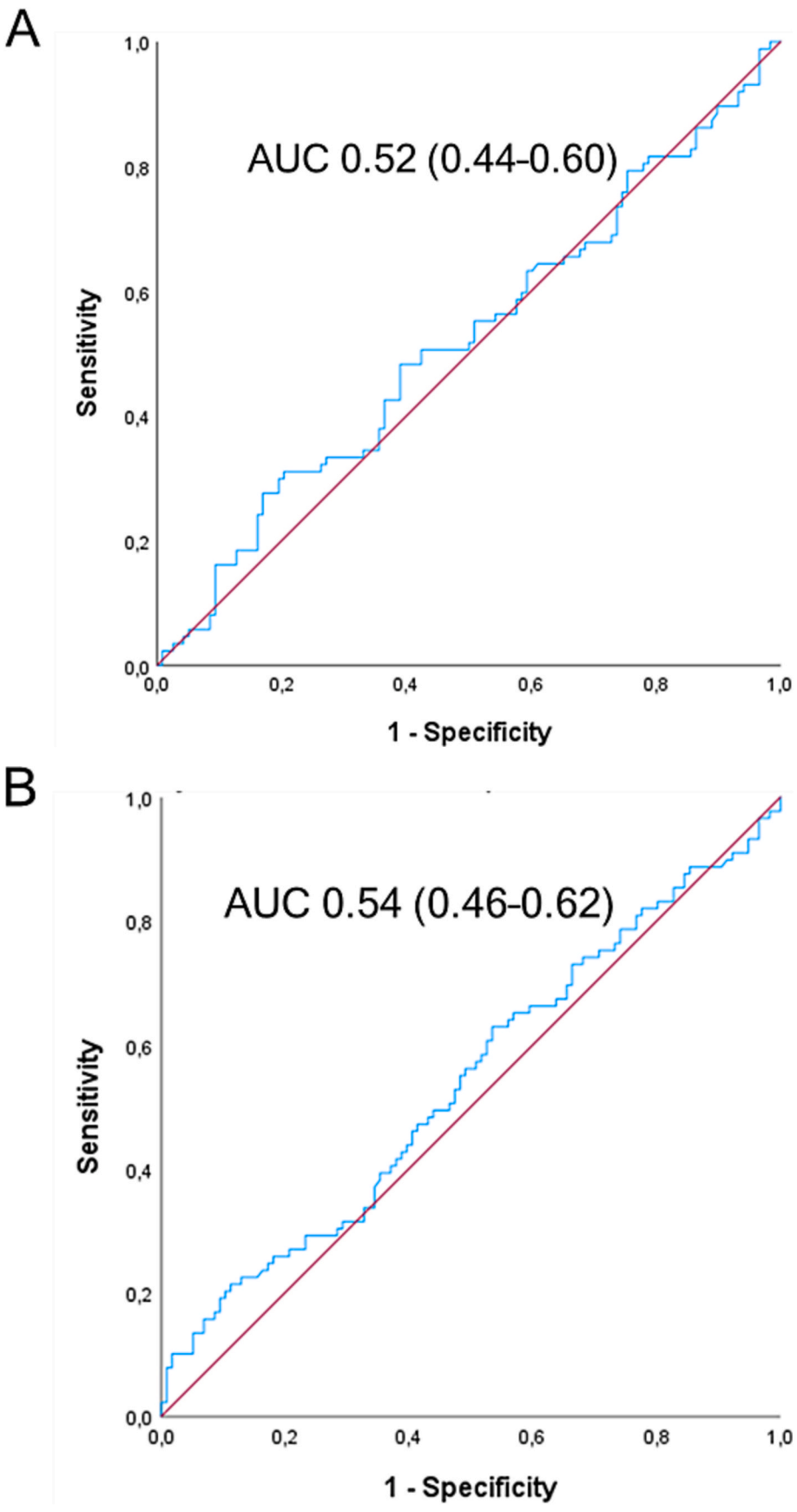

Fig. 2. AUC for plasma concentrations of (A) syndecan-1, (B) hyaluronic acid, and (C) thrombomodulin for predicting the composite outcome in women with preeclampsia.(12).

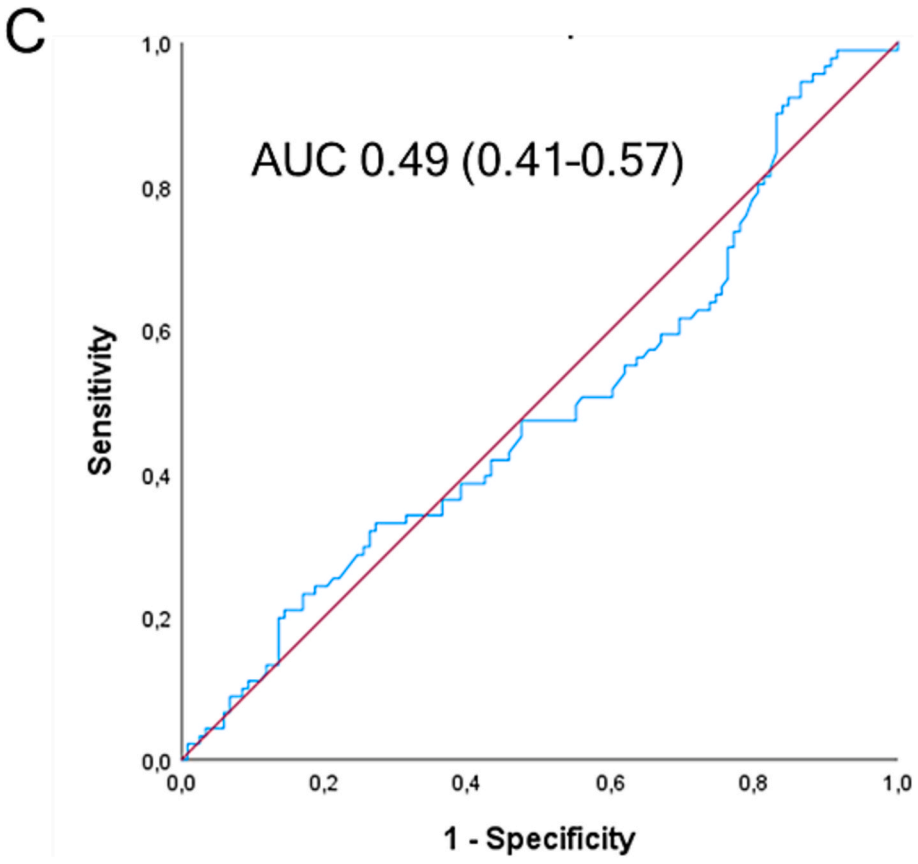

Fig. 2. (*continued*).

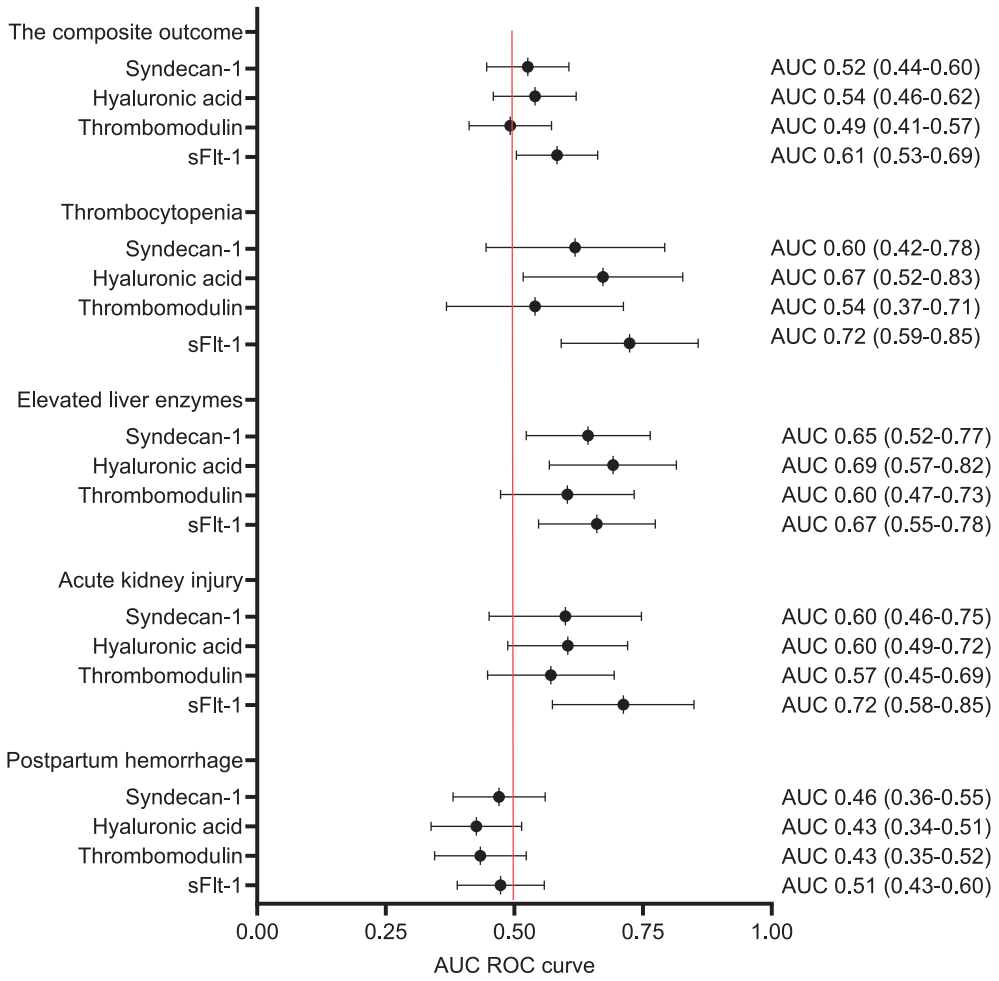

Fig. 3. Forest plot of AUC for syndecan-1, hyaluronic acid, and thrombomodulin, with sFlt-1 as a reference, for predicting the composite outcome and single outcomes in women with preeclampsia.(12) Points represent AUC, and error bars indicate 95% CI. The red vertical line denotes an AUC of 0.5, indicating no discriminatory ability. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

preeclampsia who were to an intensive care unit compared to those who were not, and reported 1.7-fold and 2.3-fold higher median plasma concentrations of syndecan-1 and hyaluronic acid, respectively, in the group who required intensive care.[14] These blood samples were taken postpartum, and organ dysfunction in the respective groups were not defined. In another study, Osmers et al. found that women with Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome had 1.7-fold higher median plasma concentrations of hyaluronic acid compared with women with preeclampsia (any complications not specified).[9] Further, Shaarawy et al. found that the median plasma concentrations of thrombomodulin were elevated by 2.6-fold and 2.1-fold in women with eclampsia and severe preeclampsia, respectively, compared with women with preeclampsia without severe features.[15] Similarly, Hsu et al. found that women with severe preeclampsia had 1.6-fold higher median plasma concentrations of thrombomodulin compared with women with preeclampsia without severe features.[16] Lastly, Sun et al. found that women with HELLP syndrome had 1.3-fold higher median plasma concentrations of thrombomodulin than both women with mild preeclampsia and women with severe preeclampsia without HELLP syndrome. Taken together these findings from previous studies formed the basis for our hypothesis.

Glycocalyx degradation is considered an important pathophysiologic pathway to organ complications in preeclampsia.[17] Yet, many factors may influence the predictive relationship between plasma concentrations of glycocalyx degradation products and subsequent development of organ complications in preeclampsia. One factor is that syndecan-1 is highly expressed on the syncytiotrophoblast surface.[18] Circulating concentrations of syndecan-1 are increased several-fold during normal pregnancy relative to those in non-pregnant women.[19–21] The contribution of syndecan-1 from the shedding of the endothelial glycocalyx might be less than the contribution from the placenta. In addition, the placenta is not the only potential source of non-endothelial glycocalyx degradation products found in plasma. Circulating concentrations of glycocalyx degradation products could be derived from various sources, such as food intake or plasma cells.[22,23] Cervical ripening and birth, both vaginal and by cesarean section, increase plasma concentrations of hyaluronic acid.[8,9] A third factor relates to interindividual variation in the breakdown and elimination of glycocalyx degradation products. The kinetics of syndecan-1 elimination are complex, and plasma concentrations are known to vary several-fold due to differences in kidney function, while elimination of hyaluronic acid from the circulation is mainly mediated by liver sinusoidal cells and is dependent on liver function.[24,25] It is also possible that plasma concentrations of glycocalyx degradation products increase concurrently with the onset of clinical symptoms of organ complications, rather than preceding them. These factors, among others, could explain why syndecan-1, hyaluronic acid, and thrombomodulin showed limited predictive performance in our study.[26,27].

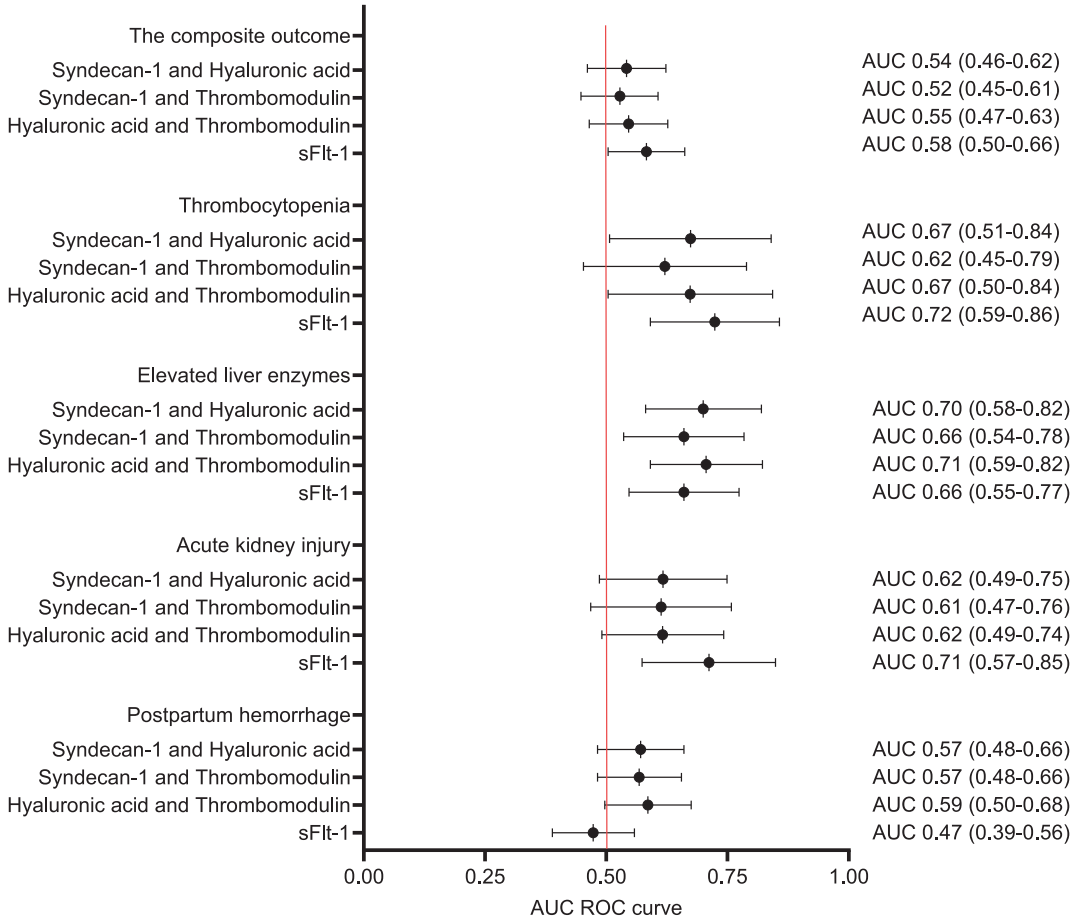

Fig. 4. Forest plot of AUC for the multivariable analysis of pairwise combinations of syndecan-1, hyaluronic acid, and thrombomodulin, with sFlt-1 as a reference, for predicting the composite outcome and single outcomes in women with preeclampsia.(12) Points represent AUC, and error bars indicate 95% CI. The red vertical line denotes an AUC of 0.5, indicating no discriminatory ability. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The best predictive performance in our study was observed for hyaluronic acid as a predictor of elevated liver enzymes. Elevated plasma concentrations of hyaluronic acid in HELLP syndrome are well-documented.[8,9] We reason that this is due to glycocalyx degradation, although high plasma concentrations of hyaluronic acid could also be amplified by reduced clearance in the liver. Sinusoidal thrombotic microangiopathy and liver cell demise are known to compromise liver function in HELLP syndrome.[28] Future studies are warranted to investigate whether hyaluronic acid could serve a biomarker for hepatic involvement in preeclampsia.

Preeclampsia is associated with a wide range of organ dysfunctions, which may be linked to multiple underlying pathophysiological pathways. While the use of a single biomarker as a predictor of composite outcomes may be limited, specific organ dysfunctions could be associated with and possibly predicted by individual glycocalyx degradation products. Our findings on hyaluronic acid predicting thrombocytopenia and elevated liver enzymes need to be validated in other populations.

If plasma concentrations of syndecan-1 derived from the placenta could be distinguished and analyzed separately from syndecan-1 derived from the endothelium, this biomarker could be more specific for endothelial injury. This was not possible with the analytical technique used in our study; however, cell surface glycosylation is a rapidly growing field with promising new techniques.[29] Future studies could address this technical challenge.

Long-term consequences of preeclampsia include stroke and cardiovascular disease, and there is a growing interest in the relationship between glycocalyx degradation and atherosclerosis.[30,31] Women with a history of preeclampsia have structural and functional vascular changes.[32] Future studies should focus on endothelial health and glycocalyx degradation products as indicators of cardiovascular health after an episode of preeclampsia.

In a clinical setting, blood tests measuring plasma concentrations of glycocalyx degradation products do not seem useful for the prediction of maternal organ dysfunction in women with a confirmed diagnosis of preeclampsia.

4.1. *Strengths and limitations*

The study has a prospective design, and the use of a core set of outcomes for preeclampsia research will enable future research to confirm or refute our results. To the best of our knowledge, this is one of the most comprehensive studies on glycocalyx degradation products in women with preeclampsia, including over 200 participants and more than 100 organ complications. Even so, many outcomes in the consensus core set of outcomes were too rare to be analyzed. Therefore, we cannot comment on the predictive performance of syndecan-1, hyaluronic acid, and thrombomodulin for these outcomes. Studies in larger populations and with a higher incidence of organ complications are warranted.

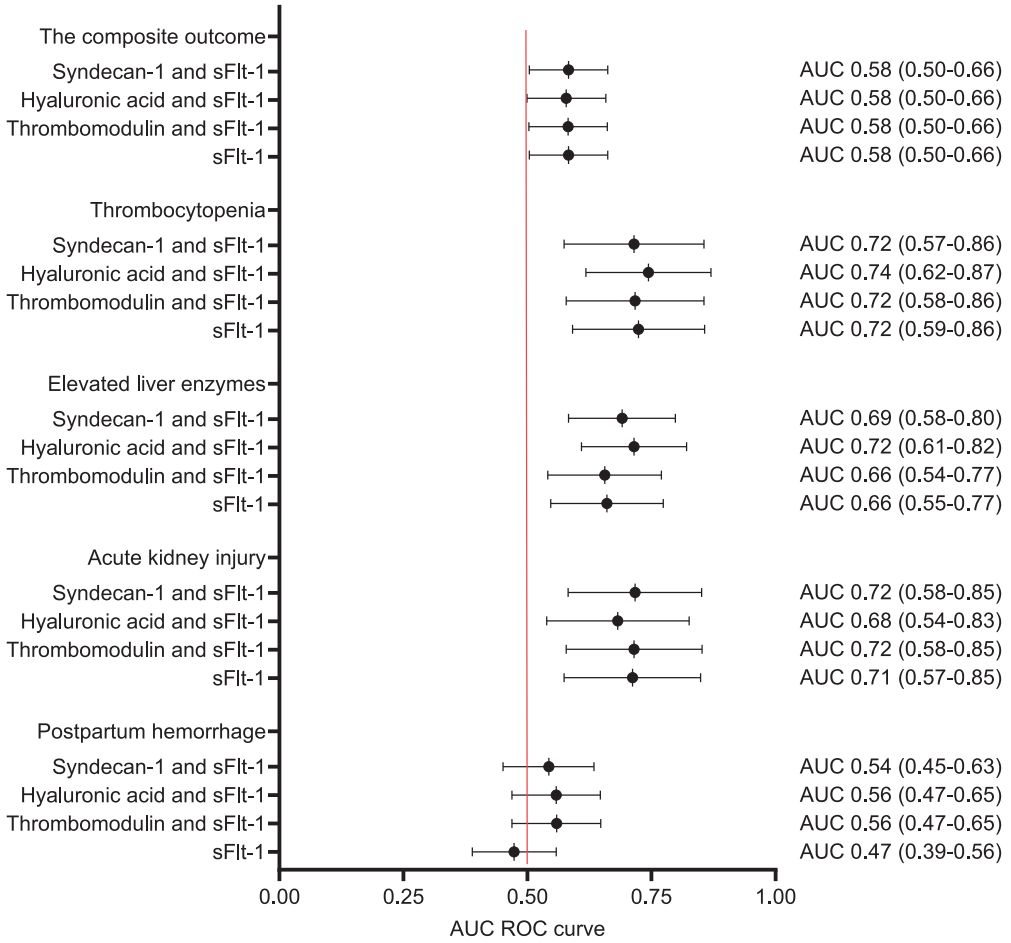

Fig. 5. Forest plot of AUC for the multivariable analysis of syndecan-1, hyaluronic acid, and thrombomodulin, in combination with sFlt-1, with sFlt-1 alone as a reference, for predicting organ complications, according to the Delphi consensus composite outcome and single outcomes, in women with preeclampsia. Points represent AUC, and error bars indicate 95% CI. The red vertical line denotes an AUC of 0.5, indicating no discriminatory ability. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5. Conclusion

In women with a confirmed diagnosis of preeclampsia, plasma concentrations of syndecan-1, hyaluronic acid, and thrombomodulin generally show poor performance in predicting subsequent maternal organ dysfunction; however, hyaluronic acid had a moderate predictive performance for the single outcomes thrombocytopenia and elevated liver enzymes.

6. Fundings

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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