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Identification of predictive biological markers of maternal-fetal complications in patients with severe preeclampsia

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ABSTRACT

Introduction
Preeclampsia (PE) is a serious pregnancy complication associated with significant risks for both mothers and fetuses. Identifying biological markers that predict adverse outcomes is essential for improving clinical management and outcomes in severe preeclampsia.

Purpose
This study aimed to identify blood and urine biological markers that are strongly associated with maternal-fetal complications among women with severe preeclampsia.

Methods
A total of 204 pregnant women hospitalized for severe preeclampsia were included. Demographic, clinical, and laboratory data were collected. Univariate and multivariate logistic regression analyses were performed to determine biological predictors of maternal-fetal complications.

Results
The mean age of participants was 28 ± 6.7 years, with 53.8% being primiparous. A history of preeclampsia was present in 19.2% of patients, and 63.5% had chronic hypertension. The median gestational age at diagnosis was 32 weeks (range: 28–36 weeks). Overall, 53.8% of patients experienced complications, most commonly retroplacental hematoma (14.4%), eclampsia (11.5%), and acute renal failure (10.6%). Biological markers significantly associated with maternal-fetal complications were uric acid > 6 mg/dl (p = 0.006), AST > 40 IU/L (p = 0.017), creatinine ≥ 1.3 mg/dl (p = 0.037), proteinuria ≥ 3 g/24h (p = 0.023), and ACR ≥ 30 (p = 0.023). After multivariate adjustment, three markers remained independently associated with complications: uric acid > 6 mg/dl (ORa: 2.26; 95% CI: 1.05–4.87), AST > 40 IU/L (ORa: 2.43; 95% CI: 1.02–5.76), and ACR ≥ 30 (ORa: 2.95; 95% CI: 1.21–7.19).

Conclusion
Preeclampsia remains a complex condition requiring vigilant monitoring. Elevated uric acid, AST, and ACR were identified as independent predictors of maternal-fetal complications and may serve as valuable markers for risk stratification. These findings support the integration of biomarker assessment into management strategies, while future research should evaluate additional markers and personalized protocols to improve maternal and perinatal outcomes.

INTRODUCTION

Preeclampsia is a severe pregnancy complication characterised by hypertension and organ involvement, most commonly affecting the kidneys and liver, usually appearing after 20 weeks of gestation (Rana et al., 2019). This condition remains a major cause of maternal and perinatal morbidity and mortality worldwide, affecting approximately 2–8% of pregnancies. Understanding and managing preeclampsia have significantly advanced over the past decades, thanks to improvements in identifying and utilising biological markers to predict associated complications (American College of Obstetricians and Gynecologists [ACOG], 2019).

Recent research has underscored the crucial role of biological markers in predicting preeclampsia complications. Studies have shown that certain biological parameters can be early indicators of disease severity and potential risks for the mother and fetus (von Dadelszen et al., 2011; Payne et al., 2014). Elevated transaminases, particularly AST, are associated with severe liver involvement in preeclampsia. Serum creatinine is a key marker of renal function, and recent studies have demonstrated that high levels of creatinine (> 1.3 mg/dL) are strongly predictive of acute renal failure in women with severe preeclampsia (Kozic et al., 2011).

Proteinuria remains a central diagnostic criterion for preeclampsia. High levels of proteinuria (≥ 3 g/24 h) are associated with adverse maternal and fetal outcomes (Bellomo, 2005). Recent recommendations emphasise the importance of precise quantification of proteinuria to assess the risk and severity of the disease (Thangaratinam et al., 2007). The albumin/creatinine ratio (ACR) has also emerged as a useful marker in predicting maternal-fetal complications. Although its use is still under evaluation, studies have shown that high ACR levels are associated with an increased risk of severe preeclampsia and complications (Thangaratinam et al., 2009).

Uric acid is a marker of endothelial dysfunction and oxidative stress. Elevated uric acid levels are frequently observed in preeclampsia and are associated with an increased risk of maternal and neonatal complications. Although its exact role as an independent marker remains to be clarified, it continues to serve as a useful indicator of disease severity (Tshibuela et al., 2017). Thrombocytopenia, often observed in severe cases of preeclampsia and HELLP syndrome, may indicate coagulopathy, requiring immediate monitoring and intervention (Laskin et al., 2011).

The prevalence of preeclampsia is estimated at 8.5% in Kinshasa, Democratic Republic of the Congo; however, no studies have been conducted there to determine the role of biological markers in predicting the occurrence of fetal-maternal complications associated with this condition (Elongi et al., 2011).

METHODS

Objective

To determine the blood and urine biological markers whose disturbances are strongly associated with maternal-fetal complications in severe preeclampsia among Congolese pregnant women in 2020.

Study Population

We conducted a multicentre study in tertiary maternity hospitals specialising in the management of preeclampsia (high prevalence) in Kinshasa, Democratic Republic of the Congo.

Inclusion Criteria

Eligible women were those hospitalised due to preeclampsia who had undergone at least one prenatal assessment of proteinuria using a reactive urine test strip, the Pr/Cr ratio of a spot urine sample, and/or a 24-hour urine collection. Proteinuria assessment was performed visually at the patient's bedside using a reactive strip.

Sampling Methods

i. Whole blood: Drawn into a dry tube without anticoagulant for measuring transaminases, creatinine, and uric acid; and into tubes with anticoagulant for platelet count.
ii. Urine: Spot urine samples for creatinine and proteins (to calculate the ratio), and 24-hour urine collection for measuring proteins and sodium.

Statistical Analyses

Statistical analyses were performed using the Student's t-test and logistic regression (univariate and multivariate

analyses). The biological determinants of maternal-fetal complications were determined using odds ratios.

Ethical Considerations

The protocol was submitted to the Ethics Committee of the Kinshasa School of Public Health and approved under number ESP/CE/069/2019. Data processing was carried out anonymously and confidentially, with fairness and without conflict of interest.

RESULTS

Complications Observed

Out of 204 pregnant women, maternal complications alone were observed in 48.5% of cases, and fetal complications alone in 58.3% of cases. Maternal and fetal complications were associated in 71.6% of cases **(Figure 1)**.

Figure 1:
Various maternal and fetal complications observed

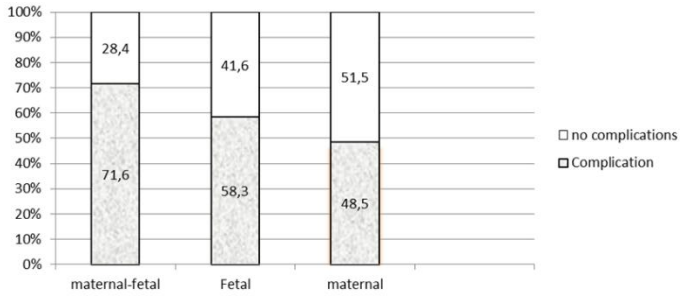

Table 1 presents the biological characteristics associated with maternal-fetal complications in patients with preeclampsia. The results highlight significant differences between patients with complications and those without. Parameters significantly higher in patients with maternal-fetal complications include: uric acid > 6 mg/dL (p = 0.014), ALT > 40 IU/L (p = 0.048), AST > 40 IU/L (p = 0.010), creatinine ≥ 1.3 mg/dL (p = 0.028), 24-hour proteinuria ≥ 3 g/24h (p = 0.027), and ACR ≥ 30 (p = 0.023).

Table 1:
Comparison of Clinical and Laboratory Variables Between Groups

Variables	**All** *(n = 204)*	**No complications MF** *(n = 58)*	**Complications MF** *(n = 146)*	*p*
Uric acid > 6 mg/dL	67	12	55	0.014
ALAT > 40 U/L	46	9	37	0.048
ASAT > 40 U/L	52	8	44	0.010
Platelets < 150,000/mm³	67	21	46	0.314
Creatinine ≥ 1.3 mg/dL	86	19	67	0.028
Proteinuria (24 h) ≥ 3 g/24 h	56	10	46	0.027
ACR ≥ 30	28	13	15	0.023
Urine output < 500 mL	83	23	60	0.489
Sodium < 135 mmol/L	60	16	44	0.095

Median values analysis shows that among the biological parameters examined, only AST (p = 0.013), creatinine (p = 0.047), and calcium (p = 0.021) were significantly higher in patients with maternal-fetal complications. Other parameters such as uric acid, ALT, proteinuria, urinary albumin, ACR, diuresis, and sodium did not show statistically significant differences between patients with and without maternal-fetal complications **(Table 2)**.

Table 2:
Median (Interquartile Range) of Laboratory Parameters

Variables	**All** *(n = 204)*	**No complications** *MF (n = 58)*	**Complications** *MF (n = 146)*	*p*
Uric acid (mg/dL)	5.2 (4.5–6.5)	5.1 (4.1–5.8)	5.2 (4.6–6.6)	0.241
ALAT (U/L)	26.2 (18.2–36.6)	25.8 (10.4–33.1)	26.6 (19.1–40.2)	0.475
ASAT (U/L)	30.0 (21.4–40.8)	27.8 (21.4–32.9)	31.0 (21.4–45.2)	0.013
Platelets × 10³/mm³	155 (140–204)	150 (140–211)	156 (140–200)	0.973
Creatinine (mg/dL)	1.2 (1.0–1.5)	1.1 (1.0–1.3)	1.2 (1.0–1.7)	0.047
Proteinuria (g/24 h)	1.6 (0.6–3.2)	1.6 (0.8–2.8)	1.7 (0.6–3.6)	0.933
Urinary albumin (mg/L)	150 (80–150)	150 (100–160)	150 (80–150)	0.293
ACR	8.5 (5.6–17.0)	8.5 (5.7–17.0)	7.6 (5.6–17.0)	0.360
Sodium (mmol/L)	137 (134–139)	137 (135–138)	137 (134–140)	0.776
Calcium (mmol/L)	2.4 (2.2–2.6)	2.4 (2.1–2.5)	2.5 (2.3–2.6)	0.021

Univariate logistic regression models revealed that the following parameters were biological determinants of maternal-fetal complications: uric acid > 6 mg/dL, AST > 40 IU/L, creatinine ≥ 1.3 mg/dL, proteinuria ≥ 3 g/24h, and ACR ≥ 30. In multivariate analysis, after adjusting for other significant univariate variables, the independent biological determinants of maternal-fetal complications were uric acid > 6 mg/dL (ORa: 2.26; 95% CI: 1.05–4.87), AST > 40 IU/L (ORa: 2.43; 95% CI: 1.02–5.76), and ACR ≥ 30 (ORa: 2.95; 95% CI: 1.21–7.19). The risk of complications was thus doubled for uric acid levels > 6 mg/dL and AST levels > 40 IU/L, and tripled for ACR levels ≥ 30 **(Table 3)**.

Table 3:
Univariate and Multivariate Logistic Regression Analysis

Variables	Univariate Analysis		Multivariate Analysis	
	p	OR (95% CI)	*p*	aOR (95% CI)
Uric acid > 6 mg/dL	0.022	2.32 (1.13–4.75)	0.037	2.26 (1.05–4.87)
ASAT > 40 U/L	0.019	2.70 (1.18–6.16)	0.044	2.43 (1.02–5.76)
Creatinine ≥ 1.3 mg/dL	0.003	3.74 (1.92–5.29)	0.248	1.51 (0.75–3.05)
Proteinuria ≥ 3 g/24 h	0.043	2.21 (1.03–4.75)	0.204	1.71 (0.75–3.92)
ACR ≥ 30	0.026	2.52 (1.12–5.71)	0.017	2.95 (1.21–7.19)

Analysis of biological variables revealed that, when examined continuously, values were generally comparable between patients at low and high risk of maternal-fetal complications. However, certain variables, such as creatinine, showed significant differences, with levels higher in patients at high risk of complications (p = 0.042). Categorical analysis of biological variables showed that the frequency of the following parameters was significantly higher in patients at high risk of complications: uric acid > 6 mg/dL (p = 0.043), ALT > 40 IU/L (p = 0.038), AST > 40 IU/L (p = 0.028), creatinine ≥ 1.3 mg/dL (p = 0.019), proteinuria ≥ 3 g/24h (p = 0.003), and sodium < 135 mmol/L (p = 0.004) **(Table 4)**.

Table 4:
Laboratory and Clinical Parameters by Risk Group

Variables	All *(n = 204)*	Low Risk *(n = 92)*	High Risk *(n = 112)*	*p*
Uric acid (mg/dL)	5.2 (4.5–6.5)	5.1 (4.3–6.2)	5.2 (4.6–6.6)	0.715
Uric acid > 6 mg/dL	67 (32.8%)	24 (26.1%)	43 (38.4%)	0.043
ALAT (U/L)	26.2 (18.2–36.6)	25.8 (14.5–33.1)	27.8 (18.3–40.3)	0.140
ALAT > 40 U/L	46 (22.5%)	16 (17.4%)	30 (26.8%)	0.038
ASAT (U/L)	30.0 (21.4–40.8)	29.7 (21.5–38.9)	30.6 (20.4–45.8)	0.082
ASAT > 40 U/L	52 (25.5%)	18 (19.6%)	34 (30.4%)	0.028
Platelets × 10^3/mm^3	155 (140–204)	150 (134–203)	160 (141.3–209.5)	0.990
Platelets < 150,000/mm^3	67 (32.8%)	36 (39.1%)	31 (27.7%)	0.057
Serum creatinine (mg/dL)	1.2 (1.0–1.5)	1.1 (1.0–1.3)	1.3 (0.9–1.9)	0.042
Creatinine ≥ 1.3 mg/dL	86 (42.2%)	31 (33.7%)	55 (49.1%)	0.019
Proteinuria (24 h, g/24 h)	1.6 (0.6–3.2)	1.6 (0.8–2.7)	1.7 (0.5–3.7)	0.458
Proteinuria ≥ 3 g/24 h	56 (27.5%)	16 (17.4%)	40 (35.7%)	0.003
ACR	8.5 (5.6–17.0)	8.5 (5.7–17.0)	5.7 (5.6–17.0)	0.709
ACR ≥ 30	28 (13.7%)	14 (15.2%)	14 (12.5%)	0.359
Urine output (mL)	1600 (1100–2100)	1580 (1162.5–2200)	1650 (1100–2000)	0.301
Urine output < 500 mL	83 (40.7%)	39 (42.4%)	44 (39.3%)	0.380
Sodium (mmol/L)	137 (134.1–139.3)	137.1 (134.6–138.1)	137.2 (134.0–139.6)	0.874
Sodium < 135 mmol/L	60 (29.4%)	24 (26.1%)	36 (32.1%)	0.004

DISCUSSION

Preeclampsia is a complex and severe condition associated with significant complications that contribute to high maternal and perinatal morbidity and mortality. Clinical symptoms, while important, often do not reliably predict adverse maternal and fetal outcomes. This study highlights the importance of biological parameters in predicting complications related to preeclampsia.

Several parameters were found to be significantly associated with the risk of maternal complications, including uric acid levels > 6 mg/dL (p = 0.014), elevated liver transaminases (ALT > 40 IU/L, p = 0.048; AST > 40 IU/L, p = 0.010), creatinine levels ≥ 1.3 mg/dL (p = 0.028), proteinuria ≥ 3 g/24h (p = 0.027), and a protein-to-creatinine ratio (PCR) ≥ 30 (p = 0.023). AST levels > 40 IU/L (p = 0.013) and creatinine levels ≥ 1.3 mg/dL (p = 0.047) were predictive of fetal complications.

Univariate analyses show that uric acid > 6 mg/dL increased the risk of maternal-fetal complications by twofold (OR = 2.32; 95% CI: 1.13–4.75), AST > 40 IU/L by threefold (OR = 2.70; 95% CI: 1.18–6.16), creatinine ≥ 1.3 mg/dL by fourfold (OR = 3.74; 95% CI: 1.92–5.29), proteinuria ≥ 3 g/24h by twofold (OR = 2.21; 95% CI: 1.03–4.75), and PCR ≥ 30 by threefold (OR = 2.52; 95% CI: 1.12–5.71). Multivariate analysis identified three key biological parameters for predicting maternal-fetal complications: uric acid > 6 mg/dL (OR = 2.26; 95% CI: 1.05–4.87), AST > 40 IU/L (OR = 2.43; 95% CI: 1.02–5.76), and significant proteinuria with PCR ≥ 30 (OR = 2.95; 95% CI: 1.21–7.19). For fetal complications, AST > 40 IU/L doubled the risk (OR = 2.43; 95% CI: 1.02–5.76).

These results align with previous studies. Koopmans et al. (2009) demonstrated that hyperuricemia is associated with an increased risk of eclampsia. Thangaratinam et al. (2006)

found that elevated uric acid levels doubled the risk of severe complications, including eclampsia and cesarean deliveries. Kumar and Singh (2019) reported a significant correlation between maternal serum uric acid, disease severity, and maternal outcome. Similarly, the urinary protein-to-creatinine ratio (UPCR) has been shown to be a simple, reliable tool for predicting abnormal fetomaternal outcomes in preeclampsia (Dong, 2017; Martins-Costa, 2011). Quantifying the severity of proteinuria may identify a subgroup of women with preeclampsia at increased risk of adverse outcomes. Dacaj et al. (2016) observed elevated liver transaminases in preeclamptic patients, particularly those with intrauterine growth restriction (IUGR). Moreover, Kozic et al. (2011) emphasized that while liver function tests are associated with adverse maternal outcomes, their predictive value improves when combined with other biological parameters.

Development of a Prediction Score

These results underscore a significant association between these biological parameters and an increased risk of maternal-fetal complications. Therefore, it is crucial to integrate these variables into a risk prediction score. Incorporating these biological parameters into a prediction score could offer a more precise approach for assessing the risk of complications in preeclampsia. Such a score would enable stratification of patients based on their risk, facilitating earlier and more tailored management. This approach could enhance decision-making regarding pregnancy termination, medical treatment, and referral to specialized care centers.

CONCLUSION

Incorporating biological parameters into a prediction score for preeclampsia complications represents a significant advancement in patient management. This score could enable more precise identification of high-risk patients, facilitating preventive and personalized interventions. Further studies are needed to validate and refine these predictive tools to optimize the management of this complex condition.

Authors' Contributions

- Tshibuela Beya Dophie: Principal investigator, protocol design and drafting, field survey, data tabulation and analysis, drafting of the article.
- Elongi Moyene JP: Supervision, protocol design and drafting, analysis of results, drafting of the article.
- Muwonga Masidi Jérémie: Protocol writing, results analysis, article drafting.
- Nkodila Natuhoyila Aliocha: Data analysis and interpretation.
- Prof. Dr. Fons Verdonck: Protocol writing, results analysis, article drafting.
- Prof. Dr. Bernard Spitz: Protocol writing, results analysis, article drafting.
- Kimema Passy: Protocol writing, results analysis, article drafting.

Ethical Approval: This study was approved by the Ethics Committee of the Kinshasa School of Public Health, University of Kinshasa (ESP/CE/115/2021).

Conflicts of Interest: None declared.

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