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Association of Postpartum Cardiovascular Biomarkers with HIV Among Women with Recent Preeclampsia in Zambia

Moses Mukosha[1,2] · Mwansa Ketty Lubeya[2,5] · Wilbroad Mutale[3] · Innocent Maposa[2,6] · Benjamin H. Chi[4] · Abigail Hatcher[2,7]

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Abstract

Objectives Women recovering from preeclampsia with elevated vascular biomarkers have a higher risk of future cardiovascular diseases. We investigated whether HIV on treatment was associated with biomarkers of cardiovascular risk in the weeks following delivery.

Methods We analyzed data from a six-month prospective cohort study conducted from January 2022 to June 2023. Following delivery and at six weeks postpartum, we measured cystatin C, high sensitivity C-reactive protein (hs-CRP), Interleukine-2 (IL-2), Interleukine-6 (IL-6) and Tumor necrosis factor-alpha (TNFa). A generalized linear regression model with Poisson distribution estimated the association between vascular biomarkers and HIV on treatment.

Results This study included 75 participants with a median age of 29 years (interquartile range [IQR] = 27–34 years), with 35 (46.7%) living with HIV on ART and 40 (53.3%) HIV-negative. Women living with HIV on ART had higher levels of hs-CRP than HIV-negative women (4.68 mg/l vs 3.60 mg/l, p = 0.025) at six weeks. On the other hand, women living with or without HIV on ART had similar levels of cystatin C (0.78 mg/l vs 0.81 mg/l, p = 0.303), IL-2 (0.64 pg/ml vs 0.67 pg/ml, p = 0.131), IL-6 (0.64 pg/ml vs 0.64 pg/ml, p = 0.422), and TNFa (24.2 pg/ml vs 24.1 pg/ml, p = 0.346). Living with HIV while on ART was associated with an increased risk of presenting as hypertensive with elevated hs-CRP (aRR = 2.88, 95% CI: 1.09–7.60).

Conclusions Women living with HIV on ART had elevated hs-CRP but similar levels of other biomarkers after preeclampsia. Further studies are needed to explore the differential impact of HIV disease vs. antiretroviral treatment on inflammatory responses.

Significance

What is already known on this subject? Women with preeclampsia have a double risk of cardiovascular diseases after giving birth and beyond, which is exacerbated by elevated levels of pro-inflammatory biomarkers.

What this study adds? This study reports on the levels of cardiovascular risk indicators in women recovering from preeclampsia. The results highlight the differences in cardiovascular risk indicators between women living with and without HIV on ART and discuss how those risks are disproportionately felt by women living with HIV. The results suggest the need for targeted support in the postpartum, particularly in women living with HIV.

✉ Moses Mukosha
mukoshamoses@yahoo.com

[1] Department of Pharmacy, School of Health Sciences, University of Zambia, P.O. Box 32379, Lusaka, Zambia

[2] Faculty of Health Sciences, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

[3] Department of Health Policy and Management, School of Public Health, University of Zambia, Lusaka, Zambia

[4] Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[5] Department of Obstetrics and Gynaecology, School of Medicine, The University of Zambia, Lusaka, Zambia

[6] Division of Epidemiology & Biostatistics, Department of Global Health, Faculty of Medicine & Health Sciences, Stellenbosch University, Cape Town, South Africa

[7] Department of Health Behavior, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Keywords Cardiovascular risk biomarkers · Preeclampsia · HIV on ART · Postpartum · Zambia

Introduction

Preeclampsia, a pregnancy-specific condition characterized by high blood pressure and systemic inflammation, is a significant public health condition (Vishnyakova et al., 2021). Preeclampsia affects about 3–5% of pregnant women globally (Chappell et al., 2021) and is responsible for over 70,000 maternal deaths and 500,000 fetal deaths per year (Rana et al., 2019). In women living with HIV, the intersection of HIV, antiretroviral therapy (ART), and preeclampsia can lead to adverse outcomes in affected women (Mukosha et al., 2022).

HIV is associated with a two-fold or greater risk of lifetime cardiovascular diseases and premature cardiovascular mortality (Sukmanee & Liabsuetrakul, 2022). Similarly, chronic hypertension is common after preeclampsia and contributes to over 2-fold higher rates of cardiovascular disease in women of reproductive age (Khosla et al., 2021). Evidence suggests a synergistic effect between HIV and preeclampsia through inflammation and endothelial dysfunction (Naidoo et al., 2021). Studies have highlighted the potential role of biomarkers of inflammation in cardiovascular disease risk monitoring, particularly after pregnancies complicated by preeclampsia (Alfaddagh et al., 2020), and have been incorporated into the risk prediction scores for cardiovascular diseases (CáceresMéndez & García-Peña, 2020). Therefore, assessing biomarkers of inflammation and renal function such as high sensitivity C reactive protein (hs-CRP), interleukin 2 (IL-2), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNFa) and cystatin C can be useful in the understanding of how HIV is associated with future risk of cardiovascular diseases in women recovering from preeclampsia in the postpartum and beyond (Liu et al., 2021).

Elevated levels of vascular biomarkers (e.g., hs-CRP, IL-2, IL-6, cystatin C and TNFa) have been documented in the general population and women with preeclampsia during pregnancy (Businge et al., 2021; Mabhida et al., 2024). A study by Kiefer and colleagues found that HIV infection was associated with inflammation, measured by higher levels of hs-CRP in the general population (Kiefer et al., 2018). However, similar associations between vascular biomarkers and HIV have not been evaluated in women with preeclampsia after giving birth. Additionally, there is a lack of evidence linking specific vascular biomarkers to postpartum outcomes among HIV-positive women recovering from preeclampsia.

In this study, we examined the association of HIV on treatment with cardiovascular risk biomarkers among postpartum women previously diagnosed with preeclampsia. We hypothesized that women living with HIV on ART would have higher levels of hs-CRP, IL-2, IL-6, TNFa and cystatin C than HIV-negative women, likely due to underlying chronic inflammation and dysfunction of the endothelium.

Methods

Study Design, Setting and Population

We analyzed data from a six-month prospective cohort study of women previously diagnosed with preeclampsia from Jan 1, 2022, to June 30, 2023, at the Kanyama General and Women and Newborn Hospitals in Lusaka Urban, Zambia. The two hospitals have obstetricians/gynecologists and nurse midwives and receive referrals of women with preeclampsia from surrounding clinics. The health services are offered free of user fees. From the two hospitals on average about 24,000 pregnant women are seen per year with over 12,000 births.

Details of the study population have been previously described (Mukosha et al., 2024). Briefly, the primary cohort included postpartum women who developed preeclampsia (With or without HIV) during pregnancy. To be eligible for inclusion, a participant should have had a documented HIV testing result in the antenatal record, show willingness to participate in the study voluntarily, and provide written informed consent and consent for blood draw. The sample for biomarker testing was drawn from the eligible participants in the primary cohort. This study is reported per the Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (Online Resource 1).

Study Procedures

A research assistant provided a full description of the study prior to obtaining informed consent. Building on our previous work, we anticipated difficulties in the recruitment of women living with HIV due to the low prevalence of preeclampsia in this population, 4.8% (Mukosha et al., 2022); therefore, in the main cohort, we purposively oversampled women living with HIV, and an equivalent number of HIV-negative women were enrolled using a systematic sampling technique. At enrolment, research assistants collected blood samples, measured blood pressure and recorded participants' sociodemographics, clinical and obstetric characteristics. Venous blood samples were collected to test hs-CRP, IL-2, IL-6, TNFa and cystatin C at enrollment and on their return at six weeks' postpartum routine hospital visit.

Laboratory Procedures

After collection into heparin bottles, blood samples were transported to the laboratory located within the hospital (within 30 min), where it was centrifuged at 3000 g for 5 min, and resultant plasma and serum were stored at − 80 degrees Celsius for biomarker testing. The assay for plasma and serum levels of biomarkers (hs-CRP, IL-2, Il-6, cystatin C and TNFa) was done through a commercially available MAGPIX MILLIPLEX MAP kit. Measurements were performed using the Bio-Plex MAGPIX Multiplex Reader (Bio-Rad Laboratories, Hercules, CA, USA) as specified by the manufacturer. All laboratory analyses were done in triplicate with standard curves calculated using a four-parameter logistic curve analysis using Graph Pad Prism 5 (San Diego, CA, USA).

Study Outcome

The primary outcome variable was hs-CRP. The secondary outcomes were IL2, IL6, TNFa and Cystatin C. The primary and secondary outcomes were categorized based on the cardiovascular risk, which was previously described as linear, with higher levels associated with high cardiovascular risk (Mossmann et al., 2022). The statistical analysis used a cutoff value of > 3 mg/l to categorize hs-CRP because levels above 3 mg/l are associated with a higher cardiovascular risk profile (Pearson et al., 2003). On the other hand, we used quartiles to categorise IL-2, IL-6, TNFa and cystatin C, with levels in the highest quartile representing a high cardiovascular risk (Hauspurg et al., 2019). We further categorized the biomarker levels based on the level of cardiovascular risk profile as moderate adverse cardiovascular risk profile (i.e., any elevated vascular biomarker) and most adverse cardiovascular risk profile (hypertensive with any elevated biomarker) (Pearson et al., 2003).

Study Exposures

The primary exposure of interest was HIV infection. All participants with a positive HIV serostatus had initiated ART, as recommended by the national Zambian clinical guidelines (Health RoZMo, 2020), though adherence was not formally assessed. In the study settings, therapy for HIV includes a combination of any regimen with three or more medications, such as protease inhibitors, integrase inhibitor-based regimens, and non-reverse transcriptase inhibitor regimens.

We also collected sociodemographic, clinical and obstetric characteristics. Using standard procedures, research assistants measured blood pressure at enrollment and six weeks postpartum. Age was measured in years based on the last birthday. Marital status was measured on two levels (unmarried and married). Food insecurity scores were assessed using the Household Hunger Scale (Nkomoki et al., 2019). The socio-economic status was scored using the principal component analysis to obtain wealth index quintiles (poorest, poorer, medium, rich, richest) (Chakraborty et al., 2016). Education status was measured based on the following categories/levels (uneducated, primary, secondary, tertiary).

Furthermore, we calculated body mass index from the participant's weight and height at six weeks postpartum. The severity of preeclampsia was measured on three levels: mild (hypertension [140/90 to 149/99 mmHg]), moderate (hypertension [150/100 to 159/109 mmHg]) and severe (hypertension [160/110 mmHg or higher]) (Markova et al., 2016). The onset of preeclampsia was measured as early-onset (less than 34 weeks gestation) and late-onset (more than 34 weeks gestation).

Adverse pregnancy outcomes were categorized as preterm birth (< 37 completed weeks gestation) or stillbirth. The Hospital Anxiety and Depression Scale, a 14-item measure for assessing mental health in primary healthcare settings (Zigmond & Snaith, 1983), was used to assess anxiety and depression. Contraceptive use was measured categorically: intrauterine, barrier, or dual methods; hormonal methods; and unknown or no contraception at six weeks postpartum.

Sample Size Consideration

In the six-month main cohort study, 55 HIV-positive and 111 HIV-negative completed postpartum visits. For this analysis, we included 35 HIV-positive with complete samples for visits 1 and 2 and sampled 40 eligible participants from the HIV-negative group using a simple random sampling technique without replacement. This sample was sufficient to achieve over 80% power to detect a difference of 0.77 mg/l of hs-CRP (smallest effect size from similar published studies) (Kiefer et al., 2018; Neuhaus et al., 2010) between women living with and without HIV at an alpha level of 0.05. This considered a mean hs-CRP level of 1.36 mg/l among women living without HIV and an equal standard deviation of 1.3 mg/l in either group (Neuhaus et al., 2010).

Data Management and Analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture), an electronic data capture tool hosted at the University of the Witwatersrand (Johannesburg, South Africa). Final data was transferred and analyzed in Stata version 17/BE (Stata Corp., College Station, Texas, USA).

We conducted a descriptive analysis of the levels of biomarkers in the HIV-positive on-ART group compared to

the HIV-negative group. We used the Shapiro–Wilk test for normality and quartile-quartile plots to assess the distribution of continuous variables. Median levels of hs-CRP, cystatin C, IL-2, IL-6 and TNFa were compared between the two groups using the Wilcoxon Ranksum test. Violin plots were used to illustrate the concentration of the biomarkers stratified by HIV serostatus. The risk of moderate adverse cardiovascular profile (any elevated hs-CRP > 3 mg/l or IL-2, IL-6, TNFa, cystatin C > 4th quartile) and most adverse cardiovascular profile (hypertensive with any elevated biomarker) at six-week follow-up was assessed using the Generalized Linear regression models with Poisson distribution. The final list of variables to be considered for inclusion in the multivariable models were identified through previous literature and p-value < 0.20. Variables identified to have a confounding association with HIV and biomarkers were included a priori, including: age and body mass index. Separate models with robust estimation of standard errors were fitted for each of the biomarkers. Interactions were assessed among the significant variables and none reached any statistical significance at $p < 0.05$. In the regression models, we reported the adjusted relative risk and 95% confidence intervals with significance set at a p-value less than 5% (two-tailed).

Ethical Statement

Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee (ref: 1785-2021) and the Human Research Ethics Committee of the University of Witwatersrand South Africa (Medical [ref: R14/49]). The study was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study. And details that might disclose the identity of the subjects under study were omitted.

Results

The study included 75 participants with a median age of 29 years (interquartile range [IQR]: 27–34 years). Overall, 64 (85.3%), were married and 54 (72.1%) attained a secondary or tertiary level of education. Slightly above half, 47(62.7%) were below the richer wealth index quintile (Table 1).

Biomarker Levels, Hypertension and HIV Serostatus

Participants living with HIV on ART had higher median cystatin C levels (0.81 mg/l, IQR: 0.68–1.14 mg/l); however, between-group differences in concentration did not reach statistical significance. The levels of IL-2, IL-6 and TNFa were similar between women living with and without HIV. Women living with HIV on ART had higher levels of hs-CRP than HIV-negative women (4.68 mg/l vs 3.60 mg/l, $p = 0.025$) (Table 2; Fig. 1). Nearly half 17 (48.6%) of HIV-positive women had hypertension, whereas just over a quarter, 11 (27.5%) of HIV-negative women had hypertension (Table 2). In sub-group analysis (Online Resource 1), participants who initiated HIV treatment during pregnancy had higher TNFa median levels than those who initiated before pregnancy (30.3 pg/ml vs 24.1 pg/ml, $p = 0.047$). Additionally, slightly above half (51.6%) of the participants who initiated ART pre-pregnancy had hypertension compared to only one participant (25%) who initiated during pregnancy.

Cardiovascular Risk Profile and HIV Serostatus

We categorized women by the presence of abnormal biomarkers at six weeks postpartum (Table 3). The majority, 22 (62.9%) of the women living with HIV on ART had elevated hs-CRP. HIV on ART was associated with increased risk (adjusted relative risk [aRR] = 2.88, 95% CI: 1.09–7.60) of the most adverse cardiovascular profile (hypertensive with elevated hs-CRP) than HIV-negative women adjusting for body mass index, age and initial hs-CRP levels. However, the risk of moderate adverse cardiovascular profile (i.e., any elevated hs-CRP, IL-2, IL-6, TNFa, and cystatin C) at six weeks postpartum was similar between women living with and without HIV (Table 3).

Cardiovascular Risk Profile and HIV Serostatus Stratified by Preeclampsia Onset

Among women who developed late-onset preeclampsia, the proportion of women with adverse cardiovascular risk profiles was higher for women living with HIV on ART than the HIV-negative. However, statistical significance was not retained among the women who had early-onset preeclampsia. Furthermore, women in the late-onset preeclampsia group living with HIV (aRR = 2.56, 95% CI: 1.10–5.95) were more likely to have the most adverse cardiovascular profile (hypertensive with elevated hs-CRP) than HIV-negative counterparts (Table 4).

Discussion

We assessed the cardiovascular risk biomarkers among postpartum women previously diagnosed with preeclampsia. We found that at six weeks postpartum, women living with HIV and on ART recovering from preeclampsia had higher blood pressure and hs-CRP, a marker of inflammation and future cardiovascular risk. HIV with ART use was associated with a 2.88-fold increase in the risk of presenting with an adverse

Table 1 Characteristics of study participants

Variable	Total population n = 75(%)	HIV serostatus		P-value
		Negative, n = 40(%)	Positive, n = 35(%)	
Age years median (IQR)	29 (26–29)	28 (23.5–30.5)	32 (27–35)	0.07
Marital status				
Unmarried	11 (14.7)	5 (12.5)	6 (17.1)	0.57
Married	64 (85.3)	35 (87.5)	29 (82.9)	
Education				
None/Primary	21 (28.0)	7 (17.5)	14 (40.0)	0.03
Secondary/Tertiary	54 (72.0)	33 (82.5)	21 (60.0)	
Wealth index				
Poorest/poorer/middle	47 (62.7)	21 (52.5)	26 (74.3)	0.05
Richer/richest	28 (37.3)	19 (47.5)	9 (25.7)	
Onset of preeclampsia				
Early (< 34 weeks)	34 (45.3)	20 (50.0)	14 (40.0))	0.26
Late (≥ 34 weeks)	41 (54.7)	20 (50.0)	21 (60.0)	
Severity of Preeclampsia				
Severe	4 (5.3)	1 (2.5)	6 (10.3)	0.24
Mild/Moderate	71 (94.7)	39 (97.5)	29 (89.7)	
Adverse pregnancy outcomes, n = 24				
Stillbirth	7 (29.2)	–	7 (63.6)	0.001
Preterm birth	17 (70.8)	13 (100)	4 (36.4)	
Parity median (IQR)	2 (1–3)	2 (1–3)	2 (1–4)	0.49
Contraceptive use				
Unknown/no contraception	24 (32.0)	10 (25.0)	14 (40.0)	0.38
Intrauterine/barrier/dual	9 (12.0)	6 (15.0)	3 (8.6)	
Hormonal	42 (56.0)	24(60.0)	18 (51.4)	
Body mass index, median (IQR)	27.5 (24.7–31.3)	27.3 (24–30.8)	29.7 (25.4–31.3)	0.29
Anxiety and depression				
No	45 (60.0)	25 (62.5)	20 (57.1)	0.64
Yes	30 (40.0)	15 (37.5)	15 (42.9)	

IQR interquartile range

Table 2 Median biomarker levels and hypertension according to HIV serostatus at postpartum visit

Variable	HIV serostatus		
	Negative, n(%)/median(IQR)	Positive, n(%)/median(IQR)	p-value[b]
Hypertension[a]			
No	29 (75.5)	18 (51.4)	**0.023**
Yes	11 (27.5)	17 (48.6)	
Hs-CRP, mg/l	3.60 (1.44–5.68)	4.68 (2.35–10.78)	**0.025**
Cystatin C, mg/l	0.78 (0.72–1.01)	0.81 (0.68–1.15)	0.303
IL-2, pg/ml	0.64 (0.64–0.64)	0.64 (0.64–0.67)	0.131
IL-6, pg/ml	0.64 (0.64–2.39)	0.64 (0.64–2.34)	0.422
TNFa, pg/ml	24.1 (15.5–32.5)	24.1 (15.5–32.2)	0.346

[a]Elevated systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or on treatment, IQR-interquartile range, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha, boldface indicates statistical significance at alpha < 0.05, [b]p-values from Wilcoxon Ranksun test/Pearson Chi-square test

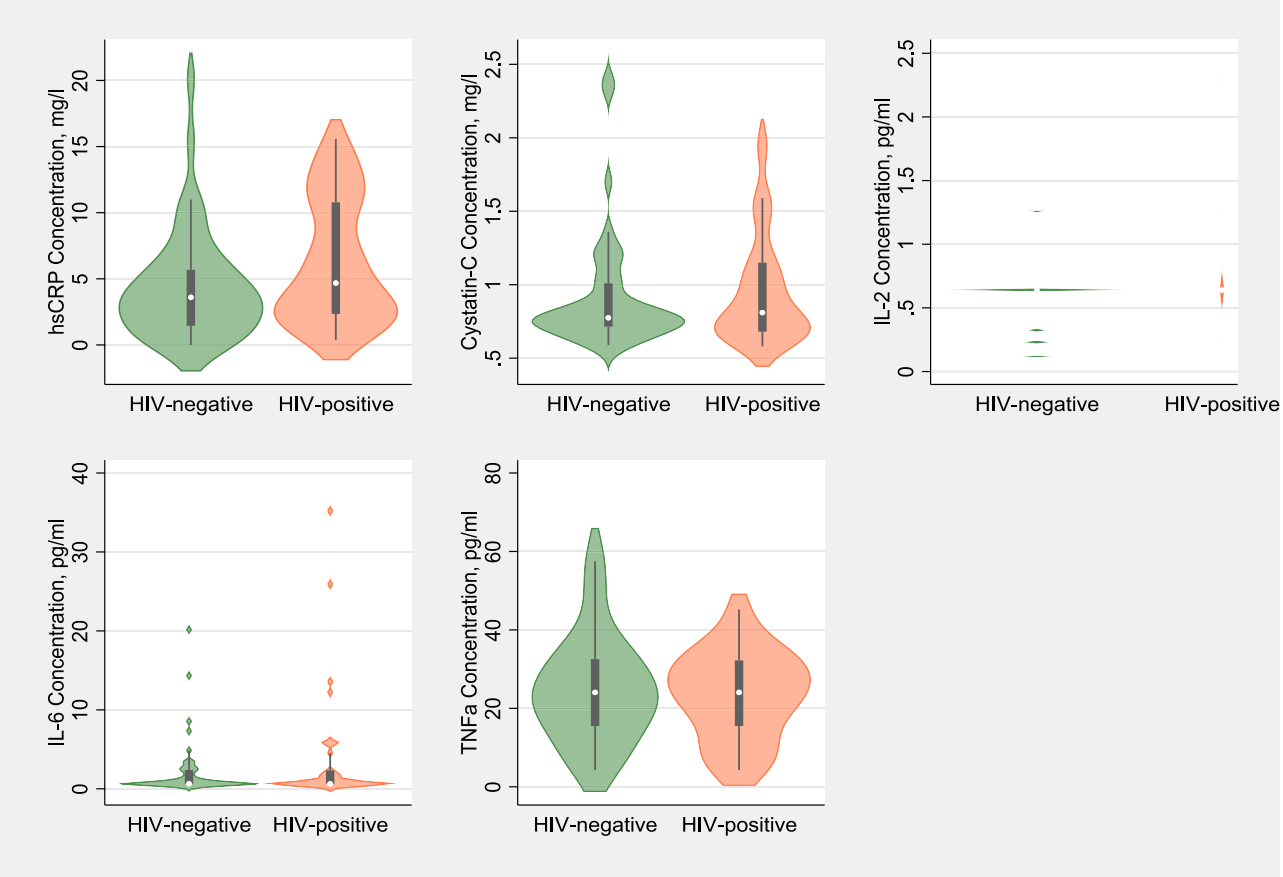


Fig. 1 Concentration of biomarker (hs-CRP, Cystatin C, IL-2, IL-6 and TNFa) levels at six weeks postpartum in women living with and without HIV, n = 75

cardiovascular profile compared to HIV-negative participants. When stratified by preeclampsia onset, statistical significance was only retained in the late-onset group. However, we did not observe IL-2, IL-6, TNFa, and cystatin C differences by HIV status and the comprehensive risk of moderate adverse cardiovascular profile at six weeks postpartum was similar between women living with and without HIV.

Consistent with the extant literature (Bigna et al., 2020; Fiseha et al., 2019), we found that most women living with HIV were in the adverse cardiovascular risk profile (hypertension with elevated hs-CRP) at six weeks postpartum. High levels of pro-inflammatory biomarkers and immune activation are linked to having HIV and are known to contribute to endothelial dysfunction and subsequent hypertension (Shiau et al., 2023). In addition, certain ART agents (e.g., protease inhibitors) may have metabolic side effects that could lead to elevated blood pressure (Mabhida et al., 2024). This was in line with our findings where we noted that more participants who initiated ART pre-pregnancy had hypertension compared to participants

Table 3 Multivariable model for prediction of various cardiovascular risk profiles at six weeks postpartum, N = 75

Cardiovascular profile	HIV negative	HIV positive	
	n(%)	n(%)	Adjusted RR[a] (95% CI)
Hs-CRP > 3 mg/l	23 (57.5)	22 (62.9)	1.09 (0.75–1.61)
Cystatin C > 97.2 mg/l	8 (20.0)	9 (25.7)	1.27 (0.51–3.21)
IL-2 > 0.64 pg/ml	4 (10.0)	6 (17.1)	1.59 (0.48–5.30)
IL-6 > 10 pg/ml	10 (25.0)	8 (22.9)	0.84 (0.38–1.87)
TNFa > 16 pg/ml	10 (25.0)	8 (22.8)	0.79 (0.32–1.94)
Hypertensive with elevated hs-CRP	6 (15.0)	12 (34.3)	2.88 (1.09–7.60)*

RR-relative risk, 95% CI- 95% confidence intervals, [a]HIV-negative was the reference group, *p < 0.05, All models adjusted for initial biomarker concentration, maternal age and body mass index as continuous variables, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha

Table 4 Multivariable model for prediction of various cardiovascular risk profiles stratified by onset of preeclampsia, N = 75

Cardiovascular profile	Early onset preeclampsia			Late-onset preeclampsia		
	HIV negative n = 20(%)	HIV positive n = 13(%)	aRR[a] (95% CI)	HIV negative, n = 20(%)	HIV positive, n = 22 (%)	aRR[a] (95% CI)
Hs-CRP > 3 mg/l	10 (50.0)	9 (69.2)	1.55 (0.84–2.83)	13 (65.0)	13 (59.1)	0.97 (0.58–1.62)
Cystatin C > 97.2 mg/l	6 (30.0)	6 (46.2)	1.65 (0.65–4.19)	2 (10.0)	3 (13.6)	1.14 (0.18–7.12)
IL-2 > 0.64 pg/ml	2 (10.0)	1 (7.7)	1.78 (0.10–32.7)	2 (10.0)	5 (22.7)	2.11 (0.42–10.5)
IL-6 > 10 pg/ml	4 (20.0)	1 (7.7)	0.39 (0.04–4.41)	6 (30.0)	7 (31.8)	1.15 (0.41–3.20)
TNFa > 16 pg/ml	3 (15.0)	1 (7.7)	0.52 (0.08–3.53)	7 (35.0)	7 (31.8)	1.04 (0.34–3.20)
Hypertensive with elevated hs-CRP	3 (15.0)	3 (23.1)	2.06 (0.44–9.75)	3 (15.0)	9 (40.9)	2.56 (1.10–5.95)*

RR-relative risk, 95% CI- 95% confidence intervals, [a]HIV-negative was the reference group, *p < 0.05, All models adjusted for initial biomarker concentration, maternal age and body mass index as continuous variables, hs-CRP-high sensitivity reactive protein, IL-2-interleukine-2, IL-6-interleukine-6, TNFa-tumor necrosis factor-alpha

who initiated during pregnancy. However, these preliminary results should be interpreted with caution since only 4 patients initiated ART in pregnancy in this cohort. As all HIV positive participants in our study were on ART, determining the relative contribution of treatment regimens is impossible, but this would be important in future studies.

Our findings on elevated hs-CRP levels indicate increased inflammation, which is recognized as a contributing factor to hypertension and future cardiovascular risk (Visser et al., 2014). Furthermore, the finding on higher blood pressure with elevated hs-CRP could be suggestive of future cardiovascular diseases in the HIV population post-pregnancy complicated by preeclampsia. Most participants in the present study had hs-CRP 3 mg/l or above, suggesting chronic rather than acute inflammation as the most likely pathway to postpartum hypertension in this population.

The similarities in the overall concentrations of cystatin C, IL-2, IL-6 and TNFa between women living with and without HIV may suggest that other mechanisms of endothelial dysfunction may contribute to high rates of hypertension in our cohort (Peprah et al., 2021). On the other hand, we speculate that the lack of significant differences in IL-6, IL-2, and TNFa between the HIV and non-HIV participants could be due to power limitations. Studies from high-income countries have reported an association between pro-inflammatory cytokines like IL-6 and TNFa and endothelial dysfunction in individuals living with HIV (Lacerda et al., 2014; Liu et al., 2019).

While HIV itself has been associated with chronic inflammation, the lack of substantial variation in the assessed biomarkers of inflammation suggests that several factors, such as socioeconomic or genetic factors (Abraham & Romani, 2022), may also play a prominent role in women recovering from preeclampsia in our cohort. Additionally, studies have demonstrated that well-controlled HIV infection with sustained ART use can lead to immune reconstitution and attenuation of systemic inflammation, which may explain the lack of significant differences in cytokine and renal function biomarker levels observed in our study (Bloch et al., 2020). Understanding the multifaceted nature of endothelial dysfunction in women recovering from preeclampsia is crucial for developing effective preventive and therapeutic strategies tailored to the unique challenges and factors at play.

In this study, the proportion of participants with adverse cardiovascular profiles was high. The within-group difference was only seen in the women presenting with late-onset than early-onset preeclampsia. This could at least be partially explained by the placental pathophysiological condition during preeclampsia which is mainly seen in later stages of pregnancy (Sharma et al., 2007). Placenta hypoxia induces the release of pro-inflammatory cytokines such as IL-6 and TNF-α that stimulate the liver to release more hs-CRP, which leads to endothelial dysfunction and hypertension (Mabhida et al., 2024).

Sustained injury to the endothelium during pregnancy may not resolve entirely even after delivery, and HIV could potentially worsen this. Testing biomarkers such as hs-CRP early postpartum could help in risk identification and stratification of future cardiovascular diseases and potentially improve outcomes in those living with HIV who are at a greater risk of cardiovascular diseases. Biomarkers of inflammation are useful in predicting future cardiovascular risk, and most risk score algorithms have incorporated them in high-income countries (Liu et al., 2019). If confirmed by larger studies the assessed biomarkers could be key in early identification of the future risk of cardiovascular diseases in women living with HIV after preeclamptic pregnancies.

Clinical Implications

If confirmed by larger studies postpartum follow-up strategies should be modified for women living with HIV

after a pregnancy complicated by hypertension. An emphasis should also be placed on the importance of postpartum follow-up for women who suffered preeclampsia when conducting continuous professional developed programs for healthcare workers. Understanding vascular biomarkers is important in patient risk identification and stratification, as suggested by moderate evidence, particularly among intermediate cardiovascular-risk women, where it is unclear whether to initiate primary preventive therapy (Pearson et al., 2003). Additionally, this creates an opportunity for targeted interventions such as lifestyle modification (Diet, exercise, smoking cessation, moderation of alcohol), pharmacological interventions such as Statins and Aspirin, and nutritional supplementation (ginger, green tea and Vitamins C,D,E).

Furthermore, the discovery of assays that can accurately identify those women at the highest risk for cardiovascular diseases early could improve management and outcomes. Studies have reported several vascular biomarkers associated with cardiovascular disease (Antonopoulos et al., 2022; Visser et al., 2014). However, among currently available vascular biomarkers, hs-CRP is the best characterised and is currently the only marker that adds prognostic information to traditional cardiovascular risk assessment (Antonopoulos et al., 2022). Therefore, our findings on hs-CRP in the HIV comorbid preeclampsia population are timely given the increasing recognition of postpartum cardiovascular risks associated with preeclampsia.

Strengths and Limitations

The study has several strengths. This study is among the first to study associations between HIV and biomarkers (hs-CRP, IL-2, IL-6, cystatin C and TNFa) in postpartum women recovering from preeclampsia. However, there are some limitations. This study enrolled women from two urban hospitals in Lusaka, Zambia, and therefore, findings may not be generalized to other settings.

Additionally, although the sample size was in line with prior findings in the medical literature (Osoti et al., 2020; Sukmanee & Liabsuetrakul, 2022), the wide confidence intervals indicate that future studies with larger sample sizes may be needed. Additionally, we could not account for the severity of preeclampsia in the multivariable models due to small numbers of women with severe preeclampsia. Furthermore, for reasons of cost, this study used case–control subsampling when population-based sampling may be more representative. Furthermore, the sample size was powered to detect differences in the primary outcome (hs-CRP) and this may have underpowered other analyses. As this study was unable to make comparisons by HIV serostatus, future studies are warranted to compare how HIV vs. pre-eclampsia vs. both conditions impact biomarkers.

Conclusion

Women living with HIV on ART had higher blood pressure levels and concentrations of postpartum hs-CRP, a marker of inflammation and risk of future cardiovascular diseases. Additionally, women living with HIV were twice as likely to have the adverse cardiovascular risk profile than HIV-negative women. However, we did not observe differences in IL-2, IL-6, TNFa, and cystatin C by HIV status. These findings suggest a potential role of hs-CRP in risk stratification and identification for future hypertension. Given the high morbidity and mortality from cardiovascular diseases globally, the ability to screen patients in a fast, reliable and cost-effective manner will have great importance. Future studies are warranted to identify accurate methods of cardiovascular disease screening to decrease preventable deaths from hypertension among women of childbearing age.

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Data Availability All data materials used for this study are available through the hospital management and data sharing agreements of the National Health Research Authority in Zambia.

Code Availability Authors can make available the STATA code used for this analysis upon request.

Declarations

Conflict of interest All the authors declare that they have no competing interests.

Ethical Approval Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee (ref: 1785–2021) and the Human Research Ethics Committee of the University of Witwatersrand Johannesburg, South Africa (Medical [ref: R14/49]).

Consent to Participate All participants signed written informed consent forms before participating in the study.

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