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Elevated central blood pressure, NT-proBNP and hs-cTnI in women with maternal complications of hypertensive disorders of pregnancy

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ABSTRACT

Objective: The main objective of the study was to compare the levels of CBP and these cardiac biomarkers in women with maternal complications of hypertensive disorders of pregnancy (HDP).

Methods: This was a cross-sectional study that enrolled 270 women with HDP and 270 normotensive pregnant controls. Data on basic characteristics and incidence of maternal complications were collected among the two groups. Additionally, information on cardiac biomarkers and CBP was gathered from the women with HDP, to compare the levels of these biomarkers with maternal complications experience by this group.

Results: Non-hypertensive controls were significantly older than hypertensive cases and had a higher median gestational age at recruitment compared to hypertensive cases The median levels of CBP and cardiac biomarkers were significantly higher among hypertensive participants with maternal complications ($n = 107/270$) than those without complications ($n = 163/270$). Specifically, central systolic blood pressure (CSBP) was 133 (120–142) mmHg vs 128 (109–129) mmHg ($p = 0.033$) and central diastolic blood pressure (CDBP) was 75 (62–86) mmHg vs 69 (56–73) mmHg ($p < 0.01$), while NT-proBNP was 446 (145–1126) vs. 57 (21–167)) pg.ml^{-1}; $p < 0.0001$, and hs-cTnI was 12 (7–35) ng.L^{-1} compared to 8 (3–8) ng.L^{-1}; $p < 0.0001$, in cases v. controls, respectively.

Conclusion: In conclusion, the study found that pregnant hypertensive women with maternal complications had significantly higher median values of CSBP and CDBP, NT-proBNP, and hs-cTnI in compared to those without complications. These findings suggest that measuring these vital signs and cardiac biomarkers in hypertensive pregnancies might be helpful for screening and monitoring maternal complications.

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Preeclampsia; systolic blood pressure; eclampsia; cardiac biomarkers

Introduction

Central blood pressure (CBP) and cardiac biomarkers such as NT-proBNP and hs-cTnI, are among several variables that have been studied in women with hypertensive disorders of hypertensive disorders (HDP)) (1–5). The inactive N-terminal pro B-type natriuretic peptide is co-secreted with a 32-amino acid polypeptide, B-type natriuretic peptide (BNP), from the left and right cardiac ventricle in response to ventricular volume expansion and pressure overload, while hs-cTnI is a cardiac enzyme whose levels in the circulation respond to cardiomyocyte damage (6–8). In general, both biomarkers are associated with cardiac injuries and can indicate future cardiac disease risk, and, to some degree, the severity of cardiovascular events generally used for diagnosing cardiomyocyte injury (6,9–11). Lam et al. (2018) demonstrated that patients with heart failure and elevated BNP are more likely to experience death and rehospitalisation compared to those with low levels (12).

HDP are a leading cause of maternal morbidity and mortality globally (13). They account for approximately 14–18% of all maternal deaths globally, with an estimated 62,000–77,000 maternal deaths, and 500,000 perinatal deaths annually (13–15). Maternal complications of HDP include stroke, pulmonary edema, Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome, abruptio placentae, acute kidney injury, intensive care unit (ICU) admission, low Glasgow coma scale (GCS), and others (16,17). Studies have shown an association between preeclampsia (PE) and cardiovascular complications during pregnancy or many years after pregnancy

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(18,19). Other long-term complications of HDP are chronic hypertension, diabetes mellitus, stroke, end-stage renal disease, and cognitive impairment (19).

Hypertension can negatively affect pregnancy outcomes in women with advanced pregnancies and those undergoing assisted reproductive technologies (ART) such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (20). Research has shown that even a slight increase in blood pressure among normotensive women undergoing IVF/ICSI is associated with a reduced live birth rate. A recent study involving 73,462 patients demonstrated that elevated systolic blood pressure (SBP) in normotensive women has a significant impact on live birth outcomes during these procedures (21). These findings are consistent with earlier research by Chen et al., which showed that both (SBP) and diastolic blood pressure (DBP) were lower in a group of 1,487 women who achieved successful outcomes after fresh embryo transfers following IVF/ICSI compared to those who did not have live births (22). Previous studies have demonstrated a significant increase in NT-proBNP in hypertensive pregnant women compared to pregnant normotensive women (1,3,4,11,23–25). A correlation between elevated systemic vascular resistance, left ventricular diastolic dysfunction, and depression of cardiac output in preeclamptic patients and elevated NT-proBNP levels has been observed ((24–26). A strong association between cardiac Troponin I and PE, has also been reported (6,8,24,25,27,28). However, there is still insufficient data evaluating relationships between NT-proBNP, hs-cTnI, and other short-term maternal complications, other than cardiac-related complications, in women with HDP.

Evidence suggests that PE is associated with increased central aortic blood pressure, pulse wave velocity as well as elastic arterial stiffness (5,29,30). Torrado and colleagues (2015) found that CSBP was significantly higher in Caucasian women with PE compared to those with gestational hypertension (GHPT) (29). They further elaborated that in their study there was no difference in PBP in those with PE compared to those with GHPT. The studies by Meeme et al. (2017) and Namugowa et al. (2017) focused on examining the CBP and arterial stiffness in black African women in South Africa with and without PE. They found that women with PE had higher arterial stiffness compared to normotensive women (5,30) However, their studies did not include women with preeclampsia with severe features such as eclampsia, imminent eclampsia, stroke, HELLP syndrome, pulmonary edema, abruptio placentae and acute kidney injury. Their studies also did not explore the relationship between the CBP and the maternal outcomes in women with PE. These unaddressed issues warrant further investigation. The aim of the current study was therefore to assess the levels of CBP, cardiac biomarkers proBNP and hs-cTnI in women with maternal complications of HDP. The study hypothesized that levels of CBP and these biomarkers would be higher in women with HDP who have maternal complications compared to those without related complications.

Methods

This was a prospective cross-sectional study evaluating the levels of CBP, NT-proBNP and hs-cTnI, in women with immediate maternal complications of HDP. A total of 540 participants were enrolled, comprising 270 inpatient women with HDP and 270 inpatient normotensive pregnant women in the maternity ward at Nelson Mandela Academic Hospital in South Africa. Data on basic characteristics and incidence of maternal complications were collected among the two groups. Additionally, information on cardiac biomarkers and CBP was gathered from the women with HDP, to compare the levels of these biomarkers with maternal complications experience by this group. All participants were followed up for up to seven days after delivery to identify maternal complications and rule out normotensive patients developing hypertension.

The inclusion criteria for the hypertensive group encompassed all hypertensive patients who were at least 20 weeks gestation, while the inclusion criteria for normotensive pregnant participants included healthy patients with singleton pregnancies and specific conditions such as placenta previa, preterm premature rupture of membranes, preterm labor, or patients admitted for repeat elective cesarean section at term.

Patients who were less than 20 weeks gestation, those who were dire emergencies with no time to seek consent for participation in the study and those who declined to participate, were excluded. Patients with diabetes mellitus, cardiac disease, chronic renal disease, and antiphospholipid syndrome or other autoimmune disease were also excluded.

The cases were not matched for maternal and gestational age. This is because most patients with HDP, especially eclampsia, are younger compared to the general population, and excluding them will cause bias. According to national guidelines, patients with HDP are delivered preterm (preferably less than 35 weeks), whereas controls such as placenta previa and previous cesarean deliveries are delivered much later (31).

Definitions of hypertensive disorders were made according to the International Society for the Study of Hypertension in Pregnancy classification recommendations (32):

- Chronic hypertension was defined as high blood pressure predating the pregnancy or recognized at less than 20 weeks' gestation.
- Gestational hypertension was defined as hypertension diagnosed after 20 weeks gestation, without any features of pre-eclampsia.
- Preeclampsia was defined as de novo hypertension or superimposed on chronic hypertension after 20 weeks' gestation, accompanied by proteinuria and/or other evidence of maternal end-organ dysfunction, and/or fetal growth restriction.
- Eclampsia was defined as the convulsive manifestation of the HDP.

HELLP syndrome was diagnosed when any two of the following abnormalities were present: increased Lactate dehydrogenase (LDH) (≥600 IU/L), increased Aspartate transaminase (AST) (≥70 IU/L), low platelet count (<100 ×10^9/L); and renal failure if creatinine was ≥ 90 umol/L (28,33).

Data collection

These data were gathered from patient and maternity case files, using a pre-designed questionnaire. It comprised socio-demographic and clinical information, including maternal and gestational age, parity, marital status, education, presence and type of hypertensive disorders of pregnancy, maternal and fetal conditions, as well as maternal and perinatal outcomes.

Blood pressure measurements, both peripheral and central, were recorded at enrollment and within a week after delivery using the Microlife WatchBP Office Central. Before using the WatchBP Office central, the correct size of cuff was chosen and placed over the left or right upper arm so that the artery mark arrow point toward the lower arm. The cuff was wrapped around the arm, making sure that the lower edge of the cuff was approximately 2 cm above the elbow. The WatchBP Office Central device automatically measured both brachial and central blood pressure, displaying the results on the screen once the measurement process was complete. To determine the central blood pressure, the WatchBP Office Central uses brachial pulse volume plethysmography (PVP) waveforms. It is designed to perform PVP at a cuff pressure of 60 mmHg. Based on the analysis of the PVP waveforms, the central systolic pressure and central pulse pressure values are automatically determined.

Blood samples were collected from each woman using two different types of tubes. For serum NT-proBNP, hs-cTnI, and platelet count, 10 ml of venous blood from the antecubital vein was drawn into tubes containing EDTA. The plasma was separated through centrifugation at 4°C for 15 minutes at 3500 rpm and then stored at −80°C until analysis. Another 10 ml of venous blood was drawn into yellow tubes containing Solution A (trisodium citrate, citric acid, and dextrose) for the measurement of creatinine, alanine transaminase (ALT), AST, and LDH. All assays, including NT-proBNP and hs-cTnI, were performed using an Alinity iSTAT analyzer (Abbott, USA).

Statistical analysis

Data were checked for completeness and consistency before being captured using the IBM SPSS STATISTICS software package version 29 for Windows (IBM Inc., Chicago IL, USA). These data were summarized into proportions (%) for categorical variables. Continuous data such as age, gestational and parity was interpreted using means and standard deviations (SD) if normally distributed or using medians, interquartile ranges, and percentiles (p25, p75) if skewed. The Chi-square test was used to delineate the degree of association between categorical variables. A $p < 0.05$ was considered statistically significant.

Results

General and clinical characteristics of the sample population

Out of the 270 hypertensive cases, 143 (53%) had preeclampsia, 102 (38%) had eclampsia, 14 (5%) had chronic hypertension, and 11 (4%) had gestational hypertension.

Two out of the eleven patients with gestational hypertension initially had normal blood pressure at recruitment but later developed hypertension during labor and were reassigned as gestational hypertension instead of normotensive controls.

The demographic and clinical characteristics of the sample population are shown in Table 1. The non-hypertensive controls (median = 28 years; $p < 0.0001$) were significantly older than the hypertensive cases (median = 25 years). The majority (63.1% $n = 341$) were in the 20 to 34 years age group and the minority (17.2% $n = 93$) were younger than 20 years.

Table 1. General and clinical characteristics of the sample population.

Characteristics	Hypertensive cases; $n = 270$ n (%)	Non-hypertensive controls; $n = 270$ n (%)	Total; $n = 540$ n (%)	Pearson X^2 Sig.
Ethnicity				
African	269 (99.6)	268 (99.2)	537 (99.4)	0.624*
Multiracial	1 (0.4)	2 (0.7)	3 (0.6)	
Marital status				
Single	210 (77.8)	207 (76.7)	417 (77.2)	0.837*
Married	60 (22.2)	62 (23.0)	122 (22.6)	
Divorced	0 (0.0)	1 (0.4)	1 (0.2)	
Gravidity				
Multigravida	149 (55.2)	209 (77.4)	358 (66.3)	<0.0001
Primigravida	121 (44.8)	61 (11.6)	182 (33.7)	
Booking status				
Booked	248 (91.9)	258 (95.6)	506 (93.7)	0.111
Not booked	22 (8.1)	12 (4.4)	34 (6.3)	
Mode of delivery				
Caesarean section	233 (86.3)	235 (87.0)	468 (86.7)	0.800
Vaginal	37 (13.7)	35 (13.0)	72 (13.3)	
Maternal complications				
Yes	107 (39.6)	2 (0.7)	109 (20.2)	<0.0001
No	163 (60.4)	268 (99.3)	431 (79.8)	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Sig.****
Gestational age at recruitment (weeks)	34 (6)	38 (3)	36 (5)	<0.0001

*Fisher's Exact p-value; ** Mann-Whitney U p-value.

There was no statistical difference ($p > 0.05$) for the other demographic characteristics observed in the hypertensive cases and non-hypertensive controls. Nearly all (99.4% $n = 537$) the participants were of African race, and the remaining were Multiracial (0.6% $n = 3$). More than three-quarters (77.2%) were single, and slightly more than a quarter (22.6% $n = 122$) were married.

Participants with HDP had a higher proportion of primigravida than the normotensive controls (44.8% Vs 11.6%, $p < 0.0001$). Most (93.7% $n = 434$) of the participants attended antenatal clinics while 34 (6.3%) did not. Antenatal clinic attendance between hypertensive cases and non-hypertensive controls was comparable statistically ($p > 0.05$). The median gestational age at enrollment to the study was 36 weeks (IQR: 5). The median gestational age at recruitment was significantly higher (38 weeks IQR = 5 weeks) among non-hypertensive controls compared to hypertensive cases (34 weeks IQR = 6 weeks) ($p < 0.0001$). The majority (86.7% $n = 468$) gave birth through cesarean section and the minority (13.3% $n = 72$) normally. No significant difference was observed in the mode of delivery between the two groups.

Maternal complications diagnosed in the study group

More than twenty percent of all participants (109/540, 20.2%) developed complications pre- or post-delivery. Only 2 out of the 270 normotensive controls (0.7%) developed maternal complications with both having abruptio placenta. In contrast 107/270 (39.6%) of the cases with HDP had various maternal complications with the most common being HELLP syndrome (78/270, 28.9%) renal failure (29/270, 10.7%), and abruptio placental (26/270, 9.6%) (Table 2). Other complications included pulmonary edema (3/270), low GCS (4/270), cerebrovascular accident, disseminated intravascular coagulopathy ($n = 1$), or posterior reversible encephalopathic syndrome (each 1/270). Multiple regression analysis indicated that maternal age and parity were not associated with maternal complications (Table 3). Only gestational age at recruitment showed an independent association with maternal complications. Specifically, as gestation progressed in weeks, the odds of experiencing maternal complications decreased by 17.4% (Table 4). However, when using Integrated Discrimination Improvement (IDI) predictive model, inclusion of gestational age, CBP and PBP did not increase the risk prediction of maternal complications in women with HDP. In this group, NT-proBNP was the most effective predictor of maternal complication risk, followed closely by hs-cTnI.

Table 2. Maternal complications diagnosed in the study participants.

	Cases; $n = 107$	Controls; $n = 2$	Total; $n = 109$
Maternal complications	n (%)	n (%)	n (%)
Abruptio placenta	24 (22.4)	2 (100.0)	26 (23.9)
HELLP syndrome	78 (72.9)	0 (0.0)	78 (71.6)
Renal failure	29 (27.1)	0 (0.0)	29 (26.6)
Pulmonary edema	3 (2.8)	0 (0.0)	3 (2.8)
Low GCS	7 (6.5)	0 (0.0)	7 (6.4)
ICU admission	7 (6.5)	0 (0.0)	7 (6.4)

Table 3. Multiple regression analysis examining the relationship between maternal complications and factors such as age, parity, gestational age, BMI, and HIV status.

	No maternal complications	Yes-Maternal complications	p-value
Age(years)	28.0 (22.0–33.0)	25.0 (19.0–30.0)	0.002
Parity	1.0 (0.0–2.0)	0.0 (0.0–2.0)	<0.0001
Gestational age at recruitment	37.0 (34.0–38.0)	33.0 (29.0–36.0)	<0.0001
Body Mass Index (kg/m^2)	29.4 (25.0–35.1)	27.8 (23.8–33.3)	0.086
HIV status			
Positive	125 (29.0)	28 (25.7)	0.571
Negative	306 (71.0)	81 (74.3)	

Table 4. Relationship between maternal complications and gestational age.

	B	S.E.	Wald	p-value	OR (95%CI)
Age(years)	−0.016	0.022	0.509	0.475	0.985 (0.943–1.028)
Parity	−0.172	0.126	1.861	0.172	0.842 (0.657–1.078)
Gestational age at recruitment	−0.191	0.027	48.664	<0.0001	0.826 (0.783–0.872)
Constant	5.818	1.046	30.926	<0.000	336.259

The serum concentrations of hs-cTnI and Nt-proBNP in women with different types of HDP

Women with eclampsia had significantly higher median serum hs-cTnI levels (15.5 ng.L^{-1}; 7.0–44.0) and log-transformed hs-cTnI levels (1.19 ng.L^{-1};0.85–1.64) than women with other phenotypes of HDP ($p < 0.0001$), as shown in Table 5. Similarly, women with eclampsia had significantly higher median serum NT-proBNP levels (577.5 pg.ml^{-1}; 236.0–1175.0) and log-transformed NT-proBNP (2.76 pg.ml^{-1}; 2.37–3.07) compared to women with other phenotypes of HDP ($p < 0.0001$), as shown in Table 5. The levels of serum NT-proBNP in women with eclampsia were well above the upper normal limit of 150 pg.ml^{-1}.

Relationship between PBP, CBP, NT-proBNP and hs-cTnI, and maternal complications in all hypertensive cases

The median levels (p25, p75) of the cardiac biomarkers and CBP were significantly higher among hypertensive participants with maternal complications (n = 107/270) than those without complications (n = 163/270). Specifically, the central systolic blood pressure (CSBP) were 133 (120–142) mmHg vs 128 (109–129) mmHg ($p = 0.033$) and the central diastolic blood pressure (CDBP) levels were 75 (62–86) mmHg vs 69 (56–73) mmHg ($p < 0.01$) while NT-proBNP levels were 446 (145–1126) vs. 57 (21–167)) pg.ml^{-1}; $p < 0.0001$, and hs-cTnI levels were 12 (7–35) ng.L^{-1} compared to 8 (3–8) ng.L^{-1}; $p < 0.0001$ (Table 6). For PBP, only the PDBP was significantly higher among hypertensive participants with maternal complications when compared to those without complications [80 (65–93) vs 72(62–86) mmHg; $p = 0.004$] (see Table 4). The median values indicate that NT-proBNP levels in individuals with maternal complications were above the normal range (<150 pg.ml^{-1} for NT-proBNP), while the values for hs-cTnI were within the normal range (<30 ng.L^{-1} for hs-cTnI). Among the participants with HDP, a significant relationship was observed between renal failure and the biomarkers (Table 6). In this hypertensive group of participants, the median hs-cTnI in cases with renal failure was significantly higher [35 (12–50) ng.L^{-1}; $p < 0.0001$] compared to those without [11 (6–19) ng.L^{-1}.

The median NT-proBNP in cases with renal failure was also significantly higher [821 (434–1894) pg.ml^{-1}; $p = 0.002$] compared to those without [348 (85–1003)].

Table 5. Serum levels of hs-cTnI and Nt-proBNP in women with the different types of HDP.

	GESTATIONAL HYPERTENSION (n = 11)	CHRONIC HYPERTENSION (n = 14)	PREECLAMPSIA (n = 68)	ECLAMPSIA (n = 102)	
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	p-value*
Hs-cTnI (ng.L^{-1})	6.0 (5.0–9.0)	5.5 (4.0–8.0)	10.0 (6.0–15.0)	15.5 (7.0–44.0)	<0.001
NT-proBNP (pg.ml^{-1})	53.0 (18.0–217.0)	44.5 (11.0–188.0)	180.0 (68.0–508.0)	577.5 (236.0–1175.0)	<0.001
Log transformed NT-proBNP (pg/mL)	1.72 (1.26–2.34)	1.65 (1.04–2.27)	2.26 (1.83–2.71)	2.76 (2.37–3.07)	<0.001
Log transformed Hs-cTnI (ng/L)	0.78 (0.70–0.95)	0.74 (0.60–0.90)	1.00 (0.78–1.18)	1.19 (0.85–1.64)	<0.001

*Kruskal-Wallis.

Table 6. Maternal complications in hypertensive cases: medial comparisons of PBP, CBP, NT-proBNP, and hs-cTnI.

		Peripheral systolic blood pressure (mmHg) Median (IQR)	Peripheral diastolic blood pressure (mmHg) Median (IQR)	Central systolic blood pressure (mmHg) Median (IQR)	Central diastolic blood pressure (mmHg) Median (IQR)	NT-proBNP ($pg.ml^{-1}$) Median (IQR)	Hs-cTnI ($ng.L^{-1}$) Median (IQR)
Composite maternal complications	Yes ($n = 107$)	131 (117–144)	80 (65–93)	133 (120–142)	75 (62–86)	446 (145–1155)	8(5–16)
	No ($n = 163$)	125 (113–139)	72(62–86)	128 (109–129)	69 (56–73)	187 (46–513)	12 (7–36)
	P	0.055	**<0.004**	**0.033**	**0.004**	**<0.0001**	**<0.0001**
Abruptio placentae	Yes ($n = 24$)	123 (112–137)	76 (65–91)	127 (119–138)	71 (56–82)	291 (140–1460)	11(7–31)
	No ($n = 83$)	133 (119–145)	82 (64–94)	134 (123–143)	76 (63–88)	475 (145–1126)	15(7–36)
	P	0.59	0.428	0.140	0.347	0.604	0.501
HELLP syndrome	Yes ($n = 78$)	132 (119–144)	82 (65–93)	133 (119–141)	74 (64–85)	469 (145–1178)	13(7–36)
	No ($n = 29$)	126 (112–144)	73 (62–93)	134 (121–147)	76 (56–87)	403 (200–821.)	12(7–35)
	P	0.426	0.408	0.383	0.975	0.716	0.528
Renal failure	Yes ($n = 29$)	131(117–144)	78 (67–93)	132 (120–145)	78 (66–87)	821 (434–1894)	35 (12–50)
	No ($n = 78$)	131(115–144)	82 (62–93)	133 (120–142)	73 (61–86)	348 (109–1013)	11(6–19)
	P	0.944	0.952	0.922	0.570	**0.002**	**<0.0001**
Pulmonary edema	Yes ($n = 3$)	112 (111–112)	73 (61–76)	105 (99–118)	62 (58–80)	85 (11–13801)	5(5–91)
	No ($n = 104$)	132(118–144)	82 (65–93)	133 (120–143)	75.5 (62–87)	451 (157–1141)	12(7–36)
	P	0.053	0.181	0.059	0.221	0.597	0.499
Low GCS	Yes ($n = 7$)	140 (122–173)	109 (67–121)	134 (123–148)	97 (73–104)	600 (77–2120)	50 (11–77)
	No ($n = 100$)	131 (116–144)	80 (63–93)	133 (120–142)	74 (61–85)	435 (151–1098)	12(7–5)
	P	0.241	0.161	0.614	0.099	0.619	0.059
ICU admission	Yes ($n = 7$)	138 (122–173)	106 (67–119)	138 (128–148)	95 (73–101)	600 (77–2120)	50 (11–77)
	No ($n = 100$)	131 (116–144)	80 (63–93)	132 (120–142)	74 (61–85)	435 (151–1098)	12(7–35)
	P	0.246	0.177	0.368	0.120	0.673	0.061

SIG.= MANN-WHITNEY.

The other readings of biomarkers were similar in participants with the named complications and those without them ($p > 0.05$).

A hs-cTnI value of 8.5 $ng.L^{-1}$ or higher predicted maternal complications of HDP with a sensitivity of 69% and a specificity of 50% ($p < 0.001$; 95% CI 0.57–0.70; AUC = 0.63), while an NT-proBNP value of 179 $pg.ml^{-1}$or higher predicted maternal complications with a sensitivity of 71% and a specificity of 51% ($p < 0.001$; 95% CI 0.59–0.73; AUC = 0.66) (Table 7 and Table 8).). A combination of NT-proBNP, hs-cTnI, and CBP (AUC: 68%; $p < 0.0001$) demonstrated a superior ability to distinguish between participants with and without maternal complications compared to NT-proBNP alone (AUC: 66 %; $p < 0.0001$). (Figure 1 and 2).

A hs-cTnI value of 11 $ng.L^{-1}$ or higher predicted renal failure with a sensitivity of 79% and a specificity of 50% ($p < 0.001$; 95% CI 0.66–0.85; AUC = 0.75), while an NT-proBNP value of 167 $pg.ml^{-1}$ or higher predicted renal failure with a sensitivity of 93% and a specificity of 65% ($p = 0.002$; 95% CI 0.58–0.80; AUC = 0.69) (Figure 3).

Relationship between CBP, NT-proBNP and hs-cTnI and maternal complications in women with eclampsia and preeclampsia

Eclamptic women with composite maternal complications had significantly higher median cSBP (138 mmHg; 124–148: p = 0.010) and cDBP (79 mmHg; 67–95: p = 0.001) compared to those without such complications (cSBP:128 mmHg; 117–136),; (69 mmHg; 58–77). The median cSBP and cDBP in eclamptic women with specific maternal complications such as abruptio placentae, HELLP syndrome, pulmonary edema, low Glasgow coma scale, ICU admission did not differ significantly from those women without the specific maternal complications (all p values > 0.05), as shown in Table 5.

Table 7: Coordinates of the ROC Curve for Highly Sensitive Cardiac Troponin I (ng/ml)

Test Result Variable	Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
Highly Sensitive Cardiac Troponin I (ng/ml)	2.000	1.000	1.000
	3.500	.935	.883
	4.500	.897	.822
	5.500	.860	.724
	6.500	.813	.663
	7.500	.729	.558
	8.500	.692	.497
	9.500	.645	.448
	10.500	.579	.405
	11.500	.523	.362
	12.500	.486	.325
	13.500	.467	.282
	14.500	.467	.264
	15.500	.421	.252
	16.500	.411	.233
	17.500	.393	.221
	18.500	.374	.215
	19.500	.355	.215
	20.500	.336	.202
	21.500	.327	.196
	22.500	.327	.178
	23.500	.327	.166
	24.500	.327	.160
	25.500	.308	.153
	26.500	.308	.141
	27.500	.308	.135
	28.500	.308	.117
	29.500	.299	.104
	30.500	.299	.098
	32.000	.290	.098
	33.500	.280	.098
	34.500	.271	.074
	35.500	.252	.074
	37.000	.234	.074
	39.500	.224	.074
	41.500	.224	.067
	43.000	.215	.067

Additionally, in eclamptic cases who had additional maternal complications, the NT-proBNP and the hs-cTnI were significantly higher compared to those without additional maternal complications: respectively 1030 (382–1894) vs. 464 (164–940) $pg.ml^{-1}$, $p = 0.003$] and 33 (12–62) vs. 10 (5–25) $ng.L^{-1}$ $p < 0.0001$ (Table 9). The cases with eclampsia who had renal failure had significantly higher hs-cTnI compared to eclamptic cases without renal failure 46 (20–175) vs.21 (8–54) $ng.L^{-1}$; $p = 0.036$. There was no difference in the median hs-cTnI and NT-proBNP in eclamptic cases with and without abruptio placenta, help syndrome, pulmonary edema, low GCS, or admission to the ICU ($p > 0.05$) (Table 9).

Table 8: Coordinates of the ROC Curve for NT-Prohormone Brain Natriuretic Peptide

Test Result Variable	Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
NT-Prohormone Brain Natriuretic Peptide (pg/mL)	9.000	1.000	1.000
	10.500	.963	.896
	11.500	.944	.883
	13.000	.935	.877
	14.500	.935	.871
	15.500	.935	.859
	17.000	.925	.859
	18.500	.925	.847
	19.500	.925	.840
	21.000	.925	.834
	22.500	.925	.828
	23.500	.925	.816
	24.500	.916	.816
	25.500	.916	.810
	27.500	.897	.810
	30.000	.897	.804
	31.500	.897	.791
	34.000	.897	.779
	37.000	.897	.773
	40.000	.897	.761
	44.000	.897	.755
	46.500	.897	.748
	47.500	.897	.736
	50.000	.879	.736
	52.500	.879	.730
	54.500	.879	.718
	56.500	.869	.718
	58.000	.869	.712
	59.500	.869	.706
	61.000	.869	.699
	65.000	.869	.693
	69.000	.860	.693
	70.500	.860	.687
	71.500	.860	.681

Overall, the median NT-proBNP [246.50 (85–673) vs.141.50 (45–381) $pg.ml^{-1}$; $p = 0.009$] were significantly higher in preeclamptic cases with maternal complications compared to those without maternal complications. There was no statistically significant difference in the medians for hs-cTnI, in preeclamptic cases with and without maternal complication.

Upon stratified analysis, participants with PE who developed renal failure had significantly higher median hs-cTnI and NT- proBNP compared to those without renal failure, respectively 20 (10–46) vs. 9 (6–12) $ng.L^{-1}$ $p = 0.001$; and [619 (233–1894) vs.200 (78–520) $pg.ml^{-1}$ $p = 0.002$. There was no difference in the median hs-cTnI and NT-proBNP of preeclamptic cases with and without abruptio placenta, HELLP syndrome, low Glasgow coma scale, pulmonary edema, and admission to the ICU ($p > 0.05$).

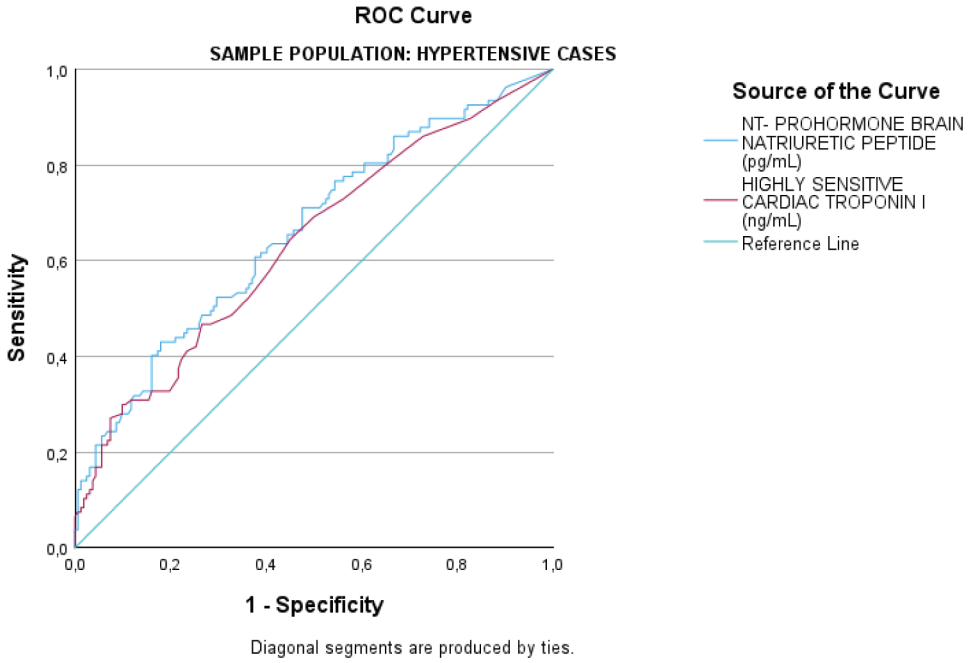

Figure 1. ROC curve analysis of hs-cTnI and Nt-proBNP in women with maternal complications of hypertensive disorders ofpregnancy.

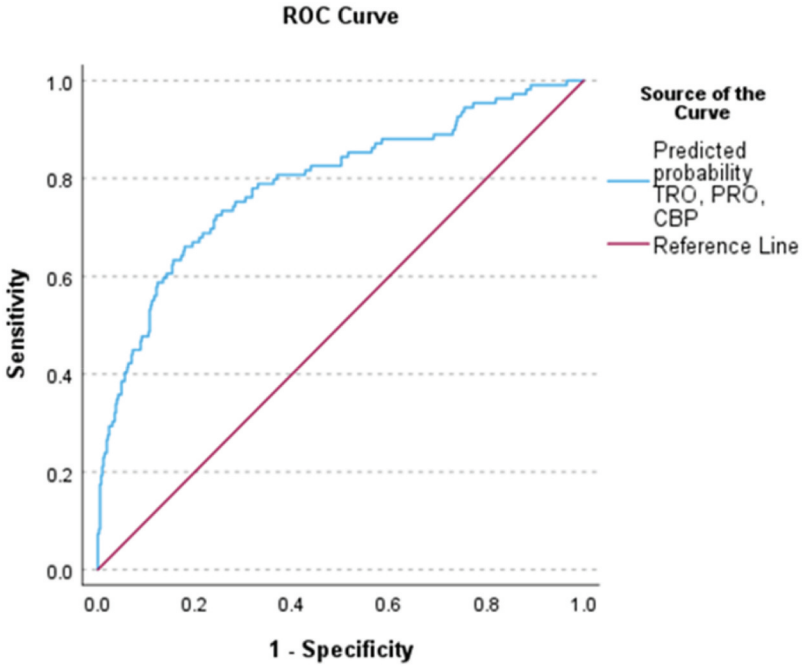

Figure 2. ROC curve analysis of the combined biomarkers hs-cTnI, NT-proBNP, and CBP in women with hypertensive disorders of pregnancy. TRO= hs-cTnI; PRO= NT-proBNP; CBP=Central blood pressure.

Discussion

This study included a total of 540 participants, consisting of 270 individuals with hypertension and 270 non-hypertensive controls.

The control group of non-hypertensive participants was significantly older and had a higher median gestational age at recruitment compared to those with hypertensive conditions. Typically, preeclampsia and eclampsia affect younger women and often lead to early delivery, which likely influenced the median maternal and gestational age of women with HDP in this study (15,34). As a result, the median age of hypertensive participants in this study was 25 years, with most falling within the age range of 25 to 35

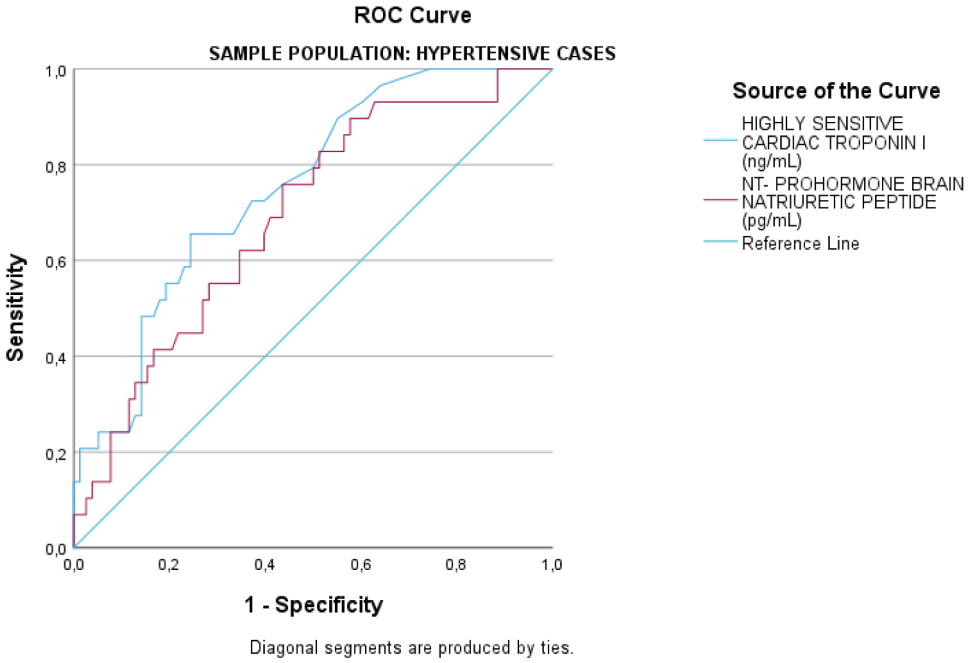

Figure 3. ROC curve analysis of hs-cTnI and Nt-proBNP in hypertensive pregnant women with renal failure.

Table 9. Maternal complications in cases with eclampsia: medial comparisons of CBP, NT-proBNP, and hs-cTnI.

		cSBP Median (IQR) mmHg	cDBP Median (IQR) mmHg	NT-proBNP Median (IQR)	hs-cTnI Median (IQR)
Composite maternal complications	Yes ($n = 45$)	138 (124–148)	79 (67–95)	1030 (382–1894)	33 (12–62)
	No ($n = 57$)	128 (117–136)	69 (58–77)	464 (164–940)	10 (5–25)
	P	**0.010**	**0.001**	**0.003**	**<0.0001**
Abruptio placenta	Yes ($n = 6$)	140.5 (120–150)	83 (79–86)	1460 (403–1894)	31 (11–46)
	No ($n = 39$)	138 (124–148)	77 (64–95)	1026 (355–2120)	34 (12–77)
	P	0.858	0.660	0.684	0.591
HELLP syndrome	Yes ($n = 33$)	134 (122–148)	79 (64–95)	1069 (434–3250)	34 (12–104)
	No ($n = 12$)	144.5 (134.5–152.0)	84 (72–92)	523 (341–1460)	22.50 (11.50–48)
	P	0.156	0.621	0.279	0.367
Acute kidney injury	Yes ($n = 14$)	139 (120–154)	82 (70–93)	1133 (434–3223)	46 (20–175)
	No ($n = 31$)	138 (124–148)	77 (64–97)	1026 (270–1673)	21 (8–54)
	P	0.883	0.951	0.500	**0.036**
Pulmonary edema	Yes ($n = 0$)	.	.	.	.
	No ($n = 45$)	138 (124–148)	79 (67–95)	1030 (382–1894)	33 (12–62)
	P	-	-	-	-
Low GCS	Yes ($n = 6$)	137 (124–155)	100.5 (74–104)	877.50 (446–2120)	52 (16–77)
	No ($n = 39$)	138 (122–148)	79 (64–89)	1030 (355–1894)	29 (11–62)
	P	0.637	0.123	0.884	0.317
ICU admission	Yes ($n = 6$)	139 (134–155)	96 (74–104)	877.50 (446–2120)	52 (16–77)
	No ($n = 39$)	138 (122–148)	79 (64–89)	1030 (355–1894)	29 (11–62)
	P	0.442	0.170	0.987	0.333

p value (Mann-Whitney).

years. This distribution is of interest, as previous research offers a mixed narrative regarding the association between maternal age and the risk of HDP. While some studies suggest that women in the 25–35 age bracket may be at higher risk, others indicate heightened risks in those older than 35 or younger than 25 (35–37). These discrepancies highlight the complexity of the relationships between age and HDP, possibly reflecting varying demographic, environmental, and healthcare-related factors influencing these outcomes.

Among the participants with hypertension, 39.6% experienced maternal complications, with HELLP syndrome being the most common complication

reported. Women with complications related to HDP presented with higher levels of both diastolic and systolic central blood pressure. Additionally, those with complications had significantly elevated levels of NT-proBNP and hs-cTnI. Hypertensive patients who also had renal failure showed even higher levels of NT-proBNP and hs-cTnI compared to those without renal failure.

These study results are consistent with existing literature which has shown increased levels of NT-proBNP in women with HDP, and a correlation between these cardiac biomarkers and maternal complications in patients with HDP ((11,38,39). Hamad et al. (2009) observed impaired diastolic left ventricular function and increased levels of NT-proBNP in pregnancies complicated by PE (477 (152) ng.L^{-1} vs 46 (6) ng.L^{-1}; $p < 0.0001$), especially early-onset PE (1243 (583) ng.L^{-1} vs 254 (57) ng.L^{-1}, $p = 0.005$) (40). Fustaret et al. (2012) also evaluated the correlation between NT-ProBNP in normotensive pregnant women and women with HDP, finding that NT-ProBNP significantly correlated with lactic dehydrogenase and platelets, which are markers for HELLP syndrome, and cardiac failure (31). The current study did not find a significant association between NT-proBNP and HELLP syndrome but found that hypertensive patients with renal failure had significantly higher NT-proBNP levels compared to those who did not have renal failure. This finding aligns with the established phenomenon that NT-proBNP clearance exclusively occurs in the kidneys, which is well-documented in patients with chronic renal failure (41). Therefore, an impairment in the renal system may result in higher levels of NT-proBNP.

The current study did not find any association between pulmonary edema and NT-proBNP levels, which is different from the results of other studies. For instance, Kumari et al. (2017) reported a significant association of serum NT-proBNP levels with pulmonary edema [997 (642.92 to 1351.08) pg.ml^{-1} ($p = 0.049$)] (42) Additionally, Kim et al. (2020) conducted a study with 124 preeclamptic patients and found that NT-proBNP levels were significantly higher in women with pulmonary edema (43). Their findings are consistent with a cross-sectional study of 30 women with severe PE conducted by Hafiz et al. (2021), in which an association between NT-proBNP and pulmonary edema was also found (33). Further studies are necessary to understand the differences between our findings and those of other studies.

In the study by Hafiz et al., a significant association was also found between NT-proBNP and HELLP syndrome in preeclamptic patients, which contradicts our findings (33). Hafiz et al. included only 35 participants with hypertension, while our study involved a larger sample size, which may explain the discrepancies between the two studies. Conversely, a study by Kumari et al., which included 45 hypertensive women and 45 normotensive women, aligns with our results, revealing no association between NT-proBNP and HELLP syndrome in pregnant women with hypertensive conditions (42).

In addition to NT-proBNP, our study also found elevated levels of hs-cTnI in women with maternal complications of HDP compared to those without maternal complications. This observation is in line with previous research indicating a potential association between hs-cTnI and PE (28,44). However, there is a lack of studies specifically examining the relationship between hs-cTnI and maternal complications of HDP. It's worth noting that, similar to the findings for NT-proBNP among pregnant women with hypertension, those who experienced renal failure had significantly higher levels of hs-cTnI. This finding is consistent with existing literature indicating that cardiac biomarkers are filtered through the glomerular filtration barrier, and a decrease in glomerular filtration can impact their levels (45).

The current study indicates that both diastolic and systolic central blood pressure are higher in women with maternal complications of HDP. Previous studies have mainly focused on the relationship between central blood pressure and HDP, rather than examining the association between central blood pressure and maternal complications (5,29,30). These studies have consistently demonstrated that CBP is elevated in women with HDP compared to those without HDP. CBP is known to be a reliable indicator of target organ damage, which may explain the association between central blood pressure and maternal complications of HDP in the current study, as these complications are largely associated with target organs (46).

In non-pregnant patients, CBP has been shown to be a good predictor of complications in certain target organs, such as cardiovascular events (myocardial infarction, coronary heart disease, sudden death, congestive heart failure, and stroke) and renal failure (47,48). However, unlike other studies that have established a correlation between CBP and the decline in renal function, the current study did not find significantly different levels of CBP between women with renal failure and those without (40–42). This may be attributed to the fact that the other studies primarily involved non-pregnant patients with chronic kidney disease rather than acute cases, and it also included some male participants. For example, Xiao et al.

(2020) conducted a study with 1426 non-pregnant participants who were followed for a median of 4.8 years to assess the prognostic significance of various blood pressure measurements for renal function decline and early chronic kidney disease (48). Their study showed that central pulse pressure emerged as an independent predictor of the decline in renal function. Their findings are consistent with the earlier community-based population study by Fan et al. (2016), which evaluated 3153 participants and found that central SBP was a stronger predictor compared with peripheral SBP for kidney function decline (49). Ohno et al. (2016) also highlighted the association between CBP and kidney function (50). They proposed a vicious cycle between chronic kidney disease (CKD) and CBP, indicating that abnormalities in central hemodynamics can hasten the progression of CKD by potentially causing renal ischemia and glomerular hypertension.

The current study found that the CSBP was significantly higher in women with maternal complications of HDP compared to women without complications of HDP. However, the peripheral systolic blood pressure did not show a significant difference. This may imply that CSBP may be better associated with complications of HDP compared to PSBP. This finding is consistent with the findings in the general population, where CBP is a better predictor of cerebrovascular accidents compared to peripheral blood pressure. For example, Matsumoto et al. conducted a study that found that higher CSBP and central pulse pressure, but not brachial blood pressure, were significantly associated with white matter hyperintensity volume (51). Han et al. also investigated the association between CBP and long-term prognosis in patients with Embolic Stroke of Undetermined Source (ESUS) and found that CBP parameters were independently associated with unfavorable outcomes, including major adverse cardiovascular events, stroke recurrence, and mortality (52). However, while the current study observed elevated CBP in relation to all maternal complications, it did not find any association between cerebrovascular events and CBP. This could be due to the short interval of exposure to high CBP in pregnant women compared to long-term exposure in the aforementioned studies. A long-term follow-up of patients in our study might be needed to address this controversial finding.

Limited data exists on relationships between CBP, hs-cTnI and NT-proBNP, and maternal complications in women with HPD, so this study offers valuable insights. However, the study had some limitations. One limitation is that the follow-up period was only up to seven days after delivery, potentially missing complications that could have occurred later. However, this may be mitigated by the fact that most immediate complications of HDP occur during the antenatal and immediate postpartum periods, which is seven days after delivery. Another limitation is that cases and controls were not matched for maternal and gestational age, which could introduce statistical bias.

In conclusion, the study found that pregnant women with hypertension and maternal complications had significantly higher levels of CBP, and cardiac biomarkers NT-proBNP and hs-cTnI compared to those without complications. These cardiac biomarkers were particularly elevated in women with renal failure. The findings may suggest that women with maternal complications of HDP during pregnancy may be at higher risk of developing chronic cardiovascular problems. Additionally, measuring these biomarkers in hypertensive pregnancies could help in screening and monitoring maternal complications, especially renal failure, and CSBP may be more effective than PSBP in screening for maternal complications of HDP.

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Author contributions

CRediT: **Mirabel Nanjoh:** Formal analysis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval

Approval to perform the study was obtained from Faculty of Health Sciences research and ethics at Walter Sisulu University. The approval number is 035/2022.

Data availability statement

The datasets used during the current study are available from the corresponding authors on reasonable requests.

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