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Systematic Review
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A Systematic Review of NT-proBNP as Prognostic Biomarker for Preeclampsia Complications

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ABSTRACT

Background: Preeclampsia can lead to maternal and fetal complications due to its ability to cause multiple organ disorders. Interestingly, N-terminal pro-brain-type natriuretic peptide (NT-proBNP) levels were higher in preeclampsia than in non-preeclampsia, representing cardiovascular mal-function as the potential cause. Moreover, NT-proBNP also has a potential role in predicting complications that will arise in preeclampsia. This systematic review was performed to determine the role of NT-proBNP plasma levels in predicting maternal and fetal complications in preeclampsia.
Subjects and Method: This systematic review was conducted based on PRISMA-P by previous observational study from scientific databases, namely Hinari, Cochrane Library, ScienceDirect, Scopus, and grey literature in OCLC's OAISTER between 2006 and 2021. The search keyword used were ((NTproBNP) OR (NT-proBNP) OR (N-terminal pro-BNP) OR (N-terminal pro-Brain Natriuretic Peptide)) AND ((preeclampsia) OR (pre-eclampsia)) AND (pregnancy complications). Newcastle - Ottawa Quality Assessment Scale (NOS) was used to assess quality of included studies.
Results: After study selection, five studies from 156 studies were considered eligible and selected in this systematic review. The results showed that pre-eclampsia complications occurred with NT-proBNP levels above 500 mg/dL, which cardiovascular complications may occurred above 700 mg/dL. NT-proBNP levels were higher in women with maternal complications such as placental abruption, HELLP (Hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome, eclampsia, pulmonary oedema, congestive heart failure, cerebrovascular accident, renal dysfunction, and hypertensive retinopathy. Furthermore, increased NT-proBNP levels were associated with fetal growth restriction, resulting in low birth weight. NT-proBNP was significantly higher in pregnant women due to a combination of pre-existing volume overload and NT-proBNP clearance dysfunction in kidney.
Conclusion: NT-proBNP levels were associated with adverse outcomes in preeclampsia. NT-proBNP serum levels could be used to predict maternal-fetal complications in preeclampsia.

Keywords: preeclampsia, fetal, maternal, complications, NT-proBNP

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BACKGROUND

Preeclampsia is a new onset of hypertension with severe features or proteinuria, leading to multiple organ disorders (Rana et al., 2019). The aetiology of preeclampsia remains elusive with two different paradigms. The first and second paradigm is placental origin of preeclampsia and extraplacental origin of preeclampsia respectively. The placental origin explains that preeclampsia is a placental disease that progresses in 2 stages (Thilaganathan, 2017). The first stage is abnormal placentation marked by triad of inadequate placentation, placental insufficiency, and vascular inflammation that leads to vascular ischemia (Melchiorre and Thilaganathan, 2011). The second stage is maternal preeclamptic syndrome mediated by inflammatory cytokine and immune cell alteration that induce multiorgan failures (Ramos et al., 2017).

The second paradigm, extraplacental origin, mainly addresses maladaptation of cardiovascular system as the aetiology of preeclampsia. Pregnancy is often considered as a physiological stress test for maternal organ system, especially cardiovascular system. During pregnancy, maternal organ system must adapt to fulfil the increase in metabolic demand. The cardiovascular system has to increase the cardiac output (CO) and decrease the systemic vascular resistance, leading to a high-volume, low-resistance circulation (Fox et al., 2019). When the alteration is failed, it might lead to organ hypoperfusion, including the placenta, kidney, liver, brain, and cardiovascular (Ker and Soma-Pillay, 2018).

Preeclampsia is associated with maternal and fetal complications due to its ability to cause multiple organ disorders. Several maternal complications could occur, including eclampsia, pulmonary oedema, antepartum haemorrhages (APH), haemolysis elevated liver enzymes and low platelets (HELLP), renal dysfunction, cardiomyopathy, and hypertension (Kim et al., 2020). Fetal complications, which affected maternal preeclampsia, could also lead to further complications, such as premature birth, fetal hypoxia, and intrauterine growth restriction (IUGR) (Giannubilo et al., 2017). These complications can harm both mother and fetus.

On the other hand, N-terminal pro-brain-type natriuretic peptide (NT-proBNP) is an inactive form of brain natriuretic peptide (BNP). It has been investigated for its role in preeclampsia (Álvarez-Fernández et al., 2016). The NT-proBNP is released from heart to systemic circulation in response to cardiac ventricular stretch and stress due to volume or pressure overload. (Kumari et al., 2017). Previous study showed that NT-proBNP could induce vasodilation, inhibit the production of renin and aldosterone, and decrease cardiac and vascular growth. The study also revealed that NT-proBNP levels were found higher in preeclampsia rather than in non-preeclampsia pregnancy. Elevated NT-proBNP levels may indicate ventricular stress and cardiac dysfunction (Hafiz et al., 2021). Therefore, this systematic review is aimed to determine the roles of NT-proBNP plasma levels in predicting maternal and fetal complications of preeclampsia in women. We also described the roles of NT-proBNP plasma levels in predicting both severity and onset of preeclampsia, also the sensitivity and specificity of NT-proBNP plasma levels in preeclamptic women.

SUBJECTS AND METHOD

1. Study Design

We conducted a systematic review for observational studies (case control, cohort, and cross-sectional) that follow the guideline established by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search of this study was conducted in online scientific databases, including Hinari, Cochrane Library, ScienceDirect, and Scopus, between 2006 and 2021 using the following keywords (Table 1). We also searched the grey literature in OCLC's OAISTER.

2. Inclusion and Exclusion Criteria

The inclusion criteria include: observational studies (including case-control, cohort, and cross-sectional), language restriction to English only publication, preeclampsia patients with HELLP syndrome, pulmonary oedema, poor cardiac function, fetal complications of preeclampsia (IUGR and prematurity), and plasma NT-proBNP examination. Meanwhile, the exclusion criteria were: experimental studies (animal and laboratory studies), review articles, case reports or series, editorial articles, and patient cardiac hereditary diseases or genetic disorders.

Table 1. Search Strategy

Search	Search Term
#1	(NTproBNP) OR (NT-proBNP) OR (N-terminal pro-BNP) OR (N-terminal pro-Brain Natriuretic Peptide)
#2	(preeclampsia) OR (pre-eclampsia)
#3	pregnancy complications
#1 AND #2 AND #3	

3. Study Selection

Two authors evaluated the articles' initial search, screening, and eligibility. We used a consensus to resolve any disagreements. After tinitial search, duplicated article records were removed. Subsequently, remaining articles were screened and excluded based on the eligibility criteria (i.e., title and abstract based on whether articles were non-research articles, non-English articles, incomplete metadata and conference abstract or poster). The full text of selected articles was retrieved and assessed for Population, Indicator, Comparators, Outcomes, and Study Design (PICOS) eligibility criteria (Table 2). The eligible studies consistent with PICOS were included in this systematic review.

Table 2. Population, indicator, comparators, outcomes, and study design criteria

Criteria	Description
Population	Preeclampsia diagnosed women
Indicator	NT-proBNP plasma level
Comparator	Low vs High NT-proBNP plasma level
Outcome	Maternal and fetal complications, severity, and onset of preeclampsia
Study design	Observational study (Case-control, cohort, or cross-sectional)

4. Quality Assessment

The Newcastle - Ottawa Quality Assessment Scale (NOS) was applied to evaluate the quality of included studies. The NOS manual contains three general parts: selection, comparability and exposure. The NOS manual for cohort comprises 8 checklists with a maximum score of 9 and the NOS manual for cross-sectional studies comprises 7 checklists with a maximum score of

10. Two authors performed quality assessment of included studies, and a consensus resolved any disagreements.

5. Data Extraction

The data extracted from included articles include first author's name, publication year, country, study design, number of participants, maternal age, gestational age, time of research, sampling time, sampling method, and outcome (including NT-proBNP level for PE complications, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV). Two authors independently performed data extraction process. Any disagreements were resolved by consensus.

6. Registered Protocol

This systematic review has been registered in PROSPERO International prospective register of systematic reviews with registration code of CRD42021243943. The protocol of present systematic review also has been published (Asaduddin et al., 2021).

Approximately 156 studies were identified from initial findings using the designed search strategy. There were 6 studies excluded due to duplications from the search engines. Furthermore, 150 studies were screened, and 145 studies were excluded because they did not meet the criteria (described in Figure 1). Finally, five studies were considered eligible and selected in this systematic review. Based on quality assessment, two articles (Hafiz et al., 2021; Kumari et al., 2017) were included as good-quality studies, whereas the others were included as poor-quality studies (Álvarez-Fernández et al., 2016; Kim et al., 2020; Sadlecki et al., 2016) (Table 3).

Table 3. Quality assessment of included studies (Newcastle-Ottawa Scale)

Author (Year)	Type of study	Selection				Comparability	Outcome			Total	Quality
		A	B	C	D	E	F	G	H		
Álvarez-Fernández (2016)	Retrospective Cohort	*	*	*	*	*	*	-	-	6	Poor
Kumari (2017)	Prospective Cohort	*	*	*	*	**	*	*	*	9	Good
Sadlecki (2018)	Retrospective Cohort	*	*	*	*	**	-	-	-	6	Poor
Kim (2020)	Retrospective Cohort	*	-	*	*	*	*	-	-	5	Poor
Hafiz (2021)	Cross-Sectional	*	-	*	**	**	**	*	None	10	Good

Cohort study: A) Representativeness of the exposed cohort; B) Selection of the non-exposed cohort; C) Ascertainment of exposure; D) Demonstration that outcome of interest was not present at start of study; E) Comparability of cohorts on the basis of the design or analysis; F) Assessment of outcome; G) Was follow-up long enough for outcomes to occur; H) Adequacy of follow up of cohorts.

Cross sectional study: A) Representativeness of the sample; B) Sample size; C) Non-respondents; D) Ascertainment of the exposure (risk factor); E) Comparability in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled; F) Assessment of the outcome; G) Statistical test.

RESULTS

1. Study Characteristics

From the 5 selected studies (described in Table 4), there were four studies using cohort design (Álvarez-Fernández et al., 2016; Kim et al., 2020; Kumari et al., 2017; Sadlecki et al., 2016) and one study (Hafiz et al., 2021) using a cross-sectional design. In addition, the number of pregnant women in these included studies was 770, and 317 of whom were patients with preeclampsia. Studies were conducted in Spain (Álvarez-

Fernández et al., 2016), India (Kumari et al., 2017), South Korea (Kim et al., 2020), Poland (Sadlecki et al., 2016), and Indonesia (Hafiz et al., 2021).

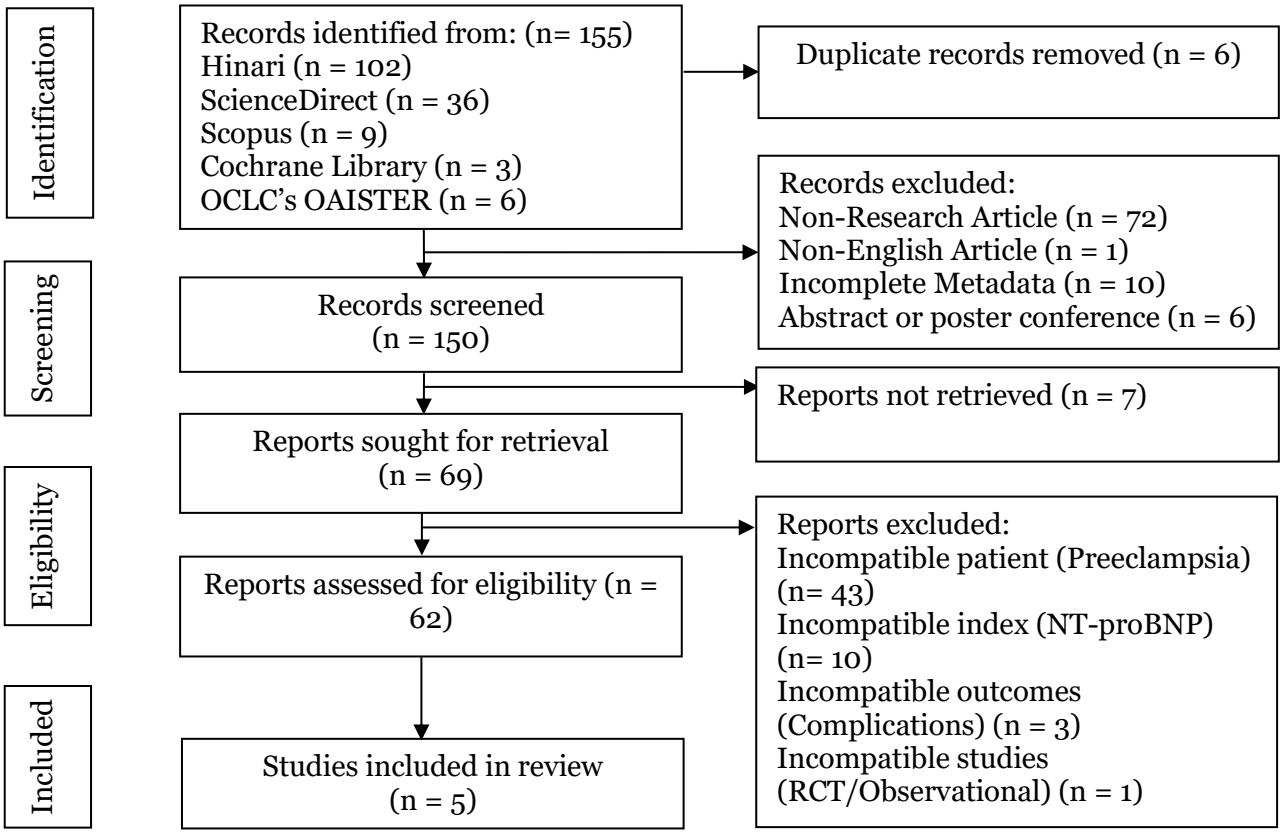

Figure 1. PRISMA Flowchart diagram of the search strategy

Table 4. Characteristics of studies included in the review

Author (Year)	Country	Study Design	Subject	Gestational Age (Weeks^{+days})	Maternal Age (Year)	Sampling time
Alvarez-Fernández (2016)	Spain	Retrospective full-blinded cohort	**Non-PE** (*n*=236) **PE** (*n*=104)	**Non-PE**: <34*w*=31^{+0}(26^{+1}-32^{+6}), ≥34*w*=37^{+5}(36^{+4}-39^{+4}) **PE**: <34*w*=31^{+1}(27^{+4}-35^{+6}), ≥34*w*=37^{+0}(36^{+0}-38^{+5})	**Non-PE**: <34=34(31-37), ≥34=34(30-37); **PE**: <34=34(30-38), ≥34=35(32-37)	At clinical presentation
Kumari (2017)	India	Prospective cohort	**NP** (*n*=45) **PE** (*n*=45)	**NP**: <34*w* (*n*=5), 34-37*w* (*n*=16), >37*w* (*n*=24); **PE**: <34*w* (*n*=5), 34-37*w* (*n*=16), >37*w* (*n*=24)	**NP**: <25 (*n*=17), 25-30 (*n*=23), >30 (*n*=5); **PE**: <25 (*n*=20), 25-30 (*n*=24), >30 (*n*=1)	At term or just before induction of labour or in early labour in both the groups

Author (Year)	Country	Study Design	Subject	Gestational Age (Weeks+days)	Maternal Age (Year)	Sampling time
Kim (2020)	South Korea	Retrospective cohort	**GPE group** (*n*=77) **SPE group** (*n*=47)	**SPE**: 32.8(28.21-37.39) **GPE**: 33,5(29.79-37.21) **PPE**: 31,66(27.16-36.16) **NPE**: 33,7(29.86-37.54)	**SPE**: 33.7(28.7-38.7); **GPE**: 32.6(28.4-36.8); **PPE**: 32.1(27.3-36.9); **NPE**: 33.3(28.9-37.7)	At clinical presentation
Sadlecki (2016)	Poland	Prospective Cohort	**GH** (*n*=26) **PE** (*n*=14) **GDM** (*n*=81) **Control** (*n*=35)	**Control**: 40(38.9-41.1) **Study group**: 38(35.2-40.8)	**Control:** 29.4(24.4-34.4) **Study group:** 29.1(24.5-33.7)	During the 3rd semester, up to 7 days before delivery
Hafiz (2021)	Indonesia	Cross-sectional	**NP** (*n*=30) **Severe-PE** (*n*=30)	**NP:**≤34 (n=2), >34 (n=28) **Severe-PE:** :≤34 (n=8), >34 (n=22)	**NP:** 20-35 (n=22), >35 (n=8) **Severe-PE:** <20 (n=2), 20-35 (n=17), >35 (n=11)	At delivery, induction or caesarean section

NP: Normotensive Pregnancy; PE: Preeclampsia; GPE: Gestational PE without chronic hypertension; SPE: Superimposed PE on chronic hypertension; GH: Gestational hypertension; GDM: Gestational diabetes mellitus; PE w/o SS: Preeclampsia without severe sign; PE w/ SS: Preeclampsia with severe sign

All studies included in this review aimed to evaluate plasma NT-proBNP levels for predicting adverse outcomes in preeclampsia (Table 5). Two other studies (Kumari et al., 2017; Hafiz et al., 2021) evaluated association of serum NT-proBNP levels and maternal complications (HELLP syndrome, eclampsia, pulmonary oedema, retinopathy, cerebrovascular accident, and renal dysfunction) between preeclampsia and normotensive pregnancy group. Similar from two previous studies which reporting maternal complications, a study from Kim et al. investigated association of NT-proBNP serum levels with the prediction of pulmonary oedema occurred in preeclamsia women (Kim et al., 2020). Fetal complications of preeclampsia found in a study conducted by Sadlecki et al. who identified the role of NT-proBNP in predicting birth weight, although there were no significant correlation found between NT-proBNP and birth weight (Sadlecki et al., 2016). Similar with Sadlecki et al. study, Alvarez et al. assessed and compared the level of a cardiac biomarker (NT-proBNP) in prognosis of fetal adverse outcomes (imminent delivery in first week since clinical presentation, intrauterine fetal death (IUFD), and early neonatal death) in pregnant women attending obstetric triage before 34 weeks of gestation (Álvarez-Fernández et al., 2016).

Table 5. Results data extraction of included studies

Author (Year)	NT-proBNP level for PE Complications (pg/mL)	Outcomes			
		Specificity	Sensitivity	PPV (%)	NPV (%)
Alvarez-Fernández (2016)	**<34*w* cut-off:** 219 Imminent delivery, fetal demise, or early neonatal death	**<34*w***: 93.6% (95% CI: 83.5-97.9)	**<34*w***: 76.2% (95% CI: 52.5-90.9)	NR	NR
Kumari (2017)	**APH (Abruption)** 678(466,61-889,39); **HELLP (complete)** 853(735.62-970,38); **HELLP (partial)** 783.22(247.597-1318.843)**; **Eclampsia** 956.71(617.15-1298.27)**; **PPE** 997(642.92-1351.08)*; **CHF** 770; **Cerebrovascular accident** 823; **Renal dysfunction** 891(228.42-1553.58); **Hypertensive retinopathy** 850	90% (cut-off >500 pg/mL), 73.09% (cut-off >200 pg/mL), 50% (cut-off >100 pg/mL)	78.94% (cut-off >500 pg/mL), 89.47% (cut-off >200 pg/mL), 94.47% (cut-off >100 pg/mL)	83.38% (cut-off >500 pg/mL), 70.83% (cut-off >200 pg/mL), 58.06% (cut-off >100 pg/mL)	87.09% (cut-off >500 pg/mL), 90.47% (cut-off >200 pg/mL), 92.85% (cut-off >100 pg/mL)
Kim (2020)	**PPE** 3473.40(-1682.3-8557.10)** **NPE** 305.10(-653,1-1263.3)**	**Prediction of PPE:** 75.8% (cut-off> 278.7 pg/mL)****	**Prediction of PPE:** 92.6% (cut-off> 278.7 pg/mL)****	NR	NR
Sadlecki (2016)	**BW PE (2500-4000 g)**: 46.30(19.80-72.80) **BW PE (>4000 g)**: 47(11-83)	NR	NR	NR	NR
Hafiz (2021)	**HELLP** 1084.30(594.01-1574.59)** **Eclampsia** 887 **PPE** 1131.5(860.68-1402.32)* **CHF** 499.50(-123.46-1122.46) **Retinopathy** 788.75(238.63-1338.87)** **Cerebrovascular accident** 2640 **Renal dysfunction** 1417.5(497.23-2337.77)**	NR	NR		

PE:Preeclampsia; APH: Antepartum haemorrhage; HELLP: HELLP (Hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome; PPE: Pulmonary edema; NPE: Non-pulmonary edema; CHF: Congestive heart failure; BW: Birth weight; w: weeks; w/o: without; HF: heart failure^; ^NHF: non-heart failure; PPV: Positive predictive value; NPV: Negative predictive value; CI: confidence intervals; NT-proBNP: N-terminal pro-brain natriuretic peptide; NR: not reported; pg/mL: picogram per liter; R; *:p<0.05; **p<0.01; ***p<0.001;****p<0.0001.

2. NT-proBNP Levels Cut-Off in Predicting Preeclampsia Adverse Outcomes

Three studies described the NT-proBNP level as a prognostic biomarker of adverse outcomes in women with preeclampsia by determining NT-proBNP level cut-off value (Álvarez-Fernández et al., 2016; Kim et al., 2020; Kumari et al., 2017). Among this three, there are two studies who reported cut-off value with its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) (Álvarez-Fernández et al., 2016; Kumari et al., 2017). Meanwhile, the remaining one study only reported cut-off value with its sensitivity and specificity.

The study performed by Alvarez et al. found cut-off values in pre-eclamptic women with gestational age of <34 weeks (n=83) and >34 weeks (n=257). There were 18 patients suffered from fetal adverse outcomes (imminent delivery within the first week since clinical presentation, fetal death, or early neonatal death) among 37 pregnant women who had preeclampsia and followed obstetric triage at <34 weeks of gestation. At gestational age of >34 weeks, there were 50 patients who developed adverse outcomes among 67 PE patients. Furthermore, at <34 weeks of gestation with ROC analysis, it was found that NT-proBNP cut-off as a predictor of preeclampsia adverse outcomes was 219 mg/dL with a sensitivity of 76.2% (95% CI= 52.5 to 90.9) and a specificity value of 93.6% (95% CI= 83.5 to 97.9). Conversely, at >34 weeks of gestation, AUC result was <0.650, thus the cut-off could not be determined because the biomarker showed lower performance (Álvarez-Fernández et al., 2016).

The study by Kumari et al. tested different cut-off levels of NT-proBNP. This study reportedt cut-off value of 500 mg/dL had a sensitivity of 78.94%, a specificity of 90%, a PPV of 83.38%, and a NPV of 87.09%. At cut-off of 200 mg/dL, they found sensitivity was 89.47%, specificity was 73.09%, PPV was 70.83%, and NPV was 90.47%. Furthermore, cut-off of 100 mg/dL had a sensitivity of 94.47%, a specificity of 50%, a PPV of 58.06%, and a NPV of 92.85%. In this study, decreasing cut-off level will increase t sensitivity and negative predictive values. On the other hand, specificity and positive predictive values will decrease. In addition, this study reported that in preeclampsia group, complications mainly occurred with NT-proBNP levels above 500 mg/dL. Meanwhile, they found cardiovascular complications in patients with preeclampsia with NT-proBNP levels above 700 mg/dL (Kumari et al., 2017). This finding was supported by another study from Hafiz et al., which stated that the most of preeclampsia patients with complications had NT-proBNP levels above 500 mg/dL (Hafiz et al., 2021).

Another study from Kim et al. reported a NT-proBNP cut-off value of 278.7 pg/mL with sensitivity of 92.6% and specificity of 75.8%. Preeclampsia patients in this study further divided into post-partum pulmonary edema (PPE) and non-post-partum pulmonary edema (NPE). PPE group (3473.4(-1682.3-8557.10) pg/ml) had significantly higher serum NT-proBNP levels than NPE group (305.1(-653,1-1263.3) pg/ml) (Kim et al., 2020).

3. NT-proBNP in Predicting Specific Diseases of Preeclampsia Complications

The eligible studies described results of NT-proBNP levels specified for every single type of diseases or accidents that arose due to complications of preeclampsia (Table 4 and 5). There are two studies that measure NT-proBNP levels on the occurrence of HELLP syndrome, eclampsia, congestive heart failure, retinopathy, cerebrovascular accident, and renal dysfunction due to complications of preeclampsia. Kumari et al. found that there were very significant results in association of serum NT-proBNP with partial HELLP syndrome (NT-proBNP levels of 783.22 (247.597 to 1318.843) mg/dL; p=0.009) and eclampsia (NT-proBNP levels of 956.71(617.15-1298.27) mg/dL; p=0.001) in pre-eclamptic women group. Other complications that arose insignificantly were complete HELLP syndrome (NT-proBNP levels of 853 (735.62 to 970.38) mg/dL; p=0.121), congestive heart failure (NT-proBNP levels of 770 mg/dL; p=0.394), cerebrovascular accident (NT-proBNP levels of 823 mg/dL; p=0.314), renal dysfunction (NT-proBNP levels 891

(228.42 to 1553.58) mg/dL; p= 0.155) and hypertensive retinopathy (NT-proBNP levels of 850 mg/dL; p=0.278) (Kumari et al., 2017). Another study from Hafiz et al. revealed significant association of serum NT-proBNP levels with HELLP syndrome (NT-proBNP levels of 1.084 (594.01 to 1574.59) mg/dL; p=0.008), retinopathy (NT-proBNP levels of 788.75 (238.63 to 1338.87) mg/dL; p=0.008), and renal dysfunction (NT-proBNP levels of 1,417.5 (497.23 to 2337.77) mg/dL; p=0.002) in preeclamptic women (Hafiz et al., 2021) (Table 5).

In the emergence of pulmonary oedema complications, three studies measured increase in NT-proBNP levels in preeclampsia group compared to non-preeclampsia group. Kumari et al. (2017) suggested that the association of serum NT-proBNP levels with pulmonary edema were 997 (642.92 to 1351.08) mg/dL (p=0.049), which had significant result (Kumari et al., 2017). The study by Hafiz et al. measured that levels of NT-proBNP in preeclamptic patients with pulmonary oedema were 1,131.5 (860.68 to 1402.32) mg/dL (p=0.027) (Hafiz et al., 2021). Meanwhile, study performed by Kim et al. showed that the levels of NT-proBNP in the appearance of pulmonary oedema were 3.473.4 (1682.3 to 8557.10) mg/dL (p=0.004). This study also added that the cut-off value for prediction of pulmonary oedema of 278.7 mg/dL had a sensitivity value of 92.6% and a specificity value of 75% (AUC=0.905, p<0.0001) (Kim et al., 2020) (Table 5).

However, the data are singular for other complications because there are none of this type of complication evaluated in any other studies, thus there is no comparison. Kumari et al. revealed the association of NT-proBNP levels in the incidence of antepartum haemorrhage was 678 (466,61 to 889,39) mg/dL (p=0.170) (Kumari et al., 2017). In study by Sadlecki et al., they showed that in a multivariate analysis, it was found that there was a significant inverse correlation between maternal NT-proBNP levels and birth weight (R= -0.22, p= 0.009) (Sadlecki et al., 2016). However, there was no significant difference in NT-proBNP levels at birth weight of 2,500—4,000 g (mean NT-proBNP levels of 46.3 (19.80 to 72.80) mg/dL) and > 4,000 g (mean NT-proBNP levels of 47 (11 to 83) mg/dL) (Hafiz et al., 2021) (Table 5).

DISCUSSION

Based on our results, NT-proBNP can predict various complications, including fetal and maternal, in pregnancy with preeclampsia. Alvarez et al. (2016) found that NT-proBNP with a cut-off value of 219 pg/mL could predict development of fetal adverse outcomes at <34 weeks' gestation (early onset preeclampsia). These fetal adverse outcomes include imminent delivery within the first week since tclinical presentation, fetal demise, or early neonatal death. This study also reported NT-proBNP level tend to be higher in early onset preeclampsia than the late one (Álvarez-Fernández et al., 2016). This finding is in line with Lafuente-Ganuza et al. who also found higher NT-proBNP level in early-onset preeclampsia than the late-onset one. The reason behind this finding is unclear. They hypothezised that diastolic dysfunction is higher in early and late-onset term PE, which ended up in similar situation as unaffected pregnancies and IUGR (Lafuente-Ganuza et al., 2021). Similar to previous study who reported fetal complications, Sadlecki et al. study found no significant correlation between birth weight and NT-proBNP values (Sadlecki et al., 2016).

In contrast to study of Kumari et al. (2017) maternal complications of preeclampsia were evaluated, including

placental abruption, HELLP syndrome (partial and complete), eclampsia, pulmonary oedema, congestive heart failure, cerebrovascular accident, renal dysfunction, and hypertensive retinopathy (Kumari et al., 2017). Hafiz et al. (2021) study also found a significant correlation between NT-proBNP and relatively similar maternal complications with Kumari et al. (2017) study, including HELLP syndrome, eclampsia, pulmonary oedema, congestive heart failure, retinopathy, cerebrovascular accident, and renal dysfunction (Hafiz et al., 2021). Complications of pulmonary oedema were also found to be significantly correlated with NT-proBNP level in other study (Kim et al., 2020). Heart failure was also being reported as a single maternal complication in association with NT-proBNP level in a study (Nguyen et al., 2022). It can be concluded that higher cut-off value of NT-proBNP implied higher specificity but lower the sensitivity and vice versa. Based on three studies (Hafiz et al., 2021; Kim et al., 2020; Kumari et al., 2017), the cut-off value of NT-proBNP is in range of 200 to 500 pg/mL, with various specificity and sensitivity.

Preeclampsia is a common complication in pregnancy identified by hypertension and proteinuria (Rana et al., 2019). Preeclampsia can progress to other life-threatening complications, such as eclamptic convulsion, HELLP syndrome, placental abruption, acute cardiovascular disease and pulmonary oedema (Melchiorre and Thilaganathan, 2011; Nankali et al., 2013). These complications came from two central dogmas of preeclampsia pathophysiology, which are placental and extraplacental origins (Leon et al., 2019). Acute cardiovascular disease rose from the extraplacental one. It subsequently disrupted hemodynamic and vascular modification in pregnant women (Thilaganathan, 2018). Over decades, researchers have discovered numerous markers elevated in pregnancy, including NT-proBNP. Myocytes produced this inactive form of BNP in response to myocardial expansion (Cao et al., 2019). NT-proBNP played a role in inhibiting myocardial hypertrophy via peripheral vasodilation and endothelial permeability elevation (Fu et al., 2018). NT-proBNP was significantly higher in pregnant women due to a combination of pre-existing volume overload and NT-proBNP clearance dysfunction in kidney (Seong et al., 2011).

Based on the systematic review results, we found that NT-proBNP was related to obstetric and non-obstetric complications of preeclampsia. Obstetric complications of preeclampsia can be divided into maternal and fetal complications (Fig.2). In terms of maternal obstetric complications, Kumari et al. showed that NT-proBNP was associated with diastolic BP, the severity of PE and eclampsia and statistically significant (p-values of 0.012 and 0.03, respectively) (Kumari et al., 2017). Another study by Adu-Bonsaffoh et al. (2014) also reported that eclampsia was the most prevalent complication of preeclampsia, with an incidence of up to 15.8% cases. However, Yücesoy G et al. showed eclampsia and HELLP syndrome with 11% cases for each complication (Yücesoy et al., 2005). HELLP syndrome is the complication of severe preeclampsia, affecting preeclampsia and eclampsia patients, which account for up to 12% of cases (Tolcher et al., 2019). Another study showed that incidence of HELLP syndrome (442 cases) was 20% among women with severe preeclampsia (Sibai et al., 1993). Ngweya reported that HELLP syndrome was the most common complication (9.1% cases) (Ngwenya, 2017). Antepartum Haemorrhage (APH) was also reported as the maternal complication of preeclampsia, even not significantly associated with NT-proBNP levels (Kumari et al., 2017). The previous

study reported that APH was the most frequent maternal complication in PE (13.97%) (Aabidha et al., 2015).

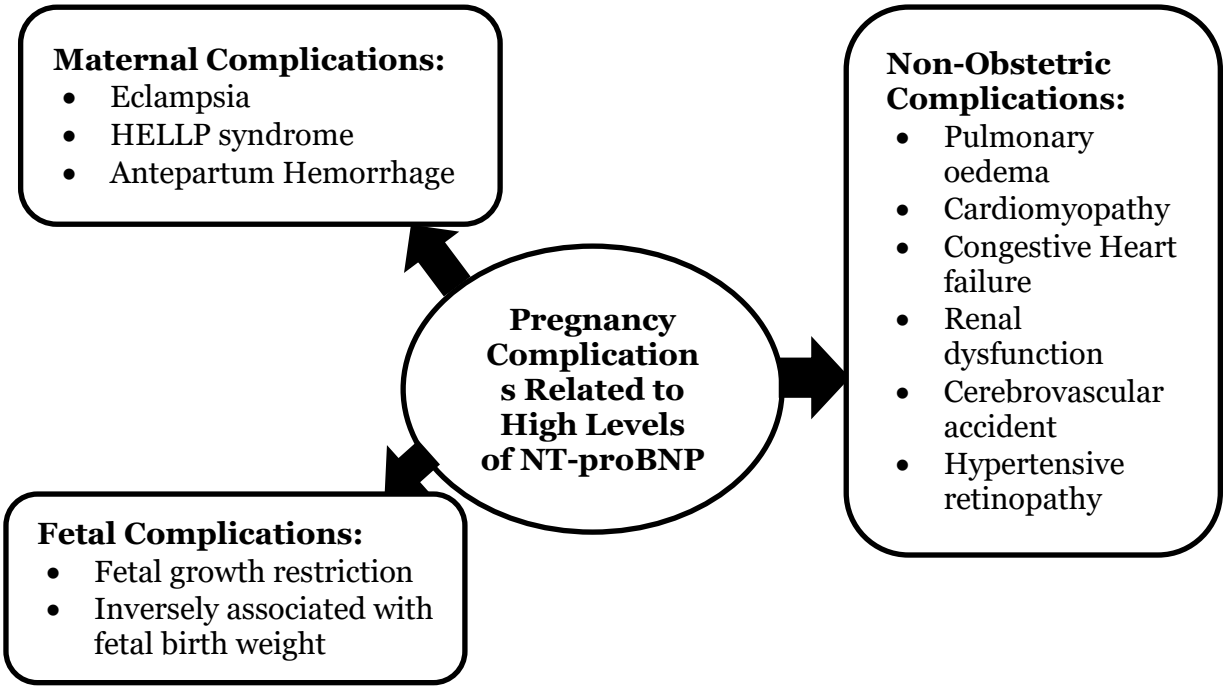

Figure 2. Pregnancy complications related to high levels of NT-proBNP

In terms of fetal complication, a study by Sadlecki et al.(Sadlecki et al., 2016) found that maternal NT-proBNP levels are inversely associated with fetal birth weight. Still, there was no significant difference in NT-proBNP levels at the birth weight of 2,500—4,000 g and >4,000 g. A study by Giannubilo et al.(2017) also reported that NT-proBNP levels are inversely correlated with birth weight and cardiac output. Preeclampsia is also associated with fetal growth restriction (FGR). Mateus et al. (2019) reported that severe preeclampsia is associated with poor fetal growth. Adequate vascularisation and transport of nutrients are important for fetal growth. The rise of the NT-proBNP level indicates the alteration of the cardiovascular system that can disturb fetal growth (Mateus et al., 2019). Therefore, FGR can be found in the fetal preeclamptic pregnancy.

Apart from obstetric complications, we also highlighted the correlation between NT-proBNP levels and non-obstetric complications, such as cardiovascular and pulmonary complications, cerebrovascular accident, retinopathy, and renal dysfunction. In terms of cardiovascular complications, a significant increase of NT-proBNP can predict complications of congestive heart failure in pregnancy (Hafiz et al., 2021; Kumari et al., 2017; Nguyen et al., 2022). Myocyte stretch will stimulate proBNP production. During secretion, proBNP will split into biologically active BNP and the remaining part, namely N-terminal proBNP. Conditions associated with heart failure can result in higher heart wall stretch, neurohormonal activity, and hypoxia. These three factors will lead to an increase in BNP production (Seong et al., 2011).

In terms of pulmonary complications, pulmonary oedema is the most common pulmonary complication associated with preeclampsia (Kim et al., 2020). Recent study showed that NT-proBNP levels were

significantly associated with pulmonary oedema. Pulmonary oedema develops in cardiomyopathy or hypertensive heart failure patients result due to of volume overload and alteration of vascular permeability (Kim et al., 2020). Level of NT-proBNP elevates as a response to volume overload in pulmonary oedema.

However, NT-proBNP elimination was only performed in kidney. Renal dysfunction will cause NT-proBNP clearance process to be disrupted so that NT-proBNP circulates a lot in blood (Srisawasdi et al., 2010). Renal dysfunction is one of the preeclampsia complications characterized by a decrease in glomerular filtration rate (GFR) due to glomerular endotheliosis (Pankiewicz et al., 2019). Glomerular endotheliosis is a histopathological change including fibrin deposition, endothelial swelling, and loss of capillary space. This process increases NT-proBNP secretion, which intends to increase the GFR (Gromadziński et al., 2019). Decreased renal function also reduces the clearance of NT-proBNP (Srisawasdi et al., 2010). Therefore, NT-proBNP level increases in renal dysfunction. Studies by Kumari et al. and Hafiz et al. showed that NT-proBNP levels were associated with renal dysfunction ($p = 0.155$ and $p = 0.002$, respectively).

Some studies stated, that in addition to being produced by ventricular myocytes, BNP is produced by hypothalamus due to stimulation of ischemic stroke. This occurs due to activating of hypothalamic-pituitary-adrenal axis in ischemic brain states. BNP can also predict the long-term severity of post-ischemic stroke. This finding is also supported by other studies which state that there is a significant relationship between BNP levels and the degree of neurological severity in acute stroke (Kuwashiro et al., 2016).

Current systematic review proved that NT-proBNP levels correlate with adverse outcomes of preeclampsia, including obstetric and non-obstetric complications. It should be kept in mind that this review only focused on complications arise from preeclampsia that could be predicted with NT-proBNP value. Other studies which reported the relationship between NT-proBNP value either with preeclampsia status or preeclampsia severity were not included.

However, this review lacks previous eligible research and patients when compared to each complication of preeclampsia. Further research is required to compare each complication finding, thus leading to more specific conclusions, including determining the universal NT-proBNP cut-off value as a predictor of complications and prognosis in preeclampsia.

In conclusion, NT-proBNP levels were associated with adverse outcomes in preeclampsia. The cut-off value of NT-proBNP to predict adverse outcome is 200 to 500 pg/ml. The greater cut-off value of NT-proBNP has a higher sensitivity but lower sensitivity. Regarding maternal obstetric complications, NT-proBNP levels are significantly associated with diastolic BP, severity of PE, eclampsia, and HELLP syndrome. Maternal NT-proBNP levels are inversely related to fetal birth weight in terms of fetal complications. NT-proBNP levels are substantially associated with pulmonary oedema and renal impairment in non-obstetric complications.

AUTHOR CONTRIBUTION

Muhammad Adrianes Bachnas and Aiman Hilmi Asaduddin conducted main study design. Agni Shalha Ali, Ardhia Fefrine Indarta and Shafira Yasmine Anshari provided a process of study selection, quality asessment and data extraction. Data analysis and interpretation were conducted

by Ratih Puspita Febrinasari and Vitri Widyaningsih. Manuscript preparation and finalization were done by Muhammad Adrianes Bachnas and Aiman Hilmi Asaduddin with approval of all authors.

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CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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