Article

Identification of Polymorphism Angiotensin Ii Type 1 Receptor (AT1) 1166 A/C Gene and Potassium Levels in Pre-Eclampsia among The Madurese Population

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Abstract: Pre-eclampsia is a hypertension disorder during pregnancy, significantly affects maternal morbidity and mortality worldwide. A Case-control research was done on 100 pregnant mothers as respondents: 50 case (pre-eclampsia) and 50 control groups (healthy pregnant mothers). Selected case the following characteristics: were aged between 20-40 years old; had a gestational age of over 20mgg; had blood pressure above 140/90mmHg; and single pregnancies. Control had the following characteristics: were healthy pregnant women patients that visited the Syamrabu Bangkalan Public Hospital; were third-generation Madura natives; without pre-eclampsia or chronic hypertension; were third-generation Madura natives; had a gestational age of over 20mgg; aged between 20-40 years; and without pregnancy complications. The results showed of those with PE, 45 had the AA genotype (homozygote) (90%), five had AC (heterozygote) (8%) and one had CC (homozygote) (2%). As for those without PE, 33 had the AA genotype (homozygote) (73.3%), 11 had AC (heterozygote) (26.7%), none had CC (homozygote) (0%). PE and non-PE cases mostly had the AA genotype (homozygote) and A alleles. AT1R 1166 A/C polymorphism was found to be a significant risk factor for pre-eclampsia, while potassium level had no significant effect on it. Meaning further research is needed on different ethnicities and races.

Keyword: polymorphism; AT1; potassium; pre-eclampsia,Madurese

Introduction

Pre-eclampsia is one of biggest morbidity and mortality causes for mothers worldwide (1). Pre-eclampsia is hypertension that generally occurs after 20 weeks of gestation followed by proteinuria (2). When proteinuria does not exist, pre-eclampsia is diagnosed related to hepatic disfunction, thrombocytopenia, pulmonary edema, new-onset renal dysfunction, or new-onset brain or visual disturbances (3). This can lead to several severe morbidity, chronic disability, and even maternal and infant mortality (4). In addition, this is related to increased risk of cardiovascular disease and type 2 diabetes in later maternal life. In developing countries, women have 14 times the risk of dying from obstetric complications compared to women in developed countries (5). In 2013, pregnancy complications caused about 289,000 female mortalities worldwide, and 99% of them were from developing countries (5). About 12% of mothers die from pre-eclampsia globally (6). As were predicted by the World Health Organization (WHO), pre-eclampsia occurrence is seven times higher in developing countries than in developed countries (7). Pre-eclampsia rates are between 1.8 to 16.7% in developing countries.

The problem this study highlights is the high pre-eclampsia incidence among the Madurese. Direct causes of the maternal mortality rate in Indonesia include bleeding, pre-eclampsia, and infection. In East Java,the major cause of maternal mortality cases has been found to be pre-eclampsia, which ranks highest after bleeding. Based on data from the East Java Public Health Office, the mortality rate in East Java dropped from 2010 to 2018

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from 598 to 370 cases. Maternal mortality in East Java in 2018 was caused by health problems such as pre-eclampsia (31%), bleeding (22%), heart failure (10%), infection (4%), and others (33%). Around 68.65% cases occurred between the reproductive ages of 20-34 years old. From theabove data, pre-eclampsia was concluded to be the major cause of mother mortality, especially among the Madurese. However, based on data per district in 2018, the Bangkalan district had eight mother mortality cases, Sumenep seven cases, Pamekasan 15 cases, and Sampang nine cases (8).

There are many factors that might cause pre-eclampsia, either internal (mother's age, obesity, parity, pregnancy spacing, genetic disease, pre-eclampsia history, stress and anxiety, hypertension history) or external (cigarette smoke exposure, antioxidant, natrium, MSG, educational status, antenatal care/ANC history, and the mother's nutritional intake) (9). Pre-eclampsia's etiology and pathogenesis remain unknown even now. Hypoxic conditions and ischemic placenta have been identified as some of the possible pre-eclampsia causes and occur due to abnormal cytotrophoblast (10). Polymorphism of the angiotensin II type 1 receptor gene will increase angiotensin II activity, resulting in susceptibility to essential hypertension. AT1R is located in chromosome 3q24. Angiotensin II activities through the type 1 receptor will cause vasoconstriction of the blood vessels and stimulate aldosterone excretion,causing increased blood pressure. Research conducted from January 2008 to 2010 in Iran by Salimi et al. showed that ACE I/D gene polymorphism played an important role in increasing the risk of pre- eclampsia, but there was no significant relationship between thisand pre-eclampsia incidence (11).

Some ways to control blood pressure are having a healthy diet, reducing salt, maintaining ideal body weight before pregnancy, and reducing excessive weight gain through yoga. Prenatal yoga during pregnancy will significantly lower pain, anxiety, and stress, as well as increase quality of life (12). Rakhsani conducted a study in India on yoga's effects on high-risk pregnancy. It showed fewer pregnancies were induced by hypertension, with pre-eclampsia, with gestational diabetes, and with intra uterine growth restriction (IUGR) in the group that did yoga (13). Doing prenatal yoga exercises for 12 weeks with a 20-minute duration might reduce hypertension during pregnancy (14). This study aimed to identify polymorphisms of the angiotensin II type 1 receptor (AT1) 1166 A/C gene and potassium levels in pre-eclampsia among the Madurese population.

Material and Methods

Case control analytical research was conducted to 100 pregnant mothers as respondents; 50 case groups (pre-eclampsia) and 50 control groups (healthy pregnancy) were selected according to inclusion and exclusion criteria. Selected case groups had the following characteristics: were pre-eclampsia patients that visited the Syamrabu Bangkalan Public Hospital; were third-generation Madura natives; aged between 20-40 years old without chronic kidney disease, diabetes mellitus, and heart disease that affect hypertension occurrence during pregnancy; had a gestational age of over 20mgg; had blood pressure above 140/90mmHg; had single pregnancies; and were willing to be respondents by signing informed consent forms. Control groups had the following characteristics: were healthy pregnant women without pre-eclampsia or chronic hypertension; were third-generation Madura natives; had a gestational age of over 20mgg; aged between 20-40 years; and without pregnancy complications.

The case and control groups were interviewed to confirm they were third generation Madurese using pedigrees before blood was drawn. Blood was drawn from patients if they met the screening examination criteria of being without heart abnormalities and diabetue mellitus. Blood samples were taken in the morning and fasting was done for accurate PGIF levels. Samples that met the inclusion criteria continued to the next step of peripheral blood mononuclear cell (PBMC) examination from separated blood.

Then, PBMC DNA was extracted and amplified in the AT1-R gene region using the PCR technique. PCR conditionsat the time of the study were initially denaturation at 94^0C

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for five minutes, followed by 35 denaturationcycles at 94^0C for one minute, annealing at 59^0C for one minute, and extension at 72^0C for one minute. The last step was dfinal extension for seven minutes at 72^0C. PCR product results measuring 856 bp was detected by electrophoresis in 2% agarose gel. Angiotensin II type 1 receptor gene fragment1166 A/C was forwarded using nucleotide primers to 5'-AAT GCT TGT AGC CAA AGT CAC CT-3' and reversed to 5'-GGC TTT GCT TTG TCT TGT TG-3'. A PCR Go Taq Green Master Mix Promega (11,15) kit was used. Potassium levels were checked with an assay kit using plasma at the Institute of Tropical Disease (ITD) at Universitas Airlangga. Sodium levels were checked using plasma, while PGIF levels were checked using ELISA and assay kits (11).

In samples where PCR, RFLP, and sequencing products were found, the DNA cutting of PCR products with restriction enzyme Dde1 was incubated for three hours at 37^0C (11). Chi-square and Mann Withney statistics tests were used to determine the relationship between variables. This research study has passed an ethical feasibility test at KEPK STIKes Ngudia Husada Madura with an approval number of 1402/KEPK/STIKES-NHM/EC/VII/2022.

Results and Discussion

Table 1. Characteristics of Potassium Level Examination Results in PE and Non-PE Cases.

Variable	Pe	Non-Pe	P-Value
Age	±29	±25	<0.05
Parity	Primigravida dan multi-gravida	Primigravida dan multi-gravida	<0.05
Body weight	±67	±62	<0.05
Potassium level	2.58	2.60	>0.05

Characteristics of PE and non-PE cases at Syarifah Ambami Rato Ebuh Bangkalan Hospital, includematernal age, parity, and body weight. Results showed a significant difference between PE and non-PE cases. The average age of those with PE was 29 years old, and those without PE was 25 years old. On average, PE parity was primigravida, and non-PE parity was primigravida and multigravida, while average body weight was67 kg for PE cases and 62 kg for non-PE cases. Judging from the logistic regression test on these three variables, the age variable greatly affected PE incidence. Every additional number in age was followed by an increased risk of PE by 1,121 times.

In line with the result of a study conducted by Zainiyah (2019) in Bangkalan Public Hospital, risk factors (i.e., age and parity) showed a significant relationship with pre-eclampsia incidence; therefore, age increased pre-eclampsia risk by 5.172 times and parity primigravida increased it by 2.112 times (8,16). Pre-eclampsia is a common pregnancy disorder and a major cause of mother, fetal, and neonatalmorbidity and mortality. The cause of pre-eclampsia lies in the placenta. Pre-eclampsia only occurs during pregnancy, and mothers with this disorder recover soon after delivery. Those with young primigravida had greater risk of developing pre-eclampsia. Various methods have been tried to reduce the impacts of pre-eclampsia, especially on the fetus and mother (17,18). The results differ from pre-eclampsia factors theory, as pre-eclampsia incidence was found to be dominated by a healthy age group. Reproductive age groups around 20-35 years old and even 20-30 years old may experience pre-eclampsia; there were many factors affecting this, such as a history of hypertension. The result showed that body weight and parity had significantly different effects on pre-eclampsiaincidence; body weight in PE cases was higher, and parity in PE cases was mostly primigravida. These results are in line with previous research that showed obesity is a risk factor for pre-eclampsia, which was also caused by unidentified multi-factors. Pre-eclampsia occurs in 5% of pregnancies, commonly in the first pregnancy and in women who previously had high blood pressure or vascular disease (8).

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Results of potassium level research showed that the average value of PE and non-PE cases was 2.58 and 2.60. There was a small decrease in potassium level for PE and non-PE cases, but statistical tests showed no significant relationship. This is in line with research conducted by Fitri et al., (2018) that found that there was no significant relationship between potassium intake and hypertension incidence with a p-value of 1.000 (p >0.05) in a chi-square test (19).

In accordance with previous research, there was a significant decrease (p <0.001) in serum potassium levels in pre-eclampsia (average significance = 3.45; SD = 0.54 mmol/L) compared to normotensive pregnant women (average = 3.98; SD = 0.36 mmol/L). In summary, serum potassium levels that decreasein pre-eclampsia cases compared to normotensive pregnant women showed there were electrolyte changes that may be associated with pe-eclampsia. This study found no correlation between potassium, potassium intake, and hypertension. This may be due to most respondents consuming sufficient amounts of potassium. Based on theory, potassium intake that meets the daily minimum requirement can reduce blood pressure in women who are suffering from mild to moderate hypertension. Otherwise, low potassium intake will cause increased blood pressure.

Table 2. Genotype and Polymorphism of A1166C Allele in Angiotension II Type 1 Receptor Gene (AT1) among the Madurese Population.

	PE	Non PE	X^2	P value	Odds ratio
A1166C polymorphism					
AA (%)	45(90)	33 (73.3)	-	-	-
AC (%)	5 (8)	11 (26.7)	-	-	-
CC (%)	1 (2)	0 (0)			
AC+CC (%)	6 (11.1)	11 (26.6)	4.478	0.03	3.273 (1.051-10.191)
Alel A (%)	0.94	0.87	-	-	-
Alel C (%)	0.06	0.13	-	-	-

The results showed genotype and polymorphism of the A1166C allele in angiotensin II type 1 receptor gene (AT1) among the Madurese population. The results found that, of those with PE, 45 had the AA genotype (homozygote) (90%), five had AC (heterozygote) (8%) and one had CC (homozygote) (2%). As for those without PE, 33 had the AA genotype (homozygote) (73.3%), 11 had AC (heterozygote) (26.7%), and none had CC (homozygote) (0%). Both PE and non-PE cases mostly had the AA genotype (homozygote) and A alleles. The AT1R 1166 gene was found to have an important role in increasing the risk of pre-eclampsia.

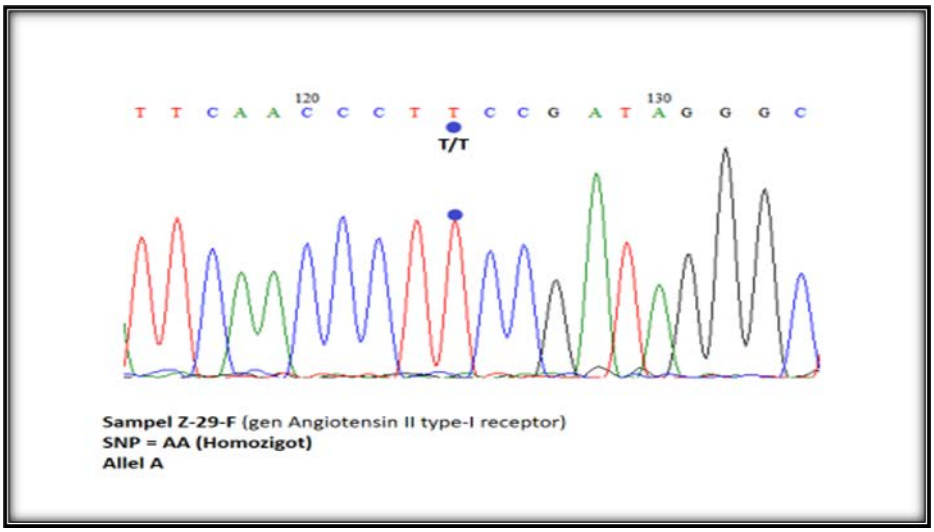

Figure 1. SNP = AA (Homozygote) Allele A.

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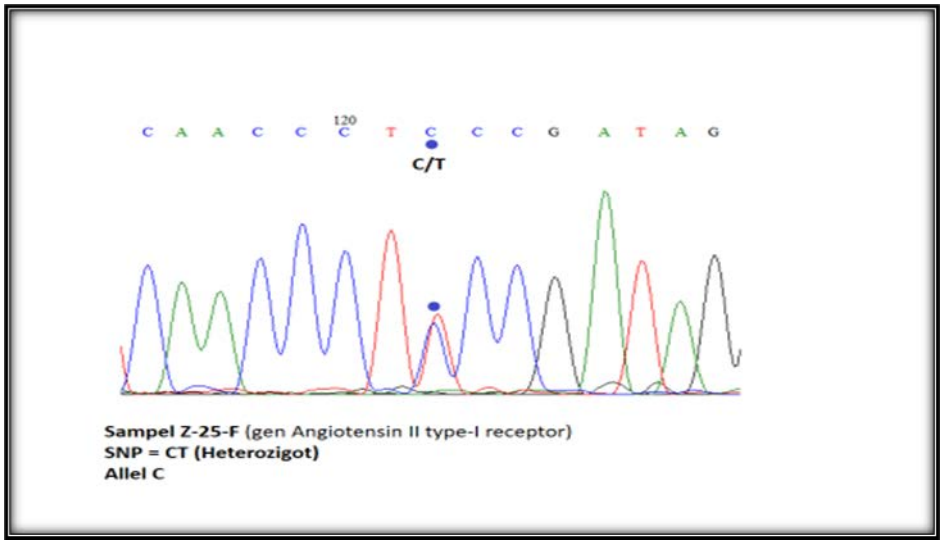

Figure 2. SNP=CT (Heterozigot) Alel C.

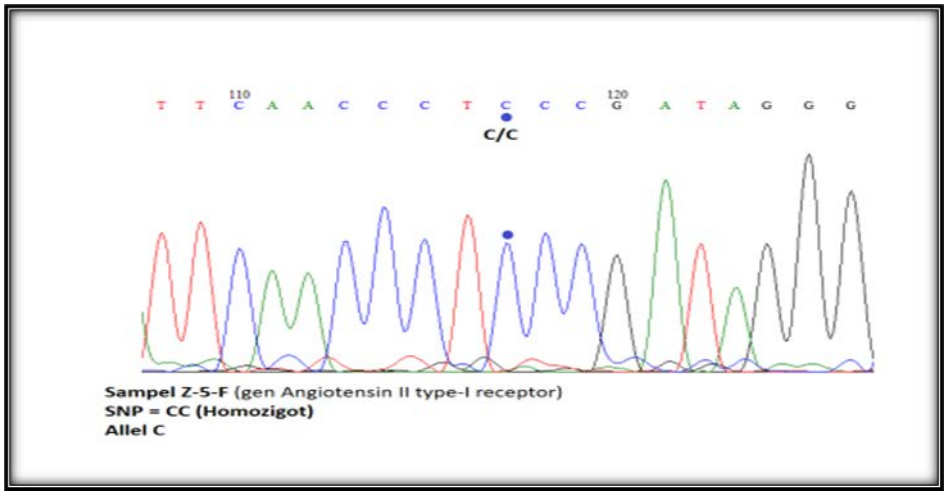

Figure 2. SNP = CC (Homozygote) Allele C.

Pre-eclampsia is a multifactorial disorder that occurs due to the interaction of various environmental and genetic factors. The exact cause of pre-eclampsia has not been determined, but many extensive analyses on animal models and human studies were conducted to find any correlation between environmental and geneticfactors linked with this disorder (20).

The results showed genotype and polymorphism of the A1166C allele in angiotensin II type 1 receptor gene (AT1) among the Madurese population. Of those with PE, 45 had the AA genotype (homozygote) (90%), five had AC (heterozygote) (8%) and one had CC (homozygote) (2%). As for those without PE, 33 had the AA genotype (homozygote) (73.3%), 11 had AC (heterozygote) (26.7%), and none had CC (homozygote) (0%). Both PE and non-PE cases mostly had the AA genotype (homozygote) and A alleles.

In line with the research conducted by Rahmadhayanti et al., (2014), the AA genotype was the highest in both the case and control groups. It was found in 91.4% of the case group and 88.6% of the controlgroup. The AC genotype was only present in 8.6% of the case group and 11.4% of the control group. However, none of the CC genotype (homozygote mutant) was found in any of the 77 respondents (15).

Based on research results from sequencing genotype and polymorphism of the A1166C allele in angiotensin II type 1 receptor gene (AT1) participants with genotypes

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AA (homozygote), AC(heterozygote), and CC (homozygote), both PE and non-PE respondents were mostly with genotype AA (homozygote), while most had the A allele. In addition, results also showed AT1R 1166 A/C polymorphism as a significant risk factor for pre-eclampsia.

These results are in accordance with previous research by Ramie et al., (2018) that revealed there were significant relationships between a familial history of pre-eclampsia and pre-eclampsia incidence (21). Polymorphismof the angiotensin II type 1 receptor gene (AT1) will increase angiotensin II activity; therefore, susceptibility emerges in essential hypertension incidence. AT1R is located in chromosome 3q24. Angiotensin IIthrough type 1 receptors will cause blood vessel vasoconstriction and stimulate aldosterone excretion; therefore, blood pressure will increase (15). This is also in line with several studies about the relationship between AT2R1 polymorphism and pre-eclampsia. Research conducted by Li et al. reported that the AT1R gene frequency was similar in pre-eclampsia and normal pregnancies (22).

This is unlike research by Salimi et al. conducted in Iran (January 2008 - February 2010), which reported that there was no significant relationship between AT1R 1166 A/C gene polymorphism with pre-eclampsia incidence (11). This is possibly due to racial differences between the Iranian and Madurese, who havedifferent characteristics and creates the need for further research with different sample and ethnicities. Several studies have identified various candidate genes involved in high blood pressure pregnancy and pre-eclampsia. Particular attention was given in gene study for the renin-angiotensin system (RAS) due to angiotensin II synthesis. The angiotensin enzyme converter converts inactive angiotensin I to vasoactive angiotensin II; therefore, this enzyme is an important member of the RAS and plays a key role in maintaining blood pressure and electrolyte balance. Angiotensin II mostly exerts through AT1R (23).

These research results are also inconsistent with a study by Morgan et al. that found incorrelation between AT2R1 A1166C polymorphism and pre-eclampsia in the United Kingdom (24). Research conducted by Hu et al. reported that the variant frequency (AC, CC) of the AT1R A1166C polymorphism gene in pregnancy-induced hypertension (PIH) cases (20.5%) was significantly higher than in control subjects (7.4%). Seremak-Mrozikiewicz et al.revealed that A1166C polymorphism is a risk factor for PIH development (25).

Research conducted by Parchwani (2018) revealed that the A1166C variant genotype and allele distribution was significantly different in hypertension and normotensive subjects. Allele frequencies at the A1166C position were 61% A and 39% C for case patients, and 52% A and 48% C for control patients. Genetic variation in the AT1R gene affects hypertension risk and may function as a predictive marker for susceptibility to hypertension (26). Research conducted on a population in Iran by Behravan (2006)reported that the C allele frequency in hypertensive women was higher than in normotensive women (27).

A study conducted on 321 hypertensive and 215 normotensive residents in Japan with matching age andsex found a relationship between the 1166C allele and hypertension incidence (28). A case-control study in a Caucasian population showed that there was a relationship between the C allele frequency and hypertension incidence (26).

Otherwise, studies in different countries did not support the hypothesis about the relationship between A1166CC AT1R polymorphism and pre-eclampsia conducted by Salimi et al.. There was no correlation between A1166C polymorphism and pre-eclampsia (11). Morgan et al. did not find any correlation between A1166C AT2R1 polymorphism and pre-eclampsia in the United Kingdom (24). These differences in studiesare common and may happen due to different races, length of study, criteria for pre-eclampsia, population size, and other factors, but should consider studies using meta-analyses. In this study, we found evidence of a correlation between the AT2R1 gene polymorphic variant and pre-eclampsia. The AT1R gene allele C frequencies were 0.06 and 0.13, while the AT1R gene allele A frequencies were 0.94 and 0.87 in control subjects and pre-eclampsia women.

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Conclusion

The results showed that there was a significant difference in the AT1R 1166 A/C polymorphism between pre-eclampsia and non-pre-eclampsia cases, meaning it can be concluded that the AT1R gene plays an importantrole in pre-eclampsia occurrence. The genotype and polymorphism Angiotension Type 1 Receptor (AT1) A1166CC gene allele among the Madurese in PE cases were mostly with the genotype AA (Homozygote) in both PE and non-PE cases, while the allele mostly had A allele in both PE and non-PE cases. Potassium levels did not differ in pre-eclampsia and non-pre-eclampsia cases. However, potassium levels were found to be lower in pre-eclampsia cases; therefore, further research withdifferent ethnicities and races is needed.

Author contribution statement

Zakkiyatus Zainiyah: conceived, designed experiments, conducted experiments, supervised thestudy, wrote the manuscript, and made manuscript revisions.

Eny Susanti: conducted experiments, collected samples and clinical information, and analyzeddata.

Novita Wulandari: conducted experiments, collected samples and clinical information, andanalyzed data.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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