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Angiotensin-Converting Enzyme Insertion/Deletion (*ACE* I/D) Gene Polymorphism as a Risk Factor for Essential Hypertension

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ABSTRACT

Background: Hypertension is the leading cause of death globally due to its complications, including coronary heart disease and stroke. In 2018, hypertension cases in West Java were the second highest among all populations in Indonesia. Genetics is one of the unmodifiable risk factors for hypertension. Angiotensin-converting enzyme insertion/deletion (*ACE* I/D) gene polymorphism could affect ACE production in the renin-angiotensin-aldosterone system (RAAS), which is linked to the blood pressure regulation.

Aims: To analyze *ACE* I/D gene polymorphism as a risk factor for hypertension in Cirebon.

Methods: An observational analysis with a case-control design was used in this study. Blood samples were collected from 30 hypertensive patients and 30 healthy individuals at Talun Health Center. DNA extraction was performed to evaluate polymorphisms using ARMS-PCR. Statistical analyses, including the Chi-square test, Fisher's exact test, Mann-Whitney test, and Kruskal-Wallis test, were conducted to compare the case and control groups. The odds ratio was calculated to see the risk of the assessed variables, including genotype, allele frequency, and the presence of *ACE* I/D gene polymorphism.

Results: In the case group, the frequency of the II genotype was 2 (6.7%), the ID genotype was 25 (83.3%), and the DD genotype was 3 (10.0%). In the control group, the frequency of the II genotype was 2 (6.7%), the ID genotype was 26 (86.7%), and the DD genotype was 2 (6.7%). Statistically, there was no significant association between *ACE* I/D gene polymorphisms in essential hypertension patients and healthy people (p=0.500; OR=1.556; 95% CI=0.241-10.049).

Conclusion: *ACE* I/D gene polymorphism was not significantly associated with essential hypertension in Cirebon, West Java, Indonesia.

Keywords: *Polymorphism, ACE gene, Insertion-deletion mutation, Blood pressure, Hypertension.*
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1. Introduction

One of the risk factors for diseases that cause death globally is hypertension, including coronary heart disease, ischemic stroke, and hemorrhagic stroke (World Health Organization, 2023, 2024). Hypertension is a condition in which systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (World Health Organization, 2023). According to the World Health Organization (WHO), an estimated 1.13 billion people in the world suffer from hypertension. Hypertension accounts for about 12.8% (estimated 7.5 million) of all deaths in the world (World Health Organization, 2023). The prevalence of hypertension in Indonesia is 34.11% of individuals aged ≥18 years, while in West Java Province, the prevalence of hypertension is 39.6% (Badan Penelitian Dan Pengembangan Kesehatan Kementerian Kesehatan RI, 2019). The estimated number of hypertension patients in Cirebon Regency in 2021 is 648.030, and 73.173, or 11.3% of the total number of hypertension patients, have received medical treatment according to standards (Dinas Kesehatan Kabupaten Cirebon, 2021). The estimated number of hypertension patients aged ≥15 years at the Talun Health Center is 12.182 (Dinas Kesehatan Kabupaten Cirebon, 2021).

Essential hypertension and secondary hypertension are the two types of hypertensions that are classified according to their causes. Essential hypertension is hypertension of unknown cause. The percentage of essential hypertension is 90%, while the percentage of secondary hypertension, whose cause is known to be 10% (Kumar & Clark, 2021; Tortora & Derrickson, 2014). Among the factors that cause essential hypertension are genetic factors. An example is the polymorphism of genes that regulate blood pressure, such as angiotensin-converting enzyme (*ACE*). (Setiati et al., 2014).

The *ACE* gene plays a crucial role in the renin-angiotensin-aldosterone system (RAAS), which raises blood pressure by converting the inert peptide angiotensin I into the potent vasoconstrictor angiotensin II. It also deactivates the vasodilator bradykinin (Sayed-Tabatabaei, Oostra, Isaacs, Duijn, & Witteman, 2006). Differences in the ACE enzymes produced can be caused by mutations in the *ACE* gene. One of the most common variations is the insertion/deletion (I/D) of *ACE* gene. Insertion (I) refers to additional deoxyribonucleic acid (DNA) segments in the *ACE* gene. On the other hand, deletion (D) denotes the absence of specific segments in the *ACE* gene. Possible genotype combinations are II, ID, and DD (Eleni et al., 2008; Sayed-Tabatabaei et al., 2006). The Alu 287 bp sequence in intron 16 is where the *ACE* I/D polymorphism is found (Sayed-Tabatabaei et al., 2006). *ACE* I/D variants have been associated in multiple studies with an increased risk of cardiovascular diseases such as hypertension, stroke, kidney disease, psoriasis, and Alzheimer's disease. (Sayed-Tabatabaei et al., 2006; X. Wang et al., 2004). Individuals carrying the D allele tend to have higher ACE enzyme activity, resulting in increased angiotensin II production, which can cause vasoconstriction and elevated blood pressure, thereby increasing the risk of essential hypertension (Eleni et al., 2008; Qadar Pasha et al., 2002; L. Wang, Song, & Dong, 2023).

Studies on *ACE* I/D polymorphisms have produced conflicting results, possibly due to population differences and other risk factors. For instance, research conducted on the Ethiopian population found a significant association between the *ACE* I/D polymorphism and the risk of hypertension (Birhan, Molla, Abdulkadir, & Tesfa, 2022). A correlation between hypertension and the *ACE* I/D gene polymorphism was discovered in studies conducted on the Chinese steelworker community (X. Zhang et al., 2022). Meanwhile, a study in the Hefei region of Anhui, China, found no relationship between *ACE* I/D gene polymorphism and hypertension in the Hefei region of Anhui, China (L. Wang et al., 2023). The *ACE* I/D polymorphism was not significantly associated with hypertension in a research conducted in South Sulawesi, Indonesia, involving 99 non-hypertensive and 104 hypertensive patients. (Rasyid, Bakri, & Yusuf, 2012).

To date, no studies have examined the connection between *ACE* I/D polymorphisms and risk factors for hypertension in the population of Cirebon, West Java, Indonesia, in 2024. Therefore, this study aims to investigate the role of the *ACE* I/D polymorphism as a risk factor for hypertension in the population of Cirebon, West Java, Indonesia, in 2024.

2. Methods

Study design and Research procedures

This observational analytical study employed a case-control design to investigate the relationship between *ACE* I/D polymorphism and essential hypertension in Cirebon, West Java, Indonesia. This study compared hypertensive patients, who represented the affected individuals (cases), and healthy individuals as the unaffected controls. Participants were selected through purposive sampling based on predefined inclusion and exclusion criteria.

The case-control approach determined a total sample size of 60 participants, comprising 30 individuals in the case group and 30 individuals in the control group. The subjects were categorized into two groups: the case group, which included patients diagnosed with essential hypertension according to JNC VIII criteria, and those with a history of essential hypertension, receiving antihypertensive medications for more than 3 months. The control group consisted of healthy individuals without a history of essential or secondary hypertension, and who were not taking antihypertensive medications. Control subjects were matched with case subjects by age (± 2 years). To reduce bias, patients who were pregnant or breastfeeding, or had a history of diabetes mellitus, renal disease, coronary heart disease, or other cardiovascular disease were excluded from the case group.

Measurements

Screening and Blood Collection of Subjects

Data collection and sample acquisition were conducted between March and August 2024 at the Talun Public Health Center in Cirebon. Genetic analysis was performed at the Research Laboratory of the Faculty of Medicine at Universitas Swadaya Gunung Jati. After obtaining informed consent, participants who met the study criteria were screened using a questionnaire. Clinical characteristics collected during screening included age, gender, occupation, ethnicity, body mass index (BMI), smoking status, dietary habits, and family history of hypertension. Furthermore, blood pressure was measured three times, with 3 to 5 minutes between each measurement. Blood samples (3–5 cc) were collected at the Talun Public Health Center, placed in EDTA tubes, and sent to the Research Laboratory at Universitas Swadaya Gunung Jati Cirebon for genetic analysis.

DNA Extraction

The DNA extraction was performed using the salting-out method with the TianGen TIANamp DNA/RNA Extraction kit. Upon completion of the extraction process, the DNA was stored at -20 ℃ in the freezer.

DNA Amplification

The extracted genomic DNA from hypertensive patients was amplified using the ARMS-PCR technique. The forward primer used was 5'–CTGGAGACCACTCCCATCCTTTCT–3', and the reverse primer was 5'–GATGTGGCCATCACATTCGTCAGAT–3'. The total volume for the amplification reaction was 25 µl, which included 12.5 µl of PCR Taq Master Mix, 1.0 µl each of upstream and downstream primers, 1.0 µl of DNA template, and 9.5 µl of deionized water. The ARMS-PCR condition included an initial pre-denaturation step at 95 °C for 5 minutes, followed by denaturation at 94 °C for 30 seconds, annealing at 58 °C for 30 seconds, and extension at 72 °C for 40 seconds. Starting from denaturation to extension, the cycle was repeated 35 times. A final terminal extension was performed at 72 °C for 5 minutes (X. Zhang et al., 2022).

PCR Visualization

An insertion/deletion site characterized the *ACE* I/D polymorphism, and genotypes were identified by visualizing ARMS-PCR amplification products under an ultraviolet analyzer. The DNA fragments were stained with GelRed and subjected to electrophoresis on a 1.5% agarose gel in TAE buffer for 30 minutes at 100 volts. The expected results were II genotype (490 bp); ID genotype (190 bp, 490 bp); and DD genotype (190 bp).

Statistical techniques

Statistical analysis was performed using Chi-square, Fisher's exact test, Mann-Whitney, and Kruskal-Wallis tests to compare case and control groups. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess the risk associated with the variables such as genotype, allele frequency, and the presence of *ACE* I/D gene polymorphism, with significance set at $p<0.05$.

Ethical Clearance

This study was conducted after receiving ethical clearance from the Medical Research Ethics Committee of Universitas Swadaya Gunung Jati on April 30, 2024, under approval number 29/EC/FKUGJ/IV/2024.

3. Results

Overview of the Characteristics of the Research Subject

Based on the results of the analysis of 60 respondents in Table 1, it was found that the frequency of the highest age characteristics was around 23 (76.7%) subjects in the age range of 40-59 years in the control group and 22 (73.3%) in the case group. The most dominant frequency of ethnic characteristics was Javanese, with 26 (57.8%) in the control group and 19 (42.2%) in the case group. The highest frequency of subjects with a family history of hypertension was observed in the control group, with 27 individuals (90.0%) categorized as having no history of hypertension. The highest frequency of BMI characteristics in both the case and control groups was Obesity I, followed by Overweight, Obesity II, and Normal. In the case group, the frequencies were 13 (43.3%), 6 (20.0%), 6 (20.0%), 4 (13.3%), and 1 (3.3%) subjects, respectively. In contrast, the BMI distribution in the control group was as follows: 12 (40.0%) subjects had Obesity I, 10 (33.3%) had Overweight, 4 (13.3%) had Obesity II, 4 (13.3%) had Normal BMI, and 0 (0.0%) subjects had other BMI categories.

Table 1. Frequency Distribution of Characteristics of Research Subjects

Characteristics	N (%)		P- Value	OR (95 % CI)
	Case	Control		
Total	30 (100)	30 (100)		
Age			0.800[a]	NA
18-39	4 (13.3)	3 (10.0)		
40-59	22 (73.3)	23 (76.7)		
≥60	4 (13.3)	4 (13.3)		
Sex			1.000[b]	1.00 (0.363-2.751)
Male	15 (50.0)	15 (50.0)		
Female	15 (50.0)	15 (50.0)		
Ethnicity			0.037*[b]	0.266 (0.073-0.964)
Javanese	19 (42.2)	26 (57.8)		
Non-Javanese	11 (73.3)	4 (26.7)		
Family History of Hypertension			0.000*[b]	15.545 (3.814-63.359)
Yes	19 (63.3)	3 (10.0)		
No	11 (36.7)	27 (90.0)		
BMI			0.533[c]	NA
Underweight	1 (3.3)	0 (0.0)		
Normal	4 (13.3)	4 (13.3)		
Overweight	6 (20.0)	10 (33.3)		
Obesity I	13 (43.3)	12 (40.0)		
Obesity II	6 (20.0)	4 (13.3)		
Smoking			0.371[b]	1.714 (0.523-5.621)
Yes	9 (30.0)	6 (20.0)		
No	21 (70.0)	24 (80.0)		

*Significant (P<0.05) [a]Mann-Whitney Test. [b]Chi-Square Test. [c]Kruskal-Wallis test.

The highest frequency of smoking status was observed in the non-smoking category, with 24 (80.0%) subjects in the control group and 21 (70.0%) in the case group. The p-value for ethnicity and family history of hypertension showed statistical significance (p=0.037; p=0.000), while age, gender, BMI, and smoking did not demonstrate significant associations with the incidence of hypertension (p=0.800; p=1.000; p=0.533; P=0.371). The OR (95% CI) value for ethnicity was 0.266 (0.073-0.964), while for family history of hypertension was 15.545 (3.814-63.359). The OR (95% CI) value for smoking status was 1.714 (0.523-5.621).

Standard Descriptive Analysis of Research Subjects

Descriptive analysis (Table 2) reveals that the case and control groups had the same age range and median age, with a range of 42 years and a median of 51 years. The standard deviation of the case group was 9.640, whereas that of the control group was 9.481.

Table 2. Standard Descriptive Analysis of Research Subjects

	Range	Median	Std. Deviation
Control Age	42	51	9.413
Case Age	42	51	9.640
Total Age	42	51	9.448

Genotype and Allele Frequency Distribution

The genotype frequency distribution of the *ACE* I/D gene was determined using ARMS-PCR, yielding three possible outcomes: II (490 bp), ID (190 bp, 490 bp), and DD (190 bp). The allele frequency distribution of the *ACE* I/D gene consisted of allele I and allele D, as shown in Table 3. According to the table, the most common genotype was ID, found in 25 subjects (83.3%) in both the case and control groups. The least common genotype was II, identified in only 2 subjects (6.7%) in the case group. The most frequent allele in the case group was allele I (51.7%), while in the control group, allele D was more prevalent (51.7%). The p-value for genotype (Kruskal-Wallis test) and allele (Fisher's exact test) did not show significance (p=0.531; p=0.715). The OR (95% CI) for the alleles was 1.143 (0.558-2.338).

Table 3. Genotype and Allele Frequency Distribution

	N (%)		P-Value	OR (95% CI)
	Case	Control		
Genotype				
II	2 (6.7)	3 (10.0)	0.531[a]	1.00 (Ref)
ID	25 (83.3)	25 (83.3)		0.667 (0.102-4.339)
DD	3 (10.0)	2 (6.7)		2.25 (0.179-28.254)
Allele				
I	31 (51.7)	29 (48.3)	0.715[b]	1.00 (Ref)
D	29 (48.3)	31 (51.7)		1.143 (0.558-2.338)

[a]Kruskal-Wallis test. [b]Chi-Square Test.

Moreover, Table 4 demonstrates that there is no significant association between hypertension and the *ACE* I/D genotype when Fisher's exact test is applied. The ID+DD vs. II (reference) comparison yielded an odds ratio (OR) of 0.643 and a 95% CI of 0.100–4.153.

Table 4. Compound Allele Analysis

		N (%)		P-Value	OR (95% CI)
		Case	Control		
Total		30 (100)	30 (100)		
DD		3 (10.7)	2 (7.4)		1.00 (Ref)
	• ID	25 (89.3)	25 (93.6)	0.518[a]	1.500 (0.230-9.763)
		3 (60.0)	2 (40.0)		1.00 (Ref)
	• II	2 (40.0)	3 (60.0)	0.500[a]	2.250 (0.179-28.254)
DD		3 (10.0)	2 (6.7)		1.00 (Ref)
	• ID+II	27 (90.0)	28 (93.3)	0.500[a]	1.556 (0.241-10.049)
II		2 (6.7)	3 (10.0)		1.00 (Ref)
	• ID+DD	28 (93.3)	27 (90.0)	0.500[a]	0.643 (0.100-4.153)

[a]Fisher's Exact Test

Gel Electrophoresis Visualization Results

Figure 1 illustrates the results of gel electrophoresis conducted on 1.5% agarose gel, run for 30 minutes at 100 volts. Bands labeled 3, 5, 8, and 11 showed a single band representing II (490 bp), while bands labeled 1, 4, 6, 7, and 9 showed two bands corresponding to ID (190 bp, 490 bp), and bands 2 and 10 indicated a single band for DD (190 bp).

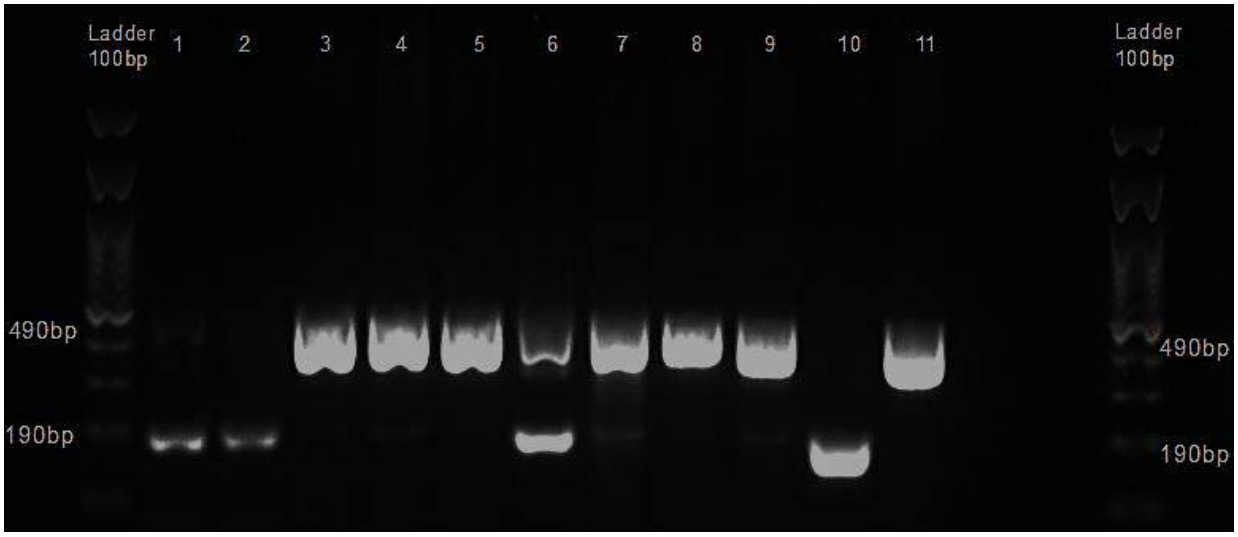

Figure 1. Gel Electrophoresis of *ACE* I/D

Relationship between *ACE* I/D Polymorphism and Essential Hypertension

Table 5 reveals that 28 (93.3%) subjects in the case group had the *ACE* I/D polymorphism, while only 2 (6.7%) did not. In the control group, 27 (90.0%) subjects had the polymorphism, while 3 (10.0%) did not. Due to the small number of subjects in each category, the data did not meet the minimum expected count for the Chi-square test. Therefore, Fisher's exact test yielded a p-value of 0.500, indicating no statistical significance ($p>0.05$). The OR (95% CI) was 1.556 (0.241-10.049), suggesting that subjects with the *ACE* I/D polymorphism were 1.556 times more likely to develop essential hypertension than those without the polymorphism. In this study, the *ACE* I/D polymorphism was considered a risk factor for essential hypertension.

Table 5. Association of *ACE* I/D Gene Polymorphism with Essential Hypertension

Polymorphism	N (%)		P-Value	OR (95% CI)
	Case	Control		
Yes (DD and ID)	28 (93.3)	27 (90.0)	0.500[a]	1.556 (0.241-10.049)
No (II)	2 (6.7)	3 (10.0)		1.00 (Ref)
Total	30 (100.0)	30 (100.0)		

[a]Fisher Exact Test

4. Discussion

One of the primary contributors to cardiovascular disease-related mortality is hypertension, a disorder characterized by elevated blood pressure. The complications of hypertension can affect multiple target organs, with the extent of organ damage depending on the severity and duration of high blood pressure. Common complications include ischemic heart disease, heart failure, stroke, kidney failure, retinopathy, and other related disorders (Muhadi, 2016).

Family history or genetic predisposition is a significant non-modifiable risk factor for hypertension (Rahmadhani, 2021). More than 150 genes have been linked to hypertension, with various genetic variations evolving according to the study population (Y. Zhang et al., 2019). One of the most critical genes involved in hypertension is the *ACE* gene, which plays a vital role in the RAAS (Sayed-Tabatabaei et al., 2006). In this study, a family history of hypertension was statistically significant ($p<0.05$), with an OR (95% CI) of 15.545 (3.814-63.359), indicating that individuals with a family history of hypertension are 15.545 times more likely to develop hypertension than those without such a history. These findings are consistent with a study conducted in 2023 in Kendari, Indonesia, which also demonstrated a significant association between family history and hypertension risk, where subjects with a family history of hypertension were 12 times more likely to develop the condition (Sudayasa, Husdaningsih, & Alifariki, 2023).

This study involved 30 hypertensive patients and 30 healthy individuals. The significance of ethnicity was observed in both groups, with a p-value of 0.037 ($p<0.05$), similar to the finding from a study conducted in India that also reported a significant association with hypertension in both the case and control groups (Qadar Pasha et al., 2002). The OR (95% CI) for ethnicity was 0.266 (0.073-0.964), suggesting that it may serve as a protective factor against hypertension in this study. A study in Banyuwangi, East Java, Indonesia, showed similar results, indicating that ethnicity was not a risk factor for hypertension (Astutik, Puspikawati, Dewi, Mandagi, & Sebayang, 2020).

BMI characteristics did not show statistical significance in either group, with a p-value of 0.585 ($p>0.05$), consistent with studies conducted in Kazakh populations in China's Barkol Pasture (X. Wang et al., 2004), Mataram, Indonesia (Rezqi, Fathana, & Dirja, 2023), and Bogor, Indonesia (Agustiani, Anggie Nauli, & Masitha Arsyati, 2023). However, studies conducted in Anhui, China (L. Wang et al., 2023), Lorestan, Iran (Hadian, Zafarmohtashami, Chaghervand, & Nouryazdan, 2022), and Yogyakarta, Indonesia (Bawazier, Sja'bani, Haryana, Soesatyo, & Sadewa, 2010) reported significant associations between BMI and hypertension. Smoking status in this study also did not demonstrate statistical significance between the two groups, with a p-value of 0.371 ($p>0.05$). This finding aligns with studies conducted in Banyuwangi (Bawazier et al., 2010), and South Hulu Sungai, Kalimantan Selatan, Indonesia (Mufaidah, 2019), which similarly found no significant association between smoking and the incidence of hypertension (Hidayat & Milenia Saputri, 2023). Likewise, a recent study in Anhui, China, reported no significant association between smoking and essential hypertension (L. Wang et al., 2023).

The *ACE* gene influences plasma ACE levels and blood pressure regulation through the RAAS. Approximately 47% of the variation in serum ACE levels is attributed to the Insertion/Deletion (I/D) polymorphism (Sudayasa et al., 2023). In this study, the ID genotype was the most common among both case and control groups, followed by the DD and II genotypes. The most frequent allele in the case group was allele I, while allele D was more prevalent in the control group. Genotype and allele frequencies were not significantly associated with hypertension, consistent with findings from a study involving 203 subjects in South Sulawesi, Indonesia (Rasyid et al., 2012). Similar results were observed in a cross-sectional study with 69 postmenopausal women in Java

(Utami, Simamora, Idawati, & Widjaja, 2024). According to that study, the II genotype was more prevalent among healthy individuals; however, the DD genotype was exclusively present among hypertensive patients. A study conducted in Japan similarly reported no significant association between genotype and allele frequencies among case and control groups (Ishigami et al., 1995).

In this study, the II genotype was more frequently observed in healthy individuals. The I allele is associated with lower concentrations of angiotensin II in tissues and reduced enzyme levels. In contrast, the D allele is linked to higher serum ACE levels, resulting in increased angiotensin II concentration and bradykinin degradation, which leads to hypertension (Barley et al., 1994). A study conducted in Yogyakarta, Indonesia (Bawazier et al., 2010) found that the ID+DD genotypes were significantly associated with hypertension compared to the II genotype. However, the comparison between ID+DD vs. II genotypes in this study was not statistically significant, although it suggested a protective effect (OR<1). Similar results were observed in a study conducted in Burkina Faso, West Africa, where the ID+DD vs. II genotypes were found to be protective, with an OR of 0.34 and a 95% CI of 0.14–0.76 (Tchelougou et al., 2015).

This study aimed to investigate the association between the risk of hypertension and *ACE* I/D gene polymorphisms. The results indicated no significant association between *ACE* I/D polymorphisms and hypertension; however, the OR values suggested that *ACE* I/D polymorphisms could still be considered a risk factor for essential hypertension. These findings are consistent with a study conducted in South Sulawesi, Indonesia, involving 99 non-hypertensive and 104 hypertensive subjects (Rasyid et al., 2012). The lack of significant differences between the two groups in that study suggests that essential hypertension may not be associated with the *ACE* I/D polymorphism. A cross-sectional study in the Spanish-Mediterranean population also found no association between the *ACE* I/D gene and hypertension, although the D allele was statistically linked to increased serum ACE activity (Martínez et al., 2000). Similarly, a study in the Perm region of Russia in 2022 reported a risk ratio of 1.87 (95% CI: 1.07–3.61), suggesting that the *ACE* I/D polymorphism may serve as a potential marker for susceptibility to essential hypertension (Starkova, Dolgikh, Kazakova, & Legostaeva, 2022). A large-scale analysis of data from 5.561 participants in the NHANES III survey found limited support for an association between the *ACE* I/D variant and blood pressure or hypertension across various racial and ethnic groups, although significant genotype-sex interactions were observed specifically in Mexican Americans. Overall, there was a notable lack of significant associations in most cases (Ned et al., 2012).

In contrast, several previous studies have demonstrated a strong association between essential hypertension and the *ACE* I/D gene polymorphism. A case-control study conducted in Lorestan Province, Iran, in 2022 found that the II genotype increased the incidence of essential hypertension among 102 hypertensive patients and 104 healthy individuals (Hadian et al., 2022). In Gondar, Ethiopia, another case-control study conducted in 2022 discovered a high association between essential hypertension and both the D allele and DD genotype (Birhan et al., 2022). Additionally, a study involving 725 male steelworkers in China concluded that the DD genotype increased the risk of essential hypertension (X. Zhang et al., 2022). A meta-analysis conducted in 2020 on the Chinese population also concluded that the *ACE* I/D gene is associated with the development of essential hypertension (Xu, Chen, Li, Zhang, & Li, 2020). Furthermore, a systematic review and meta-analysis found that the D allele of the *ACE* gene is strongly associated as a risk factor for essential hypertension across Asian, Caucasian, and mixed populations (Liu, Yi, & Tang, 2021).

The discrepancies in research findings may be attributed to several factors, including variations in sample size, ethnicity, environment, and lifestyle. This study had a limited sample size because certain factors that could bias hypertension results, such as kidney disease, diabetes mellitus, and alcohol use, were excluded. Future research should involve a larger sample size to account for broader demographic differences and ethnic diversity. Ethnic diversity worldwide significantly impacts research outcomes because genetic variations can lead to changes in the frequency distribution of *ACE* genotypes within each community (Burchard et al., 2003). Additionally, environmental factors and lifestyle variations within each ethnicity produce diverse and complex interactions that can affect research outcomes.

Lifestyle is one of the risk factors for hypertension, which includes exercise (Dida, Nayoan, & Sir, 2023), diet (Frisoli, Schmieder, Grodzicki, & Messerli, 2012), and stress levels (Bhelkar, Deshpande, & Mankar, 2019). Aerobic exercise influences blood pressure responses differently based on the *ACE* I/D genotype. In a study involving elderly hypertensive individuals, those with the D/D genotype exhibited impaired mean arterial pressure responses following exercise, particularly during sleep, as well as reduced heart rate variability and nitric oxide release (Moreira et al., 2018). High salt intake interacts with the *ACE* I/D polymorphism to affect blood pressure. A study on Japanese men found that high salt intake increased blood pressure in individuals with ID+II genotypes but not in those with DD genotypes. This interaction was more pronounced among overweight individuals, leading to diastolic blood pressure of 10.5 mmHg in those with ID+II genotypes compared to DD genotypes (L. Zhang et al., 2006). Diets high in potassium, soy protein, alpha-linolenic acid, and low in sodium can decrease ACE activity and potentially reduce hypertension risk. Conversely, diets high in sodium may increase ACE activity and contribute to higher blood pressure, especially among individuals with certain *ACE* I/D genotypes (Zambrano et al., 2023).

Therefore, further research is needed to assess these factors comprehensively. This study aims to provide an evaluation for future researchers and create opportunities for subsequent studies to expand knowledge on related topics.

5. Conclusion

In both the case and control groups, the ID genotype was the most commonly observed. Essential hypertension was not associated with genotype frequency. The case group exhibited a higher frequency of the I allele, while the control group had a higher frequency of the D allele. There was no significant association between essential hypertension and the frequency of a specific allele. Polymorphisms in the *ACE* I/D gene were not significantly associated with essential hypertension.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to the results presented.

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