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Evaluating the Role of ACE *I/D* Polymorphism in Hypertension among Balinese Patients

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Hypertension continues to pose a major public health challenge worldwide, playing a critical role in the development of cardiovascular diseases and related fatalities. Its pathogenesis is multifactorial, involving both environmental influences and genetic predispositions. Among the genetic factors, the insertion/deletion (*I/D*) polymorphism in the angiotensin-converting enzyme (ACE) gene has garnered widespread attention, with previous studies reporting inconsistent associations with hypertension across different ethnicities. This cross-sectional study investigated the relationship between *ACE I/D* polymorphism and blood pressure in 87 untreated hypertensive patients of Balinese ancestry. Genotyping revealed the II genotype as the most prevalent (63.2%), followed by ID (29.9%) and DD (6.9%). While no significant association was found between genotypes and hypertension staging (p=0.090) or systolic blood pressure (p=0.552). A statistically significant variation was observed in diastolic blood pressure (DBP), with individuals carrying the DD genotype exhibiting the lowest mean DBP (p = 0.022). Similar trends emerged in allele-based analysis, where D allele carriers had significantly lower DBP (p = 0.006). These findings demonstrate an inverse association between the D allele and diastolic blood pressure in this cohort, diverging from traditional risk patterns reported in other populations. This suggests that the ACE I/D polymorphism may act as a potential risk factor modulated by population-specific contexts, highlighting the importance of ethnic diversity in precision medicine for hypertension management.

Keywords: ACE *I/D* polymorphism, Blood pressure, Hypertension

INTRODUCTION

Hypertension continues to challenge public health systems worldwide, not only because of its high prevalence but also due to its complex and multifactorial nature. Hypertension stands as a primary contributor to the development of cardiovascular conditions, cerebrovascular events, and kidney dysfunction, playing a role in millions of deaths globally each year (DiPiro et al., 2023). From 1990 to 2019, the global prevalence of hypertension experienced a twofold increase, with the number of affected women rising from 317 million to 626 million and men from 331 million to 652 million (Zhou et al., 2021). In Indonesia, hypertension affected 34.11% of the population in 2018, with Bali reporting a prevalence of 30.97% (Indonesia, 2019). These figures highlight the growing urgency to investigate both environmental and genetic factors contributing to hypertension, particularly in region-specific populations.

Genetic factors contribute significantly to the risk of developing complex disorders, including hypertension. Variations in an individual's genetic composition can influence their susceptibility to elevated blood pressure and related cardiovascular complications (Lu et al., 2015; Patel et al., 2017). As of 2019, over 1000 genes have been identified as being associated with hypertension, underscoring the complex genetic architecture underlying this condition (Cabrera et al., 2019). The angiotensin-converting enzyme (ACE) gene stands out among the genetic determinants involved in blood pressure regulation, having garnered significant scientific interest (Kolovou et al., 2015; L. Wang et al., 2023; Z. Wang et al., 2023). The *ACE* gene plays a central role in the renin-angiotensin-aldosterone system (RAAS), which regulates vascular tone and fluid-electrolyte balance (Biotechnology Information, 2025; Fountain et al., 2023). One of the most extensively investigated polymorphisms in the *ACE* gene is the insertion/deletion (*I/D*) variant, defined by the presence (insertion, I) or absence (deletion, D) of a 287-base pair Alu repeat element in intron 16. This genetic variation has been correlated with differences in both circulating and tissue concentrations of ACE, with the D allele typically associated with elevated enzymatic activity (Ajala et al., 2012; Kutumova et al., 2024; Rigat et al., 1990). Consequently, numerous studies have explored the potential association between *ACE I/D* genotypes and susceptibility to hypertension.

Despite extensive research, the association between this polymorphism and hypertension severity remains inconclusive across different ethnic groups. These inconsistencies may be attributed to gene environment interactions, population specific allele frequencies, and epigenetic factors. Southeast Asian populations, including Indonesians, are underrepresented in global genetic studies. The Balinese population, with its distinct genetic ancestry and environmental exposures, provides a valuable context for investigating this association. Given the high prevalence of hypertension in Bali, there is a lack of evidence regarding how this genetic variant relates to clinical staging in this specific group. Therefore, this study aimed to evaluate the potential association between the ACE I/D polymorphism and the severity of hypertension in a Balinese cohort.

Considering the widespread occurrence of hypertension in Bali and the possible impact of genetic variability on both disease susceptibility and treatment outcomes, investigating the significance of this polymorphism within the Balinese population is both relevant and necessary. This research contributes to a more comprehensive understanding of hypertension pathophysiology and supports the development of population specific strategies for risk assessment and personalized treatment.

METHOD

This cross-sectional study included a total of 87 hypertensive patients who had not received antihypertensive therapy prior to enrollment. Ethical clearance was obtained from the institutional ethics committee (approval number KE/FK/0474/EC/2023). All participants provided written informed consent after a full explanation of the study's genetic procedures and data confidentiality. Inclusion criteria were as follows: individuals aged over 18 years, clinically diagnosed with hypertension, of Balinese ancestry extending to at least the third generation, capable of understanding and adhering to the study protocol, and willing to participate as indicated by signed informed consent. Exclusion criteria included the presence of secondary hypertension and prior or current use of antihypertensive medications. The study enrolled 87 hypertensive patients using a purposive sampling method.

Sample preparation

Peripheral venous blood samples were obtained from all participants, and genomic DNA was isolated utilizing the Geneaid Genomic DNA Mini Kit following the manufacturer's instructions. Briefly, whole blood was subjected to erythrocyte lysis to obtain leukocyte pellets, followed by cell lysis using lysis buffer and incubation at 60°C to ensure complete disruption. The lysate was mixed with absolute ethanol and transferred to a spin column for DNA binding. Subsequent washing steps were performed to remove impurities, and genomic DNA was finally eluted using pre-heated elution buffer. The purified DNA was stored at -20°C until further analysis.

Amplification of the *ACE I/D* polymorphism was performed using polymerase chain reaction (PCR) with the following primer sequences: forward primer 5′-CTGGAGACCACTCCCATCCTTTCT-3′ and reverse primer 5′-GATGTGGCCATCACATTCGTCAGAT-3′ (Badaruddoza et al., 2009). Each 25 µL PCR reaction mixture contained 12.5 µL of Bioline MyTaq HS Red, 1 µL of each primer, 6.8 µL of genomic DNA (approximately 100 ng), and 3.7 µL of nuclease-free water. Thermal cycling conditions used for amplification are summarized in Table 1. Amplified PCR products were electrophoresed on a 2% agarose gel, stained with FluoroVue nucleic acid gel stain, and subsequently visualized under ultraviolet illumination using the BioRad Gel Doc Go™ Imaging System. Allelic discrimination was based on band sizes, with fragments of 190 bp and 490 bp corresponding to the D and I alleles, respectively. To ensure genotyping accuracy and reproducibility, PCR conditions were optimized, specifically the annealing temperature and primer concentrations. For visual validation, electrophoresis conditions were optimized at 100V for 30 minutes using a 2% agarose gel to achieve clear separation between I and D alleles fragments. Accuracy was further verified by re-testing 10% of randomly selected samples. Additionally, negative controls (nuclease-free water) were included in every run to monitor for potential DNA contamination.

Tabel 1
Optimized Polymerase Chain Reaction (PCR) Thermal Cycling Conditions for *ACE I/D* Genotyping

Steps	Temperature (ºC)	Time (seconds)	Cycles
Initial Denaturation	95	60	1
Denaturation	95	15	30
Annealing	60	15	30
Extension	72	10	30

Note: PCR: Polymerase Chain Reaction; ACE: Angiotensin-Converting Enzyme; I/D: Insertion/Deletion; °C: Degrees Celsius.

Statistical analysis

The association between the *ACE I/D* polymorphism and hypertension severity was analyzed using bivariate Chi-square tests. Blood pressure comparisons across genotypes and alleles conducted using the Kruskal–Wallis and Mann–Whitney U tests with a 95% confidence interval. Statistical significance was determined at a threshold of $p < 0.05$, while results with p-values below 0.01 were interpreted as highly significant. Genotype distributions were evaluated for Hardy–Weinberg equilibrium (HWE) using the exact test to ensure the genetic stability of the study population. All statistical

evaluations were performed using IBM SPSS Statistics (version 27).

RESULT AND DISCUSSION

A total of 87 hypertensive patients who fulfilled the inclusion criteria were recruited for this study. In addition to genetic factors, other variables summarized in Table 2 warrant attention. The majority of participants were female (64%), with a mean age of 61.99 ± 10.51 years. This contrasts with findings by, who reported a higher prevalence of hypertension in men. The greater female representation in this study may reflect the inclusion of postmenopausal women, among whom hypertension prevalence increases after age 50. Furthermore, women tend to have higher awareness and health-seeking behaviors regarding hypertension, potentially influencing participation rates in community screenings (Everett & Zajacova, 2015).

Table 2.
Participant Characteristics of Hypertensive Patients in Bali

No.	Characteristics	Frequency (n = 87)	Percentage (%)
1	**Gender**		
	Male	31	36.0
	Female	55	64.0
2	**Age**		
	18-60 years	40	46.5
	>60 years	46	53.5
3	**Hypertension staging**		
	Stage 1	36	41.9
	Stage 2	50	58.1
4	**Hypertension history**		
	<1 year	16	18.6
	1-5 years	40	46.5
	>5 years	30	34.9
5	**BMI**		
	Obese	30	34.9
	Non-obese	56	65.1
6	**Family history of hypertension**		
	Yes	43	50.0
	No	43	50.0
7	**Smoking Status**		
	Yes	3	3.5
	No and stopped	83	96.5
8	**Educational status**		
	No formal education	29	33.7
	Primary school	20	23.3
	Junior high school	10	11.6
	Senior high school	17	19.8
	Degree and above	10	11.6

Note: BMI: Body Mass Index; *n*: Absolute number.

Table 3 summarizes the frequencies of genotypes and alleles of the *ACE I/D* polymorphism. Based on the HWE Exact Test, the observed genotype frequencies did not deviate significantly from the expected proportions (p = 0.490), indicating that the study population is in Hardy–Weinberg equilibrium. In this study population, the II genotype was the most prevalent (63.2%), followed by the ID genotype (29.9%). The DD genotype had the lowest frequency, observed in only 6.9% of participants. The association between ACE I/D genotypes and hypertension severity is summarized in Table 4. Using a dominant model (II vs. ID+DD), our findings show that the II genotype was more frequent in stage 2 hypertension (65.5%) compared to the ID+DD group (46.9%). However, this trend did not reach statistical significance (p = 0.090). The predominance of the II genotype and I allele among Balinese hypertensive patients aligns with findings from several Asian populations, where the I allele has been associated with increased hypertension risk, particularly in specific genetic backgrounds (Bawazier et al., 2010; Yang et al., 2015). In contrast, studies conducted in other ethnic populations, including those from Malaysia, India, and China, have reported a stronger association between the DD genotype and D allele with hypertension. These contrasting patterns emphasize the influence of ethnic and genetic diversity in modulating the relationship between *ACE I/D* polymorphism and hypertension susceptibility.

Table 3
Distribution of *ACE I/D* Genotypes and Allele Frequencies in the Study Population

Valiable	Frequency (n)	Percentage (%)	HWE *p*-value
Genotypes (n=87)			
II	55	63.2	0.490*
ID	26	29.9	
DD	6	6.9	
Alleles (n=174)			
I	136	78.2	-
D	38	21.8	

Note: ACE: Angiotensin-Converting Enzyme; I/D: Insertion/Deletion; HWE: Hardy-Weinberg Equilibrium; *n*: Absolute number. *p > 0.05 indicates that the genotype distribution follows Hardy-Weinberg Equilibrium.

Table 4
Association Between ACE I/D Genotypes and Hypertension Severity Category

Genotype	HT Stage 1 (n=36)	HT Stage 2 (n=51)	p-value[a]
II	19	55	0.090
ID + DD	17	32	
Total	36	51	

Note: ACE: Angiotensin-Converting Enzyme; I/D: Insertion/Deletion; HT: Hypertension; *n*: Absolute number. *Analysis using the Chi-square test; p < 0.05 is considered statistically significant.

This study examined the association between *ACE I/D* gene polymorphism and blood pressure among hypertensive patients, as presented in Table 5. No significant differences in systolic blood pressure were observed among the three genotypes (II, ID, DD), with a p-value of 0.552. However, diastolic blood pressure differed significantly by genotype (p = 0.022), with participants carrying the DD genotype exhibiting the lowest mean diastolic pressure. A comparable pattern was observed when analyzing the I and D alleles. While no significant difference was detected in systolic blood pressure between allele groups (p = 0.225), diastolic blood pressure differed markedly (p = 0.006). Individuals carrying the D allele exhibited the lowest average diastolic pressure compared to those with the I allele.

This study aimed to evaluate the association between the ACE I/D polymorphism and the severity of hypertension in the Balinese population, while specifically comparing blood pressure levels among hypertensive patients across different ACE I/D genotypes. Contrary to expectations drawn from broader literature, our findings indicate no significant differences between *ACE I/D* genotypes and systolic blood pressure. However, a noteworthy and statistically significant difference was observed in diastolic blood pressure (DBP) across genotypes, with the DD genotype demonstrating lower mean DBP compared to the II and ID genotypes. These

findings align with the results of Makris et al., (2000), who reported no significant intergenotypic differences in SBP among hypertensive individuals, suggesting that the *ACE I/D* polymorphism may not uniformly influence systolic pressure across populations. Similarly, Harrap et al., (2003) conducted a large-scale study involving both Asian and non-Asian hypertensive patients, and found no significant differences in either SBP or DBP among II, ID, and DD genotypes (p = 0.57 (SBP) ; 0.77 (DBP)). Furthermore, their study showed no genotype-based differences in blood pressure response to antihypertensive therapy, suggesting limited clinical utility of *ACE* polymorphism in predicting treatment outcomes (Handani et al., 2024; Harrap et al., 2003). Similar result are shown in other studies. Supporting this, a study by (Kovacevic et al., 2025; Öztürk & Öztürk, 2009; Pinheiro et al., 2019) in Malay hypertensive males showed that although the D allele was more frequent among hypertensives, those with the DD genotype experienced the greatest reduction in both SBP and DBP after ACE inhibitor therapy. This suggests that the DD genotype may influence vascular responsiveness rather than act as a static determinant of baseline pressure.

Table 5

Comparison of Systolic and Diastolic Blood Pressure Across ACE I/D Genotypes and Alleles

Variable	SBP (mmHg)	SD	p-value	DBP (mmHg)	SD	*p*-value
Genotype						
II	170.51	20.62	0.552	99.56	9.41	0.022[a]*
ID	169.56	16.34		94.88	9.56	
DD	165.00	19.75		91.17	4.60	
Allele						
I	170.25	19.75	0.225	98.60	9.50	0.006[b]*
D	167.84	17.02		95.24	8.23	

Note: ACE: Angiotensin-Converting Enzyme; I/D: Insertion/Deletion; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SD: Standard Deviation; mmHg: Millimeters of Mercury

[a] Kruskal–Wallis test

[b] Mann-Whitney U test

*statistically significant difference ($p < 0.05$)

This pattern diverges from the widely reported association between the D allele and elevated blood pressure, which is typically attributed to increased ACE activity and consequent upregulation of the renin–angiotensin–aldosterone system (RAAS) (Ajala et al., 2012; Espinel et al., 2007; Fountain et al., 2023; Kutumova et al., 2024). A recent meta-analysis concluded that *ACE I/D* gene polymorphism is significantly associated with susceptibility to primary hypertension (Wibowo et al., 2021). Supporting this, a study conducted in Chinese male subjects demonstrated a strong association between the polymorphism and hypertension, with individuals carrying the DD genotype exhibiting a higher risk of developing hypertension compared to those with the II or ID genotypes (Niu et al., 2016).

Interestingly, although the *ACE* DD genotype is generally linked to higher plasma *ACE* concentrations and increased angiotensin II activity, which are typically associated with elevated blood pressure. This study reveals an unexpected association with lower diastolic blood pressure in the Balinese population. The precise mechanism for the lower DBP in persons with the DD genotype is not apparent. Several hypotheses may account for this observation. One possibility is the presence of epistatic interactions with other cardiovascular-related genetic variants prevalent in this ethnic group (Q. Wang et al., 2023). Alternatively, lifestyle factors such as diet, physical activity, or traditional health practices may mitigate the physiological effects of person with the D allele (Mega, 2024; Oparil et al., 2018). Moreover, it is plausible that in certain contexts, the D allele could exert a compensatory or protective effect on vascular tone, particularly at the level of arteriolar resistance that regulates diastolic pressure (Carey et al., 2018). However, this counterintuitive finding may result from gene-environment interactions unique to this population that influence the physiological expression of the DD genotype. These results emphasize the importance of evaluating genotype-phenotype relationships within ethnically distinct groups, rather than extrapolating from broader datasets.

The contribution of ACE I/D polymorphism to hypertension should be interpreted within the broader framework of gene-environment interactions. Genetic susceptibility may be potentiated by environmental exposures such as high dietary salt intake, sedentary lifestyle, and psychosocial stress, all of which are relevant in the Balinese context. These interactions highlight that hypertension risk emerges from a dynamic interplay between inherited predisposition and modifiable factors, reinforcing the need for integrated public health approaches.

Despite providing valuable insights into the genetic profile of Balinese hypertensive patients, this study

has several limitations that warrant caution in interpreting the results. First, the cross-sectional design prevents the establishment of a temporal or causal relationship between the ACE I/D polymorphism and blood pressure levels. Second, the relatively small sample size and the absence of a normotensive control group precluded multivariable analysis to adjust for potential confounders. Furthermore, this research maintained a single-gene focus, examining only the ACE I/D polymorphism without considering gene–environment interactions or the influence of other polygenic factors that may modulate hypertension. Finally, as the study was conducted exclusively within a specific ethnic cohort, the findings have limited generalizability beyond the Balinese population. Nevertheless, these results underscore the complexity of ACE gene expression and its variable impact across different ethnic groups, serving as a critical foundational step for genomics in Bali. Taken together, this study highlights the need for larger scale, longitudinal cohorts that incorporate gene–environment interactions to fully clarify the physiological and clinical significance of these genetic polymorphisms.

CONCLUSIONS

This study contributes to the literature on the ACE I/D polymorphism by providing specific data from the Balinese population. Our results indicate that the ACE I/D polymorphism is not significantly associated with the clinical staging of hypertension. However, a significant variation was observed in diastolic blood pressure (DBP) levels, where the II genotype (I allele) was linked to higher DBP compared to D-allele carriers. These findings suggest that while the ACE I/D polymorphism may not be a definitive determinant of hypertension severity in Bali, it represents a potential risk factor for specific hemodynamic variations. Crucially, the findings of this study highlight the imperative of grounding genetic research within the specific demographic and ethnic contexts of the population under investigation. Embracing such diversity is essential for refining our understanding of hypertension risk and informing more precise, population-tailored strategies for its prevention, diagnosis, and therapeutic management.

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CONFLICT OF INTEREST

The author declares no conflict of interest in relation to this study.

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