ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 08 | August - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF GENETIC POLYMORPHISM OF ACE GENE (I/D) IN AKI OF NORTH INDIAN POPULATION

Medicine

Dr. Ahmar Mumtaz	Senior Resident, MD Medicine
Dr. Devendra Kumar	Professor, MD Medicine
Dr. Shivam Srivastava	Senior Resident, MD Medicine
Dr. Satyam Sadana	Junior Resident, MD Medicine
Dr. Daniyal Malik	Junior Resident, MD Medicine
Dr. Kanika Ahuja	MD Medicine, Mercy Oregon Clinic, Oregon, Ohio

ABSTRACT

Background: Acute Kidney Injury (AKI) remains a global health challenge, with significant morbidity and mortality. Genetic factors, particularly polymorphisms in the angiotensin-converting enzyme (ACE) gene, may influence susceptibility to AKI. **Objectives:** This study aimed to investigate the association of ACE gene Insertion/Deletion (I/D) polymorphism with the occurrence and severity of AKI in the North Indian population. **Methods:** A prospective case-control study was conducted over 24 months at a tertiary care hospital. Ninety-four AKI patients and 94 age- and gender-matched healthy controls were enrolled. Genomic DNA was extracted, and ACE I/D polymorphism was analyzed using PCR techniques. Statistical analysis was performed using chi-square test and ANOVA. **Results:** The DD genotype was significantly associated with increased AKI risk (p=0.016), while the ID genotype showed a protective association (p=0.041). No significant association was observed with AKI severity or clinical outcomes. **Conclusion:** ACE gene polymorphism, particularly the DD genotype, may contribute to AKI susceptibility in this population.

KEYWORDS

Acute Kidney Injury; ACE gene; Genetic Polymorphism; North Indian Population; Renin-Angiotensin System.

INTRODUCTION

Acute Kidney Injury (AKI) is a significant global health concern, characterized by an abrupt decline in kidney function, reflected by a rise in serum creatinine or reduced urine output, often within hours to days. According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, AKI affects approximately 40% of patients admitted to intensive care units (ICUs), contributing substantially to morbidity and mortality rates that can reach as high as 50–70% among hospitalized individuals[1,2].

In India, the burden of AKI is further compounded by socioeconomic disparities, late diagnosis, and limited access to specialized renal care, making early identification of at-risk individuals crucial. Despite advances in critical care and renal replacement therapies, predicting AKI development remains challenging due to its multifactorial pathogenesis and individual variability[3].

Among the known biological pathways, the Renin-Angiotensin-Aldosterone System (RAAS) plays a pivotal role in renal hemodynamics and pathophysiology. Angiotensin-Converting Enzyme (ACE), a key component of this system, converts angiotensin I into angiotensin II, a potent vasoconstrictor implicated in hypertension, inflammation, and renal damage[4]. Genetic variations within the ACE gene, particularly the well-characterized Insertion/Deletion (I/D) polymorphism located in intron 16, have been shown to influence ACE levels, with the deletion (D) allele associated with higher circulating and tissue ACE activity[5,6].

The association of ACE I/D polymorphism with chronic kidney disease, hypertension, and diabetic nephropathy is well documented globally. However, its role in AKI, especially among the North Indian population—recognized for its unique genetic makeup and environmental exposures—remains underexplored. Given the heterogeneity in genetic predisposition across populations, this study aimed to investigate the distribution of ACE (I/D) genotypes and alleles among AKI patients in North India and assess their association with renal function and AKI-related outcomes.

MATERIAL AND METHODS

This prospective case-control study was conducted over a period of 24 months at Era's Lucknow Medical College and Hospital to investigate the association of ACE (I/D) gene polymorphism with Acute Kidney Injury (AKI) in the North Indian population. A total of 188 individuals were enrolled, including 94 patients diagnosed with AKI according to KDIGO 2012 criteria and 94 age- and gender-matched healthy controls admitted to the medical ward. Ethical approval for the study was obtained from the Institutional Review Board of the institution, and written informed consent was obtained from all participants prior to enrolment.

Inclusion criteria for cases were patients above 18 years of age with AKI, defined as an increase in serum creatinine by ≥0.3 mg/dl within 48 hours, or an increase to ≥1.5 times baseline within seven days, or urine output less than 0.5 ml/kg/h for six hours. Patients with dyslipidemia, chronic kidney disease, glomerulonephritis, or polycystic kidney disease were excluded to avoid confounding factors. Controls were selected based on similar age and gender distribution and the absence of AKI.

The calculated sample size was 94 subjects per group, considering a 5% level of significance, 80% power, and a 10% anticipated data loss. Five millilitres of venous blood was collected aseptically from all participants using sterile 0.5M EDTA tubes. All subjects underwent laboratory investigations, including complete blood count, liver and kidney function tests, and ultrasonography of the kidneys, ureters, and bladder.

Genomic DNA was extracted using a Qiagen commercial kit. DNA quality and concentration were confirmed by spectrophotometry and agarose gel electrophoresis. Genotyping for ACE (I/D) polymorphism (rs4646994) was performed by polymerase chain reaction using specific primers. The PCR products were separated on a 2% agarose gel, stained with ethidium bromide, and visualized under ultraviolet light. Band sizes of 490 bp and 190 bp indicated the insertion (I) and deletion (D) alleles, respectively.

Statistical analysis was performed using IBM SPSS version 23. Categorical variables were compared using the chi-square test, and continuous variables were analysed using the unpaired t-test and ANOVA. A p-value <0.05 was considered statistically significant.

RESULTS

We studied the association of genetic polymorphism of the ACE gene (I/D) with the occurrence and severity of acute kidney injury (AKI) in the North Indian population.

Table 1: Distribution Of Cases And Control According To Age And Gender

Category	Sub-Category	Case		Control		Chi-Sq, p-value
		N = 94	%	N = 94	%	
Age	18 - 29 yr.	17	18.1%	23	24.5%	chi sq=9.42, p=0.094
	30 - 39 yr.	14	14.9%	23	24.5%	
	40 - 49 yr.	15	16.0%	19	20.2%	
	50 - 59 yr.	14	14.9%	12	12.8%	
	60 - 69 yr.	21	22.3%	10	10.6%	
	>=70 yr.	13	13.8%	7	7.4%	
Gender	Male	49	52.1%	56	59.6%	chi sq=1.06, p=0.304
	Female	45	47.9%	38	40.4%	

The majority of AKI cases (68.1%) were classified as Stage 1 according to KDIGO criteria, followed by 26.6% in Stage 2 and 5.3% in Stage 3, indicating that most patients presented with mild to moderate AKI severity.

Table 2: Comparison of ACE Genes in Case and Control

ACE Gene	Sub-Type	Case		Control		OR	95% CI	p-value
		N	%	N	%			
Genotype	DD	35	37.2%	20	21.3%	2.19	(1.15-4.19)	0.016
	ID	37	39.4%	51	54.3%	0.55	(0.30-0.98)	0.041
	II	22	23.4%	23	24.5%	0.94	(0.48-1.84)	0.864
Allele	D	107	56.9%	91	48.4%	1.41	(0.94-2.11)	0.098
	I	81	43.1%	97	51.6%	0.71	(0.47-1.07)	0.098

Table 3: Comparison of ACE Genes according to KDIGO Classification

ANGIOTENSIN CONVERTING ENZYME GENE	KDIGO Classification	Stage 1		Stage 2		Stage 3		Chi-sq, p-value
		N	%	N	%	N	%	
Genotype	DD	23	35.9%	8	32.0%	4	80.00%	4.59, 0.334
	ID	26	40.6%	10	40.0%	1	20.00%	
	II	15	23.4%	7	28.0%	0	0.00%	
Allele	D	72	56.3%	26	52.0%	9	90.00%	4.98, 0.083
	I	56	43.8%	24	48.0%	1	10.00%	

Table 4: Comparison of KFT and Other Biochemical Parameters among ACE Genotype

Parameters	ANGIOTENSIN CONVERTING ENZYME GENE						ANOVA	
	DD		ID		II			
	Mean	SD	Mean	SD	Mean	SD	F-value	p-value
S. UREA	71.97	34.23	74.44	16.41	111.80	40.16	1.57	0.211
S. CREAT	2.22	0.44	2.29	0.40	2.92	0.68	2.44	0.090
S. Na+	138.78	2.07	139.55	2.45	139.69	2.63	2.30	0.104
S. K+	4.04	0.61	4.00	0.42	4.10	0.43	0.67	0.514
HB	11.43	1.56	11.67	2.09	11.36	2.40	0.43	0.652
TLC	7476.36	2716.34	7501.14	2444.49	6966.67	2023.72	0.80	0.453
PLATELET	2.70	1.04	2.77	0.97	2.62	1.12	0.33	0.719
S. BILIRUBIN	1.01	1.38	0.84	0.38	1.02	1.10	0.77	0.462
SGPT	32.16	11.32	27.72	10.43	30.13	13.16	2.64	0.074
SGOT	34.84	14.88	28.81	11.69	32.20	16.62	2.26	0.123
S.ALP	104.05	40.13	88.57	30.76	96.56	37.02	2.33	0.116

Table 5: Comparison of ACE Genotype with Complications among Cases

Complications	Genotype						Significance
	DD		ID		II		
	No.	%	No.	%	No.	%	
Metabolic Acidosis	21	60.3%	23	62.2%	13	59.2%	chi sq=9.57, p=0.479
Electrolyte Imbalance	9	25.7%	6	16.2%	4	18.2%	
Pulmonary Edema	2	5.7%	4	10.8%	1	4.5%	
Uremia	1	2.9%	2	5.4%	3	13.6%	
Chronic Kidney Disease	2	5.4%	2	5.4%	1	4.5%	

Table 6: Association of ACE Genotype with need for RRT, and Ventilatory Support among Cases

Category	Sub-Category	Genotype						Significance
		DD		ID		II		
		No.	%	No.	%	No.	%	
Need for RRT	No need	29	82.9%	29	78.4%	15	68.2%	chi sq=1.70, p=0.428
	RRT need	6	17.1%	8	21.6%	7	31.8%	
Ventilatory Support	Not Needed	26	74.3%	31	83.8%	17	81.0%	chi sq=1.03, p=0.597
	Needed	9	25.7%	6	16.2%	4	19.0%	

Table 7: Comparison of ACE Gene with Outcome

ANGIOTENSIN CONVERTING ENZYME GENE		Survival in AKI				Significance
		Survivor		Non-Survivor		
		N	%	N	%	
Genotype	DD	29	34.9%	6	54.5%	chi sq=4.59, p=0.334
	ID	34	41.0%	3	27.3%	
	II	20	24.1%	2	18.2%	
Allele	D	92	55.4%	15	68.2%	chi sq=1.29, p=0.256
	I	74	44.6%	7	31.8%	

DISCUSSION

In this study, we examined the association of ACE gene polymorphisms with the occurrence, severity, and outcomes of acute kidney injury (AKI) among a North Indian population. We found a significantly higher frequency of the DD genotype in AKI cases compared to controls, indicating an increased risk of AKI in individuals carrying this genotype. In contrast, the ID genotype appeared to be protective, while the II genotype showed no significant association with AKI. These findings are consistent with studies by Saw et al. (2019)[7] and Isbir et al. (2007)[8], both of which reported an association between the ACE D allele and increased AKI risk, particularly in post-surgical and critically ill populations.

Although we observed a higher prevalence of severe AKI (Stage 3) among individuals with the DD genotype, this association did not reach statistical significance. Our results partially align with those of Van der Sman-de Beer F et al. (2005)[9], who reported a significant association between the II genotype and increased AKI risk and mortality among critically ill patients. This discrepancy may be attributed to differences in study populations and clinical settings, underscoring the complex relationship between ACE polymorphisms and AKI severity.

No significant association was found between ACE genotypes and common AKI complications such as electrolyte imbalance, metabolic acidosis, pulmonary edema, or uremia. Similarly, the distribution of biochemical parameters like serum urea and creatinine levels across different ACE genotypes did not differ significantly, although a trend toward higher levels was noted in the II genotype group, which aligns with findings from Fagyas et al. (2014)[10].

The requirement for renal replacement therapy (RRT), ventilatory support, and survival outcomes showed no significant association with ACE genotypes, consistent with reports by McLaughlin et al. (1996)[11] and Serdaroglu et al. (2000)[12], who found no significant influence of ACE polymorphisms on RRT need or disease outcomes.

Limitations:

The limitations of the study include its relatively small sample size, single-centre design, and lack of long-term follow-up, which may limit the generalizability and assessment of the long-term impact of ACE polymorphisms on AKI outcomes.

Strengths: The strengths of the study include its prospective case-control design, strict inclusion criteria, and use of precise molecular techniques for ACE genotyping, providing reliable genetic association data specific to the North Indian population.

CONCLUSION

We concluded that the DD genotype of the ACE gene is significantly associated with increased AKI risk, while the ID genotype may have a protective role. However, ACE polymorphisms showed no significant

association with AKI severity or clinical outcomes.

REFERENCES

1. Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron. 2012 Aug 7;120(4):c179–84.
2. Bhatraju PK, Zelnick LR, Chinchilli VM, Moledina DG, Coca SG, Parikh CR, et al. Association Between Early Recovery of Kidney Function After Acute Kidney Injury and Long-term Clinical Outcomes. JAMA Network Open. 2020 Apr 13;3(4):e202682.
3. Pereira M, Rodrigues N, Godinho I, Gameiro J, Neves M, Gouveia J, et al. Acute kidney injury in patients with severe sepsis or septic shock: a comparison between the "Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease" (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications. Clinical Kidney Journal. 2016 Dec 13;10(3):sfw107.
4. Cartin-Ceba R, Haugen EN, Iscimen R, Trillo-Alvarez C, Juncos L, Gajic O. Evaluation of "Loss" and "End stage renal disease" after acute kidney injury defined by the Risk, Injury, Failure, Loss and ESRD classification in critically ill patients. Intensive Care Medicine. 2009 Sep 15;35(12):2087–95.
5. Ortega-Loubon C, Fernández-Molina M, Fierro I, Jorge-Monjas P, Carrascal Y, GómezHerreras JI, et al. Postoperative kidney oxygen saturation as a novel marker for acute kidney injury after adult cardiac surgery. The Journal of Thoracic and Cardiovascular Surgery. 2019 Jun;157(6):2340-2351.e3.
6. Monedero P, García-Fernández N, Pérez-Valdivieso JR, Vives M, Lavilla J. Insuficiencia renal aguda. Revista Española de Anestesiología y Reanimación [Internet]. 2011 Jan;58(6):365–74.
7. Saw KM, Ng RG, Chan SP, Ang YH, Ti LK, Chew TH. Association of genetic polymorphisms with acute kidney injury after cardiac surgery in a Southeast Asian population. Plos one. 2019 Apr 11;14(4):e0213997.
8. Isbir SC, Tekeli A, Ergen A, Yilmaz H, Ak K, Civelek A, Zeybek U, Arsan S. Genetic polymorphisms contribute to acute kidney injury after coronary artery bypass grafting. InThe Heart Surgery Forum 2007 Oct 5 (Vol. 10, No. 6, pp. E439-E444).
9. Van der Sman-de Beer F, Verhagen C, Rombach SM, Boorsma P, Van Manen JG, Korevaar JC, van den Bogaard R, Boeschoten EW, Krediet RT, Navis GJ, Vandenbroucke JP. ACE I/D polymorphism is associated with mortality in a cohort study of patients starting with dialysis. Kidney international. 2005 Nov 1;68(5):2237-43.
10. Fagyas M, Úri K, Siket IM, Fülöp GÁ, Csató V, Daragó A, et al. (2014) New Perspectives in the Renin-Angiotensin-Aldosterone System (RAAS) II: Albumin Suppresses Angiotensin Converting Enzyme (ACE) Activity in Human. PLoS ONE 9(4): e87844.
11. MacLaughlin HL, Blacklock RM, Wright K, Pot G, Jayawardene S, McIntyre CW, et al. Obesity and recovery from acute kidney injury (Ob AKI): a prospective cohort feasibility study. BMJ Open. 2019 Mar;9(3):e024033.
12. Serdaroglu E, Mir S, Berdeli A. Hypertension and ace gene insertion/deletion polymorphism in pediatric renal transplant patients. Pediatric transplantation. 2005 Oct;9(5):612-7.