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Association Between ERG11 Gene and Azole Resistance among Candida Isolates from Chronic Kidney Disease Patients

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ABSTRACT

Background*: Chronic kidney disease patients undergoing hemodialysis are vulnerable to oropharyngeal Candida infection because of immune dysfunction, uremia-related changes, frequent healthcare exposure, and altered oral conditions. Azole antifungals remain widely used for mucosal candidiasis, but resistance is increasingly reported. The ERG11 gene encodes lanosterol 14-alpha-demethylase, the main azole target, and is therefore an important molecular marker to investigate in Candida isolates.* ***Objective****: This study evaluated the detection of ERG11 and its relationship with fluconazole and voriconazole resistance among Candida isolates obtained from chronic kidney disease patients undergoing hemodialysis.* ***Methods****: This study was designed as a hospital-based cross-sectional observational study. Oral swabs were collected from hemodialysis patients and Candida isolates were identified by conventional culture and species-level laboratory methods. Antifungal susceptibility to fluconazole and voriconazole was determined, and ERG11 was detected by PCR. Associations between ERG11 positivity and azole resistance were analyzed using categorical statistical tests, with P <= 0.05 considered significant.* ***Results****: 96 Candida-positive isolates were identified. Candida albicans was the predominant species, representing 75/96 (78.1%) isolates. Fluconazole resistance was detected in 60/96 (62.5%) isolates, while voriconazole resistance was detected in 54/96 (56.2%). ERG11 was positive in 81/96 (84.4%) isolates. Fluconazole resistance was higher among ERG11-positive isolates than ERG11-negative isolates (65.4% vs. 46.7%), but the difference was not statistically significant (P = 0.16). Voriconazole resistance was also not significantly associated with ERG11 positivity (55.6% vs. 60.0%, P = 0.74).* ***Conclusion****: ERG11 was frequently detected among Candida isolates from hemodialysis patients; however, its presence alone was not significantly associated with azole resistance. These findings suggest that ERG11 detection is useful for molecular characterization, but mutation analysis and gene expression testing are needed to clarify its functional role in resistance.*

Keywords: Candida; ERG11; Azole Resistance; Fluconazole; Voriconazole; Chronic Kidney Disease; Hemodialysis; Oropharyngeal Candidiasis

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1.INTRODUCTION

Chronic kidney disease (CKD) is a progressive clinical condition characterized by gradual and irreversible loss of renal function. In advanced stages, many patients require renal replacement therapy, especially hemodialysis. CKD is not only a renal disorder, but also a systemic disease associated with chronic inflammation, metabolic abnormalities, cardiovascular complications, immune dysfunction, and increased susceptibility to infection [1,2].

Oropharyngeal candidiasis is mainly caused by Candida species, particularly Candida albicans, although non-albicans Candida species have become increasingly important in immunocompromised patients. In chronic kidney disease patients, Candida

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colonization and infection may be influenced by diabetes, oral dryness, altered mucosal immunity, and repeated antimicrobial exposure [3-5]. Fluconazole and voriconazole are azole antifungal agents that inhibit ergosterol biosynthesis by targeting lanosterol 14-alpha-demethylase. This enzyme is encoded by ERG11. Resistance to azoles may arise through ERG11 mutations, ERG11 overexpression, efflux pump activation, and biofilm-associated tolerance [6-9]. Azole resistance among Candida isolates has become an increasing clinical concern. Resistance may occur through ERG11 mutations, ERG11 overexpression, increased efflux pump activity, or regulatory changes [10,11].

2. MATERIALS AND METHODS

2.1 Study design and sample collection

This study included chronic kidney disease patients undergoing hemodialysis. Oral swab samples were collected from Basrah teaching hospital to investigate oropharyngeal Candida infection and associated antifungal resistance. Patients were classified according to microbiological detection of Candida growth into Candida-positive and Candida-negative groups. The present manuscript focused on the 96 Candida-positive isolates.

2.2 Isolation and identification of Candida species

Oral swabs were cultured on Sabouraud dextrose agar and incubated for yeast growth. Positive isolates were further identified to species level using colony morphology, CHROMagar Candida medium, and automated biochemical identification using the VITEK 2 compact system.

2.3 Antifungal susceptibility testing

Antifungal susceptibility testing was performed for Candida-positive isolates. In this manuscript, fluconazole and voriconazole were analyzed as the main azole agents. Results were classified as sensitive, intermediate, or resistant. For association testing, resistant isolates were compared with non-resistant isolates, where non-resistant included sensitive and intermediate categories.

2.4 Molecular detection of ERG11

Genomic DNA was extracted from yeast isolates using a commercial yeast genomic DNA extraction kit according to the manufacturer's protocol. ERG11 was amplified by polymerase chain reaction using species-specific primers. PCR products were detected by agarose gel electrophoresis and visualized under ultraviolet illumination.

Table 1. ERG11 primers used for Candida species.

Species	Primer sequence (5'-3')	Product size	References
C. albicans	F 5'- GCAGCTTCATATGGTCAACAACC-3' R 5'- TAACATTGGCAACCCCATGAG-3'	100 bp	[12]
C. glabrata	F 5'- AGCTGCTTACTCCCACTTGACC-3' R 5'-AGCTTGTTGGGCATGGTCTCTC-3'	412 bp	[13]
C. krusei	F 5'- ACTCCTGTTTTCGGTAAGGGCG-3' R 5'-CACCGGCACGCTTTGTATTG-3'	421 bp	[14]
C. tropicalis	F 5'-ATCCCACAGGCTTATTTGAAA-3' R 5'-GGTCTCTTTCCTTGGTTTTG -3'	614 bp	[14]
C. parapsilosis	F 5'-CGAGATAATCATCA ACGAACATTC3' R 5'-AAAGACCGCATTGACTACCGAT-3'	648 bp	[15]

2.5 Statistical analysis

Statistical analysis was performed using SPSS. Frequencies and percentages were used for categorical variables. Chi-square or Fisher exact tests were applied to evaluate associations between ERG11 positivity and azole resistance. A P value of <0.05 was considered statistically significant.

3. RESULTS

3.1 Species distribution

Among the 96 Candida-positive isolates, Candida albicans was the most frequent species, accounting for 75 isolates (78.1%). Non-albicans Candida species collectively represented 21.9% of isolates.

Table 2. Distribution of Candida species among positive isolates

Candida species	N	%
Candida albicans	75	78.1
Candida glabrata	9	9.4
Candida parapsilosis	6	6.2
Candida tropicalis	4	4.2
Candida krusei	2	2.1

3.2 Azole susceptibility pattern

The azole susceptibility results showed high resistance rates. Fluconazole resistance was detected in 60 isolates (62.5%), while voriconazole resistance was detected in 54 isolates (56.2%).

Table 3. Fluconazole and voriconazole susceptibility among Candida-positive isolates

Antifungal	Result	N	%
Fluconazole	Sensitive	31	32.3
	Intermediate	5	5.2
	Resistant	60	62.5
Voriconazole	Sensitive	37	38.5
	Intermediate	5	5.2
	Resistant	54	56.2

3.3 ERG11 gene frequency

ERG11 was detected in 81 of 96 Candida-positive isolates (84.4%). Among Candida albicans, ERG11 was detected in 60/75 (80.0%) isolates. ERG11 was detected in all tested non-albicans isolates, although these species were represented by smaller numbers.

Table 4. ERG11 frequency according to Candida species.

Candida species	Valid No.	ERG11 positive No.	Positive %	ERG11 negative No.	Negative %
Candida albicans	75	60	80.0	15	20.0
Candida glabrata	9	9	100.0	0	0.0
Candida parapsilosis	6	6	100.0	0	0.0
Candida tropicalis	4	4	100.0	0	0.0
Candida krusei	2	2	100.0	0	0.0

3.4 Association between ERG11 and azole resistance.

Fluconazole resistance was numerically higher among ERG11-positive isolates than ERG11-negative isolates, but the difference was not statistically significant. No significant relationship was observed between ERG11 positivity and voriconazole resistance.

Table 5. Association between ERG11 positivity and azole resistance.

Antifungal	No. of isolates	R & ERG11+	Non-R & ERG11+	R & ERG11-	Non-R & ERG11-	Resistance % in ERG11+	Resistance % in ERG11-	P-value
Fluconazole	96	53	28	7	8	65.4	46.7	0.16
Voriconazole	96	45	36	9	6	55.6	60.0	0.74

PCR amplification was performed to detect the ERG11 gene among Candida isolates using species-specific primers. The amplified products were separated by agarose gel electrophoresis and visualized under ultraviolet illumination. The presence of clear bands at the expected molecular size confirmed successful amplification of the ERG11 gene in positive isolates.

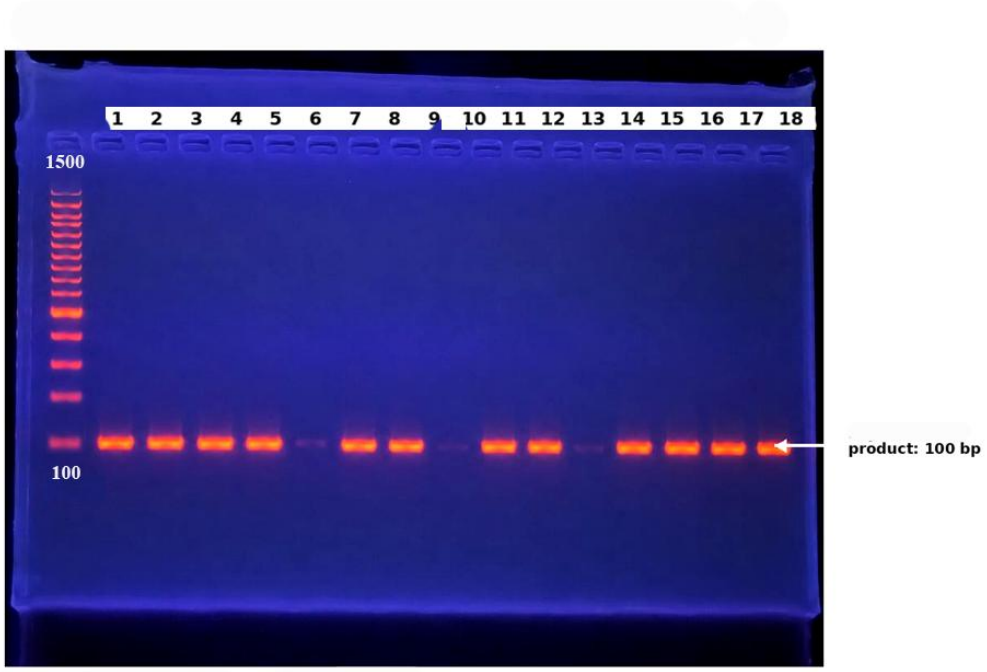

Figure 1. Agarose gel electrophoresis of ERG11 gene PCR product. Expected product size: 100 bp.

4. DISCUSSION

The present study showed a high frequency of azole resistance among Candida isolates recovered from chronic kidney disease patients undergoing hemodialysis. Fluconazole resistance was particularly prominent, and voriconazole resistance was also high. This pattern is clinically relevant because azoles are widely used for mucosal candidiasis due to their availability and oral administration. However, repeated or empirical azole exposure can select resistant Candida strains, especially in recurrent infection and in patients with repeated healthcare exposure [6,7,16].

Candida albicans was the dominant species in the current study. This agrees with the established role of C. albicans as the main cause of oral candidiasis because of its ability to adhere to oral epithelium, form hyphae, produce biofilm, and shift between commensal and pathogenic states [3,17]. The detection of non-albicans Candida species remains clinically meaningful because these species may differ in antifungal susceptibility and resistance mechanisms.

ERG11 was highly detected among the tested isolates. This finding is expected because ERG11 encodes lanosterol 14-alpha-demethylase, the target enzyme of azole antifungal drugs and an essential component of the ergosterol biosynthesis pathway [7,8]. However, the presence of ERG11 alone does not prove azole resistance. Resistance usually depends on ERG11 mutation, overexpression, copy number variation, or regulation by transcription factors rather than simple gene presence [9,18].

Although fluconazole resistance was higher among ERG11-positive isolates than ERG11-negative isolates, the association was not statistically significant. This result should not be interpreted as absence of an ERG11 role. Instead, it suggests that conventional PCR detection is insufficient to determine whether ERG11 is functionally involved in resistance. Sequencing is required to identify point mutations, and quantitative RT-PCR is needed to evaluate overexpression [8,19,20]. The lack of significant association between ERG11 and voriconazole resistance further supports the complexity of azole resistance. Cross-resistance within azoles may involve multiple mechanisms, including efflux pump activation, target modification, biofilm tolerance, and

changes in transcriptional regulators [6,9,21]. Therefore, ERG11 should be considered one component of a broader resistance network.

5. CONCLUSION

ERG11 was frequently detected among Candida isolates from chronic kidney disease patients undergoing hemodialysis. Although fluconazole resistance was numerically higher among ERG11-positive isolates, the association with fluconazole and voriconazole resistance was not statistically significant.

Declarations

Ethical approval: to be inserted according to institutional approval.

Conflict of interest: The authors declare no conflict of interest.

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Data availability: Data are available from the corresponding author upon reasonable request.

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