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Review Article

Antifungal Resistance of Clinical *Candida albicans* Isolates in Iran: A Systematic Review and Meta-Analysis

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Abstract

Background: The present systematic review aimed to investigate the drug susceptibility patterns of Iranian clinical *Candida albicans* isolates to antifungal drugs (azoles, polyenes, and echinocandins).

Methods: Six electronic databases including "PubMed," "Scopus," "Web of Science," "IranDoc", "SID", and "Magiran" were searched from May 2000 to June 2021. The susceptibility of 6322 *C. albicans* strains from 19967 patients against 14 antifungal drugs was evaluated according to CLSI method.

Results: The pooled prevalence of antifungal resistance ranged from 0% to 26%. The lowest resistance levels among azoles were observed in luliconazole with a frequency of 0% and voriconazole of 3.94%.

Conclusion: Due to the emergence of multi-drug resistant *C. albicans,* rational drug prescription based on the anti-fungal stewardship strategy and therapeutic drug monitoring is warranted.

Keywords: Antifungal susceptibility; Multi-drug resistance; *Candida albicans*; Systematic review

Introduction

Antifungal susceptibility patterns of *Candida* species can play an essential and decisive role in the treatment outcome. Differences in the susceptibility of *Candida* species to antifungals depend on strain types, individual conditions, geographical area, and health care management (1). During the past two decades, although we are witnessing an increasing incidence of non- *albicans Candida* species due to reduced susceptibility to antifungals, *C. albicans* still plays an important role in developing superficial to systemic fungal infection (2).

On the other hand, the increase of drug-resistant fungi is one of the greatest challenges in a clinical setting and may affect the disease outcome (3). Therefore, the prescription of proper antifungal

agents is essential for the management of fungal infections.

In vitro antifungal susceptibility testing is performed by different methods, such as the broth macro and microdilution, agar diffusion such as E-test, disk diffusion, and colorimetric method (4, 5). The present study aimed to investigate the drug susceptibility patterns of Iranian clinical *C. albicans* isolates to conventional antifungal drugs according to the CLSI method.

Methods

Search strategy and data extraction

This study was performed based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (6). FK and NA searched all studies on drug susceptibility of Iranian clinical *C. albicans* strains presented in databases from May 2000 to Jun 2021 independently. The national databases, including IranDoc, SID, Magiran, and international databases such as PubMed, Scopus, and Web of Science were searched with the following keywords: "*Candida*", "candidiasis", "antifungal susceptibility", "clinical laboratory standards institute", "CLSI" and "Iran". In data extraction, the following variables included references, type of disease, and the number of resistant or susceptible isolates extracted.

Statistical Analysis

The pooled prevalence of drug susceptibility with a 95% confidence interval (CI) was calculated using the random-effects model using StatsDirect software, version 2.8.0 (http://statsdirect.com). Heterogeneity was examined by Cochran's Q and I^2 statistics test. The forest plot in the random effects model was used to calculate the pooled frequency of drug resistance among Iranian clinical *C. albicans* strains.

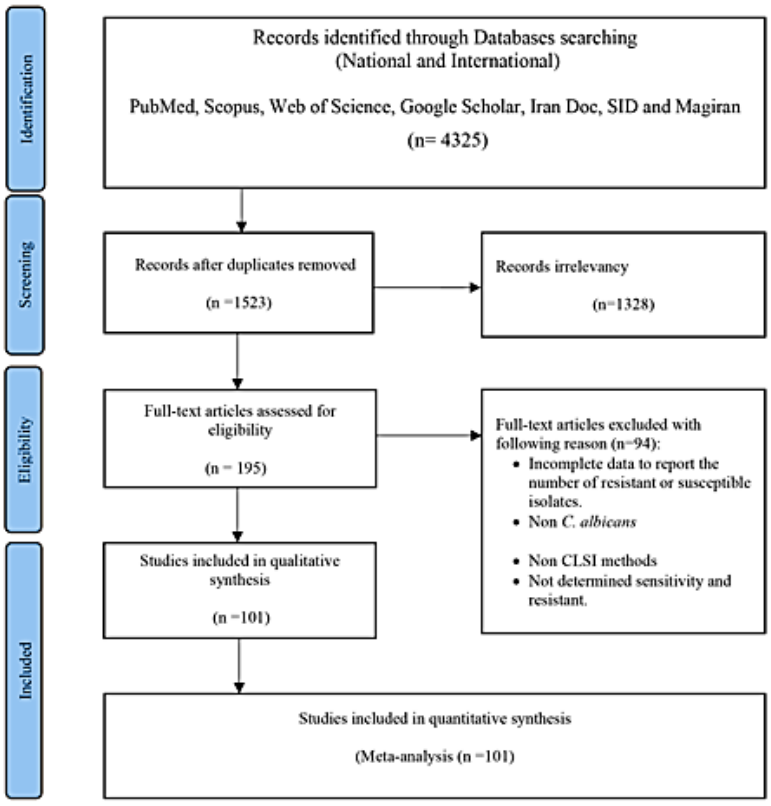

Fig. 1: PRISMA flowchart showing the search strategy

Results

In this review, 101 articles were eligible (Fig. 1). Accordingly, the susceptibility 6322 of *C. albicans* strains isolated from 19967 patients against 14 antifungal drugs was evaluated. The extracted information is summarized in Table 1.

Table 1: The detailed information from 101 included articles

Reference	*Population source*	*C. albicans no.*	*Results (R/S)*
(7)	*-	33	FLC (3/26)
(8)	-	50	FLC (25/25)
(9)	-	1	FLC (0/1)
(10)	Vaginitis	20	FLC (8/12)
(11)	Vaginitis	10	FLC (0/10)
(12)	-	11	FLC (7/4)
(13)	-	64	FLC (1/55)
(14)	-	30	FLC (16/14)
(15)	Onychomycosis	18	FLC (0/16), ITR (0/18), KTC (0/17), AMB(0/18), CAS(15/1)
(16)	Vaginitis	18	KTC (0/18)
(1)	Immunocompromised patients	172	FLC (8/159), ITR (12/22), VRC (4/164), KTC (12/160), NYS (2/170), AMB (13/159)
(17)	Vaginitis	23	FLC (19/2), CLO (1/16), KTC (8/5)
(18)	AIDS	117	FLC (12/105), KTC (0/117), NYS (0/117), AMB (0/117), CAS (0/117)
(19)	OPC	17	FLC (17/0)
(20)	Vaginitis	46	FLC (39/7), CLO (6/40), KTC (36/10), ECO (31/15), MIC (20/26), NYS (0/46)
(21)	Vaginitis	128	FLC (1/125), MIC (0/128), 5FC (0/126)
(22)	AIDS	66	FLC (15/43)
(23)	Immunocompromised patients	172	FLC (16/156), ITR (26/ND) *, VRC (4/ND), KTC (10/ND), NYS (2/170), AMB (12/160)
(24)	-	93	FLC (0/93), ITR (0/80), AMB (0/93)
(25)	OPC	38	FLC (1/31), ITR (2/18), AMB (1/37)
(26)	Peritoneal dialysis	5	FLC (0/5), AMB (0/5), 5FC (0/5)
(27)	Vaginitis	80	FLC (23/57), CLO (24/56), KTC (27/53)
(28)	Burning	6	FLC (6/0), CLO (2/2), NYS (0/2)
(29)	AIDS	103	FLC (26/57), CLO (17/78), KTC (22/65), NYS (2/101), AMB (2/99), CAS (0/100)
(30)	Vaginitis	19	FLC (18/1)
(31)	-	4	AMB (4/0)
(32)	Patients with dyspepsia	30	KTC (0/30), AMB (0/30)
(33)	-	37	AMB (0/37)
(34)	Neutropenia	117	FLC (14/103), ITR (36/84), VRC (7/109), KTC (9/108), AMB (4/113), CAS (4/113)

(35)	Superficial candidiasis	125	FLC (0/125), ITR (5/60), VRC (2/120), KTC (41/50), AMB (4/121), CAS (12/113), 5FC (5/115)
(36)	Vulvovaginitis	35	FLC (5/30)
(37)	Vulvovaginitis	6	FLC (0/5)
(38)	Vulvovaginitis	19	FLC (8/8), CLO (4/15), MIC (9/10), AMB (6/13)
(2)	Candidemia, Candiduria	19	VRC (0/19), POS (0/19), AMB (0/19), CAS (0/19)
(39)	Candiduria	4	FLC (2/2), AMB (0/4)
(40)	-	77	FLC (10/41)
(41)	AIDS, cancer, diabetic	108	FLC (8/100)
(42)	Onychomycosis	23	FLC (1/22), CLO (0/23), VRC (10/13)
(43)	OPC	60	FLC (20/34), CLO (16/39), KTC (17/38), NYS (0/59), AMB (1/58), CAS (0/59)
(44)	Superficial candidiasis	67	FLC (46/21), ITR (57/10), MIC (43/24)
(45)	Vulvovaginitis	109	FLC (0/109), VRC (0/109), POS (0/109), AMB (0/109), AFG (0/109)
(46)	Vaginitis	150	FLC (79/53), CLO (55/89), ITR (68/69), VRC (6/143), KTC (72/37), POS (7/138), NYS (1/145), AMB (0/150)
(47)	Burning, Pulmonary infection, Solid tumor	44	FLC (4/37), ITR (5/37), VRC (4/35), AMB (5/39), CAS (2/39)
(48)	Vaginitis, Cutaneous candidiasis, Candidemia	67	ITR (0/67), VRC (0/67), AMB (0/67)
(4)	ICU patients	34	FLC (10/24), ITR (12/22), VRC (5/29), AMB (6/28), CAS (0/34)
(49)	Lymphoma, Leukemia, BM transplantation	20	FLC (1/19), ITR (2/18), AMB (0/20)
(50)	-	30	KTC (25/2), AMB (2/22)
(51)	-	114	FLC (24/85), ITR (40/70), VRC (38/76), KTC (2/91)
(52)	Respiratory infection	74	FLC (14/56), ITR (19/43), AMB (46/28), CAS (1/43)
(53)	Systemic candidiasis	397	FLC (11/375), ITR (10/241), VRC (15/356), AMB (2/395), CAS (1/389)
(54)	Vulvovaginitis	65	FLC (1/64)
(55)	Vaginitis	30	FLC (0/30), CLO (3/25), CAS (2/2)
(56)	AIDS	77	FLC (20/33)
(57)	Neonatal intensive care unit	7	FLC (1/3), AMB (0/7), CAS (0/7)
(58)	Immunocompromised patients	273	FLC (13/247), ITR (34/141), VRC (18/241), AMB (9/263), CAS (1/272)
(59)	Immunocompromised patients	28	FLC (28/0)
(60)	Immunocompromised patients	510	FLC (12/273), ITR (35/273), VRC (19/273)

(61)	immunocompromised patients	223	FLC (11/202), ITR (6/163), VRC (12/202), AMB (2/221), CAS (1/216)
(62)	Vulvovaginitis	45	FLC (40/5)
(63)	Vulvovaginitis	64	FLC (7/ ND)
(64)	Vulvovaginitis	23	FLC (20/1)
(65)	Vulvovaginitis	119	FLC (97/21), CLO (54/38), KTC (85/33), NYS (18/99), AMB (20/48)
(66)	Vulvovaginitis	51	FLC (12/26), CLO (6/22), KTC (21/16), MIC (0/47),
(67)	Cancer	82	FLC (13/69), AMB (29/53), CAS (13/69), AFG (0/82)
(68)	Vulvovaginitis	38	CLO (31/7)
(69)	Denture Stomatitis	84	FLC (13/71), ITR (0/84), VRC (0/84), KTC (0/84), POS (0/84), AMB (0/84), CAS (2/82)
(70)	Diabetic	104	FLC (1/95), ITR (5/87), VRC (0/102), KTC (3/101), POS (3/101), AMB (7/84), CAS (0/100)
(71)	AIDS	54	FLC (16/310), ITR (15/9), VRI (5/45), AMB (0/54), CAS (0/54)
(72)	AIDS	40	ITR (3/3), KTC (5/21)
(73)	Idiopathic pulmonary fibrosis	4	FLC (1/0), ITR (4/0), AMB (3/1)
(74)	Immunocompetent patients	37	FLC (6/31), ITR (12/25), VRC (5/32), MIC (0/37), LLCZ (0/37), AMB (9/28), CAS (5/32), AFG (2/35)
(75)	Immunocompromised patients	10	FLC (8/0)
(76)	Malignant	55	FLC (2/50), ITR (3/33), VRC (0/53), AMB (2/53), CAS (0/55)
(77)	-	43	FLC (5/37), ITR (16/25), AMB (30/12), CAS (10/22)
(78)	Onychomycosis	7	FLC (1/6), ITR (2/5), VRC (0/7), CAS (2/5)
(3)	OPC	32	FLC (18/12), ITR (30/2), KTC (26/6), AMB (28/4)
(79)	Preterm neonates	18	FLC (0/18), ITR (2/16), VRC (0/18), AMB (7/11), CAS (4/14)
(80)	Renal transplant recipients	18	FLC (6/12)
(81)	Vulvovaginitis	40	FLC (8/32)
(82)	Vulvovaginitis, OPC	10	VRC (0/10)
(83)	Hematological malignancies	69	FLC (2/67), ITR (0/65), VRC (0/69), POS (0/69), AMB (0/69), CAS (0/69), AFG (0/69), 5FC (0/69)
(84)	Hematological malignancy, Cancer, Respiratory disorders, Vulvovaginitis, Skin lesions	105	FLC (1/104), ITR (23/ND), CAS (10/105)

(85)	-	46	FLC (2/41), ITR (3/43), VRC (1/45)
(86)	Immunocompromised patients	21	FLC (2/17), ITR (1/19), NYS (3/18), AMB (0/21)
(87)	Liver transplant recipients	34	FLC (0/34), NYS (0/34), CAS (0/34)
(88)	Onychomycosis	9	FLC (1/8), CLO (5/4), ITR (4/4), VRC (0/9), AMB (4/5), CAS (4/5), AFG (2/7)
(89)	Pemphigus Vulgaris		ECO (0/22), AMB (0/22)
(90)	Diabetics, Cancer, Maintenance hemodialysis, pregnant women	100	FLC (10/90)
(91)	Vulvovaginitis	42	FLC (36/0), ITR (42/0), CAS (18/20)
(92)	Candiduria	91	FLC (0/91), ITR (2/87), VRC (1/90)
(93)	OPC	46	FLC (0/46), VRC (0/46), CAS (0/43)
(94)	Hematological Malignancies	110	FLC (3/79), AMB (2/108), CAS (0/108)
(95)	Ocular infection	5	ITR (0/5), VRC (0/5), POS (0/5)
(96)	Onychomycosis	70	FLC (8/43), ITR (6/46), VRC (0/70), AMB (0/70)
(97)	OPC	36	FLC (1/31), NYS (0/36)
(98)	Otomycosis	3	FLC (2/1), ITR (1/2), CAS (1/2)
(99)	Vulvovaginitis	133	FLC (5/128), ITR (6/127), VRC (0/133), AMB (2/31), CAS (0/133)
(100)	Candiduria	50	FLC (1/49), ITR (4/28), VRC (0/50), POS (46/4), AMB (0/50), CAS (0/50)
(101)	Fungal otitis externa	16	FLC (2/11), COL (8/6), ITR (0/16), VRC (0/16), MIC (2/14), NYS (14/2), AMB (0/16), CAS (0/16)
(102)	OPC	33	FLC (1/31), ITR (7/22), VRC (8/25), KTC (8/25), AMB (2/31)
(103)	AIDS	50	FLC (16/29), CLO (7/35), KTC (14/31), NYS (0/50), AMB (0/48), 5FC (50/0)

***Abbreviation:** FLC; Fluconazole, CLO; Clotrimazole, KTC; Ketoconazole, ECO; Econazole, LLCZ; Luliconazole, MIC; Miconazole, VRC; Voriconazole, ITC; Itraconazole, AMB; Amphotericin B, NYS; Nystatin, POS; Posaconazole, 5FC; 5- Flucytosine, AFG; Anidulafungin, CAS; Caspofungin**,** OPC; oropharyngeal candidiasis, *-; not determined, (R/S); Resistant/Susceptible

As shown in Table 2, the pooled prevalence of antifungal resistance ranged from 0% to 26%. The pooled prevalence of FLC resistance was estimated to be 20.37% (95% CI: 15.46 to 25.72). The lowest resistance levels among azoles were observed in LLCZ in 37 isolates with a frequency of 0% and voriconazole of 3.94% in 3603 isolates (Table 2).

It is apparent from Table 2 that polyene resistance in 5355 isolates, was found at 7.28% for AMB and 4.39% for NYS. A comparison of the percentage resistance of *C. albicans* isolates to each antifungal drug by years is shown in Fig. 2.

Table 2: Meta-analysis to evaluate the prevalence of drug resistance of *C. albicans* isolates of Iranian patients

Agents	*C. albicans no.*	*AFST pattern*	*Heterogeneity*			
			Q	F	*P* value	Pooled Prevalence
Fluconazole	6002	R	211.37	95.8	0.001	20.37
		S	2390.67	96.4	0.001	72.22
Amphotericin B	4289	R	762.33	93.3	0.001	7.28%
		S	983.45	94.8	0.001	91.3%
Clotrimazole	823	R	139.11	89.2	0.001	26
		S	158.36	90.5	0.001	62.59
Itraconazole	4124	R	1049.74	95.7	0.001	16.84
		S	1149.52	96.3	0.001	68.87
Voriconazole	3603	R	279.18	87.5	0.001	3.94
		S	292.59	88.4	0.001	94.42
Ketoconazole	1981	R	766.55	96.9	0.001	21.1
		S	945.96	97.6	0.001	67.29
Econazole	68	R	45.06	-	-	26.02
		S	45.06	-	-	73.98
Miconazole	393	R	211.92	96.2	0.001	12.93
		S	217.17	96.3	0.001	74.94
Posaconazole	590	R	255.72	97.3	0.001	7.19
		S	257.59	97.3	0.001	92.35
Nystatin	1066	R	121.29	90.1	0.001	4.39
		S	135.63	91.2	0.001	93.17
Anidulafungin	306	R	13.18	69.7	.01	1.79
		S	13.19	69.7	.01	98.21
Caspofungin	3259	R	310.46	88.4	>.001	4.53
		S	610.82	94.1	>.001	91.56
5- Flucytosine	377	R	348.22	98.9	>.001	15.72
		S	318.61	98.7	>.001	81.5
Luliconazole	37	R	-	-	-	0
		S	-	-	-	100

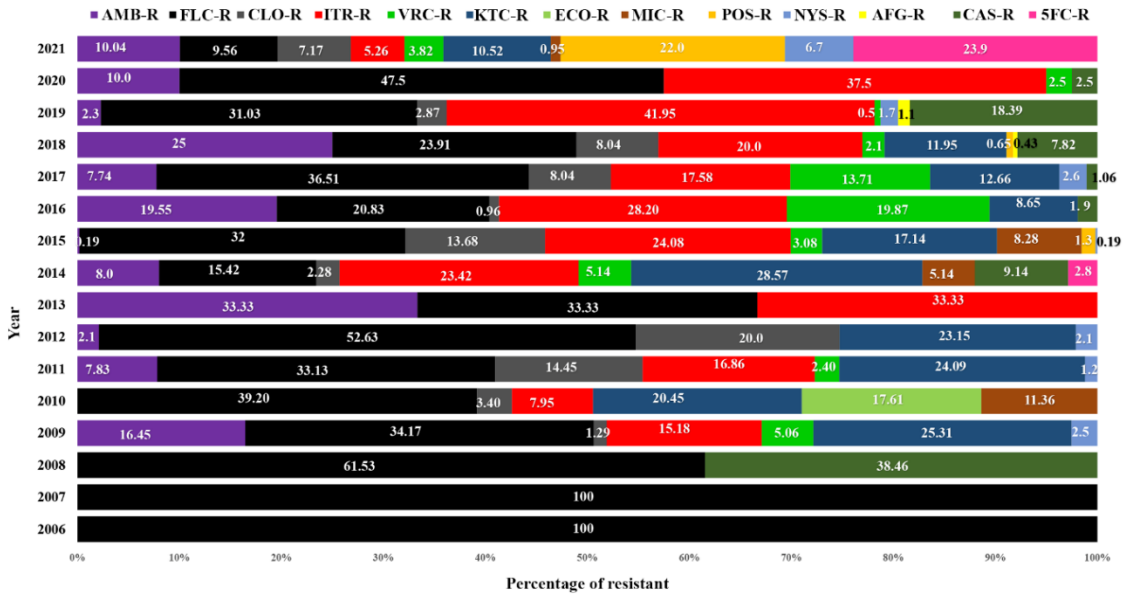

Fig. 2: A comparison chart of the percentage of resistance antifungal agents to *C. albicans* during 2006-2021

The heterogeneity of the pooled data from all the included studies in the present review was high (Table 2). An increasing trend in resistance to ITC (7%-16.65%), VRC (1.4%-6.52%), and AMB (7.50%-9.11%) was observed since 2006 in Iran, while a slightly decreasing trend was observed in fluconazole resistance (23.42%-14.42%) (Fig. 3).

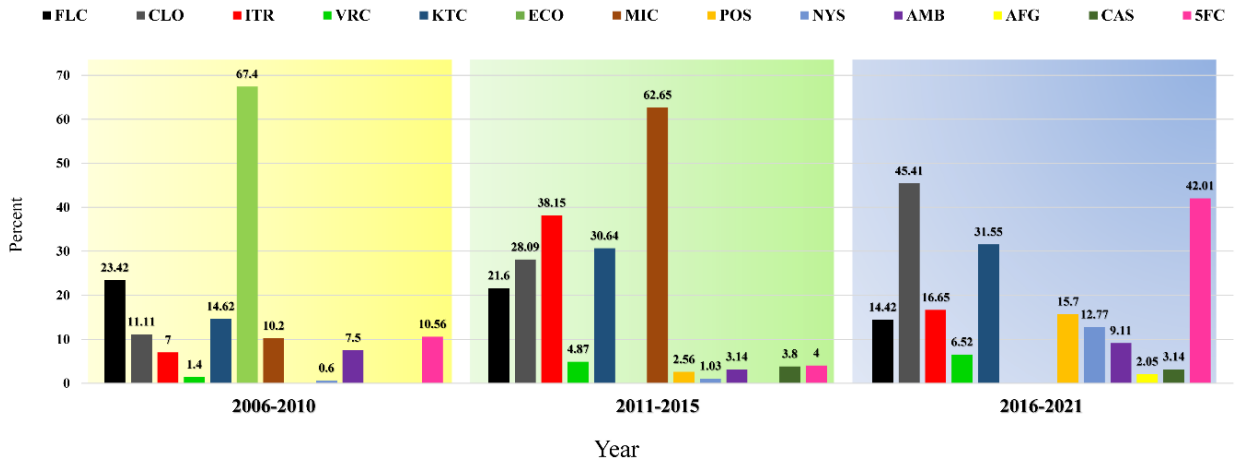

Fig. 3: The prevalence of drug resistance of *C. albicans* isolates to common antifungals

The statistical analysis results showed a clear trend of *C. albicans* strains resistance to FLC, CLO, and KTC and visually evaluated the amount of heterogeneity among disparate reported resistance levels in Iranian *C. albicans* isolates (Fig. 4- 6).

Discussion

To the best of our knowledge, the current systematic review is the first study to enhance our understanding of the antifungal susceptibility pattern of *C. albicans* in Iran.

The previous study showed an increasing trend in the azoles and echinocandins resistance among *C. albicans* as a growing worldwide public health problem (104). The most striking results of this meta-analysis are the high pooled resistance rate of *C. albicans* strains against clotrimazole and econazole (both 26%), ketoconazole (21%), and fluconazole (20%). Likewise, itraconazole, voriconazole, and clotrimazole showed an increasing trend of resistance over the years (Fig. 2).

The current literature review showed the highest resistance of vulvovaginal and oropharyngeal isolates against clotrimazole. Clotrimazole is available antifungal to treat vulvovaginal candidiasis in Iran. Therefore, vast, frequent, and incomplete treatment may lead to the emergence of clotrimazole-resistant *Candida* species.

Despite their side effects, polyenes are effective treatments for candidiasis. The current study indicated a growing trend in the resistance rate of *C. albicans* to amphotericin B over the past decade. This finding is in line with previous studies (3). However, in some of the studies, no cases of amphotericin B resistance were reported (69, 71, 96, 101). Despite numerous reports in the world and Iran about the relative resistance of *C. albicans* to polyenes, it is still used to treat candidiasis.

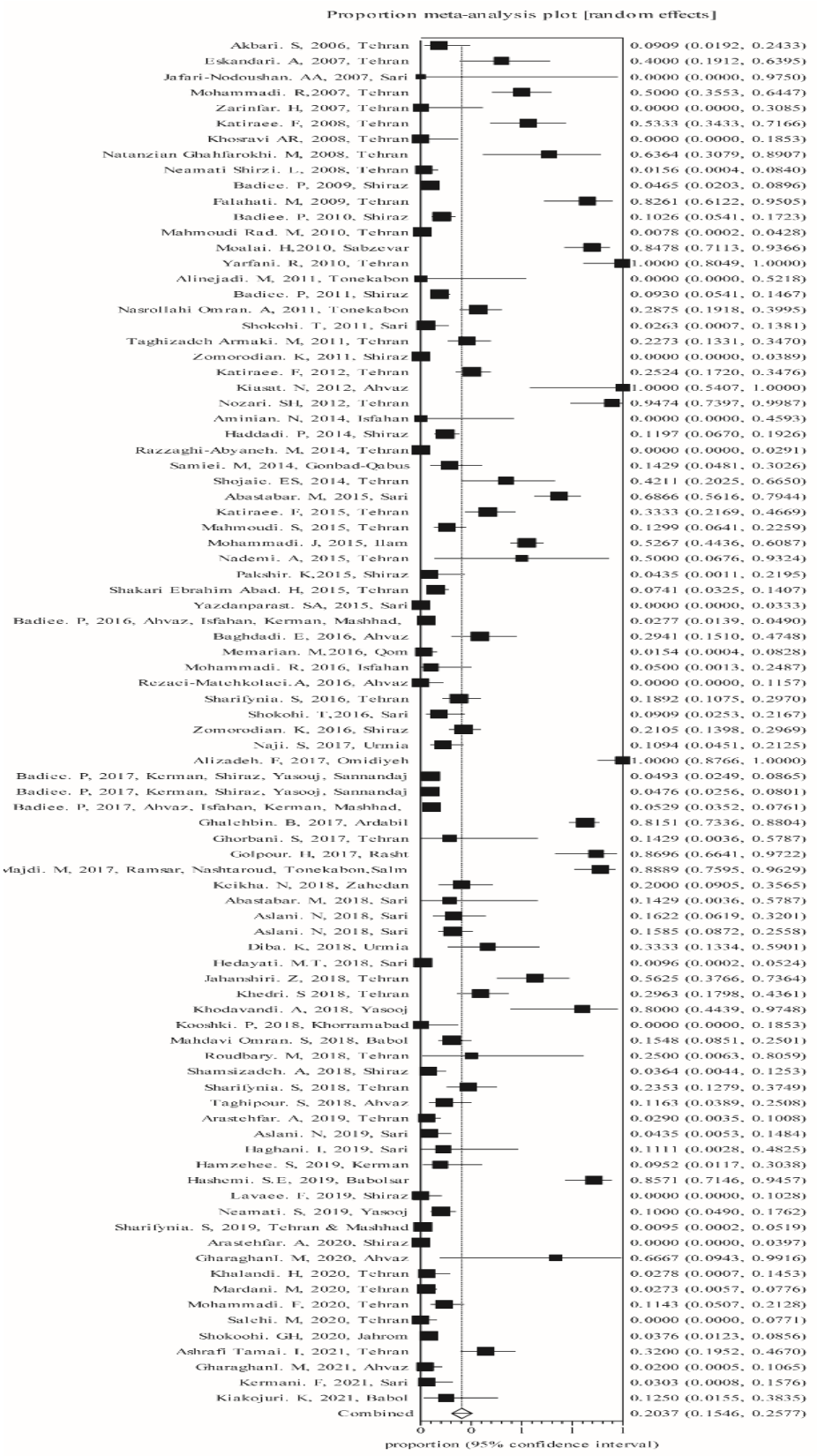

Fig. 4: The forest plot of prevalence of resistance to fluconazole

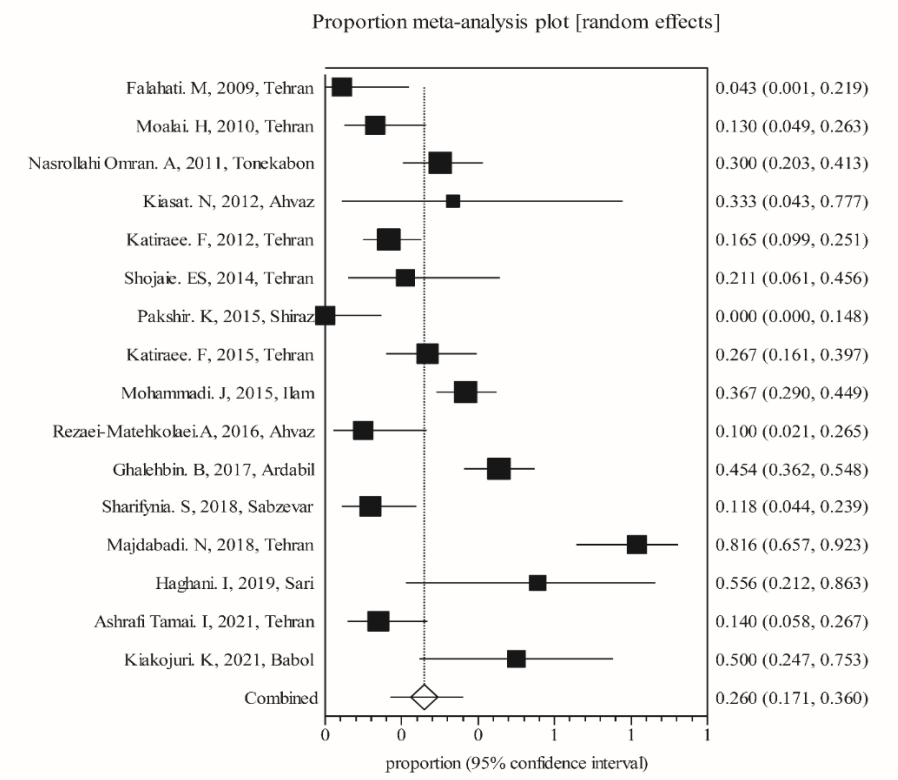

Fig. 5: The forest plot of prevalence of resistance to clotrimazole

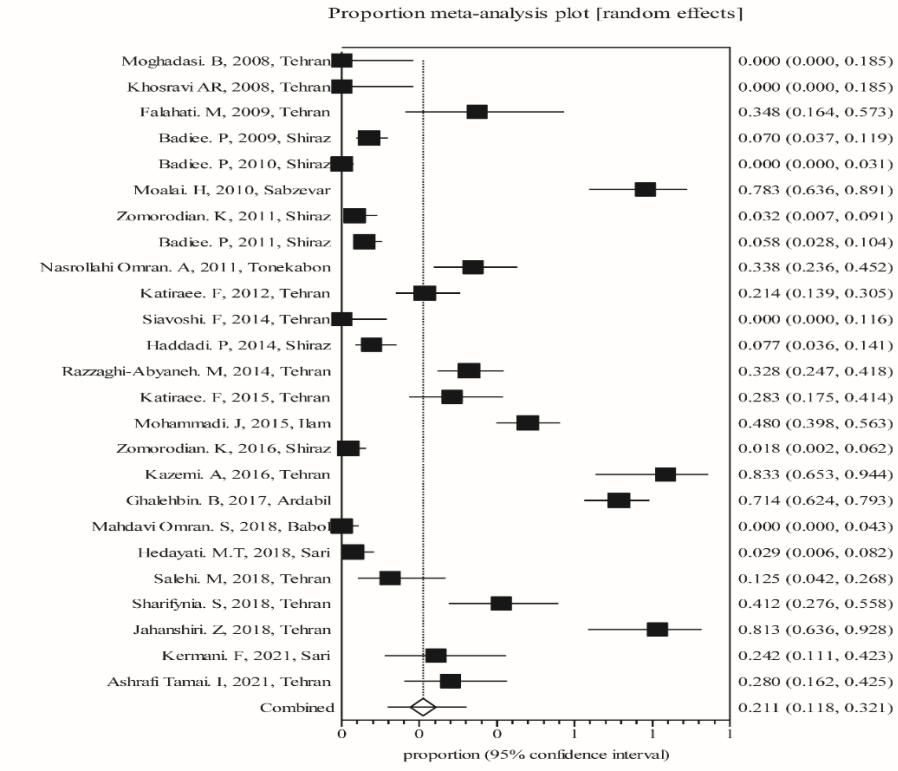

Fig. 6: The forest plot of prevalence of resistance to ketoconazole

The echinocandins are the first-line antifungals against azole-resistant *Candida* species owing to their high effectiveness. Today, the development of echinocandins resistance has led to a worldwide concern. In this review, the pooled prevalence of echinocandins resistance was estimated to be 4.53% (CI: 95% 2.53 to 7.07%) and 1.79% (95% CI: 0.006 to 5.81%) for caspofungin and anidulafungin, respectively. The highest resistance rate of caspofungin (42.8%) was reported in patients with vulvovaginal candidiasis (91). Despite the resistance to echinocandins, caspofungin and micafungin are still the best choices for treating candidemia and invasive candidiasis in adults and neonates, respectively (79).

Anidulafungin is effective against azole, amphotericin B, and other echinocandins-resistant *Candida* species (105). Given that the pattern of susceptibility to anidulafungin against *C. albicans* was evaluated in only five studies in Iran, further studies are needed to estimate its resistance trend.

In this review, resistance to 5-flucytosine increased from 10.56% to 42.01%, even in one article 100% resistance was observed in *C. albicans* isolated from oropharyngeal candidiasis (103). Even though, these results differ from some studies (106, 107).

Conclusion

The emergence of resistant species may play a role in the relapse after treatment due to long-term use, incomplete treatment, overdose, or the use of multiple antifungals during the treatment for candidiasis. Therefore, antifungals should be used via well-planned supervision, antifungal stewardship strategy combining therapeutic drug monitoring to reduce the emergence of resistant multi-drug *Candida* species.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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