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Original Article

Meta-analysis of antifungal resistance patterns of *Aspergillus* species in Iran

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ABSTRACT

Background and objectives: Aspergillus infection has several manifestations, ranging from noninvasive aspergillosis to invasive pulmonary and cerebral aspergillosis. Prophylaxis and treatment regimens for aspergillosis rely on triazoles, echinocandins, and polyenes, with specific efficacies, complications, and resistance patterns. Drug selection presents challenges, including differences in resistance rates, drug interactions, and concerns about side effects with long-term use. Aspergillus resistance to antifungal agents is an international concern and has shown an increasing trend. Each region worldwide has a resistance pattern affecting prevention and treatment regimens.

Methods: This meta-analysis started with a systematic search through PubMed, Scopus, Web of Science, Scientific Information Database (SID) and MagIran based on a combination of these keywords with "AND/OR" operators: Aspergillus/Aspergilli, resistance/resistant, susceptibility/susceptible, drug, antimicrobial(s), antifungal(s) and Iran. Search results are reported on the basis of the Preferred Reporting Items for Systematic and Meta-analyses (PRISMA).

Results: The pooled resistance rates of Aspergillus fumigatus were 6.97 % for amphotericin B, 1.40 % for caspofungin, 17.61 % for itraconazole, 4.56 % for posaconazole, and 14.68 % for voriconazole. The percentage of resistance in Aspergillus flavus was 13.16 % for amphotericin B, 13.09 % for caspofungin, 10.19 % for itraconazole, 1.23 % for posaconazole, and 0.58 % for voriconazole.

Conclusion: Our findings highlight the need for antifungal resistance surveillance in Iran. Treatment decisions should consider resistance patterns, host factors, and drug pharmacokinetics. We recommend establishing antifungal stewardship programs to develop evidence-based guidelines. Based on our findings, we suggest posaconazole or voriconazole for A. fumigatus and A. flavus, amphotericin B as alternative therapy, and caspofungin as salvage therapy.

Introduction

Aspergillus species are ubiquitous fungal molds found in all materials and environments, including air, soil, water, and food [1]. *Aspergillus* infections present a wide range of manifestations, from noninvasive aspergillosis to invasive pulmonary and cerebral aspergillosis, particularly in immunocompromised patients. High-risk populations include hematopoietic stem cell transplant (HSCT) recipients, solid organ transplant (SOT) recipients, patients with hematologic malignancies receiving broad-spectrum chemotherapy, and patients with neutropenia [2–4]. The diagnosis of aspergillosis remains challenging. Non-invasive diagnostic techniques such as serum galactomannan testing and upper respiratory tract sampling lack sufficient diagnostic power, while lower respiratory tract sampling is difficult and impractical in critical settings [5]. Prophylaxis and treatment regimens for aspergillosis rely on triazoles, echinocandins, and polyenes, each with specific efficacy, complications,

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and resistance patterns [6,7]. Azole resistance in *Aspergillus* species is increasing worldwide. Reports from Asia and Middle east suggest resistance rates exceeding 20 % in clinical isolates and up to 50 % in environmental isolates respectively. In some cases, environmental isolates of *Aspergillus fumigatus* have azole resistance rates approaching 80 % [8]. The major mechanisms of drug resistance in *Aspergillus* species include the upregulation or downregulation of cell wall modulatory proteins, alterations in the reactive oxygen species (ROS) balance, and biofilm formation [9]. Triazoles exert their antifungal effect by inhibiting the 14α-demethylase (CYP51) in the ergosterol biosynthetic pathway, leading to the accumulation of abnormal sterols in fungal cell membrane instead of functional ergosterol [9,10]. Resistance to amphotericin B develops through fungal mechanisms that counteract the oxidative stress caused by the drug, primarily through the action of heat shock proteins 70 and 90 (HSP70 and HSP90) [9]. Antifungal resistance may develop either iatrogenically or environmentally. Environmental resistance arises from exposure to agricultural fungicides, such as 14a-demethylase inhibitors (DMIs) [11,12]. These exposures select for species with mutations in the CYP51 gene, most commonly TR34/L98H which involves a 34 bp tandem repeat combined with a substitution at codon 98 [13,14]. Drug selection in aspergillosis treatment is complicated by several factors, including varying resistance rates, potential drug-drug interactions with medications used for concurrent conditions, and concerns about long-term adverse effects [3,5,15]. While antifungal resistance rates are increasing globally and becoming a pressing international issue, resistance patterns vary across different regions, affecting both prevention and treatment regimens [8,16]. The rising prevalence of antifungal resistance among *Aspergillus* species poses a significant challenge for healthcare professionals in Iran, emphasizing the need for alternative treatment strategies and continuous surveillance of resistance patterns [1]. In this meta-analysis, we systematically reviewed and analyzed antifungal resistance trends in *Aspergillus* species in Iran from 2010 to 2024. Our objectives included assessing the prevalence of resistance in clinically relevant species (*A. fumigatus, A. flavus, A. terreus,* and *A. niger*) to commonly used antifungal agents, including azoles, polyenes, and echinocandins.

Methods

Search strategy

This study was conducted based on the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement [17]. We performed a comprehensive literature search, including articles written in English from PubMed, Scopus, and Web of Science, and articles written in Persian from the Scientific Information Database (SID) and MagIran. Our search strategy employed a combination of the following keywords connected by "AND/OR" operators: *Aspergillus*/*Aspergilli*, resistance/resistant, susceptibility/susceptible, drug, antimicrobial(s), antifungal(s) and Iran.

Inclusion and exclusion criteria

This study included original articles reporting antifungal resistance of any *Aspergillus* species to antifungals agents, either as exact resistance rates or through minimum inhibitory concentration (MIC) distribution table. Only studies conducted in Iran from 2010 to 2024 were included. The exclusion criteria were studies that sampled from predefined resistant or susceptible species and studies that did not report antifungal resistance (i.e., studies lacking both exact resistance rates and MIC distribution tables).

Data extraction

Titles and abstracts were screened using the Rayyan app to identify eligible publications and exclude duplicates and irrelevant studies [18]. The full texts of the relevant articles were subsequently reviewed to extract information on authorship, publication dates, study duration, sample size and distribution, antifungal susceptibility testing methods, antifungal resistance rates of each *Aspergillus* species to various antifungal drugs and species distribution. Finally, forward and backward citation tracking was performed to identify additional relevant articles.

Almost all included studies used Clinical and Laboratory Standards Institute (CLSI) guidelines to assess antifungal resistance. For studies provided a complete report of minimum inhibitory concentrations (MICs), the number of resistant isolates was determined based on the last published CLSI guideline cutoffs. For echinocandins such as caspofungin, the Minimum Effective Concentration (MEC) was used to assess antifungal activity, as these drugs are fungistatic against *Aspergillus* species and do not produce a clear MIC endpoint. The epidemiological cutoff values (ECVs) are as follows: for amphotericin B, a MIC of 4 μg/mL for *A. flavus* and *A. terreus* and 2 μg/mL for *A. fumigatus* and *A. niger*; for caspofungin, MECs of 0.5 μg/mL for *A. flavus* and *A. fumigatus*, 0.25 μg/mL for *A. niger*, and 0.12 μg/mL for *A. terreus*; for isavoconazole and itraconazole, ECVs of 1 μg/mL for *A. flavus* and *A. fumigatus* and 4 μg/mL for *A. niger*; for posaconazole, the MICs of 0.5 μg/mL for *A. flavus* and 2 μg/mL for *A. niger* and 1 μg/mL for *A. terreus*; and for voriconazole, the ECVs of 2 μg/mL for *A. flavus* and *A. niger* and *A. terreus* and 1 μg/mL for *A. fumigatus* [19]. One study utilized the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methods for resistance measurement and reported the exact percentages of susceptible and resistant species in its manuscript [20]. For the remaining CLSI-based studies, we relied on reported numbers of resistant and susceptible species in each article's text.

Quality assessment

Information bias: We did not inform the authors of the studies included in our meta-analysis. All studies were analyzed retrospectively. Thus, there was no information bias.

Attrition bias: The data in our meta-analysis were experimental data from clinical and environmental samples rather than pure clinical data. Thus, there was no concern about attrition bias.

Confounding bias: We searched at least five databases and included studies that met the inclusion criteria. None of these were randomized controlled trials. Thus, we did not have confounding bias.

Selection bias: Due to our research question and our inclusion and exclusion criteria, the only possible source of selection bias was unpublished articles. However, the selection of studies over the past 14 years prevented publication bias.

Detection bias: Because the samples were collected from a roughly homogenous mixture of clinical and environmental settings, there was no detection bias. A risk of bias assessment is also done *via* ROBINS-E tool [21]. Fig. 1 shows a traffic light plot of this assessment.

Meta-analysis

First, a datasheet was created for each *Aspergillus* species–antifungal pair, which included the authors' names, the total number of isolates in each study, and the number of resistant isolates, using Microsoft Excel software. The data were then sorted by the study publication year and transferred to RStudio software version 2024.04.2m build 764 (RStudio, PBC, Boston, MA, USA) to perform the meta-analysis. The inverse variance method was applied to weight the studies. A restricted maximum-likelihood estimator was used to

Fig. 1. Traffic light plot for ROBINS-E risk of bias assessment [21].

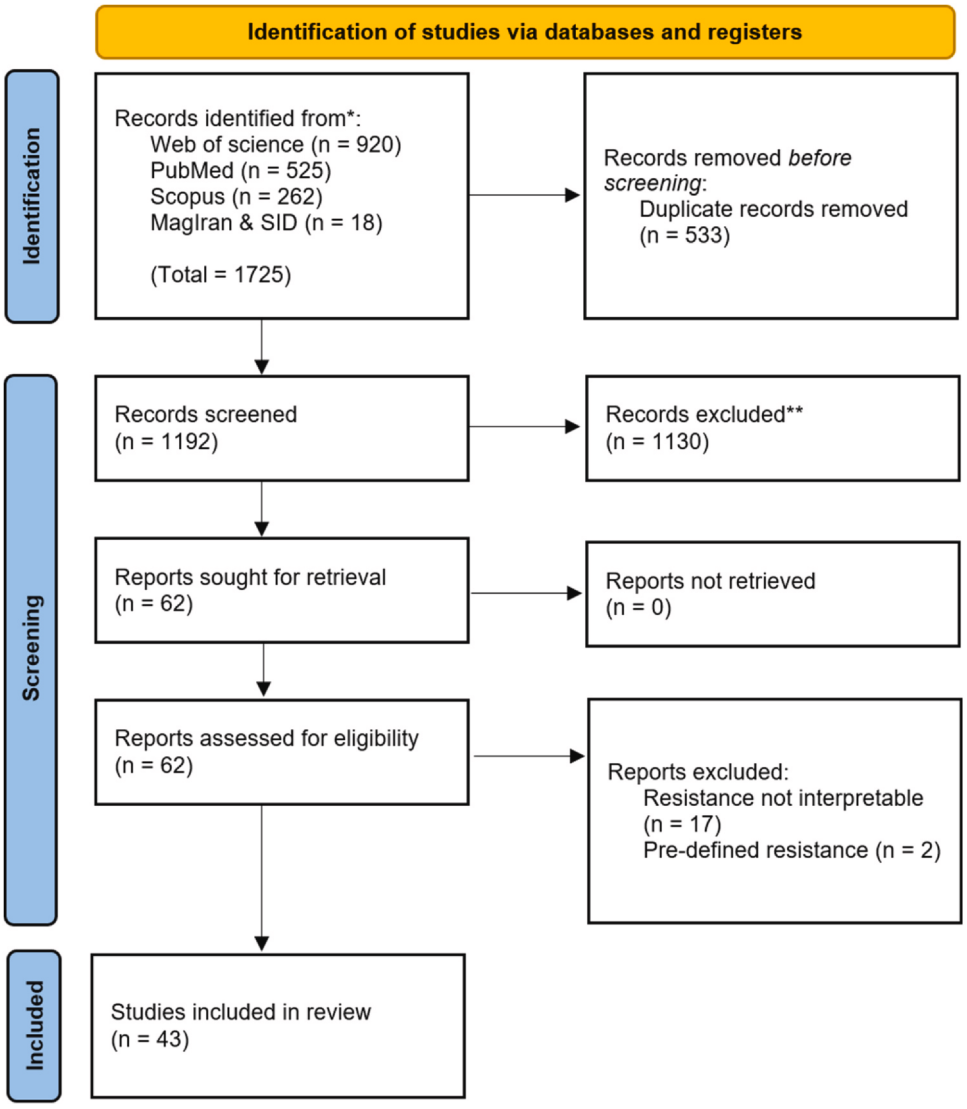

Fig. 2. Flow diagram of article selection in the current systematic review and meta-analysis [17].

calculate tau-squared, and its confidence intervals, along with those for tau, were determined using the Q profile method. Due to the high diversity in study characteristics, a random effects model was employed to calculate the pooled effects in all analyses, with the Hartung-Knapp adjustment applied. The prediction interval was calculated based on the t-distribution. The "metaprop" function from the R library "meta" was used for analyzing resistance rates, as it is the most relevant function for this purpose. This function was employed with the Freeman–Tukey double arcsine transformation, which was chosen instead of analyzing the raw data due to the large number of proportions at 0 and 1 (i.e., resistance rates of 0 % and 100 %) in the dataset. This transformation resolved variance-related issues without requiring a continuity correction (i.e., adding or subtracting small values to/from 0 or 1) [22,23]. All the data were subsequently back-transformed using the internal argument of the "metaprop" function to calculate pooled effect sizes and their confidence intervals, as well as to generate forest plots. Funnel plots were created using transformed data to avoid variance-related problems.

Results

A total of 43 articles—24 with clinical samples only, 6 with environmental samples only, and 13 with a mixture of clinical and environmental samples—were included in the systematic review (Fig. 2). The characteristics of the included articles are summarized in Table 1. Of these, 22 studies performed the fungal speciation using partial beta-tubulin DNA sequencing, 13 used morphological identification, and 7 focused on predefined isolates. Antifungal resistance was measured according to CLSI guidelines in 42 studies, while in one study, the EUCAST standard was applied. The most common sample sources for clinical studies included bronchoalveolar lavage (BAL), ear, sputum, sinus, and nail. Environmental studies primarily focused on samples collected from paddy field soils, hospital garden soils, hospital air (both indoor and outdoor), and medical equipment. The most commonly used culture media used were Sabouraud dextrose agar (SDA), Roswell Park Memorial Institute (RPMI) 1640, potato dextrose agar (PDA), and malt extract agar (MEA). Table 2 provides a comprehensive summary of antifungal resistance data.

A large proportion of I^2 measures reported in Table 3 are above 75 %, indicating high heterogeneity. This can be attributed to the diverse sample types and origins in the included studies. Among most studies examining the CYP51 gene as a mechanism of *Aspergillus* resistance, slightly more than half of the resistant isolates carried the TR34/L98H mutation [24–27]. However, several other studies reported that less than half of the resistant isolates harbored the TR34/L98H mutation [28,29]. A small proportion of resistant

Table 1
Authors, publication dates, settings and methods used in included studies.

Code	Author	Publish year	Study period	Setting	Species identification	AFST method	Number of Aspergilli
C01 [48]	Hashemi et al.	2011	2009–2010	Cln	Morphology	CLSI	40
C02 [49]	Badiee et al.	2012		Cln	Morphology	CLSI	108
C03 [50]	Fattahi et al.	2012		Cln	Predefined isolates	CLSI	45
C04 [51]	Kazemi et al.	2012	2011	Cln	Morphology	CLSI	50
C05 [1]	Badali et al.	2013		Env	PBT DNA sequencing	CLSI	41
C06 [30]	Badali et al.	2016		Env, Cln	PBT DNA sequencing	CLSI	72 (39 Cln; 33 Env)
C07 [52]	Hojatinia et al.	2016		Env, Cln	Predefined isolates	CLSI	40 (20 Cln; 20 Env)
C08 [31]	Hoseinnejad et al.	2016	2013–2015	Env, Cln	PBT DNA sequencing	CLSI	90 (30 Cln; 60 Env)
C09 [32]	Khodavaisy et al.	2016		Env, Cln	PBT DNA sequencing	CLSI	199 (171 Cln; 28 Env)
C10 [28]	Mohammadi et al.	2016	2010–2014	Cln	PBT DNA sequencing	CLSI	172
C11 [29]	Nabili et al.	2016	2012–2015	Env, Cln	PBT DNA sequencing	CLSI	150 (71 Cln; 79 Env)
C12 [53]	Ghods et al.	2017	2015–2016	Cln	Morphology	CLSI	32
C13 [39]	Nasrolahiomran et al.	2017		Cln	PBT DNA sequencing	CLSI	11
C14 [54]	Zargaran et al.	2017		Env	Morphology	CLSI	40
C15 [26]	Falahatinejad et al.	2018	2013–2016	Env, Cln	PBT DNA sequencing	CLSI	79 (50 Cln; 29 Env)
C16 [55]	Kamali Sarwestani et al.	2018		Cln	PBT DNA sequencing	CLSI	43
C17 [33]	Vaezi et al.	2018		Env, Cln	PBT DNA sequencing	CLSI	81 (36 Cln; 45 Env)
C18 [27]	Vaezi et al.	2018		Env	PBT DNA sequencing	CLSI	11
C19 [20]	Zarrin et al.	2018		Env, Cln	Predefined isolates	EUCAST	58 (9 Cln; 45 Env)
C20 [40]	Hivary et al.	2019		Cln	PBT DNA sequencing	CLSI	67 (37 Cln; 30 Env)
C21 [24]	Ahangarkani et al.	2020	2017–2018	Env	PBT DNA sequencing	CLSI	63
C22 [56]	Akbari et al.	2020	2017–2018	Cln	Morphology	CLSI	48
C23 [57]	Chadeganipour et al.	2020	2010–2018	Cln	PBT DNA sequencing	CLSI	35
C24 [41]	Gharaghani et al.	2020		Cln	Morphology	CLSI	68
C25 [11]	Mohamadnia et al.	2020		Cln	PBT DNA sequencing	CLSI	45
C26 [42]	Moslem et al.	2020	2018	Env, Cln	Morphology	CLSI	38 (20 Cln: 18 Env)
C27 [25]	Taheri Rizi et al.	2020		Env, Cln	PBT DNA sequencing	CLSI	354 (218 Cln; 138 Env)
C28 [58]	Rezaei et al.	2021		Env	Morphology	CLSI	14
C29 [59]	Shokoohi et al.	2021		Cln	PBT DNA sequencing	CLSI	33
C30 [60]	Xue Xu et al.	2021	2015–2018	Cln	PBT DNA sequencing	CLSI	48
C31 [61]	Yassin et al.	2021		Cln	PBT DNA sequencing	CLSI	14
C32 [34]	Abastabar et al.	2022		Env, Cln	Predefined isolates	CLSI	54 (35 Cln; 19 Env)
C33 [62]	Badiee et al.	2022	2018–2021	Env, Cln	PBT DNA sequencing	CLSI	233 (191 Cln; 42 Env)
C34 [63]	Fattahi et al.	2022		Cln	Predefined isolates	CLSI	8
C35 [64]	Lotfali et al.	2022	2017–2022	Cln	PBT DNA sequencing	CLSI	108
C36 [35]	Nargesi et al.	2022	2016–2019	Cln	Predefined isolates	CLSI	151
C37 [65]	Sabz et al.	2022	2018	Cln	Predefined isolates	CLSI	160
C38 [66]	Vaghar et al.	2022		Cln	PBT DNA sequencing	CLSI	163
C39 [37]	Ghazanfari et al.	2023		Env		CLSI	16
C40 [43]	Halvaeezadeh et al.	2023		Cln	Morphology	CLSI	85
C41 [67]	Khojasteh et al.	2023	2016–2021	Env, Cln	Morphology	CLSI	483 (23 Cln; 460 Env)
C42 [38]	Roohi et al.	2023	2020–2021	Cln	Morphology	CLSI	89
C43 [68]	Salehi et al.	2023	2017–2018	Cln	Morphology	CLSI	150

Cln, clinical; Env, environmental; PBT, partial beta-tubulin; PCR, polymerase chain reaction; AFST, antifungal susceptibility test.

isolates were found to carry the TR46/Y121F/T289A mutation [24–29].

As *A. fumigatus* and *A. flavus* are the most prevalent species, we briefly review their antifungal susceptibility results below. A summary of other meta-analysis results and additional information on other species can be found in Table 3. Due to the predominance of available data, forest plots of the two species–drug pairs *A. fumigatus*–itraconazole and *A. fumigatus*–voriconazole are presented in Figs. 3 and 4, respectively. Additional forest plots and all funnel plots are included in the supplementary data.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis of *Aspergillus* drug resistance in Iran. Our meta-analysis provides a comprehensive assessment of antifungal resistance among *Aspergillus* species in Iran. The findings indicate that *A. fumigatus* has the highest proportion of isolates with MIC values exceeding the ECV for azoles, particularly itraconazole, whereas *A. terreus* displays the lowest MIC values for these drugs. Caspofungin exhibited varied susceptibility across species, with *A. fumigatus* demonstrating the lowest MEC values.

Excluding Tehran province as a referral medical center in Iran, the most prevalent sampling sites in the included studies were Mazandaran and Guilan provinces [1,24,25,27,30–39], and Khuzestan province [31,40–43] prominent agricultural areas of Iran. This finding may suggest a link between agricultural poison exposure and increased antifungal resistance.

A decreasing trend in azole-resistance was observed from itraconazole to voriconazole and posaconazole. Studies conducted in Asia (Japan, China), Europe (France and Netherlands), and south America reported similar trends, with higher resistance rates for itraconazole and lower ones for voriconazole. However, there are variations in the resistance rates among different *Aspergillus* species, likely attributable to differences in antibiotic stewardship plans, healthcare resources, and fungal epidemiology [8,16,44–47].

More than half of the meta-analysis results showed high heterogeneity, likely due to the diversity in sample types and geographical origins across the included studies. A limitation of our study was the lack of sufficient grouping features for conducting subgroup analysis. This meta-analysis provides valuable guidance on the general patterns of *Aspergillus* antifungal resistance in Iran; However, further research is necessary to better characterize resistance patterns in specific region.

Four out of the 20 drug-species pairs analyzed in our study had fewer than 5 degrees of freedom, which should be addressed in future studies. Additionally, the regional data for tropical areas in our study were limited to a survey of Khuzestan Province.

Table 2
Total and resistant numbers of *Aspergillus* species to different drugs.

Code	Author	Year	Species	Total	ITC	VRC	AMB	CFG	POS	ISA	FLC	LUL	NYS	LAN	RAV
C01 [48]	Hashemi et al.	2011	*A. flavus*	40	10	0	3	NA	NA	NA	NA	NA	NA	NA	NA
C02 [49]	Badiee et al.	2012	*A. flavus*	66	12	0	36	NA	NA	NA	NA	NA	NA	NA	NA
C02 [49]	Badiee et al.	2012	*A. fumigatus*	30	15	0	3	NA	NA	NA	NA	NA	NA	NA	NA
C02 [49]	Badiee et al.	2012	*A. niger*	12	6	0	0	NA	NA	NA	NA	NA	NA	NA	NA
C03 [50]	Fattahi et al.	2012	*A. flavus*	45	45	NA	37	38	NA	NA	45	NA	45	NA	NA
C04 [51]	Kazemi et al.	2012	*A. flavus*	25	0	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
C04 [51]	Kazemi et al.	2012	*A. fumigatus*	25	0	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
C05 [1]	Badali et al.	2013	*A. fumigatus*	41	5	5	NA	NA	NA	NA	NA	NA	NA	NA	NA
C06 [30]	Badali et al.	2016	*A. niger*	72	15	20	19	0	0	NA	NA	NA	NA	NA	NA
C07 [52]	Hojatinia et al.	2016	*A. flavus*	40	4	3	NA	0	NA	NA	NA	NA	NA	NA	NA
C08 [31]	Hoseinnejad et al.	2016	*A. flavus*	90	2	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
C09 [32]	Khodavaisy et al.	2016	*A. flavus*	199	2	2	7	0	5	NA	NA	NA	NA	NA	NA
C10 [28]	Mohammadi et al.	2016	*A. fumigatus*	172	6	6	NA	NA	NA	NA	NA	NA	NA	NA	NA
C11 [29]	Nabili et al.	2016	*A. fumigatus*	150	34	11	8	5	4	NA	NA	NA	NA	NA	NA
C12 [53]	Ghods et al.	2017	*A. fumigatus*	NA	NA	NA	5	NA	NA	NA	NA	NA	NA	NA	NA
C12 [39]	Ghods et al.	2017	*A. flavus*	NA	NA	NA	10	NA	NA	NA	NA	NA	NA	NA	NA
C12 [39]	Ghods et al.	2017	*A. terreus*	NA	NA	NA	2	NA	NA	NA	NA	NA	NA	NA	NA
C13 [39]	Nasrolahiomran et al.	2017	*A. flavus*	5	0	0	0	0	NA	NA	NA	NA	NA	NA	NA
C13 [39]	Nasrolahiomran et al.	2017	*A. fumigatus*	1	1	0	0	NA	NA	NA	NA	NA	NA	NA	NA
C14 [54]	Zargaran et al.	2017	*A. terreus*	40	NA	2	21	33	9	NA	NA	NA	NA	NA	NA
C15 [26]	Falahatinejad et al.	2018	*A. fumigatus*	79	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
C16 [55]	Kamali Sarwestani et al.	2018	*A. niger*	11	NA	NA	NA	NA	NA	NA	11	NA	NA	NA	NA
C16 [55]	Kamali Sarwestani et al.	2018	*A. tubingensis*	32	NA	NA	NA	NA	NA	NA	32	NA	NA	NA	NA
C17 [33]	Vaezi et al.	2018	*A. terreus*	66	0	0	1	0	0	0	NA	0	NA	0	NA
C18 [27]	Vaezi et al.	2018	*A. fumigatus*	11	5	4	3	0	0	NA	NA	0	NA	0	NA
C19 [20]	Zarrin et al.	2018	*A. fumigatus*	54	12	41	NA	NA	NA	NA	NA	NA	NA	NA	NA
C20 [40]	Hivary et al.	2019	*A. niger*	36	NA	7	31	14	31	NA	NA	NA	NA	NA	NA
C20 [40]	Hivary et al.	2019	*A. tubingensis*	24	NA	6	24	13	17	NA	NA	NA	NA	NA	NA
C21 [24]	Ahangarkani et al.	2020	*A. fumigatus*	63	55	51	NA	NA	NA	NA	NA	NA	NA	NA	NA
C22 [56]	Akbari et al.	2020	*A. flavus*	34	0	0	5	NA	NA	NA	NA	NA	NA	NA	NA
C22 [56]	Akbari et al.	2020	*A. oryzae*	2	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
C22 [56]	Akbari et al.	2020	*A. terreus*	7	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
C22 [56]	Akbari et al.	2020	*A. tubingensis*	3	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
C22 [56]	Akbari et al.	2020	*A. welwitschiae*	2	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
C23 [57]	Chadeganipour et al.	2020	*A. flavus*	32	25	9	4	NA	NA	NA	NA	NA	NA	NA	NA
C23 [57]	Chadeganipour et al.	2020	*A. niger*	2	2	0	0	NA	NA	NA	NA	NA	NA	NA	NA
C23 [57]	Chadeganipour et al.	2020	*A. terreus*	1	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA
C24 [41]	Gharaghani et al.	2020	*A. flavus*	30	1	NA	NA	23	NA	NA	14	NA	NA	NA	NA
C24 [41]	Gharaghani et al.	2020	*A. nidulans*	1	0	NA	NA	0	NA	NA	1	NA	NA	NA	NA
C24 [41]	Gharaghani et al.	2020	*A. niger*	36	0	NA	NA	15	NA	NA	10	NA	NA	NA	NA
C24 [41]	Gharaghani et al.	2020	*A. terreus*	1	0	NA	NA	1	NA	NA	0	NA	NA	NA	NA
C25 [11]	Mohamadnia et al.	2020	*A. nidulans*	9	1	0	8	1	0	0	NA	NA	NA	NA	1
C25 [11]	Mohamadnia et al.	2020	*A. terreus*	34	9	0	29	0	0	0	NA	NA	NA	NA	2
C26 [42]	Moslem et al.	2020	*A. flavus*	38	NA	0	38	15	NA	NA	NA	0	NA	0	NA
C27 [25]	Taheri Rizi et al.	2020	*A. flavus*	66	5	0	2	7	0	NA	NA	NA	NA	NA	NA
C27 [25]	Taheri Rizi et al.	2020	*A. fumigatus*	141	25	17	2	NA	18	NA	NA	NA	NA	NA	NA
C27 [25]	Taheri Rizi et al.	2020	*A. terreus*	103	0	2	NA	0	NA	NA	NA	NA	NA	NA	NA
C28 [58]	Rezaei et al.	2021	*A. flavus*	4	0	0	0	0	NA	NA	NA	NA	NA	NA	NA
C28 [58]	Rezaei et al.	2021	*A. fumigatus*	2	0	0	0	0	NA	NA	NA	NA	NA	NA	NA
C28 [58]	Rezaei et al.	2021	*A. niger*	8	1	0	0	0	NA	NA	NA	NA	NA	NA	NA
C29 [59]	Shokoohi et al.	2021	*A. flavus*	5	1	0	0	4	NA	NA	NA	NA	NA	NA	NA
C29 [59]	Shokoohi et al.	2021	*A. niger*	28	18	4	27	28	NA	NA	NA	NA	NA	NA	NA
C30 [60]	Xue Xu et al.	2021	*A. flavus*	38	0	0	0	0	0	0	NA	NA	NA	NA	NA
C30 [60]	Xue Xu et al.	2021	*A. niger*	1	0	0	0	0	0	0	NA	NA	NA	NA	NA
C30 [60]	Xue Xu et al.	2021	*A. terreus*	3	0	0	0	3	0	0	NA	NA	NA	NA	NA
C31 [61]	Yassin et al.	2021	*A. flavus*	14	NA	NA	NA	4	NA	NA	NA	NA	NA	NA	NA
C32 [34]	Abastabar et al.	2022	*A. oryzae*	54	7	2	13	NA	6	NA	54	0	54	0	NA
C33 [62]	Badiee et al.	2022	*A. flavus*	117	0	4	0	3	1	4	NA	6	NA	NA	NA
C34 [63]	Fattahi et al.	2022	*A. flavus*	8	0	1	NA	NA	NA	NA	NA	NA	NA	NA	NA
C35 [64]	Lotfali et al.	2022	*A. fumigatus*	33	NA	5	3	NA	NA	NA	NA	NA	NA	NA	NA
C35 [64]	Lotfali et al.	2022	*A. niger*	75	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
C36 [35]	Nargesi et al.	2022	*A. flavus*	110	8	0	0	0	6	1	NA	NA	NA	NA	NA
C36 [35]	Nargesi et al.	2022	*A. niger*	41	3	1	1	0	0	0	NA	NA	NA	NA	NA
C37 [65]	Sabz et al.	2022	*A. flavus*	60	0	0	2	NA	NA	NA	NA	NA	NA	NA	NA
C37 [65]	Sabz et al.	2022	*A. fumigatus*	1	0	0	1	NA	NA	NA	NA	NA	NA	NA	NA
C37 [65]	Sabz et al.	2022	*A. niger*	43	0	0	33	NA	NA	NA	NA	NA	NA	NA	NA
C37 [65]	Sabz et al.	2022	*A. terreus*	3	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA
C37 [65]	Sabz et al.	2022	*A. tubingensis*	53	0	0	43	NA	NA	NA	NA	NA	NA	NA	NA
C38 [66]	Vaghar et al.	2022	*A. flavus*	42	1	2	5	0	0	NA	NA	NA	NA	NA	NA
C38 [66]	Vaghar et al.	2022	*A. fumigatus*	12	1	2	NA	0	0	NA	NA	NA	NA	NA	NA
C38 [66]	Vaghar et al.	2022	*A. niger*	8	NA	NA	NA	0	0	NA	NA	NA	NA	NA	NA
C38 [66]	Vaghar et al.	2022	*A. terreus*	3	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA
C39 [37]	Ghazanfari et al.	2023	*A. fumigatus*	7	NA	1	NA	NA	NA	NA	NA	NA	NA	NA	NA
C39 [37]	Ghazanfari et al.	2023	*A. tubingensis*	9	4	2	NA	NA	2	NA	NA	NA	NA	NA	NA
C40 [43]	Halvaeezadeh et al.	2023	*A. niger*	2	0	0	0	NA	NA	NA	NA	NA	1	NA	NA

(*continued on next page*)

Table 2 (*continued*)

Code	Author	Year	Species	Total	ITC	VRC	AMB	CFG	POS	ISA	FLC	LUL	NYS	LAN	RAV
C40 [43]	Halvaeezadeh et al.	2023	*A. tubingensis*	31	0	0	1	NA	NA	NA	NA	NA	11	NA	NA
C40 [43]	Halvaeezadeh et al.	2023	*A. welwitschiae*	52	0	0	0	NA	NA	NA	NA	NA	41	NA	NA
C41 [67]	Khojasteh et al.	2023	*A. fumigatus*	483	78	53	NA	NA	33	NA	NA	NA	NA	NA	NA
C42 [38]	Roohi et al.	2023	*A. flavus*	19	7	0	0	NA	NA	NA	NA	NA	NA	NA	NA
C42 [38]	Roohi et al.	2023	*A. fumigatus*	12	1	1	0	NA	NA	NA	NA	NA	NA	NA	NA
C42 [38]	Roohi et al.	2023	*A. niger*	58	8	17	0	NA	NA	NA	NA	NA	NA	NA	NA
C43 [68]	Salehi et al.	2023	*A. flavus*	101	22	9	17	8	NA	NA	NA	NA	NA	NA	NA
C43 [68]	Salehi et al.	2023	*A. fumigatus*	49	5	8	23	7	NA	NA	NA	NA	NA	NA	NA

ITC, Itraconazole; VRC, Voriconazole; AMB, Amphotericin B; CFG, Caspofungin; POS, Posaconazole; ISA, Isavoconazole; FLC, Fluconazole; LUL, Luliconazole; NYS, Nystatin; LAN, Lanoconazole; RAV, Ravoconazole.

Table 3
Results of the meta-analysis of 20 species–drug pairs analyzing the rate of drug resistance and generating a pooled resistance rate.

Antifungal_Species	Resistance Rate	CI (Lower)	CI (Upper)	I^2	τ^2	Chi^2	P (Heterogeneity)	df
AMB_flavus	13.16 %	2.34 %	29.22 %	0.96	0.1496	532.45	< 0.01	19
AMB_fumigatus	6.97 %	0 %	23.09 %	0.86	0.0517	80.95	< 0.01	11
AMB_niger	21.97 %	0.01 %	58.85 %	0.96	0.2151	263.31	< 0.01	10
AMB_terreus	24.96 %	0 %	69.93 %	0.94	0.1426	108.96	< 0.01	6
ITC_flavus	10.19 %	1.77 %	22.84 %	0.96	0.1215	479.37	< 0.01	21
ITC_fumigatus	17.61 %	5.70 %	32.77 %	0.93	0.0678	229.41	< 0.01	16
ITC_niger	12.83 %	0.25 %	34.07 %	0.87	0.0803	86.40	< 0.01	11
ITC_terreus	0 %	0 %	5.89 %	0.76	0.0354	29.23	< 0.01	7
VRC_flavus	0.58 %	0 %	02.72 %	0.68	0.0120	59.53	< 0.01	19
VRC_fumigatus	14.68 %	3.68 %	29.41 %	0.94	0.0769	282.82	< 0.01	16
VRC_niger	4.64 %	0 %	14.86 %	0.78	0.0302	46.08	< 0.01	10
VRC_terreus	0 %	0 %	0 %	0.00	0.0006	4.91	0.67	7
POS_flavus	1.23 %	0 %	3.74 %	0.42	0.0022	8.56	0.13	5
POS_fumigatus	4.56 %	0.39 %	11.53 %	0.68	0.0062	12.64	< 0.01	4
POS_niger	6.61 %	0 %	73.41 %	0.97	0.2343	137.16	< 0.01	4
POS_terreus	0.62 %	0 %	17.07 %	0.82	0.0366	21.83	< 0.01	4
CFG_flavus	13.09 %	0.95 %	32.83 %	0.96	0.1476	352.57	< 0.01	14
CFG_fumigatus	1.40 %	0 %	10.02 %	0.44	0.0085	7.21	0.13	4
CFG_niger	16.41 %	0 %	61.88 %	0.97	0.2361	209.98	< 0.01	7
CFG_terreus	26.42 %	0 %	96.29 %	0.97	0.3537	0.3537	< 0.01	5

CI, confidence interval; df, degree of freedom; AMB, amphotericin B; ITC, itraconazole; VRC, voriconazole; POS, posaconazole; CFG, caspofungin; I^2 (I-squared), represents the percentage of total variation across studies that is due to heterogeneity rather than chance (A higher I^2 value indicates greater heterogeneity); τ^2 (tau-squared) is the estimate of the between-study variance in a random-effects meta-analysis model which quantifies the degree of variability in the effect sizes across studies.

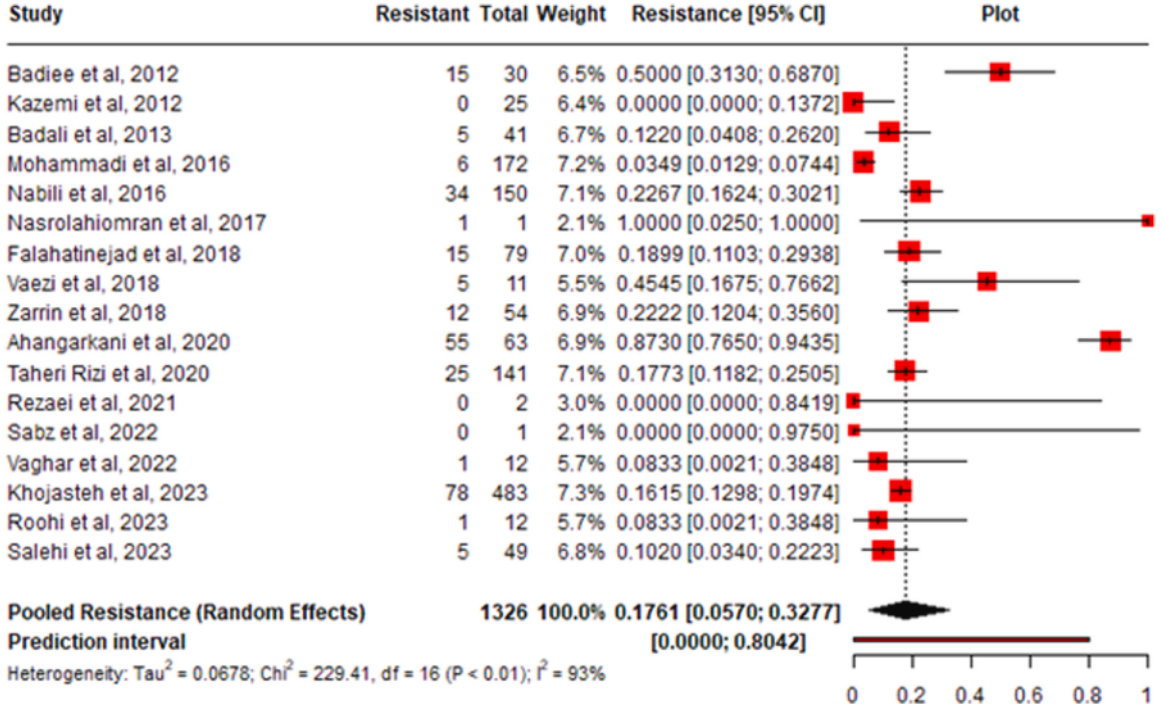

Fig. 3. Meta-analysis forest plot showing *A. fumigatus* resistance rates to itraconazole.

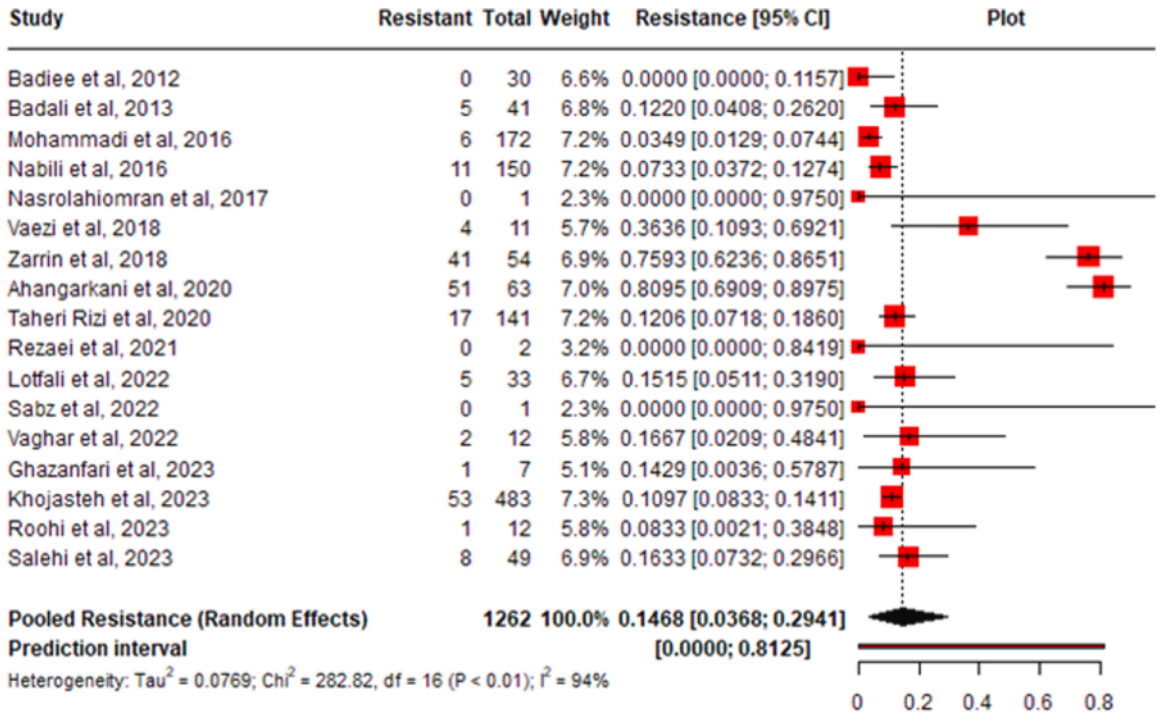

Fig. 4. Meta-analysis forest plot showing *A. fumigatus* resistance rates to Voriconazole.

Information on the resistance mechanisms of *A. flavus* remains incomplete.

While our study provides valuable insights into *Aspergillus* resistance patterns in Iran, it is important to emphasize that the selection of antifungal therapy should not rely solely on resistance rates. Host factors, including the patient's immune status, underlying conditions, drug tolerability, and potential drug interactions, are crucial in determining the most appropriate treatment. Future studies should aim to correlate resistance rates with clinical outcomes, incorporating host factors and the pharmacokinetic properties of antifungal agents. This would provide a more comprehensive framework for optimizing antifungal therapy in clinical practice.

Conclusion

Our findings highlight the critical importance of antifungal resistance surveillance in Iran. However, the choice of antifungal therapy should not rely solely on resistance rates. A multidisciplinary approach, involving antifungal stewardship specialists, infectious disease physicians, and clinical pharmacists, is essential for optimizing treatment regimens based on resistance patterns, host factors, and drug pharmacokinetics.

We recommend establishing antifungal stewardship programs in Iran to develop evidence-based guidelines for the managing *Aspergillus* infections. These programs should include experts in infectious diseases, microbiology, and pharmacology to ensure that treatment recommendations are tailored to local resistance patterns and patient populations.

Based on our findings, we propose the following approach to antifungal therapy for *Aspergillus* infections in Iran:

- **First-line therapy**: For infections caused by *A. fumigatus*, consider posaconazole or voriconazole, due to their relatively low resistance rates. For *A. flavus*, voriconazole may be preferred given its low resistance rate and favorable pharmacokinetic profile.
- **Alternative therapy**: For patients who cannot tolerate azoles or have infections caused by highly resistant strains, amphotericin B can be considered, particularly for *A. fumigatus* infections. However, close monitoring for renal toxicity is essential.
- **Echinocandins**: Caspofungin may serve as salvage therapy or be used in combination with other antifungals, particularly for infections caused by *A. terreus* or *A. niger*. However, its use should be guided by

List of abbreviations

A. flavus *Aspergillus flavus*
A. fumigatus *Aspergillus fumigatus*
A. niger *Aspergillus niger*
A. terreus *Aspergillus terreus*

BAL	Bronchoalveolar Lavage
CLSI	Clinical and Laboratory Standards Institute
DNA	Deoxyribonucleic Acid
ECV	Epidemiological Cutoff Value
EUCAST	European Committee on Antimicrobial Susceptibility Testing
MEC	Minimum Effective Concentration
MIC	Minimum Inhibitory Concentration
PDA	Potato Dextrose Agar
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PLOGIT	Logit Transformation with Continuity Correction
RPMI	Roswell Park Memorial Institute
SDA	Sabouraud Dextrose Agar
SID	Scientific Information Database

CRediT authorship contribution statement

Data curation, IBM; methodology, IAD; validation, IAD; formal analysis, IBM; investigation, IBM; writing—original draft preparation, IBM; writing—review and editing, FJG, SK and MA; supervision, IAD; All authors have read and agreed to the published version of the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2025.102838.

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