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General review

Trends in the Prevalence of Amphotericin B-Resistance (AmBR) among Clinical Isolates of *Aspergillus* Species

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ABSTRACT

The challenges of the invasive infections caused by the resistant *Aspergillus* species include the limited access to antifungals for treatment and high mortality. This study aimed to provide a global perspective of the prevalence of amphotericin B resistance (AmBR), geographic distribution, and the trend of AmBR from 2010 to 2020. To analyze the prevalence of in vitro AmBR in clinical *Aspergillus* species, we reviewed the literature and identified a total of 72 articles. AmBR was observed in 1128 out of 3061 *Aspergillus terreus* (36.8%), 538 out of 3663 *Aspergillus flavus* (14.9%), 141 out of 2691 *Aspergillus niger* (5.2%), and 353 out of 17,494 *Aspergillus fumigatus* isolates (2.01%). An increasing trend in AmB-resistant isolates of *A. fumigatus* and a decreasing trend in AmB-resistant *A. terreus* and *A. flavus* isolates were observed between 2016 and 2020. AmB-resistant *A. terreus* and *A. niger* isolates, accounting for 40.4% and 20.9%, respectively, were the common AmB-resistant *Aspergillus* species in Asian studies. However, common AmB-resistant *Aspergillus* species reported by European and American studies were *A. terreus* and *A. flavus* isolates, accounting for 40.1% and 14.3% in 31 studies from Europe and 25.1% and 11.7% in 14 studies from America, respectively. The prevalence of AmB-resistant *A. niger* in Asian isolates was higher than in American and European. We found a low prevalence of *A. terreus* in American isolates (25.1%) compared to Asian (40.4%) and European (40.1%). Future studies should focus on analyzing the trend of AmBR on a regional basis and using the same methodologies.

1. Introduction

Aspergillus species is one of the most common airborne saprobic fungi which is widely distributed in environments and colonizes various ecological niches [1]. It tolerates multiple physical conditions, persists in hospital settings, and causes a wide range of infections from superficial to potentially life-threatening systemic infections in patients with underlying severe conditions [2–4]. Invasive aspergillosis is often associated with compromised host defenses, such as neutropenia, allogeneic hematopoietic stem cell transplantation, and solid organ transplantation [4]. Over the last decades, azole compounds have been the first line of therapy to prevent *Aspergillus* infections. Therapeutic options are dramatically limited due to the continued emergence and ongoing spread of azole-resistant isolates, but this has not been found in the majority of regions. As a result, resistant *Aspergillus* infections indicate prolonged antifungal therapy, higher healthcare, therapeutic failures, and high morbidity and mortality [5, 6]. In the United States, the high rate of invasive aspergillosis resulted in an increase in the duration of hospitalization from 32.1 to 45.7 per 1 million persons between 2000 and 2013 (Annual percent change (APC)= ++3.0; P<0.001) [7]. Given the severity of invasive aspergillosis and the recent reports of emerging azole resistance in *Aspergillus* species, alternative antifungal prevention and treatment strategies should be prioritized. Amphotericin B (AmB) has become the drug of choice in the era of azole resistance [8] and can be the gold standard in this context due to demonstrating a broad range of activity against yeasts and filamentous fungi in the treatment of

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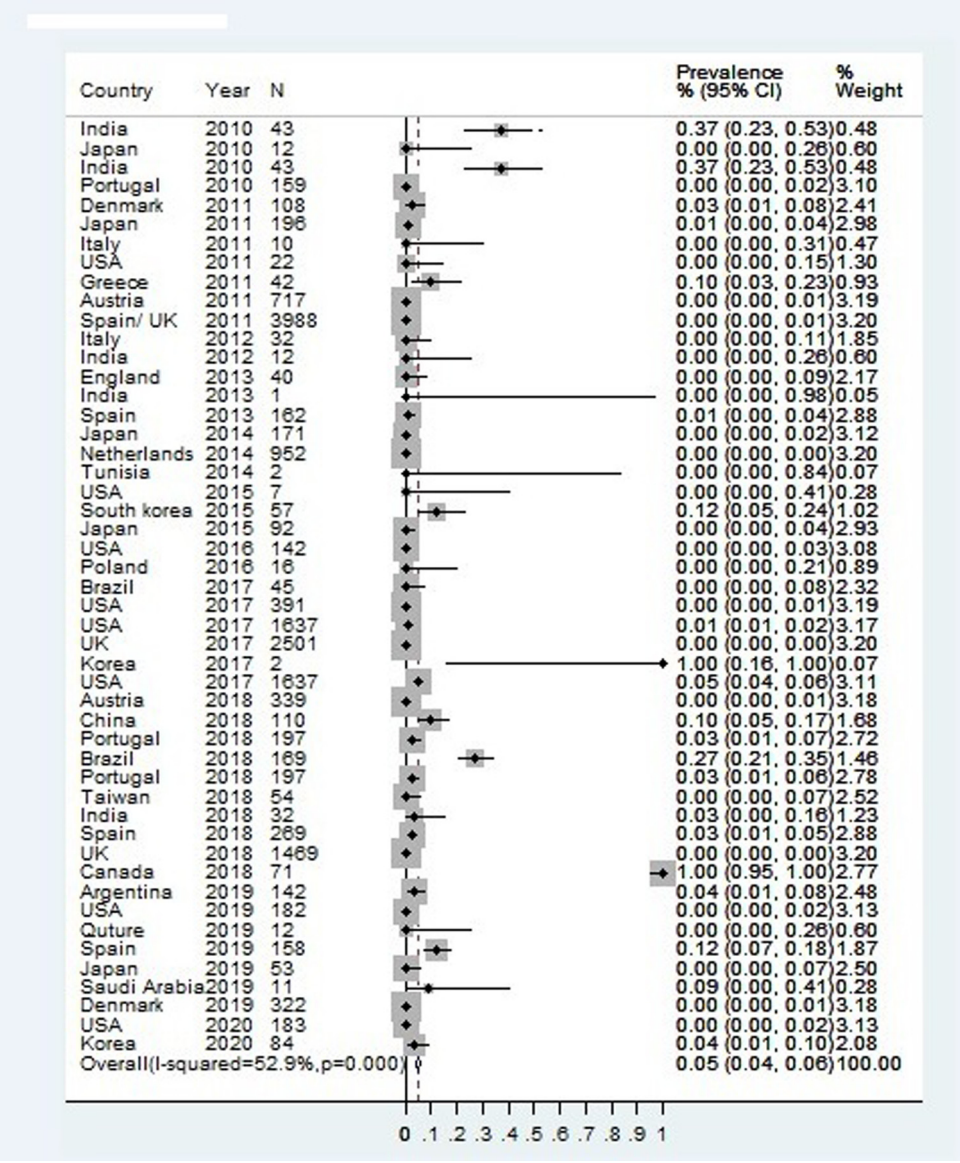

Fig. 1. Forest plot of the proportion of AmB resistant *Aspergillus fumigatus*.

severe fungal infections [9]. However, treatment of invasive aspergillosis with AmB is associated with a mortality rate as high as 65–71% [6, 10, 11]. Recently, an increase was reported in the minimal inhibitory concentration (MIC) value of AmB against *Aspergillus* species [12–15]. This led to the appearance of fully resistant isolates against AmB and azoles. Although AmBR has remained extremely rare and is less common than azole resistance in the *Aspergillus* species, many reports have described resistance to AmB among the isolates of *A. terreus, A. flavus, A. lentulus*, and *A. ustus* [13, 16–20]. As determined by in vitro susceptibility tests, resistance is often an independent factor for therapeutic failure in infected patients treated with antifungal agents [13, 21]. There is a lack of data or information regarding the relationship between the MIC values of AmB and clinical outcomes. Different rates of AmBR have been observed in various studies [22–25]. Although the exact prevalence of AmB-resistant *Aspergillus* species have not been determined to date, this rate was estimated to be 10.8% among 280 patients in nine hospitals in Spain [24]. Heo et al. reported a high rate (26.5%) of resistance to AmB in a study conducted on 136 clinical *Aspergillus* isolates from Korea [25]. The elevated AmB MICs among clinical *Aspergillus* isolates in different studies [12–15, 25] can be the reason for concern. However, despite the importance of the issue, there is a lack of review studies on the prevalence of AmBR in clinical *Aspergillus* species. Therefore, the present study was designed to systematically evaluate the shift in AmB MICs to offer a global picture of AmBR in clinical *Aspergillus* isolates within ten years (2010–2020).

2. Methods

This study reviews the existing published literature on in vitro susceptibility testing of AmB against clinical *Aspergillus* species isolates from 2010 to 2020. The studies to be included were retrieved from Medline database through PubMed, Embase through Scopus, ISI, Web of Science, Science Direct, and Google Scholar with the search terms “amphotericin B AND resistance”, and “in vitro AND susceptibility AND testing” and, “azole AND resistant AND *Aspergillus* species” OR “azole AND resistance” OR “*Aspergillus* species OR *Aspergillus terreus* OR *Aspergillus flavus* OR *Aspergillus fumigatus OR Aspergillus niger*”. We also searched the reference lists of the retrieved articles, and the primary data extracted from each study were independently verified by two authors (AV and KA). The collected data

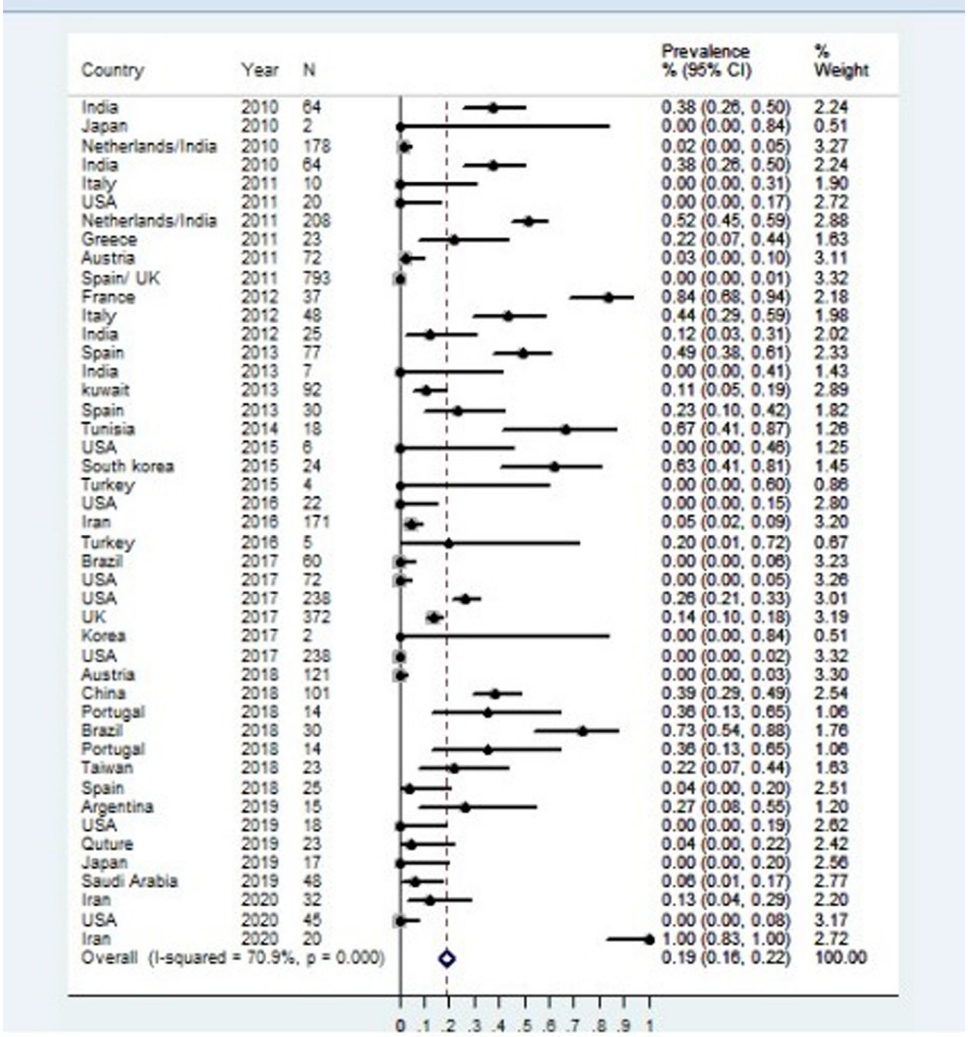

Fig. 2. Forest plot of the proportion of AmB resistant *Aspergillus flavus*.

included authors' names, year of publication, country, type of study, setting, participants' demographic information, study population, underlying condition, *Aspergillus* species, AmB resistant *Aspergillus* species, antifungal susceptibility testing method, AmB MIC cut-off value, and the prevalence of AmBR. The extracted data were then analyzed using R software (version 3.4.1). To determine the methodological quality of the included studies, the researchers used a 12-item tool adopted from STARD 2015 checklist (http://www.equator-network.org/reporting-guidelines/stard). The Chi-square test was utilized to evaluate the associations among nominal variables, and the p-value was estimated using the Monte Carlo method. Odds ratios (ORs) were also used to compare the differential prevalence of AmBR and determine the differences in causative agents of fungal infections. The significance of all ORs was calculated using a 95% Bayesian credible interval (CI) and Bayesian logistic regression.

3. Results

3.1. Characteristics of the included studies

To analyze the prevalence of in vitro AmBR in clinical *Aspergillus* species, we reviewed the literature and identified 88 relevant articles, of which16 studies were excluded owing to the small sample size (including less than 10 *Aspergillus* species isolates). The remaining 72 studies were eligible for inclusion [12–15, 23–90]. In total, 10 (13.8%), 46 (63.8%), and 16 (22.2%) studies were of high, moderate, and low quality, respectively. The studies were conducted between 2010 and July 2020 in 29 countries. The most represented countries included the United States (9 studies), Spain (8 studies), India (7 studies), Iran and South Korea (6 studies each). The retrospective cohort study was the most commonly used study design (79%) followed by prospective studies (21%). In total, 23 (31.9%), 28 (38.8%), and 21 (29.1%) studies evaluated the effect of antifungal susceptibility testing on infection, colonization, and both infection and colonization, respectively.

3.2. The pooled prevalence of AmBR among clinical Aspergillus isolates

Out of the total 26,909 *Aspergillus* isolates tested in these studies, *A. fumigatus* (n = 17,494; 65.0%), *A. flavus* (n = 3663; 13.6%), *A. terreus* (n = 3061; 11.3%), and *A. niger* (n = 2691; 10%) represented the main isolates. In most studies, the in vitro AmB susceptibility was evaluated by the antifungal broth microdilution method of the Clinical and Laboratory Standards Institute (CLSI) [n = 53; 73.6%], followed by the broth microdilution MIC determination method of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [n = 17; 23.6%], and E-test [n = 7; 9.7%]. In vitro antifungal susceptibility testing was also performed using the EUCAST in combination with CLSI (n = 3; 4.1%), CLSI in combination with E-test (n = 2; 2.7%), EUCAST in combination with E-test, and EUCAST in combination with CLSI and E-test (one study each, 1.3%). Out of 72 studies, 55 (76.3%) articles used the MIC breakpoint of ≥2 μg/mL to define AmBR against *A.*

fumigatus. In addition, 18 (25%) and 1 (1.3%) studies used the MIC breakpoints of ≥4 μg/mL and ≥1 μg/mL, respectively, and the AmB MIC breakpoint was not determined for one study.

The highest resistance rate was reported in a study conducted in India (n = 128; 92%) [26], followed by a study in France (n = 37; 84%) [13], and a prospective international *A. terreus* survey performed by Risslegger et al. (n = 370; 52.4%) [41]. In 19 (26.3%) studies, all isolates were fully susceptible to AmB. AmBR was observed in 1128 out of 3061 *A. terreus* (36.8%), 538 of 3663 *A. flavus* (14.9%), 141 out of 2691 *A. niger* (5.2%), and 353 out of 17,494 *A. fumigatus* isolates (2.0%). Overall, the pooled mean prevalence of AmBR was 0.17% (95% CI: 0.18%–0.19%) for 26,909 *Aspergillus* isolates. Pooled mean AmBR were 0.05% (95% CI: 0.04%–0.06%; Fig. 1) for *A. fumigatus* isolates (n = 17,494), 0.19% (95% CI: 0.16%–0.22%; Fig. 2) for *A. flavus* isolates (n = 3663), 0.36% (95% CI: 0.20%–0.53%; Fig. 3) for *A. terreus* (n = 3061), and 0.04% (95% CI: 0.02%–0.06%; Fig. 4) for *A. niger* isolates (n = 2691).

3.3. Trends in the prevalence of AmBR among Aspergillus isolates

To analyze the trends of changes in the prevalence of AmBR in recent years in different continents, we performed a subgroup analysis of the prevalence of AmBR based on the study year. Analysis of AmBR in a 5-year interval between 2010 and 2015 revealed the highest AmBR of 41.9% (519 of 1237) for *A. terreus* isolates, followed by *A. flavus* (16.9%), *A. niger* (7.3%), and *A. fumigatus* (0.93%). Moreover, it decreased from 41.9% of 1237 *A. terreus* isolates in 2010–2015 to 33.4% of 1824 *A. terreus* isolates in 2016–2020. The prevalence of AmBR was 12.5% for *A. flavus* isolates (n = 1861), 3.7% for *A. niger* isolates (n = 1521), and 2.7% for *A. fumigatus* isolates (n = 10,626) between 2015 and 2020. The prevalence of AmB-resistant *A. fumigatus* isolates increased gradually from 0.93% of 6868 *A. fumigatus* isolates in 2010–2015 to 2.7% of 10,626 *Aspergillus* isolates in 2015–2020. Table 1 presents the pooled prevalence of AmB-resistant *Aspergillus* species based on the study year.

3.4. Prevalence of AmBR in different geographic regions

The prevalence of AmB-resistant *Aspergillus* isolates differed in geographic regions in this subgroup analysis. The pattern of AmB-resistant *Aspergillus* species isolates in Asian studies was different from those in European and American studies; AmB-resistant *A. terreus* and *A. niger* isolates accounting for 40.4% and 20.9%, respectively, were the common AmB-resistant *Aspergillus* species in Asia. Common AmB-resistant *Aspergillus* species reported European and American studies were *A. terreus* and *A. flavus* isolates, accounting for 40.1% and 14.3% in 31 studies from Europe and 25.1% and 11.7% in 14 studies from America, respectively. This finding is essential as it indicates a

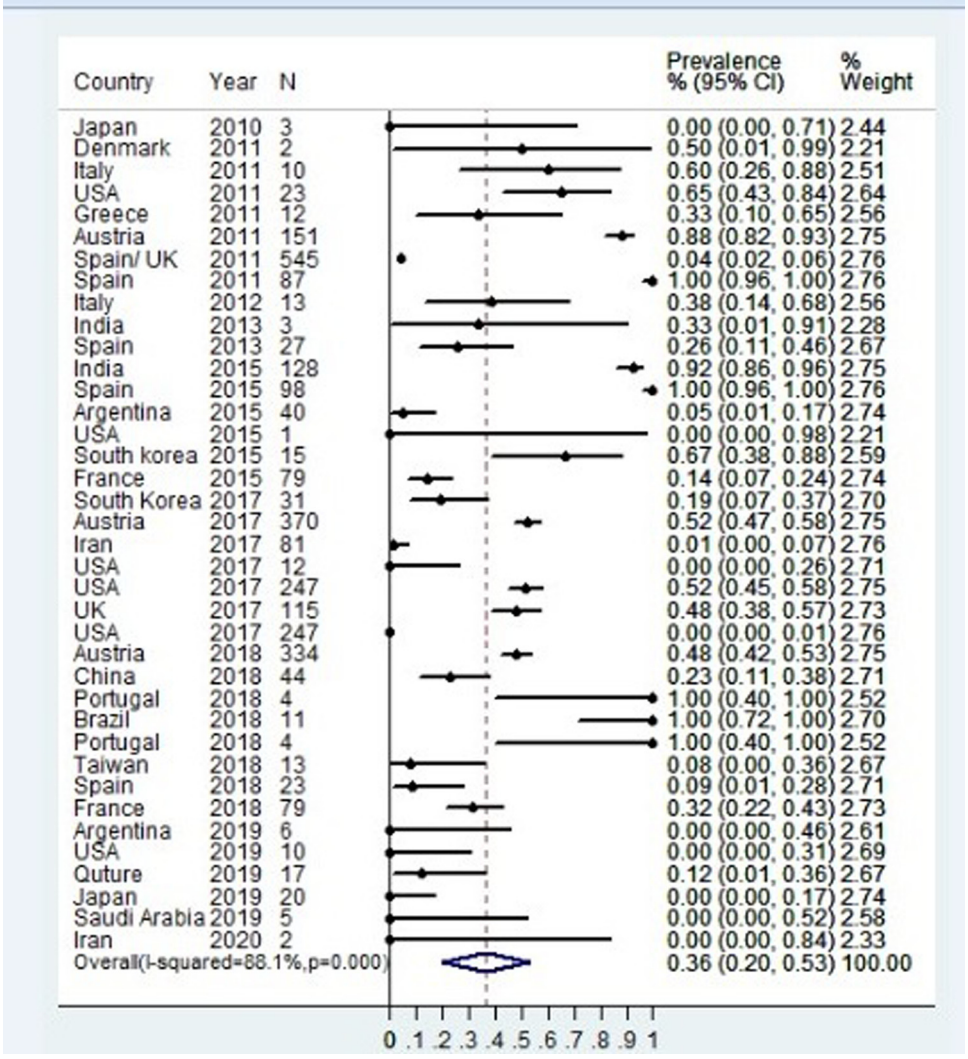

Fig. 3. Forest plot of the proportion of AmB resistant *Aspergillus terreus*.

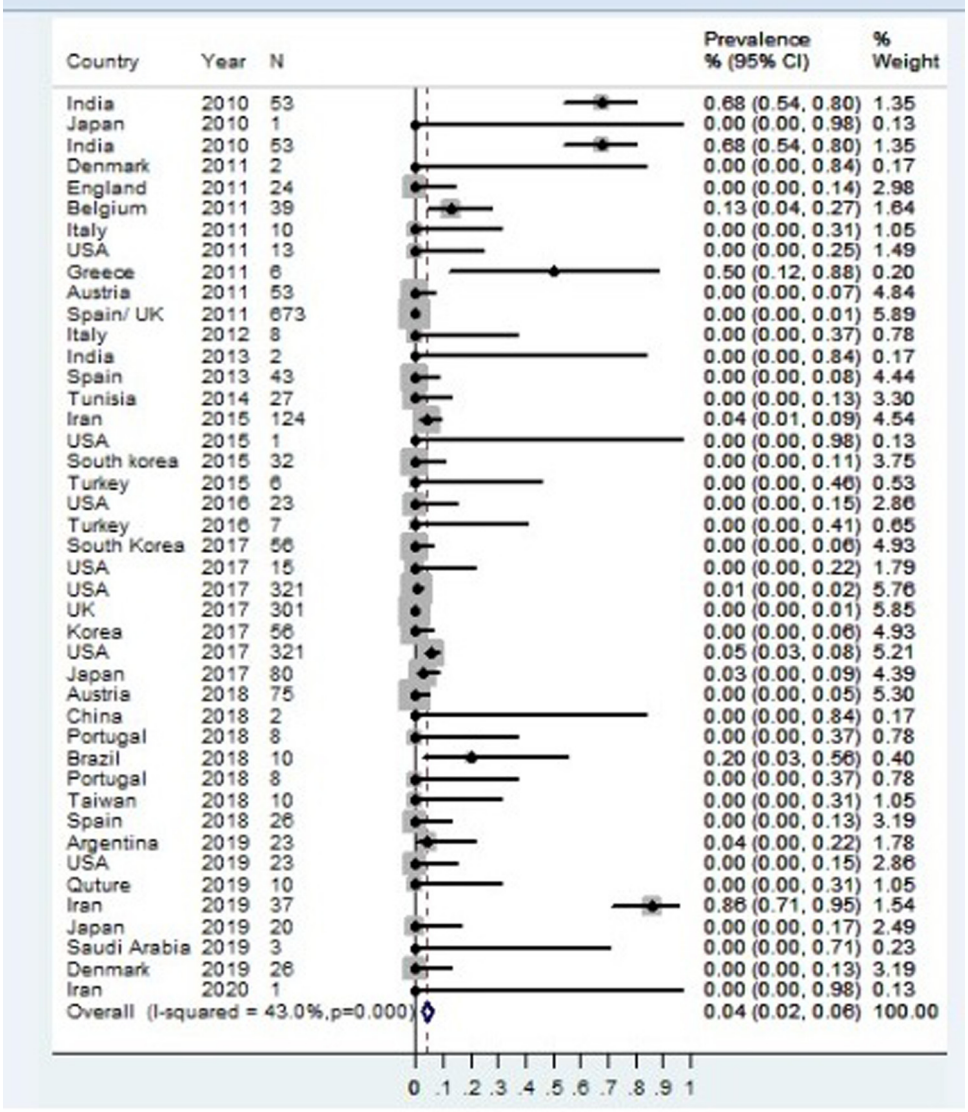

Fig. 4. Forest plot of the proportion of AmB resistant *Aspergillus niger*.

Table 1
The pooled prevalence of AmB-resistant *Aspergillus* isolates determined by in vitro susceptibility testing methods over time.

Year	*Aspergillus flavus*		*Aspergillus fumigatus*		*Aspergillus niger*		*Aspergillus terreus*	
	N of Studies	Pooled Prevalence	N of Studies	Pooled Prevalence	N of Studies	Pooled Prevalence	N of Studies	Pooled Prevalence
2010	4	0.039 (0.017–0.061)	4	0.004 (0.007–0.016)	3	0.655 (0.564–0.747)	1*	0 (0–0.354)
2011	6	0.007 (0.002–0.012)	7	0.003 (0.001–0.005)	8	0 (0–0.003)	7	0.454 (0.441–0.467)
2012	3	0.493 (0.412–0.573)	2*	0 (0–0)	1*	0 (0–0.185)	1*	0.385 (0.112–0.657)
2013	4	0.197 (0.143–0.251)	3	0.01 (0.009–0.029)	2*	0 (0–0.041)	2*	0.269 (0.105–0.433)
2014	1*	0.667 (0.438–0.895)	3	0 (0–0)	1*	0 (0–0.064)	0*	–
2015	3	0.279 (0.144–0.415)	3	0.005 (0.014–0.024)	4	0.026 (0–0.057)	6	0.915 (0.898–0.931)
2016	3	0.04 (0.009–0.072)	2*	0 (0–0)	2*	0 (0–0.07)	0*	–
2017	6	0.009 (0.002–0.016)	6	0.002 (0.001–0.003)	7	0.004 (0–0.009)	7	0.02 (0.013–0.027)
2018	7	0.018 (0.004–0.033)	10	0.003 (0.001–0.004)	7	0.001 (0–0.023)	8	0.439 (0.399–0.478)
2019	5	0.038 (0.008–0.084)	6	0.002 (0–0.007)	7	0.083 (0.047–0.119)	5	0.015 (0–0.079)
2020	3	0.175 (0.141–0.21)	2*	0.002 (0–0.11)	1*	0 (0–0.488)	1*	0 (0–0.421)

*The number of included studies is less than the minimum expected for analysis.

relationship between AmB-resistant *Aspergillus* isolates and specific geographic occurrences of this resistance.

4. Discussion

The challenges of the invasive infections caused by the azole-resistant *Aspergillus* species include the limited access to antifungals for treatment and high mortality [91, 92]. This study is the first review to investigate the trends in the global prevalence of AmBR from 2010 to 2020. The major study finding was that *A. flavus* accounted for over 24.9% of the resistant *Aspergillus* isolates in the reviewed studies, while the majority of the AmB-resistant *Aspergillus* species were *A. terreus* (52.2%). The ongoing spread of antifungal resistance can threaten the successful treatment of invasive

aspergillosis. Although AmB has been generally used as an option for the chemotherapy of azole-resistant invasive *Aspergillus* infection, an increase was observed in the treatment failure rate for AmB [93–95]. Another concern that raises questions about currently employed treatments is the association between the large particle sizes of various AmB formulations and high nephrotoxicity [96–99]. Flörl, et al. showed that the mortality related to resistant *flavus* aspergillosis (AmB MIC≥2 μg/mL) was significantly higher, compared to that in patients infected with low (<2 μg/mL) AmB MIC isolates [93]. In the same vein, Hadrich et al. investigated AmBR in *A. flavus* infection and defined to correlate the treatment failure with increased mortality [13]. However, Mosquera et al. found no correlation between in vitro AmB susceptibility and clinical outcome for *A. fumigatus* and *A. flavus* infections [100]. Although clinical *A. flavus* isolates with MIC≥2 μg/mL can be an AmB-resistant isolate in vivo [20], the variation observed in breakpoints for AmB susceptibility testing should be considered a critical issue. Remarkably, different breakpoints cause various reports of AmB susceptibility profiles for *Aspergillus* isolates, leading to an unreliable comparison of resistance rates in surveillance studies in different countries [26, 45, 48]. However, these differences may be influenced by the antifungal susceptibility testing method (E-test or broth microdilution) [101–103]. Although broth microdilution remains the common method for measuring MIC, many laboratories utilize the E-test method as an alternative [104]. However, Barchiesi et al. suggest that the E-test may be the most appropriate method to measure MIC since its results have the best correlation the outcome [20]. In the evaluation of 26,909 *Aspergillus* isolates, AmBR was observed in 36.8% of *A. terreus*, 14.9% of *A. flavus*, 5.2% of *A. niger*, and 2.01% of *A. fumigatus* isolates. The study duration was divided into two periods 2010–2015 and 2016–2020 to analyze the trends in the prevalence of AmBR in recent years. A gradually increasing trend in AmB-resistant *A. fumigatus* isolates and a decreasing trend in AmB-resistant *A. terreus* and *A. flavus* isolates were found in the studies published between 2016 and 2020. The trend of AmB-resistant *A. fumigatus* isolates has been increasing, which may be explained by the frequent use of AmB for *A. fumigatus* infections. The improper management of drug-resistant isolates can enhance the spread of resistance [105]. The changing epidemiology of *Aspergillus* infections in immunocompromised patients may increase the prevalence rate over time. This study also enabled the evaluation of the prevalence of AmB-resistant *Aspergillus* isolates by geographical region. In this review, the prevalence of AmB-resistant *A. niger* in Asian isolates (20.9%) was found to be higher than that in American (2.7%) and European (0.62%). This may be related to the existence of different species within the niger complex in Asia, America, and Europe. AmB-resistant against *A. terreus* dominates, but the frequency varied based on the region. We found a low prevalence of AmB-resistant *A. terreus* in American isolates (25.1%) compared to Asian (40.4%) and European (40.1%). Although we cannot exclude other causative factors, our data support the notion that some differences in the prevalence of AmB resistance in specific geographic regions could contribute to ecological and environmental factors for AmBR development. To enable preventative measures, it is therefore critical to investigate under what conditions and to what extent environmental selection for the resistance occur. However, the prevalence of the AmB-resistant *Aspergillus* species showed variation in the studies conducted in different European countries, such as France (84%) [13], Spain (49.4%) [15], Italy (25.2%) [43], Greece (17.5%) [60], Belgium (12.8%) [40], Portugal (6.6%) [35], and Denmark (3.5%) [28]. Although the reasons for these gaps are still unknown, the possible causes include the difficulties in determining the accurate AmBR in clinical *Aspergillus* isolates given several external factors, such as the MIC testing method employed, discrepancies in definitions, changes in AmB susceptibility breakpoints, *Aspergillus* species isolated, and/or storage period of isolates. Variations in patient populations and drug usage patterns may also explain the differences in the prevalence of AmBR in these isolates. Amphotericin B remains the gold standard for the treatment of azole-resistant invasive *Aspergillus* infections. However, renal toxicity of all AmB formulations and the emergence of isolates with reduced susceptibility to AmB [106], and the substitution of AmB with alternative agents in the treatment of high AmB MICs should lead to better patient outcomes. Isavuconazole, a new triazole agent approved by the United State Food and Drug Administration, has been developed recently to treat invasive aspergillosis [107]. However, this agent has not been yet evaluated to be used as a prophylaxis for the treatment of invasive aspergillosis in solid organ transplant recipients, patients in intensive care units, and high-risk patients without hematological malignancy [108]. Combination therapy can be regarded as another effective approach for treating patients with *Aspergillus* infection [109]. The present study had some limitations. There were significant heterogeneities among the studies which can be explained by the differences in variables, including the testing methodologies used, patient populations, and study duration. The results of different studies may have been affected by the application of the random-effects model (REM) to accommodate the existing heterogeneity and obtain a normal distribution [110]. However, the final results may have been affected by the heterogeneity of the sample.

5. Conclusion

The current study reviewed a total of 72 published studies in the literature, which provides more insight into the shift in AmBR in clinical *Aspergillus* isolates within 10 years. Amphotericin B resistance was found to be more prevalent in *A. terreus* and *A. flavus* isolates. However, some differences found in the prevalence of AmBR among *Aspergillus* species in various geographic regions highlighted the role of the environment as an essential component in this regard. In addition, the trend of AmB-resistance among *Aspergillus* species was different in the studies published within the two periods. We recommend that future studies should focus on analyzing the trend of AmBR resistance on a regional basis using the same methodologies.

6. Author contributions

AV and HF conceptualized the study, gathered resources, and wrote the manuscript. AV, HF, FJ, KA and NV curated the data. AV, HF, and MN performed the formal analysis of the study. AV contributed to funding acquisition, project administration, and data validation. HF and AV investigated the data. AV and MN provided the methodology for this study. HB and AV supervised the study. AV, HF, and HB wrote the original draft of the manuscript and ED reviewed the manuscript.

Declaration of Competing Interest

All authors report no potential conflicts of interest. The authors alone are responsible for the content and writing of the paper

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Ethics statement

This study was approved by the Research and Ethics Committee (IR.IUMS.REC.1400.526) of Iran University of Medical Sciences, Tehran, Iran.

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