International Wound Journal

WILEY | IWJ

REVIEW ARTICLE OPEN ACCESS

Candida Drug Resistance in Patients With Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis

Mohammad Hossein Ekvan[1] | Hojjat Sayyadi[2] | Sarina Alidadpour[1] | Masoume Karimi[3] | Muhammad Ibrahim Getso[4] | Ahmad Reza Ebrahimi[1] | Mohammad Mirpanahi[1] | Omid Raiesi[5,6]

[1]Student Research Committee, Ilam University of Medical Sciences, Ilam, Iran | [2]Department of Biostatistics, School of Health, Non-Communicable Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran | [3]Department of Biostatistics, Faculty of Health, Ilam University of Medical Sciences, Ilam, Iran | [4]Department of Medical Microbiology and Parasitology, College of Health Sciences, Bayero University, Kano, Nigeria | [5]Department of Parasitology, School of Allied Medical Sciences, Ilam University of Medical Sciences, Ilam, Iran | [6]Zoonotic Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran

Correspondence: Omid Raiesi (o.raissi69@gmail.com)

Received: 11 September 2025 | **Revised:** 24 February 2026 | **Accepted:** 28 March 2026

Keywords: *Candida* | diabetic foot | drug resistant | meta-analysis | systematic review

ABSTRACT

Diabetic foot ulcers (DFUs) are one of the most serious and common complications that, if not treated properly, can lead to potential damage and even amputation. The aim of this systematic review and meta-analysis was to assess the drug-resistant *Candida* species in DFU. PubMed, Web of Science, Scopus and Google Scholar databases were systematically searched for eligible articles up to 22 June 2024. All articles on *Candida* diabetic foot infections that reported data on drug resistance were included in the study. In addition to general information, data on the type and number of fungi and the percentage of resistance to each drug were collected for analysis. A total of 238 studies were screened and finally, 16 articles were selected and analysed. *Candida albicans* was the most frequently isolated species in DFUs, followed by *Candida tropicalis* and *Candida parapsilosis*. For antifungal agents, the highest resistance was reported to Nystatin (32.48%, p-value = 0.30), Itraconazole (19.46%, p-value = 0.001) and Fluconazole (16.4%, p-value = 0.001). Miconazole (1.18%, p-value = 0.54) and Caspofungin (4.69%, p-value = 0.01) had the lowest resistance rates. For all drugs, resistance was higher in *C. albicans* than in non-*albicans*. This study found that antifungal drug resistance in *Candida* species is high in patients with DFUs, especially to itraconazole and fluconazole. Caspofungin, micafungin and voriconazole were more effective. Antifungal treatment in these patients should prioritize agents with lower resistance rates to improve outcomes and reduce the risk of treatment failure.

Protocol Registration: PROSPERO—CRD42024567133.

1 | Introduction

Diabetes is a group of metabolic disorders characterized by elevated blood sugar levels resulting from defects in insulin secretion, insulin action or both [1]. The World Health Organization reports an increasing incidence of diabetes worldwide, especially in developing countries [2]. Chronic hyperglycaemia in diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels [1]. Among the complications of diabetes, diabetic foot is known to be one of the critically important complication, with an incidence rate ranging between 15% and 25% [3]. Diabetic foot is a wound or ulcer usually on extremities of lower limbs most often

Key Points

- Antifungal resistance among Candida species in diabetic foot ulcers is substantial and clinically significant.
- Candida albicans remains the dominant pathogen and exhibits higher resistance compared to non-albicans species.
- Azole antifungals, particularly itraconazole and fluconazole, show considerable resistance rates.
- Echinocandins and newer antifungals demonstrate lower resistance and may represent more effective treatment options.
- Optimizing antifungal selection based on resistance patterns is critical to reducing treatment failure and improving DFU management.

associated with secondary infections. Peripheral neuropathy, muscle atrophy, foot deformity and vasculopathic features are the root cause to this condition [4]. The wound progresses and heals slowly, sometimes degenerates in to serious complications such as osteomyelitis, gangrene and even amputation. Clinical manifestations vary greatly depending on the extent and duration of the infection and the patient's degree of sensory impairment [5]. The principles of diabetic foot ulcer (DFU) management include: diabetes control, infection control, frequent debridement and amputation, if necessary [6]. Lack of proper treatment, age, male gender and long duration of diabetes are the most important risk factors for amputation [7]. It is necessary to identify the cause of the disease and take prompt steps for management and treatment to prevent progression and amputation [8]. Bacteria are the predominant infectious agent in this disease, and past studies have focused mostly on it. In fact, the standard approach is to identify the bacterial infection and treat it with appropriate antibiotics, regardless of the possibility of opportunistic fungal infections [9]. Thus, eliminating the infection is often difficult due to the failure to consider concomitant pathogenic fungi. The possibility of co-infection is high due to the fungal colonization on skin and the diversity of opportunistic species in the micro environment [9]. Treatment of fungal infections can be challenging because, unlike the diverse options of antibacterial drugs, antifungal drugs are limited—there are only three main classes: azoles, echinocandins and polyenes against invasive fungal infections caused by *Candida*, which is the most predominant fungal isolates from DFUs [10, 11]. Although these drugs are available, mortality and disability from *Candida* infections remain high due to increased resistance to some of them, such as the azoles [12, 13]. To the best of our knowledge, there is unavailability of a single comprehensive and accurate analysis of drug resistance of fungal species causing DFUs. The aim of this systematic review and meta-analysis was to estimate the drug resistance of Candida species in DFUs. Thus, the current analysis would impact a speedy and effective decision-making while managing patients with DFUs and might herald cutting down use of unnecessary medication during empirical treatment of DFUs.

2 | Methods

This systematic review was conducted according to the PRISMA guidelines [14]. The protocol for this study is registered in PROSPERO.

2.1 | Search Strategy

A comprehensive and systematic search was conducted in electronic databases including PubMed, Web of Science, Scopus and Google Scholar. All articles related to fungal DFU infection and drug resistance of *Candida* species were collected until July 22, 2024. In the systematic search, the keywords 'Diabetic Foot Ulcer,' 'Drug Resistance' and '*Candida*', along with all related words and terms, were used to find maximum articles.

2.2 | Eligibility Criteria

All articles on *Candida* diabetic foot infections that reported data on drug resistance were included in the study. Studies were excluded from the article if they met any of the following conditions: (1) studies that were descriptive other than cross-sectional studies, (2) studies that focused on unspecified fungal species, (3) studies that did not have a standard or specific diagnostic method and (4) studies that were in a language other than English.

2.3 | Study Selection

Screening was performed to identify articles related to the input and output criteria specified in EndNote 21 software. Screening was conducted by two independent researchers in a three-stage process. First, titles, then abstracts and finally full text of articles were reviewed. Disagreements at each stage were resolved by consultation with a third researcher.

2.4 | Data Extraction

General information including author name, year of publication, study location, sample size, mean age, gender, type of diabetes and duration of diabetes were extracted from the studies. Information on the type and number of fungi and the percentage of resistance to each drug were then collected for analysis.

2.5 | Quality Assessment

To assess the quality of the studies, two independent investigators used a modified version of the Newcastle–Ottawa scale (NOS) [15], adapted specifically for cross-sectional studies, as previously used in another study [16]. This version was based on the original NOS instrument designed for cohort studies, rewritten to fit the structure of cross-sectional studies and included seven questions in the three domains of selection, confounders and exposure assessment. This tool covered key

methodological aspects such as sampling method, response rate, exposure assessment method and accuracy of statistical reporting. The maximum possible score on this scale was 10 and based on the total score, the quality of the studies was classified into four levels: very good (9–10 points), good (7–8), moderate (5–6), and poor (0–4 points). Studies that were classified as unsatisfactory were excluded from the final analysis. Any disagreement between the two reviewers was resolved independently by a third reviewer.

2.6 | Meta-Analysis

Data analysis was performed using Stata software version 11. To estimate the combined drug resistance with a 95% confidence interval, the metaprop command was used and the results were displayed as a forest plot. To assess the heterogeneity between studies, the chi-square test and the I^2 index were used. According to the Hygienist classification, an I^2 value above 75% signifies a state of very high heterogeneity; between 50% and 75%, high heterogeneity; 25% to 50%, moderate heterogeneity; and less than 25% indicates low heterogeneity. Where the I^2 index was greater than 50%, a random effects model was used to estimate the combined drug resistance and meta-regression was used to examine possible factors of heterogeneity. To assess publication bias, the metabias command and Egger's test were employed. Where a bias was detected, the metatrim command and the Trim-and-Fill methods were applied. In cases of heterogeneity, meta-regression was used to explore possible sources. Analyses such as meta-regression were only conducted when a drug was reported in more than 10 studies, as fewer studies reduce the reliability of estimates.

3 | Results

A total of 238 studies were screened in which 68 studies were duplicates. Of the remaining 170 studies, 16 were eligible for inclusion (Figure 1). These studies examined a variety of drugs. Drugs that were in at least five studies were analysed. Table 1 shows the data of 16 included studies. Seven studies were from India. Most of the data were from patients with type 2 diabetes. The duration of diabetes varied from 2 months to 20 years. The number of positive fungal samples per study is listed. The number of *Candida albicans* and non-*albicans Candida* (NAC) species is also shown separately. Non-*Candida* fungi were not examined and analysed.

Table 2 shows the quality assessment of the including articles. Due to the type and purpose of the study, the Non-responders and Comparability sections were not able to be answered. All articles received a minimum score of 'good' and were analyzed.

The NAC group of this study included more than eight strains. *Candida tropicalis* and *Candida parapsilosis* were the most important fungi in this group. Then *Candida glabrata*, *Candida dubliniensis* and *Candida lusitaniae* were the most frequent. Drug resistance in DFUs in *Candida* species is shown in Table **3**. Fluconazole, amphotericin B and voriconazole were the most common drugs reviewed in the article. According to the results, the highest drug resistance was related to nystatin, itraconazole, fluconazole and amphotericin B, respectively. Miconazole with 2.06% and caspofungin with 4.69% had the lowest drug resistance.

Based on the results of Egger's test and the presence of heterogeneity, meta-regression testing was used to find the causes of heterogeneity. This test was performed for three drugs, fluconazole, voriconazole and amphotericin B, which were present in more than 10 articles.

Meta-regression for fluconazole showed that for each unit increase in sample size, the relative risk decreased by 0.001, which was statistically significant; however, for each year increase in the year of publication of the studies, the relative risk increased by 0.0006, but this was not statistically significant. The results

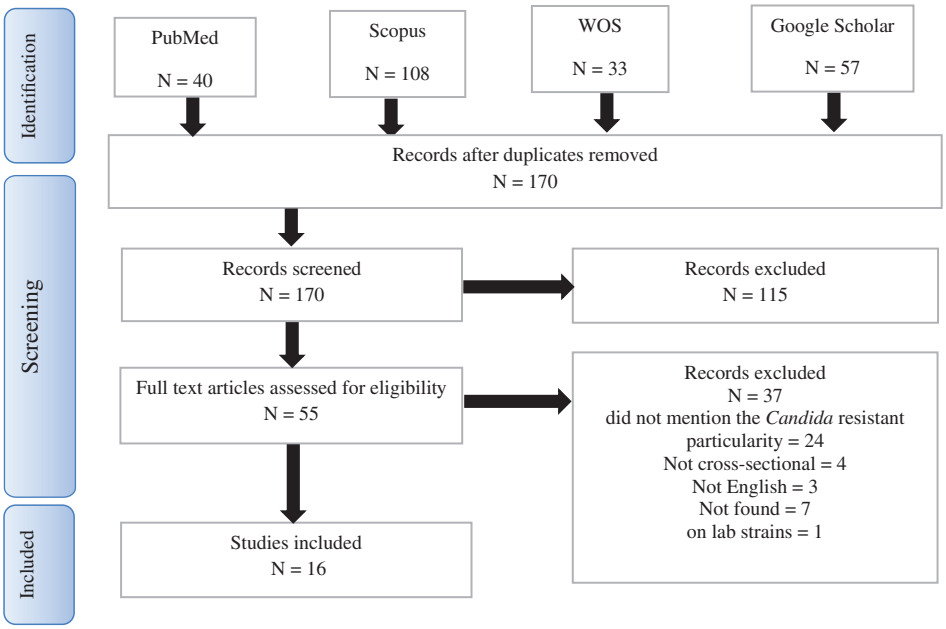

FIGURE 1 | Flow chart of study selection for inclusion in the meta-analysis.

TABLE 1 | Characteristics of articles reviewed on the drug resistance of diabetic foot ulcers.

Authors, year	Country	Study period	Total number of study participants (m:f)	Mean age (range)	Diabetes type	Total number of fungal isolates (m:f)	*Candida albicans*	*Candida* non-*albicans*
Ali et al., 2024 [17]	Pakistan	2020–2021	600	(41–78)	All type 2	200 (10:98)	88	112
Chincholikar et al., 2002 [18]	India	1994–1996	105 (71:34)	(30–86)	25 type 1 to 80 type 2	55	7	37
Chellan et al., 2010 [19]	India	2008	518 (382:136)	60.8	All type 2	141	15	90
Tascini et al., 2011 [20]	Italy	2006–2008	1295	NR	NR	81	25	45
Johargy et al., 2016 [21]	Saudi Arabia	2011–2012	138	NR	NR	9	4	5
Kumar et al., 2016 [22]	India	2012–2013	155	52.9	All type 2	75 (31:44)	22	53
Raiesi et al., 2017 [23]	Iran	2014–2015	122	61.5	78 type 1 to 44 type 2	30 (19:11)	13	5
Sugandhi et al., 2017 [24]	India	2014–2015	160 (82:78)	56.18	All type 2	25	7	18
Musyoki et al., 2019 [25]	Kenya	2017–2018	152 (93:59)	50.7	3 type 1 to 149 type 2	36	27	8
Manikandan et al., 2020 [26]	India	2014–2016	300 (189:111)	(55–65)	NR	56	35	21
Liu et al., 2023 [27]	China	2018–2021	581 (378:203)	61.29	8 type 1 to 573 type 2	21	7	11
Zubair et al., 2023 [28]	Saudi Arabia	2021–2023	122	NR	NR	28	28	0
Matei et al., 2024 [29]	Romania	2016–2022	60	73.4	NR	60 (26:34)	1	0
Wu et al., 2018 [30]	China	2014–2017	428 (273:155)	65.1	NR	67	27	40
Manikandan et al., 2021 [31]	India	2017	100	(40–69)	NR	36 (26:10)	16	16
Arun et al., 2019 [32]	India	2014–2015	1438	62.0	All type 2	250 (157:43)	151	

TABLE 2 | Quality assessment of reviewed articles on drug resistance in diabetic foot ulcers.

	Quality assessment								
Author	**Representativeness of the sample**	**Sample size**	**Non-responders**	**Ascertainment of the exposure (risk factor)**	**Comparability**	**Assessment of outcome**	**Statistical test**	**Sum/ max = 7**	**Descriptive score: 6–7 = very good, 4–5 = good, 2–3 = satisfactory, 1–0 = unsatisfactory**
Ali et al.	0	0	N/A	**	N/A	**	0	4	Good
Chincholikar et al.	*	0	N/A	**	N/A	**	0	5	Good
Chellan et al.	*	*	N/A	**	N/A	**	*	7	Very good
Tascini et al.	0	0	N/A	**	N/A	**	*	5	Good
Johargy et al.	*	0	N/A	**	N/A	**	0	5	Good
Kumar et al.	0	0	N/A	**	N/A	**	0	4	Good
Raiesi et al.	*	0	N/A	*	N/A	**	*	5	Good
Sugandhi et al.	0	*	N/A	**	N/A	**	*	6	Very good
Musyoki et al.	0	*	N/A	**	N/A	0	*	4	Good
Manikandan et al.	0	0	N/A	**	N/A	**	0	4	Good
Liu et al.	0	0	N/A	**	N/A	**	*	5	Good
Zubair et al.	0	0	N/A	**	N/A	**	*	5	Good
Matei et al.	0	0	N/A	**	N/A	**	*	5	Good
Wu et al.	0	0	N/A	**	N/A	**	*	5	Good
Manikandan et al.	0	0	N/A	**	N/A	**	0	4	Good
Arun et al.	0	0	N/A	**	N/A	**	*	5	Good

TABLE 3 | Drug resistance of *Candida* species in diabetic foot ulcers.

Type	Study (*n*)	Drug-resistant	CI 95%	I^2	*p*
Fluconazole	16	16.4	7.39–26.84	91.35	< 0.001
Flucytosine	8	6.10	0.21–16.30	86.58	0.02
Itraconazole	9	19.46	7.79–34.46	94.27	< 0.001
Voriconazole	10	7.30	1.03–16.74	89.41	< 0.001
Amphotericin B	14	10.43	2.27–21.02	91.78	< 0.001
Micafungin	5	7.28	0.06–21.72	93.48	0.04
Caspofungin	5	4.69	0.45–11.88	82.06	0.01
Nystatin	5	26.99	0.00–98.49	98.69	0.30
Miconazole	5	2.06	0.00–21.57	90.96	0.54

TABLE 4 | Meta-regression analysis of antifungal resistance in *Candida* species.

Drug	Variable	Coef	Adj R^2 (%)	*p*, 95% CI	*p**
Fluconazole	Years	0.006	46.25	0.470 (−0.011 to 0.024)	< 0.05
	Sample size	−0.001	46.25	0.042 (−0.003 to −0.000)	
Voriconazole	Years	0.014	74.53	0.172 (−0.007 to 0.036)	< 0.05
	Sample size	−0.0002	74.53	0.747 (−0.001 to 0.001)	
Amphotericin B	Years	0.014	47.31	0.096 (−0.002 to 0.031)	< 0.05
	Sample size	−0.001	47.31	0.161 (−0.002 to 0.00)	

TABLE 5 | Drug resistance of *Candida albicans* in diabetic foot ulcers.

Type	Study (*n*)	Drug-resistant	95% CI	I^2	*p*
Fluconazole	15	25.94	10.05–45.02	89.07	< 0.001
Flucytosine	7	8.35	0.36–21.68	59.63	0.02
Itraconazole	8	24.46	5.53–49.72	91.98	< 0.001
Voriconazole	9	10.74	1.35–24.75	78.74	0.01
Amphotericin B	13	13.91	3.03–28.85	83.03	< 0.001
Nystatin	5	32.48	0.00–99.68	94.72	0.23
Miconazole	5	1.18	0.00–21.73	76.73	< 0.001

TABLE 6 | Drug resistance of *Candida* non-*albicans* species in diabetic foot ulcers.

Type	Study (*n*)	Drug-resistant	95% CI	I^2	*p*
Fluconazole	13	10.65	3.80–19.66	80.59	< 0.001
Flucytosine	6	5.08	0.00–19.12	86.70	0.13
Itraconazole	7	19	6.69–35.05	87.61	< 0.001
Voriconazole	8	7.48	1.56–16.20	78.32	< 0.001
Amphotericin B	11	8.78	1.49–19.72	86.59	< 0.001

indicated that year and sample size did not play a role in this heterogeneity (p-value > 0.05), but based on the meta-regression results, the type of drug was likely to be influential in causing this observed heterogeneity. Data for voriconazole and amphotericin B are also presented in Table 4. The most common fungal species causing DFUs was *C. albicans*. In this study, fungi were divided into two groups: *C. albicans* and NAC species, and their analysis is presented in Tables 5 and 6, respectively. In *C. albicans*, nystatin had the highest resistance with 32.48%. Fluconazole and itraconazole were the next resistant strains. Miconazole was the most effective drug with only 1.18% resistance. In NAC species, only five drugs were present in at least five articles. Itraconazole recorded the highest and flucytosine the lowest drug resistance.

Several included studies reported that DFUs frequently presented as polymicrobial infections; however, detailed stratified data distinguishing fungal mono-infections from mixed bacterial–fungal infections were inconsistently reported. Therefore, subgroup analysis based on co-infection status was not feasible.

4 | Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis that investigates the prevalence of fungal drug resistance in DFU. Several similar reviews were done on drug resistant fungal strains various diseases, which indicates the importance of the topic. Dhasarathana et al. have investigated this issue in tuberculosis patients [33] and Habibzadeh et al. in coronavirus patients [34]. In a review study, Kessler et al. collected and analysed articles related to drug resistance of *C. albicans* in AIDS, cancer, kidney disease, candidemia and organ transplantation [35]. Others were also done on diabetes, but specifically not on DFUs. Although it occurs in a small proportion of diabetic patients, DFU is a serious complication that is being linked to other factors such as the duration of diabetes; increased body fat and body mass index; age; and the presence of retinopathy, nephropathy and neuropathy [36]. DFUs occur when there is prolonged poor diabetes control that leads to frequent exacerbation of the disease, weakened immunity, uncontrolled proliferation of opportunistic pathogens, including fungi in these patients. Chronic hyperglycaemia in diabetic patients has been shown to impair innate immune responses, including neutrophil chemotaxis, phagocytosis and intracellular killing capacity, thereby increasing susceptibility to persistent fungal colonization [37]. Furthermore, hyperglycaemic conditions may promote *Candida* biofilm formation in chronic wounds, which significantly reduces antifungal penetration and contributes to reduced azole susceptibility [38]. In addition, patients with DFUs are frequently exposed to repeated courses of broad-spectrum antibiotics, potentially altering the local microbiota and creating selective pressure favouring fungal overgrowth and antifungal resistance development [39]. However, it should be emphasized that the present meta-analysis did not include a non-diabetic comparator group and therefore no direct causal relationship between diabetes and antifungal resistance can be inferred. The fungal drug resistance of DFUs is different from diabetes itself. It should be noted that in Kessler's study, amphotericin B, itraconazole and ketoconazole recorded much higher resistance rates in diabetes than in other diseases. For these reasons, resistance is expected to be higher in DFU patients than in diabetic patients. However, it has been observed that the susceptibility of Candida species to antifungal agents varies over time and between countries and regions [40]. In the current review, 16 articles with the required quality were found legible and included. Most of the screened articles included all patients present at the sampling site and did not perform randomization of the sample. In some, the study sample included patients at the time of the study, not based on previous studies and formulas. Therefore, almost all studies were weak in the selection section. *C. albicans* is the most common fungal pathogen in humans, causing a wide range of infections from superficial mucosal to disseminated candidiasis [41]. Due to the dominance of this species, many studies aimed at investigating drug resistance divided fungi into two groups: *C. albicans* and NAC [13, 42]. In this study, for the same reason and, of course, the lack of information regarding any specific NAC species, this classification was adopted and reported alongside total drug resistance. Predictably, *C. albicans* was the predominant fungal species in DFUs. This finding was similar to previous reports [43, 44]. In the NAC group, *C. tropicalis* and *C. parapsilosis* were the most common fungi, followed by *C. glabrata*, *C. dubliniensis* and *C. lusitaniae*. Surprisingly, some studies have reported *C. parapsilosis* as the predominant species in DFU [19, 45]. This might be related to the age of the study population being paediatric or elderly (over 60) [13]. Kandregula et al. found *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. lusitaniae* and *C. glabrata* to be the dominant fungi in DFU [46]. Another hospital-based study reported *C. tropicalis*, *C. parapsilosis*, *C. glabrata* and *Candida krusei* as the most common *Candida* species, in that order, after *C. albicans* [13]. Also, one similar study reported *C. tropicalis*, *C. albicans* and *Candida guilliermondii*, respectively [42]. These reports were very similar to our findings in which *C. tropicalis* was identified as the most important species of NAC. In the current study, nystatin with 26.99% (p-value = 0.30) and miconazole with 2.06% (p-value = 0.54) resistance were identified as the best and worst drugs for treating *Candida* fungal infection in DFUs, but neither had sufficient p-value. Itraconazole with 19.46%, fluconazole with 16.4% and caspofungin with 4.69% resistance were the most important drugs with p-value < 0.05. Itraconazole and fluconazole were the most resistant in both *C. albicans* and NAC. Fluconazole was slightly higher in *C. albicans*. For all drugs, resistance was higher in *C. albicans* than in non-*albicans Candida*. The reason for this could be the limited data on non-*albicans* species. In our analysis, data from more than eight fungal species were lumped and analysed together, causing the overall resistance to be lower, even though some candidate species with high resistance were present in the present study. Our results revealed high resistance of *C. albicans* to Itraconazole (24.46%, p-value < 0.001). Similarly, another study on *Candida* blood stream infection reported 37.5% resistance to itraconazole [47]. In HIV-positive patients, resistance was 19% in *C. albicans* and varied between 8% and 48% in other species [48]. *Candida* samples from hospitals in India showed resistance of 4.2% [13]. These varied levels of resistance could be related to types of disease and the predominant *Candida* species in the study. Analysis of study on diabetic patients showed 27.77% resistance for *C. albicans* species [35], which was close to our result. Following the reports of increasing resistance after the high use of fluconazole increases the tendency to use itraconazole in clinical settings. This could be the reason for the high resistance to this drug. 16.4%, 25.94% and 10.65% of drug resistance to fluconazole was

found in total, *C. albicans* and non-*albicans* species (p-value < 0.001). Resistance to fluconazole in the United States has been reported to be up to 2% in *albicans* species and up to 13% in some non-*albicans* species [49, 50]. An analysis of 5 articles reported a 9.24% prevalence of resistance in *albicans* in diabetics [35]. Fluconazole is one of the most commonly prescribed antifungal drugs and this increase in resistance was expected [51]. The salient genetic adaptability of *C. albicans* allows it to rapidly adapt to and develop resistance to the drug. On the other hand, other *Candida* species have shown resistance to fluconazole through different mechanisms [52]. The overall resistance to amphotericin B was 10.43%. Musyoki et al. reported 0%, 4% and 10% resistance to this drug [25]. However, other results of the analysis of five studies showed a 9.24% resistance rate in *C. albicans* in diabetic patients [35], which is lower than in the present study (13.91%). In another report, the resistance rate of NAC to amphotericin B was 8.19%, which is similar to our finding. A variable resistance of *Candida* species to flucytosine has been reported in 4%–10% [19, 25, 53, 54]. In our study, resistance to flucytosine was 6.10%. Flucytosine resistance was somewhat higher in *C. albicans*. Voriconazole and micafungin had resistance rates of 7.30% and 7.28%, respectively. Resistance to these drugs was lower because aggressive drugs and are usually used in special cases and when resistance to other drugs was observed [55]. Miconazole had only 1.18% drug resistance in *C. albicans* (p-value < 0.001) and was identified as a highly effective drug. Polymicrobial infection is common in DFUs and has been widely reported in chronic wound settings [56]. Such microbial coexistence may influence antifungal susceptibility patterns through interspecies interactions, increased biofilm complexity and prior antimicrobial exposure [57]. The absence of consistent reporting on bacterial co-infection across studies represents a potential confounding factor in interpreting pooled resistance rates. Future investigations should stratify antifungal resistance data according to monomicrobial versus polymicrobial infection status to improve clinical applicability. Although this meta-analysis provides a quantitative synthesis of antifungal resistance patterns in DFU-associated *Candida* isolates, the findings should be interpreted with caution. The relatively small number of eligible studies, along with substantial heterogeneity observed across several analyses ($I^2 > 75\%$ in multiple drug categories), limits the generalizability of the pooled estimates. Therefore, these findings should be considered exploratory and hypothesis-generating rather than definitive.

5 | Limitations

This study has several limitations. First, the number of eligible studies was relatively small, which may reduce the statistical power and external validity of the pooled estimates. Second, substantial heterogeneity was observed in several analyses, possibly due to variations in study design, geographic distribution, antifungal susceptibility testing methods and patient characteristics. Third, for some antifungal agents such as miconazole and nystatin, the number of included studies was limited, reducing the reliability of the estimates. Finally, limited data regarding individual non-*albicans Candida* species prevented species-specific resistance analysis. Additionally, the lack of consistent data regarding concomitant bacterial infections limited our ability to adjust for polymicrobial infection as a potential confounder.

6 | Conclusion

The findings of this study suggest that antifungal resistance among *Candida* species isolated from DFUs appears to be considerable, particularly for azole antifungals such as itraconazole and fluconazole. However, given the limited number of studies and observed heterogeneity, these results should be interpreted cautiously. Larger, well-designed multicentre studies are warranted to provide more definitive evidence. Although biological mechanisms may plausibly link chronic hyperglycaemia to altered antifungal susceptibility, our findings do not establish a causal relationship between diabetes severity and antifungal resistance. Among the drugs examined, itraconazole and fluconazole showed the highest rates of resistance, which should be considered when prescribing drugs to diabetic patients with DFUs. Caspofungin, micafungin and voriconazole have been observed to be more effective treatment options for fungal infections in this group of patients. Future studies shall be more comprehensive and detailed to specifically examine each *Candida* species individually and analyse their drug resistance patterns. Also, a complete and systematic evaluation of the efficacy and resistance to all available antifungal drugs could lead to design of more targeted and efficient treatment protocols for patients with DFUs.

Acknowledgements

Sincere gratitude to all professors and students of the Department of Parasitology, School of Allied Medical Sciences, Ilam University of Medical Sciences, Iran.

Funding

This study was funded by Ilam University of Medical Sciences, Ilam, Iran, under grant number IR.MEDILAM.REC.1403.191.

Ethics Statement

The Ethical Committee of Ilam University of Medical Sciences, Ilam, Iran approved this research with the code IR.MEDILAM.REC.1403.191.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

In this study, all data and materials are included. If more information is needed, please contact the author for data requests.

References

1. American Diabetes Association, "Diagnosis and Classification of Diabetes Mellitus," *Diabetes Care* 33, no. Suppl 1 (2010): S62–S69.

2. A. Hadadi, H. O. Ghiasi, M. Hajiabdolbaghi, M. Zandekarimi, and R. Hamidian, "Diabetic Foot: Infections and Outcomes in Iranian Admitted Patients," *Jundishapur Journal of Microbiology* 7, no. 7 (2014): e11680.

3. D. G. Armstrong, A. J. Boulton, and S. A. Bus, "Diabetic Foot Ulcers and Their Recurrence," *New England Journal of Medicine* 376, no. 24 (2017): 2367–2375.

4. S. G. Rooh-Ul-Muqim and M. Ahmed, "Evaluation and Management of Diabetic Foot According to Wagner's Classification a Study of 100 Cases," *Skin* 66, no. 10.4 (2003): 22.9.

5. S. Singh, G. Banerjee, J. Agarwal, V. Kumar, and K. Usman, "Spectrum of Microbiota in Diabetic Foot Infections in a Teaching Hospital of Uttar Pradesh," *International Journal of Medical Science and Public Health* 7, no. 9 (2018): 741–748.

6. F. Rizvi, Z. H. Khawaja, N. Mehmood, S. Zeeshan, M. Afzal, and A. Baig, "Frequency and Extent of Foot Lesion and the Susceptibility Pattern of Infective Organisms in Diabetic Foot," *Annals of Punjab Medical College* 3, no. 1 (2009): 36–40.

7. S. H. Won, C. Y. Chung, M. S. Park, et al., "Risk Factors Associated With Amputation-Free Survival in Patient With Diabetic Foot Ulcers," *Yonsei Medical Journal* 55, no. 5 (2014): 1373–1378.

8. M. Polikandrioti, G. Vasilopoulos, I. Koutelekos, et al., "Quality of Life in Diabetic Foot Ulcer: Associated Factors and the Impact of Anxiety/Depression and Adherence to Self-Care," *International Journal of Lower Extremity Wounds* 19, no. 2 (2020): 165–179.

9. L. Kalan, M. Loesche, B. P. Hodkinson, et al., "Redefining the Chronic-Wound Microbiome: Fungal Communities Are Prevalent, Dynamic, and Associated With Delayed Healing," *MBio* 7, no. 5 (2016): e01058-16, https://doi.org/10.1128/mBio.01058-16.

10. A. Devasia, L. A. John, S. U. Velladath, P. Y. Prakash, C. A. Mohammad, and K. S. Shettigar, "Bacterial and Fungal Profile of Diabetic Foot Ulcer," *Biomedicine* 42, no. 6 (2022): 1372–1375.

11. J. Kaur and C. J. Nobile, "Antifungal Drug-Resistance Mechanisms in Candida Biofilms," *Current Opinion in Microbiology* 71 (2023): 102237.

12. M. B. Marak and B. Dhanashree, "Antifungal Susceptibility and Biofilm Production of Candida spp. Isolated From Clinical Samples," *International Journal of Microbiology* 2018, no. 1 (2018): 7495218.

13. N. Pahwa, R. Kumar, S. Nirkhiwale, and A. Bandi, "Species Distribution and Drug Susceptibility of Candida in Clinical Isolates From a Tertiary Care Centre at Indore," *Indian Journal of Medical Microbiology* 32, no. 1 (2014): 44–48.

14. D. Moher, A. Liberati, J. Tetzlaff, and D. G. Altman, "PRISMA Group* t. Preferred Reporting Items for Systematic Reviews and meta-Analyses: The PRISMA Statement," *Annals of Internal Medicine* 151, no. 4 (2009): 264–269.

15. W. Ga, "The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses," in *Proceedings of the 3rd Symposium on Systematic Reviews: Beyond the Basics* Oxford, UK, 3–5 July (2000).

16. R. Herzog, M. J. Álvarez-Pasquin, C. Díaz, J. L. Del Barrio, J. M. Estrada, and Á. Gil, "Are Healthcare Workers' Intentions to Vaccinate Related to Their Knowledge, Beliefs and Attitudes? A Systematic Review," *BMC Public Health* 13 (2013): 1–17.

17. H. Ali, S. Khaliq, B. Ali, N. Ali, and S. A. Abbasi, "Frequency and Antifungal Susceptibility of *Candida albicans* and Non-*albicans Candida* Isolates From Diabetic Foot Ulcer at Tertiary Care Hospitals of Peshawar," *Journal of the Liaquat University of Medical and Health Sciences* 23, no. 2 (2024): 107–111.

18. D. A. Chincholikar and R. B. Pal, "Study of Fungal and Bacterial Infections of the Diabetic Foot," *Indian Journal of Pathology & Microbiology* 45, no. 1 (2002): 15–22.

19. G. Chellan, S. Shivaprakash, S. Karimassery Ramaiyar, et al., "Spectrum and Prevalence of fungi Infecting Deep Tissues of Lower-Limb Wounds in Patients With Type 2 Diabetes," *Journal of Clinical Microbiology* 48, no. 6 (2010): 2097–2102.

20. C. Tascini, A. Piaggesi, E. Tagliaferri, et al., "Microbiology at First Visit of Moderate-To-Severe Diabetic Foot Infection With Antimicrobial Activity and a Survey of Quinolone Monotherapy," *Diabetes Research and Clinical Practice* 94, no. 1 (2011): 133–139.

21. A. K. Johargy, "Antimicrobial Susceptibility of Bacterial and Fungal Infections Among Infected Diabetic Patients," *Depression* 8, no. 9 (2016): 1291–1295.

22. D. Kumar, T. Banerjee, J. Chakravarty, S. K. Singh, A. Dwivedi, and R. Tilak, "Identification, Antifungal Resistance Profile, in Vitro Biofilm Formation and Ultrastructural Characteristics of Candida Species Isolated From Diabetic Foot Patients in Northern India," *Indian Journal of Medical Microbiology* 34, no. 3 (2016): 308–314.

23. O. Raiesi, M. Siavash, F. Mohammadi, et al., "Frequency of Cutaneous Fungal Infections and Azole Resistance of the Isolates in Patients With Diabetes Mellitus," *Advanced Biomedical Research* 6, no. 1 (2017): 71.

24. P. Sugandhi and D. A. Prasanth, "Prevalence of Yeast in Diabetic Foot Infections," *International Journal of Diabetes in Developing Countries* 37 (2017): 50–57.

25. V. M. Musyoki, "Speciation and Antifungal Susceptibility of candida Isolates From Diabetic Foot Ulcer Patients in Kenyatta National Hospital: University of Nairobi," 2019.

26. J. Manikandan, S. Jaikumar, and T. Sandhya Rani, "Microbiological Profile and Drug Resistant Organism's Pattern in Diabetic Foot Ulcer Patients at Tertiary Care Hospital Puducherry," *International Journal of Research in Pharmaceutical Sciences* 11, no. 4 (2020): 6692–6697.

27. W. Liu, L. Y. Song, W. Sun, W. J. Fang, and C. J. Wang, "Distribution of Microbes and Antimicrobial Susceptibility in Patients With Diabetic Foot Infections in South China," *Frontiers in Endocrinology* 14 (2023): 14.

28. M. Zubair, F. M. Husain, M. Al-Amri, et al., "In Vitro Inhibition of Biofilm and Virulence Factor Production in Azole-Resistant Strains of *Candida albicans* Isolated From Diabetic Foot by *Artemisia vulgaris* Stabilized Tin (IV) Oxide Nanoparticles," *Frontiers in Cellular and Infection Microbiology* 13 (2023): 1322778.

29. S.-C. Matei, C. S. Dumitru, A. M. Fakhry, et al., "Bacterial Species Involved in Venous Leg Ulcer Infections and Their Sensitivity to Antibiotherapy—An Alarm Signal Regarding the Seriousness of Chronic Venous Insufficiency C6 Stage and Its Need for Prompt Treatment," *Microorganisms* 12, no. 3 (2024): 472.

30. M. X. Wu, H. Pan, W. L. Leng, X. T. Lei, L. Chen, and Z. W. Liang, "Distribution of Microbes and Drug Susceptibily in Patients With Diabetic Foot Infections in Southwest China," *Journal of Diabetes Research* 2018 (2018): 1–9.

31. J. Manikandan and S. Jaikumar, "Prevalence and Characterization of Opportunistic Candidal Infection Among Diabetic Foot Ulcer Patients, Puducherry," *Annals Of The Romanian Society For Cell Biology* 25 (2021): 3490–3500.

32. C. S. Arun, P. Raju, V. Lakshmanan, A. Kumar, A. Bal, and H. Kumar, "Emergence of Fluconazole-Resistant candida Infections in Diabetic Foot Ulcers: Implications for Public Health," *Indian Journal of Community Medicine* 44, no. Supp 1 (2019): S74–S76.

33. P. Dhasarathan, M. S. AlSalhi, S. Devanesan, et al., "Drug Resistance in *Candida albicans* Isolates and Related Changes in the Structural Domain of Mdr1 Protein," *Journal of Infection and Public Health* 14, no. 12 (2021): 1848–1853.

34. A. Habibzadeh, K. B. Lankarani, M. Farjam, et al., "Prevalence of Fungal Drug Resistance in COVID-19 Infection: A Global

meta-Analysis," *Current Fungal Infection Reports* 16, no. 4 (2022): 154–164.

35. S. Q. S. Kessler, P. M. Lang, T. S. Dal-Pizzol, and F. Montagner, "Resistance Profiles to Antifungal Agents in *Candida albicans* Isolated From Human Oral Cavities: Systematic Review and meta-Analysis," *Clinical Oral Investigations* 26, no. 11 (2022): 6479–6489.

36. W. Tang, Y. Zhao, Z. Cheng, J. Xu, Y. Zhang, and X. Liu, "Risk Factors for Diabetic Foot Ulcers: A Systematic Review and meta-Analysis," *Vascular* 32, no. 3 (2024): 661–669.

37. H. Lee, M.-J. Kim, I.-K. Lee, C.-W. Hong, and J.-H. Jeon, "Impact of Hyperglycemia on Immune Cell Function: A Comprehensive Review," *Diabetology International* 15, no. 4 (2024): 745–760.

38. A. Malik, Z. Mohammad, and J. Ahmad, "The Diabetic Foot Infections: Biofilms and Antimicrobial Resistance," *Diabetes and Metabolic Syndrome: Clinical Research and Reviews* 7, no. 2 (2013): 101–107.

39. R. Howell-Jones, M. Wilson, K. E. Hill, A. Howard, P. E. Price, and D. W. Thomas, "A Review of the Microbiology, Antibiotic Usage and Resistance in Chronic Skin Wounds," *Journal of Antimicrobial Chemotherapy* 55, no. 2 (2005): 143–149.

40. M. A. Pfaller, D. Diekema, and Group IFSP, "Twelve Years of Fluconazole in Clinical Practice: Global Trends in Species Distribution and Fluconazole Susceptibility of Bloodstream Isolates of Candida," *Clinical Microbiology and Infection* 10 (2004): 11–23.

41. F. Fan, Y. Liu, Y. Liu, et al., "*Candida albicans* Biofilms: Antifungal Resistance, Immune Evasion, and Emerging Therapeutic Strategies," *International Journal of Antimicrobial Agents* 60, no. 5–6 (2022): 106673.

42. S. Gupta and R. Goyal, "Species Distribution and Antifungal Drug Susceptibility of candida in Clinical Isolates From a Tertiary Care Centre at Bareilly," *IOSR Journal of Dental and Medical Sciences* 16 (2017): 57–61.

43. S. Abilash, N. Kannan, K. Rajan, M. Pramodhini, and M. Ramanathan, "Clinical Study on the Prevalance of Fungal Infections in Diabetic Foot Ulcers," *International Journal of Current Research and Review* 7, no. 23 (2015): 8.

44. A. M. Ozturk, M. Taşbakan, D. Y. Metin, et al., "A Neglected Causative Agent in Diabetic Foot Infection: A Retrospective Evaluation of 13 Patients With Fungal Etiology," *Turkish Journal of Medical Sciences* 49, no. 1 (2019): 81–86.

45. A. Gitau, W. Sigilai, C. Bii, and M. Mwangi, "Fungal Infections Among Diabetic Foot Ulcer-Patients Attending Diabetic Clinic in Kenyatta National Hospital, Kenya," *East African Medical Journal* 88, no. 1 (2011): 9–17.

46. S. Kandregula, A. Behura, C. R. Behera, et al., "A Clinical Significance of Fungal Infections in Diabetic Foot Ulcers," *Cureus* 14, no. 7 (2022): e26872.

47. T. Y. Tan, A. L. Tan, N. Tee, and L. Ng, "A Retrospective Analysis of Antifungal Susceptibilities of Candida Bloodstream Isolates From Singapore Hospitals," *Annals of the Academy of Medicine, Singapore* 37, no. 10 (2008): 835–840.

48. A. Keyvanfar, H. Najafiarab, N. Talebian, et al., "Drug-Resistant Oral Candidiasis in Patients With HIV Infection: A Systematic Review and meta-Analysis," *BMC Infectious Diseases* 24, no. 1 (2024): 546.

49. A. A. Cleveland, M. M. Farley, L. H. Harrison, et al., "Changes in Incidence and Antifungal Drug Resistance in Candidemia: Results From Population-Based Laboratory Surveillance in Atlanta and Baltimore, 2008–2011," *Clinical Infectious Diseases* 55, no. 10 (2012): 1352–1361.

50. M. Pfaller, P. Rhomberg, S. Messer, R. Jones, and M. Castanheira, "Isavuconazole, Micafungin, and 8 Comparator Antifungal Agents' Susceptibility Profiles for Common and Uncommon Opportunistic fungi Collected in 2013: Temporal Analysis of Antifungal Drug Resistance Using CLSI Species-Specific Clinical Breakpoints and Proposed Epidemiological Cutoff Values," *Diagnostic Microbiology and Infectious Disease* 82, no. 4 (2015): 303–313.

51. M. A. Pfaller, D. Diekema, D. Gibbs, et al., "Results From the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: A 10.5-Year Analysis of Susceptibilities of Candida Species to Fluconazole and Voriconazole as Determined by CLSI Standardized Disk Diffusion," *Journal of Clinical Microbiology* 48, no. 4 (2010): 1366–1377.

52. E. L. Berkow and S. R. Lockhart, "Fluconazole Resistance in Candida Species: A Current Perspective," *Infection and Drug Resistance* 10 (2017): 237–245.

53. A. Schmalreck, B. Willinger, G. Haase, et al., "Species and Susceptibility Distribution of 1062 Clinical Yeast Isolates to Azoles, Echinocandins, Flucytosine and Amphotericin B From a Multi-Centre Study," *Mycoses* 55, no. 3 (2012): e124–e137.

54. P. Mnge, B. Okeleye, S. Vasaikar, and T. Apalata, "Species Distribution and Antifungal Susceptibility Patterns of Candida Isolates From a Public Tertiary Teaching Hospital in the Eastern Cape Province, South Africa," *Brazilian Journal of Medical and Biological Research* 50, no. 6 (2017): e5797.

55. Z. Javorova Rihova, L. Slobodova, and A. Hrabovska, "Micafungin Is an Efficient Treatment of Multi Drug-Resistant *Candida glabrata* Urosepsis: A Case Report," *Journal of Fungi* 7, no. 10 (2021): 800.

56. P. J. Buch, Y. Chai, and E. D. Goluch, "Treating Polymicrobial Infections in Chronic Diabetic Wounds," *Clinical Microbiology Reviews* 32, no. 2 (2019): e00091-18, https://doi.org/10.1128/cmr.00091-18.

57. C. B. Costa-Orlandi, J. C. Sardi, N. S. Pitangui, et al., "Fungal Biofilms and Polymicrobial Diseases," *Journal of Fungi* 3, no. 2 (2017): 22.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** iwj70900-sup-0001-Supinfo.pdf.