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Effects of biofilm formation and plethora of *Candida* species causing ailments: a mini review

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Abstract

Biofilm formation is an independent predictor of higher mortality rate and significant virulence factor that increase the dissemination ability and persistence of *Candida* species. However, *Candida* species distribution differs in population based studies evaluated in different geographical locations. This study aimed to evaluate the biofilm associated mortality rate, spectrum and resistance profile of *Candida* species. A systemic literature review was carried out to evaluate all current epidemiology that reports the incidence of the biofilm associated mortality rate, spectrum and resistance profile of *Candida* species. Several studies used optical density of the biomass from culture to measure biofilm formation. Data regarding the prevalence of *Candida* species, in vitro biofilm assay and rate of biofilm-related *Candida* species in clinical isolates were also extracted from the case-control, cohort, and retrospective studies. The result of this study shows that the mortality rate due to biofilm associated infections ranged from 6.9% to 70.0% and biofilm formation varied greatly from 27.2% to 100% evaluated from different published studies. *Candida albicans* was the predominant pathogen and the percentage frequency of the isolates ranged from 36.3% to 78.5%. The distribution of *Candida* species from 2016 to 2020 revealed that *Candida albicans* (39.42%) had the highest percentage frequency. High prevalence of *Candida* species was reported in 2018 (28.2%). The current data revealed that United Kingdom, Spain, Austria and Norway shows resistance profile for *Candida tropicalis*, *Candida albicans*, *Candida parapsilosis* and *Candida glabrata*. Biofilm formation is considered as potential risk factor of higher mortality rate and effective antifungal agents to eliminate or reduce this menace is urgently needed. The reports of the biofilm-forming potentials and properties among *Candid*a species could provide a remarkable step toward the improvement of *Candida* infection therapies.

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1.0 Introduction

Candida species have emerged as one of the most common causes of invasive fungal infections, and described as an opportunistic infection or systemic mycosis. National Institutes of Health reported that biofilms are significantly responsible either directly or indirectly, for more than 80% of all microbial infections in the United States (Atiencia-Carrera *et al*., 2022). *Candida* species can produce well-structured biofilms, contained multiple types of cell and microbial species, resulting to an intrinsic resistance against various forms of stress factors such as immune defense mechanisms and multiple antifungal agents (Polke *et al*., 2015). The population group that are more prone for invasive candidiasis includes patients with a central venous catheter, hematopoietic cell and solid organ transplantation, parenteral nutrition, recent abdominal surgery, hematological and solid organ malignancy or critical ill patients (Tsay *et al*., 2020). Premature newborns and patients that received broad spectrum of antibiotics are also prone to invasive candidiasis. In the early 1990s, the number of episode

of sepsis and fungal infections has been increasing and have become a major challenge in hospitals (Guinea, 2014). Several studies have reported the incidence of candidemia as 72.8 per million in population and *Candida* species remains the most predominant causative agents of invasive fungal infections compared to mucormycosis and aspergillosis (Rees *et al*., 1998). *Candida* related infection is a consequence of advances in health care especially in developing countries. Currently, the incidence of candidemia has been increasing, even with the progressive development in diagnostic criteria, commercialization of new antifungal agents and the implementation methods to prevent the dissemination of fungal infections (Pfeller and Diekema, 2007). Most of the infections caused by invasive *Candida* species, the diagnosis still remain complicated to laboratory scientists or clinicians using blood cultures for identification of the clinical isolates (Berenguer *et al*., 1993). The true incidence and epidemiology of invasive candidiasis is uncertain in most of the reported studies. The hospitalization bill for each episode of *Candida* related infections is approximately 40, 000 USD with attributable mortality rate of 15 – 35% in adults and 10 – 15% for neonates in some studies (Guinea, 2014). Late mortality is associated with factors such as baseline condition of the host, and early mortality is associated with factors related to the early removal of central venous catheters and appropriate antifungal treatment in patients (Puig-Asensio *et al*., 2014). Currently, this systemic fungal infection is the 4th leading nosocomial infection and reported about 40% of mortality rate in the United Sates (Thompson *et al*., 2019). Systemic mycosis caused by *Candida* species can be categorized into three classes which include deep-seated candidiasis, bloodstream infection (candidemia) or combination of both classes (Lagunes and Rello, 2016). Some culture media are used specifically to diagnose deep candidiasis from tissue biopsies, and blood culture is used commonly to diagnose candidemia. However, the gold standard for the diagnosis of invasive fungal infection is the culture media (Pappas *et al*., 2015). Nosocomial infections are closely related with biofilms growing attached to host tissues or medical devices (Chandra and Mukherjee, 2015). *Candida* biofilm formation strains are associated with significant mortality rate, apparently correlated with the poor permeability of the matrix to the antifungal agents (Tascini *et al*., 2017). Biofilms are the common growth state of numerous microorganisms, being a zone of irreversible adherent cells with different structural and phenotypic properties when compared to planktonic cells (Atiencia-Cerrera *et al*., 2022). It was reported that *Candida* biofilms suppress the innate immunity system of the host and the dynamics of biofilm-host association is not fully understood (Johnson *et al*., 2016). The biofilm formation forming fungal cells are commonly found on hospital surfaces which usually persist on biomedical devices and nosocomial environment (Tascini *et al*., 2017). *Candida* species resist many antifungal agents, indicated a serious menace for public health. In Europe, the incidence of *Candida* bloodstream increased from 2.2 cases in every 100,000 population to 3.2 cases in 100,000 population annually (Koehler *et al*., 2019). The trends in resistance profile against echinocandines and azole can distort the treatment of *Candida* bloodstream infection due to inadequate therapeutic options. *Candida glabrata* and *Candida parapsilosis* are also common clinical isolates causing invasive candidiasis and prevalence changes at different locations. In Northern Europe, *Candida glabrata* account for 9% to 21.1% of *Candida* bloodstream infection cases while in the Mediterranean region, *Candida parapsilosis* is more common (Galia *et al*., 2022). Currently, surveillance studies have raised the concern regarding the context of multidrug resistant data among non-*albicans Candida* species and *Candida albicans* (Arendrup *et al*., 2017). In the global context of *Candida auris*, the preservation of current antifungal therapy has increased due to nosocomial outbreak with high mortality and morbidity. The Centers for Disease Control and Prevention (CDC) added fungal infections in the priority list of the Antibiotic Resistance Threats Report in 2019 (Galia *et al*., 2022).

2.0 Materials and Methods

2.1 Data Selection and Search Strategy

This study was carried out following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategies (Zeng *et al*., 2015). Google Scholar, Web of Science, PubMed and Scopus databases were searched for relevant published articles using the following terms: candidemia, invasive candidiasis, candidiasis, bloodstream infections, effective antifungal drugs, biofilm formation, *Candida* species, biofilm associated infections, resistance data of *Candida* species, mortality rate associated with biofilm formation, prevalence and distribution of *Candida* species. In each electronic database, a combination of the mentioned terms was used to conduct the search again. The references of the relevant published articles was also searched for finding additional information. The data selection was based on human clinical isolates.

2.2 Eligibility Criteria

The major inclusion criteria included the published articles that reports the prevalence of biofilm associated to *Candida* species and the rate of biofilm formation including retrospective, cohort and case-control studies. The information regarding the geographical region of the study, the mortality rate,

and the use of antifungal therapy in clinical isolates were also extracted from the relevant studies. All studies without relevant data about prevalence of *Candida* species, biofilm formation, antifungal therapy against *Candida* isolates were excluded. Concerning antifungal resistance rate, only studies that used European Committee on Antimicrobial Susceptibility Testing EUCAST or standard susceptibility tests according to the Clinical and Laboratory Standards Institute (CLSI) was considered for this current study. Finally, articles without duplicate reports on different databases, full text available and studies with missing or unclear information was also excluded.

2.3 Statistical Analysis

Descriptive statistics (Frequency) of the distribution of *Candida* species were enumerated and subjected to graphic profile using IBM® SPSS® Statistics version 25.0 (IBM® Corp., Armonk, NY, USA).

3.0 Results

Table 1 is the prevalence of biofilm formation and mortality rate. The result shows that the biofilm formation in this study varied greatly from 27.2% to 100% evaluated from different published studies. The mortality rate due to biofilm associated infections ranged from 6.9% to 70.0%. Figure 1 is the distribution of *Candida* species from the studies. The result shows that *Candida albicans* (34.1%) had the highest percentage frequency followed by *Candida tropicalis* (22.7%), *Candida glabrata* (15.9%), *Candida parapsilosis* (13.6%), *Candida krusei* (9.1%), *Candida dubliniesis* (2.3%) and *Candida guilliermondii* (2.3%) respectively. Table 2 is the prevalence of *Candida albicans* and predominant *Candida* species. The result shows that the *Candida albicans* are the predominant pathogens and the percentage frequency of the isolates ranged from 36.3% (102 clinical isolates) to 78.5% (177 clinical isolates). Table 3 is the prevalence of *Candida* species from 2016 to 2020 in Istanbul, Turkey. The result from 2016 to 2020 shows that the common pathogen was *Candida albicans* (39.42%) followed by *Candida parapsilosis* (34.02%) and least pathogens were *Candida guilliermondii* (0.41%) and *Candida dubliniensis* (0.41%). High prevalence of *Candida* species was reported in 2018 (28.2%) compared to 2016 (14.1%), 2017 (18.3%), 2019 (24.5%) and 2020 (14.9%) respectively. Table 4 is the resistance data of *Candida* species from blood specimen. The result shows that the United Kingdom, Spain, Austria and Norway reported resistance profile for *Candida tropicalis*, *Candida albicans*, *Candida parapsilosis* and *Candida glabrata*. Currently, no study reported the resistance profile for other *Candida* species. Amphotericin B, anidulafungin, micafungin, voriconazole, fluconazole, posaconazole and itraconazole resistance in *Candida* species were the most frequent drug-species combination reported.

Table 1. Prevalence of biofilm formation and mortality rate

Country	Technique used to measure biofilm	Biofilm rate in number and percentage	Biofilm formation in number and percentage			Association between biofilm and resistance	Attributable mortality rate in number and percentage	References
			Low	Medium	High			
Hungary	Using micro plate reader with crystal violet staining (550 nm)	127/127 (100.0%)	28 (22.0%)	69 (54.4%)	30 (23.6%)	No	70 (55.1%)	(Vitalis *et al.*, 2020)
Thailand	Using micro plate reader with yellow tetrazolium salt (490 nm)	38/46 (82.6%)	13 (28.3%)		25 (54.3%)	No	13 (34.2%)	(Pham *et al.*, 2019)
Brazil	Using micro plate reader with crystal violet staining (570 nm)	13/13 (100.0%)	3 (23.1%)	7 (53.8%)	3 (23.1%)	No		(Herek *et al.*, 2019)
Mexico	Using micro plate reader with crystal violet staining (595 nm)	89/89 (100%)				No	32 (35.9%)	(Trevino-Rangel *et al.*, 2018)
Italy	Using micro plate reader with	190/190 (100.0%)	68 (35.8%)	38 (20.0%)	84 (44.2%)	No	89 (46.8%)	(Soldini *et al.*, 2018)

Country	Technique used to measure biofilm	Biofilm rate in number and percentage	Biofilm formation in number and percentage			Association between biofilm and resistance	Attributable mortality rate in number and percentage	References
			Low	Medium	High			
	crystal violet staining (540 nm)							
India	Using micro plate reader with crystal violet staining (570 nm)	55/74 (74.3%)				No		(Tulasidas *et al*., 2018)
Italy	Using micro plate reader with yellow tetrazolium salt (490 nm)	57/89 (64.0%)				No	25 (43.9%)	(Tascini *et al*., 2017)
Scotland	Using micro plate reader with crystal violet staining (570 nm)	245/280 (87.5%)	56 (22.9%)	44 (17.9%)	144 (58.9%)	Yes		(Rajendran *et al*., 2016)
India	Branchini's method	31/80 (38.8%)				No	5 (16.1%)	(Banerjee *et al*., 2015)
Spain	Using micro plate reader with crystal violet staining (550 nm)	45/54 (83.3%)				No		(Guembe *et al*., 2014)
Brazil	Christensen's method	15/28 (53.6%)				No	6 (40.0%)	(Rodrigues *et al*., 2014)
Italy	Using micro plate reader with yellow tetrazolium salt (490 nm)	160/451 (35.5%)	44 (27.5%)		116 (72.5%)	No	11 (6.9%)	(Tortorano *et al*., 2013)
Italy	Using micro plate reader with yellow tetrazolium salt (490 nm)	297/297 (100.0%)	60 (20.2%)	141 (47.5%)	96 (32.3%)	No	65 (21.9%)	(Prigitano *et al*., 2012)
Italy	Phosphate Buffered Saline (405 nm) and Using micro plate reader with yellow tetrazolium salt (490 nm)	84/207 (40.6%)				No	43 (51.2%)	(Tumbarello *et al*., 2012)
Italy	Phosphate Buffered Saline (405 nm) and Using micro plate reader with yellow tetrazolium salt (490 nm)	80/294 (27.2%)				No	56 (70.0%)	(Tumbarello *et al*., 2007)

Table 2. The prevalence of *Candida albicans* and predominant *Candida* species

S/N	Country	Number of Clinical Isolates	Clinical Specimen	Number and percentage of *Candida albicans* Isolates	Predominant *Candida* Species	References
1.	Ethiopia	194	Numerous	104 (49.8%)	*Candida krusei*, *Candida albicans*	(Seyoum *et al*., 2020)
2.	Ethiopia	81	Vaginal swab	51 (58.6%)	*Candida krusei*, *Candida dubliniesis*, *Candida albicans*	(Bitew and Abebaw, 2018)
3.	India	102	Numerous	37 (36.3%)	*Candida albicans*, *Candida tropicalis*, *Candida guilliermondii*	(Sida *et al*., 2017)
4.	Egypt	63	Vaginal Swab	38 (60.3%)	*Candida krusei*, *Candida glabrata*, *Candida albicans*	(Elfeky *et al*., 2016)
5.	India	90	Numerous	33 (36.7%)	*Candida tropicalis*, *Candida glabrata*, *Candida albicans*	(Kaur *et al*., 2016)
6.	India	90	Numerous	33 (36.7%)	*Candida tropicalis*, *Candida parapsilosis*, *Candida albicans*	(Das *et al*., 2016)
7.	Brazil	103	Oral (HIV patients)	80 (77.8%)	*Candida tropicalis*, *Candida parapsilosis*, *Candida albicans*	(Ribeiro *et al*., 2015)
8.	Thailand	250	Oral Cavity	154 (61.6%)	*Candida tropicalis*, *Candida glabrata*, *Candida albicans*	(Muadcheingka and Tantivitayakul, 2015)
9.	Ethiopia	177	Oral (HIV patients)	139 (78.5%)	*Candida tropicalis*, *Candida glabrata*, *Candida albicans*	(Mulu *et al*., 2013)
10.	Germany and Austria	1062	Numerous	573 (54.0%)	*Candida glabrata*, *Candida parapsilosis*, *Candida albicans*	(Schmalreck *et al*., 2012)
11.	India	111	Numerous	44 (39.6%)	*Candida tropicalis*, *Candida krusei*, *Candida albicans*	(Mohandas and Balla, 2011)
12.	Iran	428	Numerous	273 (63.8%)	*Candida parapsilosis*, *Candida tropicalis*, *Candida albicans*	(Badiee and Alborzi, 2011)
13.	Taiwan	108	Blood	61 (56.5%)	*Candida tropicalis*, *Candida glabrata*, *Candida albicans*	(Chi *et al*., 2011)
14.	America	580	Vaginal swab	420 (72.4%)	*Candida parapsilosis*, *Candida glabrata*, *Candida albicans*	(Richter *et al*., 2005)
15.	Latin America	103	Blood	43 (42.0%)	*Candida parapsilosis*, *Candida tropicalis*, *Candida albicans*	(Godoy *et al*., 2003)

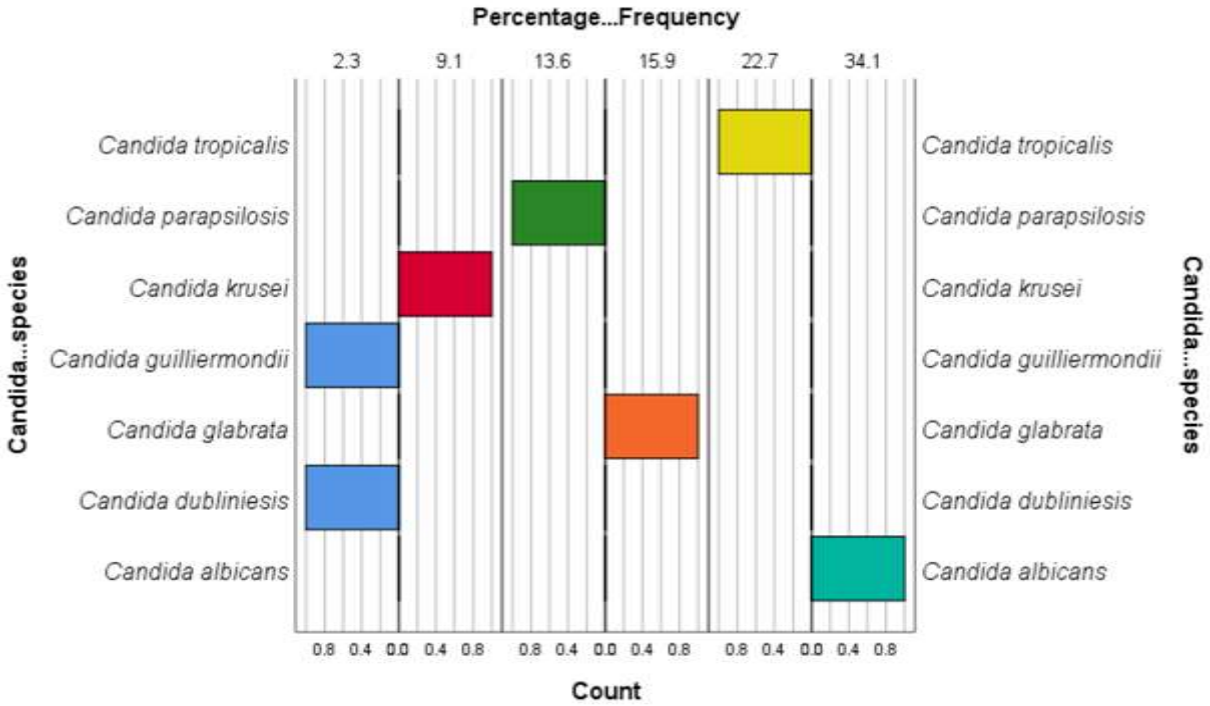

Figure 1. Distribution of Candida species from the clinical specimens

Table 3. Distribution of *Candida* species from 2016 to 2020 in Istanbul, Turkey

S/N	Isolated *Candida* species	2016	2017	2018	2019	2020	Total (%)	References
1.	*Candida guilliermondii*	0	0	0	1	0	1 (0.41)	(Yardimci and Arman, 2021)
2.	*Candida kefyr*	1	2	1	0	0	4 (1.66)	
3.	*Candida albicans*	18	18	28	17	14	95 (39.42)	
4.	*Candida dubliniensis*	0	0	0	1	0	1 (0.41)	
5.	*Candida parapsilosis*	7	13	26	22	14	82 (34.02)	
6.	*Candida rugosa*	0	1	0	0	0	1 (0.41)	
7.	*Candida glabrata*	3	3	3	7	2	18 (7.47)	
8.	*Candida famata*	0	1	1	0	1	3 (1.24)	
9.	*Candida tropicalis*	1	4	5	5	2	17 (7.05)	
10.	*Candida lusitaniae*	1	1	1	1	0	4 (1.66)	
11.	*Candida krusei*	3	1	3	5	3	15 (6.22)	
	Total	34 (14.1)	44 (18.3)	68 (28.1)	59 (24.5)	36 (14.9)	241(100)	

Table 4. Resistance data of *Candida* species from blood specimen

S/N	Antifungal Class	Antifungal Drug	*Candida tropicalis*	*Candida albicans*	*Candida parapsilosis*	*Candida glabrata*	Reference
1.	Polyene	Amphotericin B	Austria; Norway	United Kingdom; Austria; Spain; Norway	United Kingdom; Austria; Spain; Norway	United Kingdom; Austria; Spain; Norway	(Galia *et al*., 2022)
2.	Echninocandin	Anidulafungin	Norway; Austria	Norway; Austria	Norway; Austria	Norway; Austria	
		Micafungin	Austria	Norway; Austria	Norway; Austria	Norway; Austria	
3.	Azole	Voriconazole	Norway; Austria	United Kingdom; Austria; Spain; Norway	United Kingdom; Austria; Spain; Norway	United Kingdom; Austria; Spain	
		Fluconazole	Norway; Austria	United Kingdom; Austria; Spain; Norway	United Kingdom; Austria; Spain; Norway	United Kingdom; Austria; Spain; Norway	
		Posaconazole	Austria	Austria	Austria	Spain; Austria	
		Itraconazole	Austria	Spain; Austria	Spain; Austria	Spain; Austria	

4.0 Discussion

The most commonly reported *Candida* species with clinical importance in human is relatively finite. The World Health Organization (WHO) have concerned to develop a priority pathogen list for fungal ailments of public health important and to define research and development priorities to enhance innovation for new drugs, diagnostics and strategies (Galia *et al*., 2022).The most common clinical isolates of *Candida* species include *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, *Candida dubliniesis* and *Candida guilliermondii* respectively, and was consistent to the studies conducted by Mamali *et al*. (2022). Mohandas and Ballal (2011) reported that 70.0% of *Candida* bloodstream infections were caused by biofilm-forming agents. Biofilm formation was uncommon in isolates from respiratory tract infection and urogenital infections (Marak and Dhanashree, 2018). This study is in line with the Institute of Health in the United States, reported that biofilms are significantly responsible either directly or indirectly for more than 80% of all microbial infections (Nobile and Johnson, 2015). However, studies related to *Candida* associated biofilm infections differs apparently due to the number of *Candida* isolates in the studies, inadequate differentiation between *Candida* species, quantification methodologies and diversity of the biofilm detection (Lagunes and Rello, 2016). High mortality rate was reported in *Candida* infections caused by biofilm formation when compared to planktonic infections and the result agreed to the current study that reports mortality rate due to biofilm associated infections. Tsay *et al*. (2020) revealed the effect of antifungal resistance and biofilm formation as a major risk factors among critical ill patients. This study reported a mortality rate ranged from 6.9% to 70.0% and biofilm formation varied greatly from 27.2% to 100% which is consistent with the studies reported by Ghrenassia *et al*. (2019). The potential ability to establish biofilms among *Candida* species is an important virulence factor resulting to critical infection in patients (Silver *et al*., 2017). Rajendran *et al*. (2022) reports that *Candida albicans* is the most predominant *Candida* species across the globe, being responsible for the most of systemic candidiasis and oral infections which is in agreement with this study. Silva *et al*. (2017) shows that *Candida tropicalis* demonstrated high biofilm-forming ability related to infections in ulcerative colitis, prosthetic joints and endodontic issues which is not consistent to current findings. Some studies reported that the matrix material extracted from the biofilms of *Candida albicans* and *Candida tropicalis* composed of uronic acid, carbohydrate, phosphorus, proteins and hexosamine (Silva *et al*., 2012). Guinea (2014) reported that the most predominant *Candida* species are *Candida albicans*, *Candida glabrata* and *Candida*

parapsilosis which is agreed to this study. Studies from Brazil and Spain reported high prevalence of *Candida parapsilosis* and USA and Northern Europe demonstrated high prevalence of *Candida glabrata*. In general population, studies reported that fungal infection caused by *Candida tropicalis* and *Candida parapsilosis* are increasing concomitantly. Regardless of the geographical locations, individual immune system and antifungal therapy have a significant effect on the frequency and distribution of *Candida* species. Fungal infections caused by *Candida glabrata* is more common in old aged people whereas *Candida albicans* is more common among teenagers. The horizontal transmission of clinical isolates of *Candida* species can potentially influence the species distribution. *Candida krusei* is the causative agent of numerous mucosal infections and pneumonia (Atiencia-Carrera *et al*., 2022). *Candida glabrata* is commonly related with infections among patients with non-healing surgical wounds, total parenteral nutrition, ventilator associated and periodontal disease (Rodrigue *et al*., 2014). The biofilm formation of *Candida glabrata* are well-structured on multilayers of blastospores with high cohesion compared to other *Candida* species (Silva *et al*., 2012). Galia *et al*., (2022) reported some countries such as United Kingdom, Austria, Spain and Norway that integrate antifungal resistance profile for *Candida* bloodstream infection in their surveillance systems at the European level. However, Spain included their resistance profile under the surveillance of health care associated infection in intensive care unit, and Austria, United Kingdom and Norway reported their antifungal resistance profile under the surveillance system for invasive fungal infection which is in line with current study. The remaining countries did not report any profile data on *Candida* resistance of infections (Galia *et al*., 2022). Regarding the *Candida* species within the surveillance among four reported countries providing resistance profile, *Candida albicans* was the most predominant species observed including *Candida glabrata* and *Candida parapsilosis*. However, Norway and Austria reported resistance profile of *Candida tropicalis*. No any reports on resistance profile data on other *Candida* species. Amphotericin B, fluconazole and voriconazole are the most commonly evaluated antifungals agents. Amphotericin B, fluconazole and voriconazole in *Candida glabrata*, *Candida parapsilosis* and *Candida albicans* are the most common species drug combination agents usually evaluated in national surveillance studies. However, some *Candida* species like *Candida auris* is not mentioned in any surveillance network across the Europe. The mucocutaneous preference of antifungal resistant of *Candida* species in patients treated with systemic antifungals for invasive fungal infections has already been reported (Jensen *et al*., 2015). Galia *et al*. (2022) reported that an early implementation protocol on invasive candidemia caused by *Candida* species, developed by the Global Antimicrobial Resistance Surveillance System of Fungal Antimicrobial Resistance.

5.0 Conclusion

More research is urgently needed about the biofilm-forming ability among *Candida* species. High mortality rate was reported from different studies due to complications of *Candida* infections, caused by biofilm-forming strains. The mortality rate of invasive candidiasis remains high despite new antifungal agents and recent advances in an antifungal treatments. However, *Candida* species isolates vary in their potential ability to form biofilms and can be categorized according to biomass production. Multiple antifungal resistance among *Candida* infections has become a serious public health challenge, leading to expensive cost and clinical complications. A preponderance of *Candida albicans* compared with other *Candida* species varies between countries. *Candida albicans* was the most commonly isolated yeast in this study followed by other *Candida* species. The incidence and distribution of *Candida* species vary geographically and among different age groups, populations, hospital units, study periods and types of hospitals. Few countries integrate antifungal resistance profiles for *Candida* infections in their surveillance system. Regular reporting of *Candida* species distribution would help in better understanding the different epidemiological patterns between *Candida* species. It would be important to implement a module reporting profiles for resistance to antifungal drugs in *Candida* infections within existing surveillance systems for antibiotic resistance.

Declarations

Ethics approval and consent to participate

Not Applicable

Availability of data and material

Not Applicable.

Competing interests

Author declare no competing interests.

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