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ORIGINAL ARTICLE

Nosocomial infection of *C. auris* in COVID-19 Intensive Care Unit in Türkiye and Phylogenetic Analysis of Isolates

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Abstract
Background The difficulties in the identification of *C. auris* and the delays in the implementation of infection control precautions contribute to outbreaks. This study analyzed 10 patients with COVID-19 and *C. auris* candidemia, their characteristic and clinical features and phylogenetic features, and the antifungal susceptibilities of the isolates.
Method *C. auris* were detected in the COVID-19 ICU of a university hospital between January and August 2021. Identification to species level was performed using MALDI-TOF MS. Antifungal susceptibilities were determined by the Sensititre YeastOne YO10 panel. The isolates were whole genome sequenced to assess genetic relatedness and a phylogenetic tree was drawn including various *C. auris* clades.
Results The mean growth time in blood cultures was 38.8 h. *C. auris* candidemia developed on the average 27th day of ICU admission. All were susceptible to anidulafungin and micafungin, while they were resistant to fluconazole and amphotericin B. Only three isolates were found to be resistant to caspofungin. All patients died. With the WGS method, all isolates were found in a close resemblance to each other in terms of total nucleotide similarity (with a minimum of 96% pairwise alignment). Our isolates showed the closest similarity to South Asian clade (Clade I).
Conclusions This study is the first to evaluate the phylogenetic characteristics of C. auris using WGS and to determine antifungal susceptibilities in Türkiye on COVID-19 patients. The mortality rate was very high in patients who have both COVID-19 and *C. auris* candidemia.

Keywords *C. auris* · *COVID-19* · Infection control and prevention · Whole genome sequencing

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Introduction

Candida auris is an emerging multidrug-resistant (MDR) fungal pathogen that has been associated with nosocomial outbreaks worldwide. It causes serious illness in hospitalized patients through invasive infections, and misidentification by conventional diagnostic methods is quite common [1–3]. Due to the MDR phenotype, the misidentification of the organism, and invasive infections, it causes treatment failure and high mortality rates [4]. The four clades of the organism were identified in different geographical locations: Clade I (the South Asian clade), Clade II (East Asian clade), Clade III (African clade), and Clade IV (South American clade). In 2018, the Iranian clade has also been described as a potential fifth clade [5].

In addition to the well-known risk factors for *Candida spp*. infections, such as the presence of respiratory disease (e.g. COVID-19), immunosuppression, diabetes, recent intraabdominal surgery, central venous catheter, and using a broad-spectrum antibiotic, the presence of respiratory disease (e.g. COVID-19), and longer stay in the intensive care unit (ICU) are also identified as common risk factors for *C. auris* infection [6, 7].

The ability to colonize surfaces in the hospital environment and anatomic sites of the patients results in patient-to-patient transmission and causes outbreaks that have been difficult to control through spread among patients in healthcare settings [4, 8]. Infection control and prevention (IPC) measurements, especially isolation of the patients, contact precautions, and cleaning of equipment and surfaces, are crucial [9, 10]. Once it is isolated from culture, even if colonized, the patient should take contact precautions [1].

During the coronavirus disease 2019 (COVID-19) pandemic, since the healthcare personnel underestimated contact precautions measurements among the patients in open spaces, and due to a shortage of personal protective equipment (PPE), the pandemic facilitated contact transmissions and outbreaks in the hospital [7, 11].

In Türkiye, the first *C. auris* candidemia cases were identified in 2021 as case reports [12–14]. In this study, we aimed to determine the clinical features and consequences of the patients with *C. auris* candidemia, and the phylogenetic features and antifungal susceptibilities of *C. auris* isolates for the first time in Türkiye.

Material and Methods

This retrospective study was performed between January and August 2021 at Marmara University Pendik Training and Research Hospital, 1100-bed tertiary care, and two-separate buildings in İstanbul, Türkiye. A waiver of informed consent was issued by the Marmara University School of Medicine Institutional Ethical Review Board (reference number: 09.2021.578). Only the patients who stayed in COVID-19 ICUs and had *C. auris* candidemia were included in the study. As the number of COVID-19 patients increased, all seven ICUs were allocated for these patients. Some of the patients had to be transferred between two buildings or ICUs because of the need for dialysis, extracorporeal membrane oxygenation (ECMO), isolation, and cohorting. The patient's demographics and clinical, microbiological, and laboratory data were obtained from patient records.

In case of high suspicion of invasive candidiasis, we screened the patients for the candida colonization index. After determining *C. auris* in any body side other than blood, we re-evaluated the clinical situations of the patients to distinguish the infection from colonization. While the patients had no symptoms (fever, hypotension, tachycardia, tachypnea, etc.), we accepted them as colonized, on the contrary, in the presence of clinical signs and symptoms of illness we accepted them as infected.

Identification

All blood cultures were incubated in the BACT/ALERT® 3D system (bioMérieux, France) until growth was detected. The yeast cells were observed in Gram stain prepared from bottles with positive signals, and the bottled fluid aspirates were inoculated onto Sabouraud dextrose agar. After 24–48 h of incubation at 37 °C, yeast colonies were identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (VITEK MS, v3.0, bioMérieux, France). Antifungal susceptibility of the *C. auris* isolates was determined by Sensititre YeastOne YO10 panel (Trek Diagnostic

Systems, UK) according to the manufacturer's instructions. The MIC results of the isolates were interpreted according to the Centers for Disease Control and Prevention (CDC) tentative breakpoints [15].

gDNA Isolation

Ten *C. auris* culture plates belonging to patients with candidemia were obtained and preserved at + 4 °C for near-future use. The cultures were meticulously collected from the plates under Biosafety 2 conditions while the gDNA extraction processes, done under Biosafety 1 conditions, were started in the first week after the culture plates were obtained. The whole genome sequencing of the ten *C. auris* isolates was carried out with Oxford Nanopore Technologies (ONT, Oxford, UK)—MinION (Mk1B) device.

The collected samples were dissolved in separate 2 ml tubes in Tris–EDTA (10 mM-100 mM) by means of pulse vortexing 10–15 times. The 2 ml tubes with cells and Tris–EDTA mixture were centrifuged for 5 min at 20,000 × *g* and + 4 °C constant temperature. The supernatant was removed, and the extraction process was continued by following the ZymoBIOMICS DNA Miniprep Kit (Zymo Research, Cat. No. D4300) DNA isolation procedure. Afterward, the real DNA concentrations were measured with Qubit 2.0 (Thermo Fisher, Cat. No. Q32866) using Qubit dsDNA HS Assay Kit (Invitrogen, Cat. No. Q32854), and the DNA purity was determined with NanodropOne (Thermo Fisher, Cat. No. ND-ONE-W). The reference values to confirm the purity of the gDNA samples were obtained from ONT (260/280 ∼ 1.80 and 260/230 ∼ 2.0–2.2). The samples that could not reach the purity requirements were purified using Agencourt AMPure XP beads (Beckman Coulter, Cat. No. A63881).

Whole Genome Shotgun Sequencing

To perform the sequence of the whole genome of *C. auris* with approximately 12.5 million base-pairs length genome and 7 main chromosomes excluding other chromosomal copies and a mitochondrial plasmid, the study was planned to use ONT-Rapid Barcoding Kit (ONT, Cat. No. SQK-RBK110-96) for the multiplex sequencing experiment. The prepared library of 10 genomic DNA (*MaCa01, MaCa02, MaCa03, MaCa04, MaCa05, MaCa06, MaCa07, MaCa08, MaCa09*, and *MaCa10*) with adapters, sequencing buffers, and loading beads were mixed and loaded on the ONT MinION Flowcell (v. 9.4.1, Cat. No. FLO-MIN106D).

Bioinformatics and Phylogenetic Analyses

During the sequencing, the data were obtained as.fast5 files using MinKNOW (v. 22.03.5) GUI program. The adapter and barcode removal and first quality filtering were performed with ONT-guppy (v. 6.0.6) CLI program, and the.fastq formatted sequencing files were made ready for downstream analyses after this process for each sample. The quality score of the completed NGS assay was determined with FastQC (v. 0.11.9) and the average score was found to be Q19 (Phred score). By using the flye (v. 2.8) pipeline for Nanopore reads de novo assembler, the contig fasta sequences were obtained and these contigs were mapped to NCBI nt reference database (as 20/10/2022), as a result, the average of 99.89% of identity to the NCBI reference sequence *C. auris* (RefSeq [Candida] auris Cand_auris_B11221_V1) was observed.

The obtained blast (using blastn function of blast + v. 2.13.0) results were used to determine reference clades and strains of *C. auris*. These results were used to create the consensus sequences of each isolate. Finally, a phylogenetic tree was generated to determine the relationship between the isolates (Fig. 1). Unlike using multiple alignments and plotting the tree using these calculated distances, which are done with shorter genomes, ANI (average nucleotide identity) algorithm was used for distance calculation and R (v. 4.1.6) (stringr, reshape2, Matrix, MASS, ape and phangorn packages) was used to create the phylogenetic tree. In the process, ANI technique was applied using the tANI_Matrix tool and blast + (v. 2.13.0) with 80% coverage, 80% identity, and megablast options were fed into the blastn (v. 2.13.0) as the cut-off arguments [16]. Along with the 10 *MaCa* labeled isolate, 13 other *C. auris* complete genomes were included in the construction of the phylogenetic tree with tANI_Matrix R tree-building script. Among the *C. auris* sequences in the NCBI database, having complete genome records, 5 from Clade I, 2 from Clade II, 2 from Clade III, and 3 strains from Clade IV were randomly selected along with the Clade V (the Iran strain) [5] and added to the tree

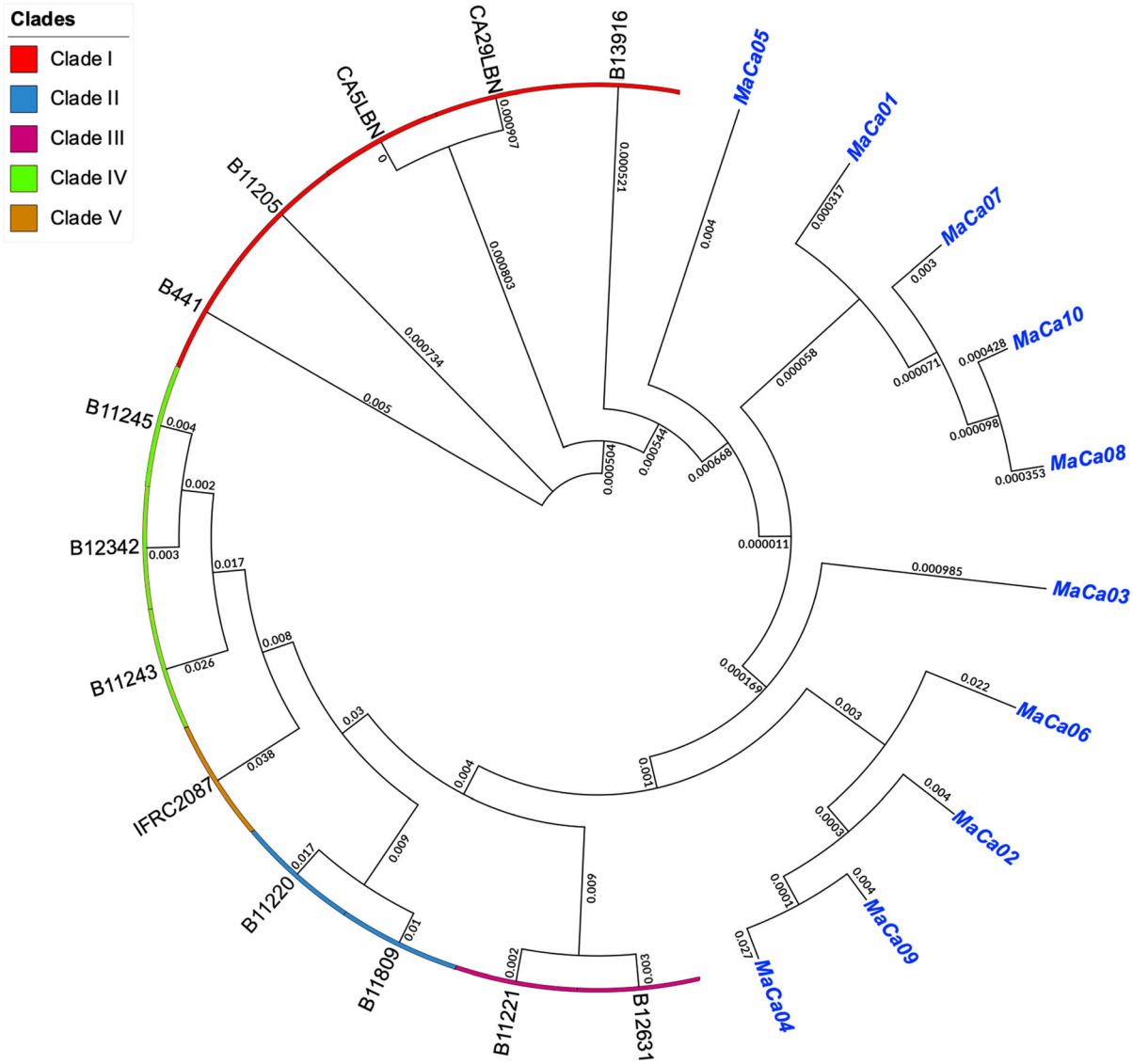


Fig. 1 The figure above shows the five clades (with the Iran variant) and isolates (*MaCa01…10*) in a phylogenetic cladogram. The blue-marked organisms represent the isolates while the others were obtained from previous studies. The numbers represent the distances between each branch separation. As reference points, 5 strains from Clade I, 2 from Clade II and III, 3 from Clade IV, and Clade V (the Iran strain) were included in the study

generation process (In respective order: [Candida] auris B8441, [Candida] auris 11,205, [Candida] auris B13916, [Candida] auris CA5LBN, [Candida] auris CA29LBN, [Candida] auris B11220, [Candida] auris B11809, [Candida] auris B11221, [Candida] auris B12631, [Candida] auris B11243, [Candida] auris B11245, [Candida] auris B12342 and [Candida] auris IFRC2087). After the tree was generated as a text document with the ANItree R script, it was visualized using iTOL web application [17]. The process was repeated 9 more times with different sets of strains, and a similar result was reached for each of them.

Results

In this study, the mean age of the patients was 67 (range: 50–83), and 60% of them were men. The first case of *C. auris* bloodstream infection (P1) was reported in the ICU in mid-February. The patient's

Table 1 The characteristic features of the patients, drug information, and significant dates

Patient	Age	Sex	Comorbidities	Broad-spectrum antibiotic use[a]	Day to candidemia[b]	*C. auris* colonization	First blood culture[c]	Treatment drug/date	Time to death (day)[d]
P1	59	F	HT, DM	Yes	30	–	11 Feb	A /15 Feb	8
P2	73	F	HT	Yes	4	–	23 Mar	–	3
P3	61	M	HT, CAD	Yes	18	02 Apr, wound	05 Apr	–	1
P4	68	M	HT	Yes	19	–	16 Apr	A /18 Apr	23
P5	76	F	–	Yes	21	–	21 May	–	1
P6	64	M	–	Yes	52	12 May, urine	30 May	–	0
P7	83	M	HT, COPD	Yes	14	–	01 Jun	A /04 Jun	15
P8	63	M	HT, DM, COPD, Morbid obesity	Yes	25	28 May, skin	03 Jun	A /28 May	2
P9	50	F	HT, DM	Yes	72	07 Jun, urine	08 Jul	A /11 Jul	26
P10	75	M	HT, ALL	Yes	20	14 Aug, urine	18 Aug	V /14 Jul AB /27 Jul A /20 Aug	15

A anidulafungin; *AB* liposomal amphotericin B; *ALL* acute lymphoblastic leukemia; *CAD* coronary artery disease; *DM* diabetes mellitus; *F* female; *HT* hypertension; *ICUs* intensive care units; *M* man; *V* voriconazole

[a]Carbapenems, glycopeptides, piperacillin-tazobactam, polymyxin

[b]The duration of ICU admission prior to candidemia onset

[c]The day of first positive blood culture for *C. auris* candidemia

[d]The duration from detecting candidemia to death

characteristic features, drug information, and significant dates were summarized in Table 1. A total of five of 10 patients (50%) were colonized with *C. auris* before detecting candidemia. The urogenital system was the most common (3/5 patients) colonized system. All patients died, and the mortality rate was 100%. Four out of 10 patients did not get a chance to take an antifungal agent before they died.

The mean time from incubation to detection of growth *C. auris* on culture was 38.8 h (range 17.2–52.9 h).

The mean duration from ICU admission to *C. auris* candidemia diagnosis was 27 days (range 4–72 days).

Before *C. auris* was detected, all patients were receiving broad-spectrum antibiotics. In addition, one patient (P10) was taking broad-spectrum antifungal prophylaxis (voriconazole and liposomal amphotericin B) because of ALL (acute lymphoblastic leukemia) prior to candidemia.

Assembly results of the isolates, from *MaCa02* to *MaCa10*, had an average coverage of 11.2 × (Table 2), with partial genomes for each, in addition to *MaCa01*, which had an average coverage of 56 × with a complete genome of 7 chromosomes, 1 mitochondrial plasmid, and copies of 3rd and 4th chromosomes. The *[Candida] auris* isolates were analyzed with a phylogenetic cladogram and 13 other *[Candida] auris* strains from previous studies were obtained from the NCBI database (Fig. 1). Of the isolates included in the study, all showed a close resemblance to each other in terms of total nucleotide similarity with a maximum of 99.9% and a minimum of 96% pairwise similarity. While each clade was grouped close within itself, Clade 1, which was formerly known as the South Asian clade, of the *[Candida] auris* groups showed the closest similarity to *MaCa* labeled isolates (Fig. 1). All the isolates having grouped together indicated the closeness and high similarity between the isolates taken from

Table 2 The list of *C. auris* sequences is given in the below table, along with the sequencing and assembly statistics

Organism	Read quality score (Phred)	GC%	Raw reads N50 (bp)	# of raw sequences	Min–max sequence length (bp)	Length of the assembled genome (bp)	Assembly coverage depth	# of the aligned contigs*/ # of total contigs
MaCa01	Q18	43	3898	162,457	1000–41395	12,373,670	56x	9 / 12
MaCa02	Q20	43	2659	44,697	1000–27914	12,357,997	10x	30 / 31
MaCa03	Q20	43	2231	55,851	1000–28110	12,358,398	11x	17 / 18
MaCa04	Q20	43	2440	27,627	1000–32920	12,358,427	6x	196 / 197
MaCa05	Q20	43	3596	24,675	1000–41994	12,360,492	7x	44 / 45
MaCa06	Q20	43	2665	23,858	1000–29458	12,371,023	6x	122 / 123
MaCa07	Q20	43	3688	29,377	1000–43290	12,362,196	10x	19 / 21
MaCa08	Q20	43	2579	94,461	1000–31829	12,369,868	22x	9 / 10
MaCa09	Q20	43	2521	44,704	1000–35906	12,357,225	10x	46 / 47
MaCa10	Q20	43	2241	86,969	1000–28064	12,357,969	18x	10 / 11

The quality (phred) score of the reads, genome's GC content, N50 of the sequencing assay, number of sequences obtained in the assay, minimum and maximum read lengths, assembled genome total length, assembly coverages, and the total amount of contigs and contigs aligned to the other *C. auris* sequences* belonging to each isolate listed. * *Excluding the mitochondrial genome*

different candidemia patients. The similarity of the isolates from *MaCa01* to *MaCa10* demonstrated to us that our isolates originated from the same *C. auris* strain. On another note, *C. auris* Clade 1, formerly identified as the South Asian clade, was seen in Iran, India, Pakistan, Saudi Arabia, Oman, Kenya and Spain, the United Kingdom, and Canada [18, 19].

Given the CDC tentative breakpoints, all isolates were susceptible to anidulafungin and micafungin, while they were resistant to fluconazole and amphotericin B. Only three isolates were resistant to caspofungin. The caspofungin MIC values of these isolates were 8 and above. The MIC range, MIC_{50}, and MIC_{90} values (μg/mL) of the antifungal agents are summarized in Table 3.

Table 3 In vitro antifungal susceptibility profiles of *C. auris* isolates (MIC values; μg/mL)

Antifungal	MIC Range	MIC_{50}	MIC_{90}
Anidulafungin	0.12	0.12	0.12
Micafungin	0.06–0.25	0.12	0.12
Caspofungin	0.06- > 8	0.12	> 8
5-Flucytosine	≤ 0.06–0.12	≤ 0.06	0.12
Posaconazole	< 0.008- > 8	2	> 8
Voriconazole	0.25- > 8	> 8	> 8
Itraconazole	< 0.015–8	8	> 16
Fluconazole	> 256	> 256	> 256
Amphotericin B	2–4	4	4

*MIC values have been interpreted due to CDC tentative breakpoints[15]

Discussion

Candida auris poses a serious threat to healthcare settings because of the misidentification, colonizing patient's skin and environment, the delay of infection control precautions, and its multidrug resistance phenotype [20]. In Türkiye, this is the first study addressing bloodstream isolates of *C. auris* in ICU patients with COVID-19 and classifying the molecular epidemiological features of the isolates using the whole-genome sequencing (WGS) method. After we identified *C. auris* species by MALDI-TOF MS, an accurate and rapid method for identification, we aimed determination of which clade of *C. auris* presented in Türkiye. We found that all our isolates are close to Clade I by WGS.

The different *C. auris* clades were reported from different geographic regions. The most prevalent clades are Clade I and Clade III in literature. Clade I (South Asian) was mainly reported from Asian countries such as India, Pakistan, Kuwait, Malaysia and the United States, Italy, Germany, and the Netherlands, etc. [21]. Due to the difficulty of

identification of *C. auris*, it has been thought that there are several undiagnosed cases. In Türkiye, there is no report on a molecular epidemiological investigation of *C. auris* cases until now. Isolates confirmed as *C. auris* with MALDI-TOF were evaluated for genetic relatedness using WGS. We found that all our isolates are the closest similarity to Clade I. Additionally, it may be said that the origins of our *MaCa* isolates are the same due to their genomic proximity within the clade. During the study period, the patients had to be transferred between certain areas of the hospital due to the COVID-19 pandemic. For this reason, they used the same or close to each other beds. These findings may support the view that they spread from a common origin in the hospital.

ICU patients have already several risk factors for developing a fungal infection. These factors include severe pneumonia, prolonged stay in ICU, presence of a central venous and urinary catheter, and using broad-spectrum antibiotics [6, 22]. Severe COVID-19 has also emerged as a predisposing factor for all these risk factors and therefore invasive fungal infections. In some reports, the incidence of candidemia in patients with COVID-19 has been founded two- to tenfold higher than in patients without COVID-19 [23, 24]. In our study, all patients had severe pneumonia due to COVID-19, and invasive vascular accesses, and all were using broad-spectrum antibiotics. Just as antibiotic exposure, antifungal exposure is anticipated as a major risk factor for acquiring *C. auris* infection. In a previous study, it has been shown that patients with *C. auris* candidemia had significantly higher prior antifungal exposure than patients with non-auris candidemia ($p < 0.001$) [6]. When the species were evaluated individually, there was no difference between *C. auris* and resistant species such as *C. krusei*, *C. glabrata*, and *C. parapsilosis* in terms of prior antifungal use and candidemia risk. This may be a result of broad-spectrum antifungal agents wiping out susceptible species in flora. We detected broad-spectrum antifungal agent use in one patient as a prophylaxis and then empirical treatment before *C. auris* candidemia. Long-term stay in ICU is another well-known risk factor for invasive candidiasis. In a meta-analysis, the mean intervals between ICU admission and the candidemia onset were demonstrated as 28.5 days in Europe, 17.4 days in Asia, and 48.5 days in South America [25]. In our study, this duration was found as similar to Europe, 27.7 days.

Once *C. auris* detected in any body site other than blood, it may not always be an infection and does not need to treat. However, strict contact precautions should be implemented even if it is colonization. Otherwise, cross-transmission between patients may be inevitable [1]. Public Health England (PHE) and CDC recommend periodic screening of the units with ongoing *C. auris* colonization and cases [1, 26]. In our study, we first screened the candida colonization index in case of high suspicion of invasive candidiasis. After we determined a colonized or infected patient, we repeated the screening according to the recommendation of these guidelines. However, since distinguishing the infection from colonization is not easy, especially in critically ill patients, empirical antifungal treatment should be considered when a colonized patient's clinical suddenly deteriorates [10]. We detected *C. auris* colonization in five patients, and only one out of them (P8) was treated empirically due to clinical deterioration. Also, *C. auris* was detected in this patient's blood culture taken six days later. Two patients died soon after determining candidemia without taking any antifungal agent. One of the other two patients took amphotericin B prophylaxis when *C. auris* candidemia was detected, and immediately switched to anidulafungin. Candidemia was detected 1 month later than colonization in the last patient and immediately started antifungal treatment.

During the pandemic, patients with COVID-19 have been separated from non-COVID patients in our hospital, as in many countries, and the IPC measurements have been applied against COVID-19. However, the burden of the pandemic both on healthcare workers (HCWs) and on healthcare settings resulted in breakings in IPC measurements [7, 27]. Firstly, HCWs had to work in different COVID-19 ICUs in different shifts. Also, the patients had to be transferred from one ICU to another because of cohorting, and the need for dialysis or extracorporeal membrane oxygenation. Therefore, both the contamination of the environment and the patients and the transmission of the microorganisms between patients were facilitated. Secondly, the IPC measurements against COVID-19 primarily targeted respiratory transmission and the protection of healthcare personnel. HCWs were afraid of getting infected during the change of protective equipment, avoiding changing gloves and gowns during the transition from patient to patient, and not following hand hygiene rules. The low compliance with the

appropriate use of PPE resulted in environmental contamination and the spread of *C. auris* [28, 29].

Despite the appropriate treatment, the mortality rate of *C. auris* candidemia is variable in literature according to the geographical region [10]. In a previous study, while the overall mortality of candidemia was 68%, this rate was found to be 59% for *C. auris* [30]. However, the overall attributable mortality rate is not clear since the patients have other serious illnesses. The MDR pattern of *C. auris* contributes to treatment failure and mortality. CDC has defined tentative antifungal breakpoints based on susceptibility data of hundreds of clinical *C. auris* isolates [15]. Based on these breakpoints, the reduced susceptibility to fluconazole and other triazoles, and variable susceptibility to amphotericin B have been determined in previous studies [10]. Therefore, the use of echinocandins for empirical treatment is primarily considered. However, it should be kept in mind that frequent use of this class of agents may lead to reduced susceptibility to *C. auris* [30, 31]. Our study evaluated the antifungal susceptibility of *C. auris* isolates according to CDC tentative breakpoints. It has been found that all isolates showed high MIC values for fluconazole and amphotericin B. Only three of ten isolates were resistant to caspofungin, while all were susceptible to anidulafungin and micafungin. Since the breakpoints for voriconazole, other triazoles, and 5-flucytosine have not been determined, we could not interpret the MICs of these drugs. All but four patients were empirically treated with anidulafungin before determining the antifungal susceptibility results. Unfortunately, four patients died before identifying *C. auris* in blood culture. The culture results were available after the patients died.

Besides the significant findings, this study also had limitations. The main limitation of this study is its retrospective design. Second, we could not evaluate the overall attributable mortality rate of *C. auris* candidemia due to severe COVID-19 and other underlying medical conditions. Moreover, since we conducted the study only in COVID-19 ICU the comparison with non-COVID-19 patients could not be performed. Finally, we could not implement internal infection control precautions such as screening for skin and environmental colonization.

In conclusion, this is the first clinical study to evaluate *C. auris* species' phylogenetic features by using the WGS method in Türkiye. In our hospital, among the most important university hospitals in Türkiye, all *C. auris* isolates included in the study have been found a similarity to Clade I. Moreover, as a result of this study, it has been found that COVID-19 and *C. auris* candidemia cause very high mortality when they are together.

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Declarations

Conflict of interest The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Ethical approval Marmara University School of Medicine Institutional Ethical Review Board issued approval 09.2021.578. The collected data did not include any patient or employee identifying information.

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