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REVIEW ARTICLE

# Characteristics of fungaemia caused by *Trichosporon* species in South-Eastern Europe

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**ABSTRACT**

The incidence of fungaemia caused by rare yeasts, particularly *Trichosporon* species, is rising globally, posing diagnostic and therapeutic challenges—especially in immunocompromised patients. This systematic review aims to analyse the epidemiology, diagnostic approaches, antifungal susceptibility, and clinical outcomes of *Trichosporon* fungaemia (TF) in South-Eastern Europe, including Turkey. A comprehensive search was conducted in PubMed and Scopus in August 2025. A total of 59 cases from 12 studies were identified, with *Trichosporon asahii* being the most prevalent species (86.4%). Cases originated from Turkey (79.7%), Greece (18.6%), and Croatia (1.7%). Diagnostic techniques varied, with phenotypic methods still widely used. MALDI-TOF MS and DNA sequencing were mainly applied as confirmatory methods. Haematologic disorders were the most frequently reported underlying conditions among the patients. Sixteen breakthrough fungaemia cases—occurring despite empirical or prophylactic antifungal therapy—were identified. Although rare, TF represents a severe infection with significant mortality in South-Eastern Europe. Early and accurate species identification—facilitated by advanced diagnostic tools—is crucial for effective management. In addition to diagnostic difficulties, treatment is also challenging. Voriconazole appears to be the preferred antifungal agent, even in breakthrough fungaemia cases. Enhanced awareness, routine use of molecular diagnostics, and ongoing epidemiological monitoring are essential to improve patient outcomes.

**KEYWORDS**

*Trichosporon*, fungaemia, breakthrough fungaemia, voriconazole

## 1. INTRODUCTION

The global incidence of fungaemia has significantly increased in recent decades, becoming an important public health concern [1, 2]. Its epidemiology is evolving and varies geographically [1, 3]. *Candida* species are the predominant cause of bloodstream yeast infections [4–6], but in the last two decades, rare yeasts—other than *Candida* and *Cryptococcus* spp.—have emerged as opportunistic pathogens, causing invasive fungal disease (IFD) and fungaemia [3, 7, 8]. These uncommon pathogens include basidiomycetous yeasts, such as *Trichosporon*, *Malassezia*, *Pseudozyma* (now classified as *Moesziomyces* or *Dirkmeia*), *Rhodotorula*, *Sporobolomyces* and ascomycetous yeasts, such as *Geotrichum*, *Kodamaea*, *Saccharomyces*, *Saprochaete* and *Magnusiomyces* [9–11]. Although these yeasts account for a small proportion of overall fungaemia cases, their incidence is rising, from 1.1 to 10.0%, depending on the patient

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population and clinical setting. This trend is likely driven by the growing number of immunocompromised patients and the widespread antifungal use—particularly echinocandins, which are commonly used as prophylaxis in haematological patients, and to which many rare yeasts are intrinsically resistant [3, 9, 11–13]. IFDs due to rare yeasts tend to have high mortality due to diagnostic delays, limited treatment options, and insufficient epidemiological data [7].

*Trichosporon* species are among the most prominent of these rare yeasts and have emerged as important human pathogen over the past four decades, in parallel with the increasing number of immunocompromised hosts [14–17]. These basidiomycetous fungi are widely distributed in the environment, particularly in soil and fresh water, and are known to colonize human skin, the upper respiratory tract, perigenital areas, and the gastrointestinal tract of humans [8, 18–20]. Presently, fifty *Trichosporon* species are recognized, of which 16 are known to be pathogenic [18]. *Trichosporon asahii* is the most common, followed by *T. inkin*, and *T. asteroides* [9].

*Trichosporon* species cause a wide spectrum of infections, ranging from conditions such as white piedra and hypersensitivity pneumonitis in immunocompetent patients to severe invasive diseases like fungaemia, endocarditis, peritonitis and central nervous system (CNS) infections in immunocompromised patients. Esophagitis and urinary tract infections have also been documented, while haematological patients with fungaemia may develop pneumonia, hepatosplenic abscesses and metastatic skin lesions [8, 9]. Risk groups include patients with haematological malignancies and other forms of cancer, haematological patients exposed to antifungals, patients with severe neutropenia, acquired immunodeficiency syndrome, those who have undergone bone marrow or solid organ transplantation, those receiving corticosteroids. Affected populations also include premature infants with low birth weight, intravenous drug users, burn patients, patients with prosthetic heart valves or indwelling catheters, and patients who have undergone ophthalmic surgery [8, 9, 20]. *Trichosporon* fungaemia (TF), including catheter-related cases, represents the most common form of this opportunistic infection, accounting for 58.8–74.7% of all *Trichosporon* infections. Although it represents a relatively small proportion of all invasive fungal infections, *Trichosporon* spp. have been identified as the second or third most frequent cause of yeast fungaemia [14, 16, 21, 22].

Diagnosis of TF is primarily based on blood cultures, with species identification achieved using phenotypic methods, molecular techniques, and Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS). Although serum β-D-glucan may be detectable, its sensitivity for *Trichosporon* infections is limited [8]. According to the global guidelines for the diagnosis and management of rare yeast infections—developed by the European Confederation for Medical Mycology (ECMM), the International Society for Human and Animal Mycology (ISHAM), and the American Society for Microbiology (ASM) [9]—voriconazole appears to be the preferred antifungal for treating trichosporonosis, while posaconazole and isavuconazole also demonstrate activity. Fluconazole shows variable effectiveness. *Trichosporon* spp. are intrinsically resistant to echinocandins. Amphotericin B and flucytosine are also not recommended for the treatment of trichosporonosis [8, 9, 13, 23, 24].

The low antifungal susceptibility of *Trichosporon* species and their potential for developing resistance pose significant challenges in the management of their infections [3]. Furthermore, limitations in routine laboratory capabilities often hinder accurate identification of *Trichosporon* spp., resulting in a paucity of data regarding species distribution and antifungal susceptibility in haematogenous infections [14]. Delayed diagnosis and the difficulties in determining an optimal treatment strategy due to the scarcity of data, contribute to the high mortality associated with TF [8, 9, 14, 16].

Accurate epidemiological analysis of *Trichosporon* infections can highlight risk factors for infection and improve patient diagnosis, treatment, and prognosis [18]. Understanding which species are most prevalent may support more accurate identification and informed therapeutic decisions, as different *Trichosporon* species exhibit varying levels of antifungal susceptibility [14, 18]. Reported cases of TF have increased over time, particularly among patients with haematological malignancies—a trend partly attributed to improved diagnostic methods and heightened clinical awareness—underscoring the need for continued epidemiological surveillance [18].

The existing literature from South-Eastern Europe seems to remain limited to individual case reports, small case series from single institutions, and national studies. To address this gap, a review of published TF cases from South-Eastern Europe was conducted including both original case reports and case series, with the aim of elucidating the regional epidemiology and identifying potential prognostic indicators.

## 2. MATERIALS AND METHODS

A research methodological protocol was developed based on the PRISMA 2020 statement [25] to collect and evaluate studies related to subject under investigation.

### 2.1. Formulation of the research question

To clearly formulate the research question and guide the literature review process, the PICO (Population, Intervention, Comparison, Outcome) framework was applied:

- Population: Patients of any age in South-Eastern Europe
- Intervention: *Trichosporon* species
- Comparison: Not applicable for this review
- Outcome: Cases of *Trichosporon* fungaemia

### 2.2. Development of the review protocol

Research question: To conduct a review of all cases of *Trichosporon* fungaemia in the countries of South-eastern Europe reported in the international literature.

Inclusion criteria:

- Case reports, case series and outbreak investigations reporting on cases of *Trichosporon* fungaemia in the countries of South-Eastern Europe. Although only part of Turkey lies geographically in South-Eastern Europe, data from the entire country were included in the analysis because of the rarity of TF and the availability of relevant national data from across Turkey. Study designs focused on invasive infections caused by *Trichosporon* spp., with confirmed bloodstream involvement as evidenced by positive blood cultures

Exclusion criteria:

- Studies referring to fungaemia by other fungi
- Cases of other forms of trichosporonosis, without confirmed TF
- Cases of TF not originating from countries of South-Eastern Europe
- Studies not referring to human infections
- Duplicate publications of the same cases
- Review articles, systematic reviews, meta-analyses and conference proceedings

## 2.3. Outcomes of interest

The main outcomes assessed in this review were:

1. Epidemiological data, including species distribution by country and year
2. Demographical and clinical characteristics of the affected population
3. Risk factors and infection outcomes, including mortality
4. Laboratory methods used for the diagnosis of TF
5. Antifungal susceptibility profiles of *Trichosporon* spp. causing fungaemia, including minimum inhibitory concentration (MIC) values and reported resistance to commonly used antifungal agents

## 2.4. Search strategy – data sources

The systematic literature review was conducted in August 2025, and studies were included regardless of their publication date. A systematic review of the existing literature was performed by searching the electronic databases PubMed and Scopus, with a final search day of August 15, 2025. The literature review was conducted using the following keywords: "non-candida", "rare yeasts", "*Trichosporon*", "*Trichosporon* spp.", "trichosporonosis", "trichosporosis", "bloodstream infection", "bloodstream infections", "blood stream infection", "blood stream infections", "fungemia", "fungemias", "fungaemia", "fungaemias", "fungal infection", "fungal infections", "South-eastern Europe", "Southeastern Europe", "South Eastern Europe", "South-east Europe", "Southeast Europe", "South East Europe", "Balkan", "Balkans", "Greece", "greek", "Bulgaria", "bulgarian", "Romania", "romanian", "Serbia", "serbian", "Montenegro", "montenegrin", "Kosovo", "kosovar", "Bosnia and Herzegovina", "Bosnia", "bosnian", "North Macedonia", "north macedonian", "Albania", "Albanian", "Croatia", "croatian", "Slovenia", "slovenian", "Turkey", "turkish", "case reports", "case series", "cases", "case", "outbreak", "outbreaks" in combination with Boolean operators (AND, OR). To minimize the risk of missing relevant studies and to ensure comprehensive coverage of the available literature, a manual electronic search and a review of the reference lists of each selected study were conducted. No time restriction was applied during the search strategy, in order to include all available published cases of TF in Southern-East Europe, regardless of publication year.

Studies published in languages other than English were not excluded, due to the rarity of the condition and the need to include all available evidence. When necessary, non-English articles were translated to extract relevant data. In cases where specific data were missing from the original articles, the corresponding fields in the tables were marked as 'Not available'.

Additionally, all reported *Trichosporon* species were included in the review, even when species identification was based on outdated taxonomy (e.g., *Trichosporon beigelii*, now revised [18]), or when species-level identification was not performed (i.e., reported as *Trichosporon* spp.). In such cases, data were extracted as presented in the original reports, without reinterpretation or retrospective reclassification. These cases were included in the epidemiological analysis (e.g., species distribution by country), but not in antifungal susceptibility presentation. For the purpose of MIC presentation, only isolates that were clearly identified at the species level according to current taxonomic classification were included.

## 2.5. Conflict resolution

Screening, data extraction, and quality assessment were conducted independently by two researchers (S.V. and I.P.), with conflicts resolved through discussion and consensus between the researchers or, if necessary, by a third researcher (M.C.).

## 2.6. Data synthesis and presentation

Data were systematically recorded in tabular format based on the following parameters: country of origin, year of publication, first author, year(s) in which the cases occurred, number of cases included in the study, hospital(s) where the cases were reported, *Trichosporon* species identified as the causative agents of fungaemia, methods used for species identification, patients' age and gender, associated risk factors, and clinical outcomes of the infections. To identify duplicate or overlapping cases, the following criteria were used: author names, location and setting, year and date of incidence, and specific details of the patients' demographic data. When multiple reports referred to the same clinical case, only the publication that contained the most complete and relevant data was included. Overlapping publications were excluded from the final selection to prevent duplication of information. Due to the heterogeneity of the data and the

absence of comparable quantitative outcomes, a meta-analysis was not performed. The results were synthesized narratively and presented in tabular form, highlighting microbiological findings, risk factors, outcomes and antifungal susceptibility.

## 3. RESULTS

A total of 44 studies were initially identified: 31 were retrieved from the PubMed database and 13 from Scopus. Among the 44 records, 10 duplicate entries were identified and removed using the duplicate detection tool in the reference management software (Zotero 7). Titles and abstracts of the remaining 34 studies were screened, and 16 were excluded, either because the content was not relevant to the aim of the review or because they met exclusion criteria evident at the title and abstract level. Eighteen full-text articles were retrieved for further assessment. Additionally, hand-searching the reference lists of these articles yielded two more records, resulting in a total of 20 articles that were reviewed for potential eligibility. In total, 12 full-text articles were included, reporting 59 cases of TF. Of these, 11 studies were published in English and 1 was translated from Croatian. The flow diagram is presented in Fig. 1.

### 3.1. Geographical distribution, species classification, and identification methods

The TF cases included in this review originated from three countries in South-Eastern Europe: Turkey, Greece, and Croatia. The first case was reported in Turkey in 2001 (Kustimur et al., 2002) [26]. Over the past 21 years, a total of 59 TF cases were reported (Table 1, Fig. 2).

The most frequently identified *Trichosporon* species was *T. asahii*, accounting for 51 of the 59 cases (86.4%). Species-level identification was not available in three cases, which were reported as *Trichosporon* spp. (5.1%). *T. mucoides* was identified in two cases (3.4%), while *T. beigelii*, *T. coremiiforme*, and *T. asteroides* were each reported in one case (1.7% each). *Trichosporon* species other than *T. asahii* were reported exclusively in Turkey (Fig. 3).

A more detailed presentation of the identification methods used for *Trichosporon* species is provided in Table 2; identification methods were available for 50 species, while for 9 species such information was not reported.

### 3.2. Clinical and demographic characteristics of the patients, minimum inhibitory concentrations of the strains, and outcome

The clinical characteristics of the cases of most articles included in this review are presented in Table 3, while the

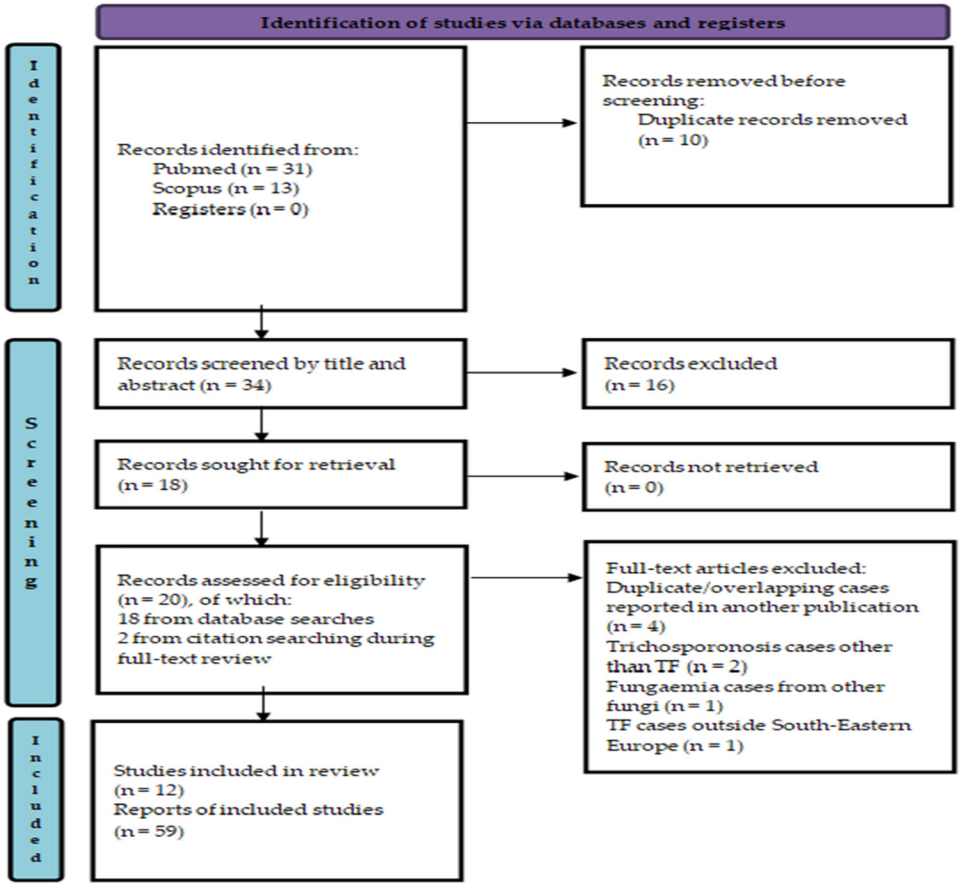


*Fig. 1.* Flow diagram illustrating the identification and screening process of studies included in this review

*Table 1.* Reported cases of *Trichosporon* fungaemia in South-Eastern Europe

| Location | Reference | Year of publication | Year(s) of cases | Number of cases and *Trichosporon* species identified | Identification method* |
|---|---|---|---|---|---|
| Turkey | Kustimur et al. [26] | 2002 | 2001 | 1 – *T. asteroides* ($n = 1$) | Morphology**, API ID 32C, VITEK***, API Candida, Fungifast/Twin system, DNA sequencing |
| Turkey | Yildiran et al. [27] | 2003 | 2003 | 1 – *T. asahii* ($n = 1$) | API ID 32C |
| Greece | Antachopoulos et al. [28] | 2005 | 2005 | 1 – *T. asahii* ($n = 1$) | API ID 32C |
| Turkey | Karabay et al. [29] | 2006 | 2005 | 1 – *T. asahii* ($n = 1$) | API 20C AUX |
| Turkey | Bayramoglu et al. [30] | 2008 | 2008 | 1 – *T. asahii* ($n = 1$) | API 20C AUX |
| Croatia | Paradzik et al. [31] | 2012 | 2012 | 1 – *T. asahii* ($n = 1$) | Morphology, Biochemical tests, API ID 32C |
| Greece | Noni et al. [32] | 2020 | 2011, 2017, 2018 | 3 – *T. asahii* ($n = 3$) | Morphology, API ID 32C, RapID Yeast Plus, VITEK, MALDI-TOF MS, DNA sequencing |
| Turkey | Alp et al. [33] | 2020 | Not specified (2002–2016) | 9 – *T. asahii* ($n = 8$), *T. mucoides* ($n = 1$) | Not available |
| Turkey | Akaslan et al. [34] | 2022 | Not specified (2010–2020) | 28 – *T. asahii* ($n = 22$), *Trichosporon* spp. ($n = 3$), *T. mucoides* ($n = 1$), *T. beigelii* ($n = 1$), *T. corremiiforme* ($n = 1$) | VITEK, API ID 32C, MALDI-TOF MS |
| Turkey | Sig et al. [35] | 2023 | Not specified (2017–2021) | 1 – *T. asahii* ($n = 1$) | Morphology, Phoenix 100 |
| Greece | Spiliopoulou [36] | 2023 | Not specified (2018–2021) | 7 – *T. asahii* ($n = 7$) | Morphology, API 20C AUX, VITEK, MALDI-TOF |
| Turkey | Oz et al. [37] | 2024 | Not specified (2011–2025) | 5 – *T. asahii* ($n = 5$) | Morphology, API 20C AUX, MALDI-TOF MS |

*All identification methods that were used are included, regardless of whether or not they led to the correct diagnosis, **The term "morphology" refers to both macroscopic morphology (colony morphology after cultivation) and microscopic morphology, ***Different versions of the same system (e.g., VITEK/VITEK 2) were grouped under a single entry.

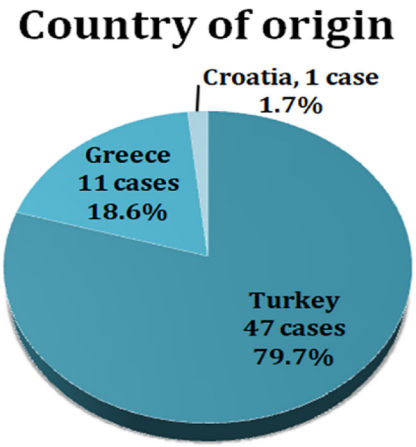


*Fig. 2.* Geographic distribution of published TF cases across South-Eastern European countries

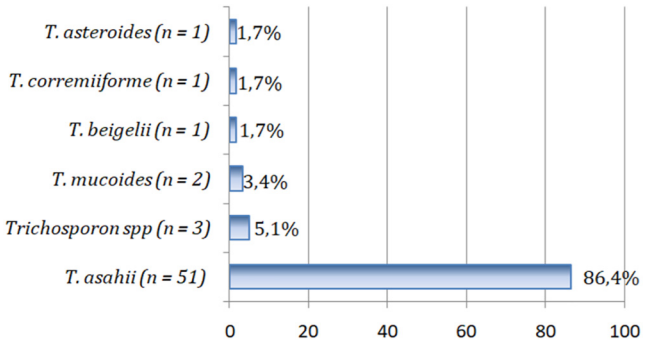


*Fig. 3. Trichosporon* species causing fungaemia in South-Eastern Europe

MICs, shown as values and ranges, for most isolates are summarised in Table 4a and b.

The study by Sig et al. [33] reports a case of *T. asahii fungaemia* in Turkey; however, it provides no detailed demographic or clinical information about the patient (except that they were hospitalised in an internal medicine unit), nor does it include MIC data for the isolate.

In the study by Alp et al. [33], the *T. asahii* strains were grouped with other rare yeasts causing fungaemia, and clinical characteristics were not available, except for data on breakthrough fungaemia (BF), defined as fungaemia developing during antifungal treatment [38], in three cases. In the first case, the patient that was receiving an echinocandin, developed breakthrough fungaemia due to *T. asahii,* and was

*Table 2.* Identification methods reported for the diagnosis of TF in South-Eastern Europe

| Identification method* | No. of cases using this method | No. of cases in which the method was used as a primary method | No. of cases in which the method was used as a confirmatory method | No. of cases in which the method was used as the only method | No. of cases in which the method led to incorrect identification (used alone or in combination with other methods); misidentified *Trichosporon* species |
|---|---|---|---|---|---|
| Morphology | 18 | 18 | 0 | 0 | 1, (*T. asteroides*) |
| Biochemical tests (manual) | 1 | 0 | 0 | 0 | 0 |
| API ID 32 C | 13 | 0 | 0 | 8 | 1, (*T. asteroides*). No specific data for 3 strains of *T. asahii*** |
| API 20 C AUX | 14 | 0 | 0 | 2 | 0 |
| API Candida | 1 | 0 | 0 | 0 | 1, (*T. asteroides*) |
| Fungifast/Twin system | 1 | 0 | 0 | 0 | 1, (*T. asteroides*) |
| RapID Yeast Plus | 3 | 0 | 0 | 0 | No specific data for 3 strains of *T. asahii*** |
| VITEK*** | 24 | 0 | 0 | 13 | 1, (*T. asteroides*). No specific data for 3 strains of *T. asahii*** |
| Phoenix 100 | 1 | 0 | 0 | 0 | 0 |
| MALDI-TOF MS | 18 confirmed cases; no specific data for 3 strains of *T. asahii*** | 0 | 12 confirmed cases, no specific data for 3 strains of *T. asahii*** | 6 | No specific data for 3 more strains of *T. asahii*** |
| DNA sequencing | 4 | 0 | 4 | 0 | 0 |

**The identification methods presented in the table account for 50 out of the 59 cases included in this review; data were not available for the remaining 9 cases. All identification methods used are listed, regardless of whether they resulted in a correct diagnosis*, **MALDI-TOF MS was used for confirmation and for the identification of non-identified isolates across all rare yeasts in the study that included the three *T. asahii* strains (Noni et al. [30]) — possibly including them in the MALDI-TOF MS analysis, although this is not explicitly stated. DNA sequencing was definitively applied to these three *Trichosporon* strains. However, it remains unclear whether the *T. asahii* strains were initially unidentified by conventional methods prior to the use of MALDI-TOF MS or DNA sequencing, ***Different versions of the same system (e.g., VITEK and VITEK 2) are grouped under a single entry.*

successfully treated with voriconazole. In the second case, the patient, who was receiving amphotericin B and developed breakthrough fungaemia by *T. asahii*, was cured with fluconazole. In the third case, the patient, that was also receiving amphotericin B, and developed breakthrough fungaemia by *T. asahii* was successfully treated with voriconazole. The available MIC values and ranges reported in this article are presented in Table 4a (for the T. *mucoides*-strain) and in Table 4b (for 7 out of 8 *T. asahii* strains).

Oz et al. [37] also reported the demographic and clinical characteristics of patients with TF alongside those with fungaemia caused by other non-Candida yeasts. The MIC ranges for 4 of the 5 *T. asahii* strains are presented in Table 4b.

Akaslan et al. [34] conducted a national study in Turkey investigating bloodstream infections caused by *Trichosporon* species in paediatric patients. The demographic and clinical characteristics of the 28 patients included in the study were reported in aggregated form and are therefore not presented in Table 3. The median age of the patients was 44.5 months (range: 2 months to 18 years), comprising 15 females and 13 males. An underlying disease was present in 27 patients (96.4%), with only one patient (3.6%) lacking a known comorbidity. The most frequently reported underlying condition was paediatric cancer (11/28, 39.3%), which included three cases each of acute lymphoblastic leukaemia (ALL) and acute myeloblastic leukaemia (AML). This was followed by neurodevelopmental and metabolic disorders (7/28, 25%) and congenital heart diseases (5/28, 18%). Immunosuppressive conditions were identified in 15 patients (53.6%), including paediatric malignancies ($n = 11$), severe combined immunodeficiency ($n = 2$), liver transplantation ($n = 1$), and sickle cell anaemia with hypersplenism ($n = 1$). At the time of fungaemia diagnosis, 10 patients (35.7%) were neutropenic, while 18 (64.3%) were not. Indwelling central venous catheters were present in 17 patients (60.7%), and 11 patients (39.2%) had a history of admission to the paediatric intensive care unit (PICU). MICs were determined

*Table 3.* Demographic and clinical characteristics of patients with TF as reported in the majority of the articles reviewed. The Table does not include data when reported in the original articles together with other yeasts or reported in aggregated form

| Yeast species | Gender | Age | Unit | Medical history, risk factors | Antifungals administered as prophylaxis/empiric treatment | Therapy | Outcome |
|---|---|---|---|---|---|---|---|
| *T. asteroides* | Female | 75 years | Intensive Care Unit (ICU) | Pulmonary embolism, broad spectrum antimicrobial treatment, central venous catheter (CVC) | – | CVC removal plus Amphotericin B | Death |
| *T. asahii* | Female | 27 weeks gestational age | Neonatal Intensive Care Unit | Prematurity, respiratory distress syndrome, broad spectrum antimicrobial treatment | Amphotericin B empirically, increased dose after *T. asahii* isolation | Amphotericin B | Cure |
| *T. asahii* | Male | 13 years | Pediatric Oncology Department | T-cell Acute Lymphoblastic Leukemia (ALL), neutropenia, ALL BFM (Berlin–Frankfurt–Münster) protocol initiated, mechanical ventilation, broad spectrum antimicrobial treatment | Liposomal amphotericin B | Liposomal amphotericin B plus Voriconazole | Death by other cause (3 weeks after the first isolation of *T. asahii* in blood while blood cultures remained negative for yeasts) |
| *T. asahii* | Female | 75 years | ICU | Renal failure, T2 transitional cell carcinoma of the bladder, pneumonia, urinary tract infection, broad spectrum antimicrobial treatment, extensive abdominal surgery, intravascular catheter | Fluconazole (for *Candida albicans* deep-wound infection), changed to Caspofungin (*T. asahii* 1st positive blood culture during Caspofungin therapy) | Caspofungin | Death |
| *T. asahii* | Male | 47 years | Hematology Unit | Acute Myeloblastic Leukemia (AML), non-insulin-dependent diabetes mellitus, neutropenia, broad spectrum antimicrobial treatment, induction chemotherapy | Caspofungin empirically | Liposomal Amphotericin B, Voriconazole | Death |
| *T. asahii* | Male | 22 years | Department of Neurosurgery, ICU | Severe polytrauma and neurotrauma, mechanical ventilation, surgery, 2 reoperations, Pudenz catheter, broad-spectrum antibiotics, urinary catheter* | – | Removal of urinary catheter plus Fluconazole | Cure |
| *T. asahii* | Female | 2.5 years | Hematology and Oncology Unit | Malignancy of the yolk sac, surgical history | N.A. | N.A. | N.A. |
| *T. asahii* | Male | 14 years | Bone Marrow Transplant Unit | ALL relapse after bone marrow transplantation | N.A. | N.A. | N.A. |
| *T. asahii* | Female | 10 years | Pediatric Intensive Care Unit | Blackfan-Diamond anaemia, renal failure | N.A. | N.A. | N.A. |
| *T. asahii* | Male | 68 years | Internal medicine services** | Obstructive and reflux uropathy, reflux nephropathy, malignant neoplasma of the bladder* | – | Voriconazole plus nephrostomy replacement | Cure |
| *T. asahii* | Male | 28 years | Surgery services** | Skull base tumor-cranial nerves palsies-surgery | – | Voriconazole | Cure |

*(continued)*

*Table 3.* Continued

| Yeast species | Gender | Age | Unit | Medical history, risk factors | Antifungals administered as prophylaxis/empiric treatment | Therapy | Outcome |
|---|---|---|---|---|---|---|---|
| *T. asahii* | Male | 73 years | Internal medicine services** | Myelodysplastic syndrome/mixed lymphocytic acute leukemia, chemotherapy-induced myelotoxicity | Posaconazole as prophylaxis | Liposomal Amhotericin B plus Voriconazole plus peripherally inserted central catheter (PICC) removal | Death |
| *T. asahii* | Male | 62 years | ICU | Neurosurgical excision of meningioma | – | Voriconazole plus CVC removal | Cure |
| *T. asahii* | Male | 67 years | ICU | Traumatic brain injuries | Empiric treatment with Anidulafungin for 17 days | Voriconazole | Cure |
| *T. asahii* | Male | 72 years | Internal medicine services** | Non-Hodgkin lymphoma, chemotherapy-induced myelotoxicity | – | Voriconazole plus PICC replacement | Cure |
| *T. asahii* | Male | 65 years | Internal medicine services** | AML, chemotherapy-induced myelotoxicity | Posaconazole as prophylaxis | Voriconazole plus CVC removal | Cure |

*The yeast was isolated from urine as well as from blood.
**There is no specific department reported.

*Table 4a.* Minimum inhibitory concentrations (MICs, μg $mL^{-1}$) of the strains, reported specifically in the original articles and not as aggregated data

| *Trichosporon* species* | Method | Amhotericin B | Fluconazole | Itraconazole | Ketoconazole | Voriconazole | Posaconazole | Isavuconazole | Caspofungin |
|---|---|---|---|---|---|---|---|---|---|
| *T. asteroides* | Microdilution method | <0.0312 | <0.125 | <0.0625 | <0.0625 | – | – | – | – |
| *T. asahii* | *E* test | 2 | 12 | 0.50 | 0.38 | – | – | – | – |
| *T. asahii* | Microdilution method | 0.25 | 2 | 0.25 | – | ≤0.06 | 0.25 | | – |
| *T. asahii* | Microdilution method | – | 16** | – | – | – | – | | 16** |
| *T. asahii* | Microdilution method | >32 | 4 | 0.5 | – | <0.015 | – | | 16 |
| *T. asahii* | Microdilution method | 4 | 1 | 0.250 | – | 0.060 | – | | – |
| *T. asahii* | Microdilution method | 0.125 | 4 | 0.03 | – | 0.01 | 0.031 | | 8 |
| *T. asahii* | Microdilution method | 8 | 6 | 0.031 | – | 0.031 | 0.25 | | 16 |
| *T. asahii* | Microdilution method | 6 | 16 | 4 | – | 0.19 | 0.031 | | 8 |
| *T. mucoides* | Microdilution method | 2 | 0.25 | 0.25 | – | – | – | | – |
| *T. asahii* | *E* test | 0.25 | 2 | 0.75 | – | 0.032 | 0.5 | 0.093 | >32 |
| *T. asahii* | *E* test | 0.50 | 2 | 0.50 | – | 0.032 | 0.5 | 0.047 | >32 |
| *T. asahii* | *E* test | 0.25 | 2 | 0.75 | – | 0.064 | 0.25 | 0.047 | >32 |
| *T. asahii* | *E* test | 0.064 | 2 | 0.50 | – | 0.064 | 0.50 | 0.094 | >32 |
| *T. asahii* | *E* test | 0.25 | 3 | 0.5 | – | 0.047 | 0.50 | 0.032 | >32 |
| *T. asahii* | *E* test | 0.19 | 0.75 | 0.75 | – | 0.023 | 0.25 | 0.094 | >32 |
| *T. asahii* | *E* test | 0.50 | 1.50 | 1 | – | 0.047 | 0.75 | 0.125 | >32 |

*Trichosporon* spp. ($n = 3$) and *T. beigelii* ($n = 1$) were excluded from the table because of imprecise current classification and the absence of relevant data for these strains.
**MIC-2 Minimal Inhibitory Concentration (prominent reduction of growth).

*Table 4b.* Minimum inhibitory concentration (MIC) ranges of isolates as reported in the original articles

| | MIC ranges (μg mL$^{-1}$) by microdilution method | | | | | | |
|---|---|---|---|---|---|---|---|
| | Amphotericin B | Fluconazole | Itraconazole | Voriconazole | Posaconazole | Caspofungin | Anidulafungin |
| *T. asahii* (11 strains) | 0.5–4 | 1–8 | 0.25–1 | ≤0.015–0.25 | 0.03–1 | 2–8 | 1–4 |

for 14 out of the 28 isolates. Thirteen MIC values were detected by an automated system (VITEK/liquid microdilution), and one by E-test method. Voriconazole MICs were <0.12 mg mL$^{-1}$ in 12 of the 14 tested strains (85.7%). Among the strains tested for amphotericin B, 10 of 13 (76.9%) had MICs ≤1 mg mL$^{-1}$, and 4 of 13 (30.7%) had MICs <0.5 mg mL$^{-1}$. Caspofungin MICs exceeded 8 mg mL$^{-1}$ in 4 out of 6 tested strains (66%). In terms of treatment, amphotericin B was administered to 10 patients (35.7%), voriconazole to 8 patients (28.6%), and combination therapy with amphotericin B and voriconazole to 9 patients (32.1%). Caspofungin was used as empirical therapy in one patient (3.6%). Empirical treatment was initiated with fluconazole in 3 patients, which was continued with amphotericin B after the isolation of *Trichosporon* spp. Two patients with ALL were treated with caspofungin for prolonged neutropenic fever, and treatment proceeded with other regimens after the isolation of *Trichosporon* spp. from the blood cultures. Two patients with ALL were treated with caspofungin for prolonged neutropenic fever, and treatment proceeded with other regimens after the isolation of *Trichosporon* spp. from the blood cultures. The overall mortality rate was 28.5% (8/28 patients). Culture clearance, when achieved, occurred after a mean duration of 8.2 days (range: 2–25 days). Mortality rates by treatment group were as follows: 12.5% (1/8) in the voriconazole group, 30% (3/10) in the amphotericin B group, and 33.3% (3/9) in the combination therapy group. The single patient who received only caspofungin did not survive.

The outcome of TF is known in 41 out of 59 cases. In two studies, data from 14 cases are reported collectively as mortality due to non-*Candida* yeasts, with overall mortality rates of 47 and 72% in these studies, respectively. Additionally, the outcome is not reported for 4 cases. Among the cases with available outcome data, the overall mortality rate is 11 out of 41 (26.8%).

Voriconazole—regardless of whether breakthrough fungemia occurred or whether treatment involved additional interventions such as catheter removal—was associated with clinical improvement in: 7 out of 9 patients presented in Table 3; 7 out of 8 patients in the voriconazole monotherapy group in the study by Akaslan et al. [34]; 6 out of 9 patients in the voriconazole plus amphotericin B group in the same study; and 2 out of 2 patients in the study by Alp et al. [33].

## 4. DISCUSSION

This systematic review presents a comprehensive analysis of published cases of *TF* in South-Eastern Europe, comprising a total of 59 cases reported from three countries—Turkey, Greece, and Croatia—over a 25-year period (2001–2025). Although TF appears to be a rare clinical condition over time, the findings of this review underscore a gradual increase in reported cases through the years, consistent with global trends reflecting improved detection and growing awareness of rare yeast infections, particularly among immunocompromised and critically ill patients [3, 8, 9, 39, 40]. Specifically, while nine cases were reported between 2002 and 2016 without precise dating, among the remaining 50 cases for which a time frame could be established, 45 were identified after 2010. This temporal distribution aligns with the findings of Liao et al. [16], who also observed an increasing global trend in TF reports, beginning in 1975 and continuing through 2014.

It is also noteworthy that, whereas 65 cases of TF were reported globally between 1975 and 1994 [16], the first recorded case in South-Eastern Europe did not appear until 2001. This delay may reflect regional differences in diagnostic capacity, clinical awareness or publication practices during earlier decades.

In our review, published cases of TF were identified in only three South-Eastern European countries (Turkey, Greece, and Croatia). Examination of the available literature indicates that, for several other countries in the region—such as Bulgaria, Kosovo, North Macedonia, Albania, Bosnia and Herzegovina, and Montenegro—published data on fungal bloodstream infections, even on candidaemia, remain limited. By contrast, apart from Turkey and Greece—where a substantial body of literature exists [41–46]—countries such as Serbia, Slovenia, Croatia, and Romania (where, in this review, only one article on TF was identified from Croatia) do show published research on candidaemia and also participate in multinational European cohort studies on candidaemia organised by the ECMM [47–52]. However, no published cases of TF from these countries were identified during our search.

Moreover, TF is often overlooked or clinically misdiagnosed with forms of yeast fungaemia, particularly candidaemia [11, 16]. In addition, the laboratory investigation of *Trichosporon* spp. presents significant challenges and diagnostic difficulties [14]. Phenotypic methods used for the identification of *Trichosporon* species often yield inconsistent results, and commercially available diagnostic systems—such as VITEK systems 1 and 2—do not always fully incorporate the updated taxonomic classification of the genus in their reference databases [14, 53–56]. For example, Ahmad et al. [54] reported that four isolates previously identified as *T. asahii* by VITEK 2 were later reclassified as *T. asteroides* using molecular techniques.

These concerns are further confirmed by one of the studies included in our review. In the study by Kustimur et al. [26], significant difficulties were encountered in

identifying a *T. asteroides*isolate—not only at the species level but also at the genus level. Initially, based on morphology, the isolate was misidentified as *Candida* spp. The ID 32C system proposed two possible identifications (30% probability for *Candida curvata* and 70% for *T. asahii*), the VITEK system misidentified it as *T. asahii*, the API Candida system failed to provide a confident identification, and the Fungifast/Twin system misidentified it as *Cryptococcus* spp. Ultimately, the isolate was accurately identified by DNA sequencing.

The review findings on identification methods used for *Trichosporon* spp. in South-Eastern Europe suggest that newer techniques such as MALDI-TOF MS and DNA sequencing have been predominantly applied as confirmatory tools rather than primary diagnostic methods. Specifically, among the 18 cases where MALDI-TOF MS was used, it served as a confirmatory method in 12 cases, while it was the sole diagnostic method in only 6 cases. DNA sequencing, applied in 4 cases, was used exclusively for confirmatory purposes.

Furthermore, the studied data indicate that conventional phenotypic and biochemical methods (including morphology, biochemical tests, API 32C, API 20C, API Candida, Fungifast, RAPID ID, VITEK, and Phoenix systems) continue to be widely employed in routine laboratories across the region. These methods were employed in a total of 76 cases, whereas newer techniques such as MALDI-TOF MS and DNA sequencing were used in only 22 cases.

Given the limited accuracy of phenotypic and biochemical methods for species-level identification and their time-consuming nature [14, 16], broader and earlier implementation of MALDI-TOF MS and DNA sequencing could facilitate faster and more accurate species-level diagnoses. This, in turn, may enable earlier and more targeted therapeutic interventions —an important consideration given the high mortality rate associated with TF [20, 57]. This conclusion aligns with the general consensus that molecular methods are essential for accurate identification, although their higher cost and limited accessibility could prevent their widespread use in routine diagnostics [14, 58, 59].

Besides, global guidelines for the diagnosis and management of rare yeast infections—developed by the ECMM, ISHAM, and ASM—strongly recommend species identification following the obtainment of an isolate through microscopy and culture, and moderately support phenotypic identification (particularly for *T. asahii*) and MALDI-TOF MS, while strongly recommending molecular-based methods [9].

The distribution of *Trichosporon* species isolated in the region and examined in this study is consistent with the findings of Liao et al. [16], who, after documentation of global cases of *Trichosporon* fungaemia, found that the vast majority of infections were also attributed to *T. asahii*, followed by *T. mucoides*. This distribution also aligns with current knowledge on the prevalence of *Trichosporon* species in human infections more broadly [9]. Notably, one isolate of *T. coremiiforme* was identified in Turkey [34], despite this species being rarely isolated from human clinical specimens [60].

The most frequently reported underlying condition among patients included in the present study was haematologic disorders, observed in 31.8% of cases (14 out of 44 patients with clearly reported data). This category includes primarily haematologic malignancies, as well as conditions such as sickle cell anaemia and Diamond–Blackfan anaemia. It is noted that in one study by Sig et al. [35], data on underlying disease were not available, and in 14 additional patients from the studies by Alp et al. [33] and Oz et al. [37], relevant information was presented in aggregated form as part of a broader cohort of non-*Candida* yeast fungaemia. Nevertheless, in both studies, haematologic disorders were again the predominant underlying conditions, reported in 42% of cases in the Alp et al. study [33] and in 48% of cases as haematologic malignancies in the Oz et al. study [37]. Based on these findings, increased awareness of TF is particularly warranted in Haematology Departments across South-Eastern Europe. Nonetheless, clinical vigilance should not be confined to haematology settings, as TF has also been reported in patients without neutropenia or haematologic malignancies, as noted by Karabay et al. [29]. Moreover, cases have been documented in individuals without any identifiable immunosuppressive condition, including those with congenital heart diseases, neurodevelopmental or metabolic disorders, and even in an otherwise healthy child, as described by Akaslan et al. [34].

With regard to the antifungal susceptibility patterns of *Trichosporon* species, no clinical breakpoints have yet been established for this genus or for other rare non-*Candida*, non-*Cryptococcus* yeasts [10]. In the present study, statistical analysis and MIC comparisons among *Trichosporon* species were not feasible due to the limited number of isolates belonging to species other than *T. asahii*. However, when considered individually, non-*T. asahii* isolates exhibited lower MIC values for azoles compared to *T. asahii* strains. Specifically, *T. asteroides* demonstrated lower MICs for fluconazole, itraconazole, ketoconazole, and even amphotericin B, compared to the *T. asahii* isolates. Similarly, *T. mucoides* displayed among the lowest MICs for fluconazole and itraconazole. The low azole MICs observed for *T. asteroides* are consistent with the findings of Francisco et al. in Brazil, while the lower amphotericin B MICs for this species align with the results of Guo et al. [61], who also reported reduced amphotericin B MICs in non-*asahii* species compared to *T. asahii*.

Regarding the *T. asahii* isolates in this study, the MIC profiles largely concurred with those reported internationally [10, 62]. Voriconazole exhibited the lowest MIC values and was generally associated with favorable clinical outcomes when administered. Posaconazole and isavuconazole also demonstrated low MICs in the tested isolates; however, their clinical use was limited among the studied cases. In contrast, fluconazole, itraconazole, and amphotericin B showed variable MIC values. As expected, the highest MICs were observed for caspofungin and anidulafungin, as *Trichosporon* spp. are known to exhibit intrinsic resistance to echinocandins [63]. These findings align with international treatment guidelines for invasive *Trichosporon* infections, as outlined by the ECMM, ISHAM, and ASM [9]. It should be noted, however, that

current treatment recommendations are primarily based on data from animal models, in vitro studies, and case series—mainly involving haematological or oncology patients—due to the absence of randomised clinical trials [9].

One noteworthy finding of this review was the identification of a considerable number of cases of breakthrough fungaemias (BF) caused by *Trichosporon* spp., occurring despite ongoing empirical or prophylactic antifungal therapy. Specifically, BF due to *Trichosporon* spp. was identified in 16 cases, based on available data from 50 of the 59 reported cases. This observation is consistent with existing evidence that *Trichosporon* spp. is a frequent cause of breakthrough infections [15, 40, 57]. In 7 of these 16 cases, voriconazole was either introduced as part of the treatment regimen or replaced the initial therapy, which included an echinocandin, a triazole, or a polyene. In 2 cases, caspofungin was substituted with other antifungals, though specific details are lacking. Breakthrough fungaemia may occur in patients receiving echinocandins—commonly used as prophylactic agents in haematologic settings—due to the intrinsic resistance of *Trichosporon* spp. to this class of antifungals [9]. Notably, among the 7 patients treated with voriconazole, 5 were either cured or had negative blood culture for *Trichosporon* spp. This outcome is in line with the current international guidelines (developed by the ECMM, ISHAM, and ASM), which state that breakthrough infections occurring during treatment with echinocandins or polyenes may be successfully managed with voriconazole [9]. When attempting to document the underlying conditions and risk factors associated with the development of BF caused by *Trichosporon* in the patients of this study, it becomes evident that BF is not exclusively observed in patients with haematological malignancies (e.g., one patient had traumatic brain injuries). The most frequently identified risk factors among these patients included broad-spectrum antimicrobial therapy, neutropenia, and chemotherapy (in those with haematological disorders). Neutropenia as a risk factor for the development of breakthrough TF in patients with haematological disorders was also demonstrated by the study of Kimura et al., where it was found to be a statistically more significant risk factor for breakthrough TF compared to candidaemia [38].

The overall mortality rate of TF in the cases from the present study with available outcome data (26.8%) is lower than the 32.3% reported by Stewart et al. [10] in an Australian study from 2025, and clearly lower than the rate reported by Liao et al. [16] in a global review of TF cases, which included data from 1975 to 2014. Overall, possibly following the management guideline for rare yeasts published in 2014 by the European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group (ESCMID) and the ECMM, as well as the 2021 global guidelines for the diagnosis and management of rare yeast infections by the ECMM, ISHAM, and ASM [9], there appears to be an improvement in treatability over time.

In earlier studies, such as those by Suzuki et al. (2010) [57] and Krcmery et al. (1999) [22], the overall mortality rate of TF ranged between 76 and 83.3%. This gradual improvement may be attributed to advances in diagnostic methods, increased clinical awareness, and the use of voriconazole, which is recommended by these more recent guidelines [9] and was also associated with favorable outcomes in the majority of cases (whether or not breakthrough fungaemia was present) in this review.

## 5. LIMITATIONS

In this systematic review, complete clinical and laboratory data were not available for many clinical cases, as in specific studies [33, 37] these data were reported collectively for rare yeasts and not separately for *Trichosporon* spp. In one study that included a single case [35], only minimal data were provided. Finally, statistical analysis of MIC values was not possible, as the same antifungal susceptibility testing method and the same antifungal agents were not consistently used across the cases.

## 6. CONCLUSIONS

Although more rarely reported, TF in South-Eastern Europe can be characterised as a particularly severe clinical entity that may lead to death and is often associated with breakthrough fungaemia. Diagnostic methods, such as MALDI-TOF MS and DNA sequencing offer a promising perspective for improving the speed and accuracy of diagnosis. Regarding treatment, voriconazole appears to offer good outcomes, even in cases of breakthrough fungaemia. The documentation of all cases is a helpful tool for supporting the epidemiological monitoring.

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