

Predictors of Invasive Fungal Infection in Patients Receiving Extracorporeal Membrane Oxygenation: A Single-Center Retrospective Cohort Study

S. S. Andreev

nerowolf@mail.ru

Moscow Clinical Research Center Hospital 52 of the Moscow Department of Health (MKNIC Hospital 52 DZM)

M. V. Ketskalo

National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov"

P. O. Narusova

Moscow Clinical Research Center Hospital 52 of the Moscow Department of Health (MKNIC Hospital 52 DZM)

D. S. Kuznetsova

Moscow Clinical Research Center Hospital 52 of the Moscow Department of Health (MKNIC Hospital 52 DZM)

R. N. Trushkin

Moscow Clinical Research Center Hospital 52 of the Moscow Department of Health (MKNIC Hospital 52 DZM)

T. K. Isaev

Moscow Clinical Research Center Hospital 52 of the Moscow Department of Health (MKNIC Hospital 52 DZM)

P. V. Troshin

National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov"

M. A. Lysenko

Moscow Clinical Research Center Hospital 52 of the Moscow Department of Health (MKNIC Hospital 52 DZM)

I. V. Dmitriev

Pirogov Russian National Research Medical University (Pirogov University, Ministry of Health of the Russian Federation)

Keywords: extracorporeal membrane oxygenation, invasive aspergillosis, invasive candidiasis, antifungal therapy

Posted Date: September 23rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10910941/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background.

Invasive fungal infections (IFI) are considered as one of the significant complications of prolonged extracorporeal membrane oxygenation (ECMO). Published estimates of the incidence of IFI in ECMO patients vary widely, ranging from 1–2% to 30–40%. A key clinical problem is the distinction between cases of true mycotic infection, confirmed microbiologically or histologically, and cases of clinical suspicion, in which antifungal therapy begins empirically and is not confirmed. The consensus definitions of EORTC/MSGERC 2019/2020 distinguish the categories of "proven", "probable" and "possible" IFI, FUNDICU 2024 does not recommend using the definition of "possible" IFI for research purposes. Only the "proven" and "probable" IFI categories are considered a valid basis for clinical and epidemiological studies.

To determine the frequency, etiological spectrum, and independent predictors of confirmed IFI — defined as "proven" or "probable" — in adults on ECMO for > 48 hours, and to describe patients who received empirical antifungal therapy without microbiological confirmation.

Methods.

This retrospective single-centre cohort study included 235 consecutive adult patients who received ECMO for > 48 hours between 2019 and 2026. Confirmed IFI was defined as a diagnosis from the "proven" or "probable" categories according to the EORTC/MSGERC 2019/2020 criteria (for patients with classical risk factors for IFI in the host) or FUNDICU 2024 (for the rest). Cases of the "possible" category were not included in the main analysis and were analyzed separately. Univariate and multivariable logistic regression analyses were applied.

Results.

Confirmed IFI was diagnosed in 29 of 235 patients (12.3%): invasive candidiasis in 21 (8.9%), invasive aspergillosis in 7 (3.0%), and cryptococcosis in 1 (0.4%). The diagnosis was proven in 23 patients and probable in 6. A further 58 patients (24.7%) were diagnosed with possible IFI, 55 of whom received empirical antifungal therapy without microbiological confirmation. In multivariable logistic regression, the independent predictors of confirmed IFI were lymphocytopenia duration (adjusted odds ratio [aOR] 1.02 per day; 95% CI 1.00–1.05; $p = 0.037$) and the need for renal replacement therapy (RRT; aOR 12.23; 95% CI 1.55–96.40; $p = 0.017$); veno-venous ECMO showed a borderline association (aOR 3.80; 95% CI 0.98–14.75; $p = 0.053$). In the multivariable model, viral pneumonia was paradoxically associated with reduced odds of a confirmed diagnosis (aOR 0.14; 95% CI 0.04–0.50; $p = 0.002$), reflecting the predominance of the "possible" IFI category with empirical treatment without verification in this particular group of patients.

Conclusions.

In patients on prolonged ECMO, confirmed IFI develops in approximately 12.3%, with invasive candidiasis predominating. Prolonged lymphocytopenia and the need for RRT are the independent risk factors. The ratio between the number of confirmed cases (29) and the number of patients with clinical suspicion and/or empirical antifungal therapy (87) is 1:3 and highlights the significant proportion of unnecessary prescribing of antifungal drugs. Managing ECMO patients requires both clinical vigilance for fungal infection and rigorous microbiological confirmation to avoid unnecessary antifungal use and its associated toxicity.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a method of temporary replacement of lung and/or heart function in patients with refractory organ failure. Over the past decade, ECMO has become a routine treatment option for severe acute respiratory distress syndrome (ARDS), including viral aetiologies, and for cardiogenic shock. With an increase in the duration of the procedure and the expansion of indications, attention to infectious complications has increased, among which invasive fungal infections (IFI) occupy a special place.

Published estimates of the incidence of invasive fungal infections (IFI) in ECMO patients vary widely across studies. In the largest registry study to date, Cavayas et al. (2018) reported a prevalence of aspergillosis of 1.4% (including both infection and colonisation with *Aspergillus spp*) and of invasive candidiasis with candidemia of 1.2% among > 19,000 adult patients in the ELSO registry; both conditions were independently associated with reduced survival [1]. An accompanying editorial by Mongardon et al. emphasised that the predictors of aspergillosis and candidiasis differ fundamentally: aspergillosis more often arises in the context of pre-existing immunosuppression or severe lung injury, whereas the risk factors for candidemia are non-specific markers of severity—older age, sepsis, and renal replacement therapy (RRT) [2]. Poth et al. (2024) confirmed an association between IFI and markedly reduced survival in veno-arterial ECMO (hospital mortality rising from 67% to 94%), although they suggested that IFI served more as a severity marker than as a direct cause of death [3]. Single-centre studies with frequent empirical antifungal use often report much higher incidence rates, up to 30–40%, largely driven by cases of clinical suspicion without mycological confirmation. An important research area is distinguishing respiratory tract colonisation from clinically significant infection [9].

Russian clinical guidelines on antimicrobial therapy regard IFI as a major problem in modern intensive care. The authors show that in the context of critical illness, invasive procedures, broad-spectrum antibiotics, organ dysfunction, and critical illness-associated immunosuppression, the frequency of IFI is high and adversely affects prognosis [11, 12]. Invasive candidiasis, particularly candidemia, remains the leading fungal infection in ICUs [13]. The COVID-19 pandemic highlighted the clinical importance of other fungi — particularly moulds — with invasive aspergillosis, mucormycosis, fusariosis, and other rare fungal infections gaining major clinical attention [6, 11, 14]. Russian researchers have proposed diagnostic and therapeutic algorithms for COVID-19-associated candidiasis and aspergillosis (COVID-IA) that are broadly consistent with the international ECMM/ISHAM 2020 consensus [10, 15].

Differences in reported IFI frequency largely reflect variation in diagnostic approaches and the inclusion of different mycosis categories in the primary outcome – not true epidemiological differences. A "proven" diagnosis requires culture from a normally sterile site or histologic confirmation. A "probable" diagnosis requires a combination of clinical, radiological, and mycological criteria, along with host risk factors. In contrast, a "possible" diagnosis is based solely on clinical and radiological findings, without mycological confirmation. In practice, the "possible" category mainly comprises patients with severe lung injury in whom empirical antifungals are started without evidence of IFI. Including this category in the primary outcome inflates the reported IFI frequency and shifts the focus from infection epidemiology to the practice of empirical antifungal therapy [4, 5]. The FUNDICU 2024 consensus provided definitions for adult non-neutropenic ICU patients without classical risk factors, aiming to unify the definition of IFI (mainly candidiasis and aspergillosis) for research purposes. There is no separate universal category of "possible IFI" in FUNDICU in the same form as in EORTC/MSGERC [5].

ECMO patients are in a unique clinical situation: prolonged mechanical ventilation, prolonged standing of multiple invasive lines (both ECMO cannulas and central venous catheters), prolonged use of massive antibacterial therapy, immunomodulatory therapy, repeated blood transfusion, and the need for RRT. This combination of factors does not fit easily within the classical host factor framework of EORTC/MSGERC 2019/2020 [4]. In 2024, the international expert consensus FUNDICU published consensus definitions for immunocompetent adult ICU patients, with separate criteria for "proven" and "probable" invasive candidiasis and aspergillosis [5]. In domestic practice, the recommendations of the Ministry of Health of the Russian Federation (interim guidelines on COVID-19, version 19, 2025) [15] and recommendations edited by N. N. Klimko [12] identify a separate algorithm for mycological diagnosis in critically ill patients using galactomannan in bronchoalveolar lavage (BAL) fluid, serological tests, and culture testing.

This study aimed to assess the frequency of confirmed IFI (probable or proven categories) in a single-centre Russian cohort of patients on prolonged ECMO, to identify predictors of confirmed IFI using ECMO-specific parameters, and to describe patients who received empirical antifungal therapy without mycological confirmation.

Materials and methods

Design and population

A single-center retrospective cohort study was conducted. We included all consecutive adults (≥ 18 years) who received ECMO for > 48 hours between January 2019 and February 2026 at the ECMO Centre of Moscow Clinical Research Center Hospital 52 DZM (formerly City Clinical Hospital No. 52), regardless of indication or circuit configuration. Patients on ECMO for < 48 hours or with incomplete IFI data were excluded.

Data collection

Demographic data (age, sex), underlying and concomitant conditions (diabetes, obesity, chronic lung disease, cancer, haematological disorders), pre-ECMO hospitalisation length, presence of viral pneumonia (including influenza and COVID-19), ECMO type and duration, and weaning status were extracted from electronic medical records and ICU charts, along with laboratory parameters for the entire ECMO run: minimum and maximum values of leukocytes, lymphocytes, neutrophils, platelets, maximum values of procalcitonin and C-reactive protein, duration of lymphocytopenia (lymphocytes $< 1.0 \times 10^9/L$). Use of systemic corticosteroids, other immunosuppressants (IL-6 inhibitors, JAK inhibitors, cytostatics, etc.), RRT, antifungal therapy, and hospital outcome were also recorded.

Diagnosis of IFI and outcome definition

The IFI was classified under the modified EORTC/MSGERC 2019/2020 criteria [4] for patients with classical host risk factors and the FUNDICU 2024 definitions [5] for patients without them. Three categories of IFI were defined: "proven", "probable", and "possible". The primary endpoint was confirmed IFI, defined as "proven" or "probable" cases. Cases of clinical suspicion of IFI without mycological verification were classified as "possible", they were excluded from the primary analysis and were described separately. Proven invasive candidiasis was defined as isolation of *Candida* spp. from blood or a normally sterile site; proven invasive aspergillosis – with histological confirmation (including autopsy data) in the presence of appropriate clinical and radiological signs. In fatal cases, the diagnosis was reassessed based on autopsy findings.

Statistical analysis

Continuous variables are described as the median [interquartile range (IQR)], categorical variables as frequencies (percentages). The groups were compared using the Mann–Whitney test and the Fisher exact test or chi-squared test, depending on the applicability. Independent predictors of confirmed IFI were assessed using binary logistic regression. Variables with $p < 0.1$ in univariate analysis, as well as clinically relevant variables, were entered into the multivariable model. The results are presented as an odds ratio (OR) with a 95% confidence interval (95% CI). A two-sided p -value < 0.05 was considered statistically significant. The calculations were performed in Python 3.12 (libraries *scipy*, *numpy*, *pandas*, *statsmodels*).

Results

Baseline characteristics of the cohort

The analysis included 235 patients. The median age was 48 [39–59] years, and 161 patients (68.5%) were male. The primary indication for ECMO was pneumonia (188 cases, 80.0%), with viral aetiology confirmed in 145 patients (62.0%). The veno-venous configuration was used in 179 patients (76.2%), the veno-arterial configuration in 36 (15.3%), and other configurations in 20 (8.5%). The median ECMO duration was 10 [6–22] days, and the median pre-ECMO hospital stay was 24 [13–37] days. Successful

weaning from ECMO was achieved in 90 patients (38.5%), and hospital mortality was 73.6% (173 patients). Systemic corticosteroids were administered to 156 patients (66.4%), other immunosuppressants (mainly IL-6 receptor and JAK inhibitors) to 119 (50.6%), and RRT to 186 (79.1%). Case distribution over time mirrored the COVID-19 pandemic trajectory, peaking in 2020–2021 (133 cases, 56.6%).

Frequency and etiological structure of confirmed IFI

Confirmed IFI was diagnosed in 29 of 235 patients (12.3%). The etiological structure was dominated by invasive candidiasis: 21 patients (72.4% of confirmed cases, 8.9% of the entire cohort), followed by invasive aspergillosis: 7 patients (24.1% and 3.0%, respectively). One patient was diagnosed with cryptococcosis (0.4%). By diagnostic category, 23 cases were proven (20 candidemia confirmed by blood culture; 3 invasive aspergillosis with histological confirmation at autopsy) and 6 were probable (1 candidiasis with positive mannan test; 4 aspergillosis based on combined clinical, radiological, and mycological criteria; 1 cryptococcosis). (Fig. 1)

Among *Candida* isolates, *C. albicans* predominated (11 isolates), followed by *C. auris* (4), *C. glabrata* (3), and *C. parapsilosis* (2); in one case the species was not specified. Of the 29 confirmed cases, 21 met EORTC/MSGERC 2019/2020 criteria; application of FUNDICU 2024 criteria identified an additional 6 patients (28.6% increase). Two patients with histologically proven aspergillosis, according to autopsy data, did not meet the formal criteria of IFI of any of the systems ante-mortem.

A diagnosis of "possible IFI" was made in 58 patients (24.7%) based on clinical and radiological findings without microbiological or histological confirmation. In one patient, the suspicion of IFI was ruled out after further investigation. This group is described in detail in a separate section below.

Comparison of groups with and without confirmed IFI

Patients with (n = 29) and without (n = 206) confirmed IFI did not differ significantly in sex distribution. Patients with confirmed IFI tended to be older (56 vs 48 years; p = 0.052). Significant differences were found in a number of clinical and laboratory parameters (Table 1).

Table 1
Baseline characteristics of patients with and without confirmed IFI.

Characteristic	No confirmed IFI (n = 206)	Confirmed IFI (n = 29)	p
Age, years, median [IQR]	48 [38–58]	56 [46–60]	0.052
Male gender, n (%)	141 (68.4)	20 (69.0)	1.000
Duration of hospitalisation before ECMO, days	22 [13–35]	38 [23–55]	0.001
ECMO duration (days)	10 [6–21]	12 [8–28]	0.126
Lymphocytopenia duration (days)	14 [6–24]	26 [19–40]	< 0.001
Viral pneumonia, n (%)	134 (65.0)	11 (37.9)	0.007
VV-ECMO, n (%)	154 (74.8)	25 (86.2)	0.245
Weaning from ECMO, n (%)	73 (35.4)	17 (58.6)	0.024
In-hospital mortality, n (%)	156 (75.7)	17 (58.6)	0.070
Systemic GCS, n (%)	141 (68.4)	15 (51.7)	0.093
Other immunosuppressants, n (%)	108 (52.4)	11 (37.9)	0.167
Renal replacement therapy, n (%)	158 (76.7)	28 (96.6)	0.013
Minimum white blood cells, $\times 10^9/L$	4.3 [2.5–6.8]	3.5 [2.5–4.9]	0.301
Minimum lymphocyte count, $\times 10^9/L$	0.3 [0.2–0.4]	0.2 [0.2–0.3]	0.398
Minimum neutrophil count, $\times 10^9/L$	3.0 [1.5–5.1]	2.4 [1.5–3.7]	0.237
Minimum platelet count, $\times 10^9/L$	35 [21–61]	32 [26–44]	0.527
Peak procalcitonin, ng/ml	2.0 [0.7–4.5]	22.3 [13.5–31.0]	0.004
Maximum CRP, mg/l	271 [170–364]	295 [236–386]	0.374
<i>Note: continuous variables are the median [IQR]; Mann-Whitney U test for continuous and Fisher's exact test for categorical variables. GCS—glucocorticosteroids; ECMO—extracorporeal membrane oxygenation; VV—veno-venous; CRP—C-reactive protein.</i>			

Univariate and multivariable analyses

In univariate analysis, confirmed IFI was significantly associated with lymphocytopenia duration (OR 1.02 per day; 95% CI 1.01–1.04; $p = 0.007$) and need for RRT (OR 8.51; 95% CI 1.13–64.17; $p = 0.038$). Viral pneumonia was associated with lower odds of IFI (OR 0.33; 95% CI 0.15–0.73; $p = 0.007$). Age, ECMO duration, VV-ECMO, systemic corticosteroid use, and other immunosuppressants were not significant in

univariate analysis. Patients with confirmed IFI tended to be older (56 vs 48 years; $p = 0.052$), approaching statistical significance by the Mann–Whitney U test.

In multivariable analysis adjusted for ECMO duration, lymphocytopenia duration, ECMO type, RRT, immunosuppressant use, and viral pneumonia, only lymphocytopenia duration and RRT remained independent predictors of confirmed IFI. VV-ECMO showed a borderline association ($p = 0.053$), while viral pneumonia was consistently associated with lower odds of a confirmed diagnosis (Table 2).

Table 2
Multivariable logistic regression analysis of predictors of confirmed IFI (n = 233).

Predictor	Corrected OR	95% CI	p
Duration of lymphocytopenia (per day)	1.02	1.00–1.05	0.037
Renal replacement therapy	12.23	1.55–96.40	0.017
Veno-venous ECMO	3.80	0.98–14.75	0.053
ECMO duration (per day)	1.00	0.96–1.04	0.916
Other immunosuppressants	1.08	0.32–3.62	0.901
Viral pneumonia	0.14	0.04–0.50	0.002
<i>Note: OR—odds ratio; CI—confidence interval; ECMO—extracorporeal membrane oxygenation. The negative association between viral pneumonia and confirmed IFI is further addressed in the Discussion and likely reflects the classification of patients with viral ARDS as "possible mycosis" treated empirically without mycological confirmation.</i>			

Empirical antifungal therapy group without microbiological confirmation

A diagnosis of "possible IFI" was made in 58 patients (24.7%) based on clinical and radiological findings without mycological confirmation. Of these, 55 patients (94.8%) received antifungal therapy, mainly amphotericin B (38 cases) or combinations containing it (5 cases), and less frequently echinocandins (5) or azoles (3). Table 3 compares this group with patients without suspected IFI and those with confirmed IFI.

Table 3

Comparison of patients without suspected IFI, those receiving empirical antifungal therapy without confirmation, and those with confirmed IFI.

Characteristic	Without suspicion of IFI (n = 148)	Empirical therapy without IFI confirmation (n = 58)	Confirmed IFI (n = 29)
Age (years)	48 [38–59]	47 [39–57]	56 [46–60]
ECMO duration (days)	8 [5–15]	22 [12–32]	12 [8–28]
Lymphocytopenia duration (days)	12 [5–18]	24 [14–35]	26 [19–40]
Pre-ECMO hospitalisation (days)	17 [11–29]	34 [22–47]	38 [23–55]
Minimum platelet count, $\times 10^9/L$	42 [25–70]	27 [13–35]	32 [26–44]
Peak procalcitonin, ng/ml	2.0 [0.6–4.4]	2.0 [2.0–9.1]	22.3 [13.5–31.0]
Viral pneumonia, n (%)	85 (57.4)	49 (84.5)	11 (37.9)
VV-ECMO, n (%)	103 (69.6)	52 (89.7)	25 (86.2)
Systemic GCS, n (%)	95 (64.2)	46 (79.3)	15 (51.7)
Other immunosuppressants, n (%)	68 (45.9)	40 (69.0)	11 (37.9)
Renal replacement therapy, n (%)	104 (70.3)	54 (93.1)	28 (96.6)
Received antifungal therapy, n (%)	4 (2.7)	55 (94.8)	24 (82.8)
In-hospital mortality, n (%)	104 (70.3)	52 (89.7)	17 (58.6)
<i>Note: continuous variables are presented as median (IQR). GCS—glucocorticosteroids.</i>			

Patients receiving empirical antifungal therapy without IFI confirmation were the most severely ill across most parameters. They had the longest median ECMO duration (22 vs 8 days in patients without suspected IFI and 12 days in those with confirmed IFI), the lowest platelet count ($27 \times 10^9/L$), and the highest rates of viral pneumonia (84.5%), VV-ECMO (89.7%), glucocorticoid use (79.3%), and other immunosuppressants (69.0%). In-hospital mortality in this group was 89.7%, significantly higher than in patients with confirmed IFI (58.6%; $p = 0.002$, Fisher's exact test) and in those without suspected IFI (70.3%; $p = 0.004$).

In five patients with confirmed IFI, the diagnosis was made posthumously, and antifungal therapy was therefore not administered.

Discussion

In our single-centre cohort of 235 adults on prolonged ECMO, the incidence of confirmed IFI (proven or probable) was 12.3%. This characteristic is significantly higher than that from the ELSO registry: 1.4% for aspergillosis and 1.2% for candidemia [1], but significantly lower than the values from single-center studies that included the "possible" cases as a primary outcome. If all three categories (including "possible" cases) were included, the IFI incidence in the study cohort would be 37.0% – three times higher than the confirmed rate. This difference is crucial for interpretation of the data.

The obtained frequency of 12.3% (with a predominance of confirmed candidiasis over aspergillosis) is in good agreement with prospective multicentre studies using consensus criteria and active mycological diagnosis. Thus, the prospective multicentre APICOVID study in France (Desmedt et al., 2024), which included 566 patients, reported a COVID-IA prevalence of 5.1%, rising to 9.1% among those on mechanical ventilation [16]. The prospective MSG-017 study in seven US centers (Zilberberg et al., 2024) on 212 patients on mechanical ventilation reported a CAPA rate of 7%, with only 7% of these cases being "proven" by EORTC/MSGERC, and in 14% of cases formally classified as COVID-IA, the authors considered invasive aspergillosis unlikely; the mortality rate among COVID-IA was 71% and did not differ from patients without COVID-IA [17]. A two-centre study in China (Alpha and Omicron periods) reported a COVID-IA rate of 5.1–7.5%, a prospective cohort in the UK showed 0.9% of probable COVID-IA in the absence of proven cases [18, 19]. The prevalence of IFI in a large systematic review by Feys et al. (48 studies, 2,953 ICU patients with COVID-19) was 15.1% with significant heterogeneity, largely due to the depth of mycological diagnosis [20]. A systematic review and meta-analysis by Gioia et al. (2024) confirmed that immunosuppression, prolonged mechanical ventilation, and RRT are key independent risk factors for COVID-IA, and mortality in confirmed COVID-IA in most cohorts is 50–60% [21].

Russian ECMO-specific data on IFI incidence are scarce, although a substantial body of evidence on IFI epidemiology in the ICU is available. Studies by Klimko et al. and Khostelidi et al. described the etiological structure and risk factors of invasive aspergillosis in Russia, describing the prevalence of *Aspergillus fumigatus* and confirming the importance of prolonged neutropenia and lymphocytopenia as risk factors [14, 11]. The Russian national guidelines for the diagnosis and management of ICU-related mycoses, edited by Klimko et al. [12], along with subsequent work on invasive aspergillosis in severe viral respiratory infections, standardise domestic practice and closely align with the international ECMM/ISHAM 2020 [10] and FUNDICU 2024 [5] recommendations.

The pathogen spectrum in our cohort, when limited to confirmed cases, differs from that obtained when "possible" mycoses are included in the analysis. With a strict approach, invasive candidiasis predominates (21 cases, mainly candidemia), whereas proven or probable invasive aspergillosis was diagnosed in only 7 patients. This is diagnostically consistent as the cultural confirmation of candidemia is achievable with standard blood cultures, whereas invasive aspergillosis in ECMO patients is extremely rarely confirmed in life: routine determination of galactomannan in bronchoalveolar lavage (BAL) and (1→3)-β-D-glucan in our cohort was not performed, and histological confirmation was obtained only

postmortem (3 of 7 cases). This limitation is well known in the literature: according to global autopsy data, 53–60% of cases of invasive aspergillosis in the ICU are not diagnosed during life [14]. The prevalence of candidiasis in the confirmed part of the cohort is consistent with the ELSO data [1], and the low number of confirmed aspergillosis cases likely reflects the challenges of ante-mortem diagnosis, rather than the actual absence of invasive mold infection in patients.

The spectrum of *Candida* species warrants special attention. In addition to *Candida albicans*, *Candida auris* (4 cases) and *Candida glabrata* (3 cases), species with reduced susceptibility to azoles and echinocandins, were documented in our cohort. The Russian ARTEMIS DISK study, conducted in eight Russian centers in the early 2000s, showed a significant proportion of *non-albicans Candida* in the spectrum of candidiasis, primarily *C. glabrata* (5.2%), *C. parapsilosis* (3%) and *C. krusei* (2.8%), while maintaining high sensitivity of *C. albicans* to fluconazole (98.9%) and the borderline sensitivity of *non-albicans* species [22]. Since then, global and domestic epidemiology has shifted toward an increasing proportion of *non-albicans* species. The spread of *C. auris*, a multidrug-resistant micromycete, is of particular concern [23, 24]. Our data on four cases of *C. auris* candidemia in ECMO patients highlight the relevance of this pathogen.

The key result of this study is the identification of two independent predictors of confirmed IFI: the duration of lymphocytopenia and the need for RRT. Prolonged lymphocytopenia reflects acquired immune deficiency in sepsis and severe ARDS. In our cohort, its median duration was nearly twice as long in patients with confirmed IFI (26 days) than in those without (14 days). This finding is consistent with multicentre domestic data, where prolonged neutropenia and lymphocytopenia were identified as key risk factors for both invasive aspergillosis and mucormycosis in haematological patients [13]. In our study, lymphocytopenia was a risk factor for poor outcomes in the general population of patients with candidemia [25]. In relation to ICU patients who do not meet the EORTC/MSGERC criteria, prolonged lymphocytopenia becomes an indicator of critical illness-associated immunosuppression, which becomes an independent risk factor for opportunistic infections and their outcome.

On the one hand, the need for RRT is a marker of combined multiple organ failure, on the other hand, it is an independent risk factor for fungal invasion: constant intravascular access, frequent use of antibiotic therapy, and the need for repeated transfusions of blood components. The association of IFI with RRT is consistent with the findings of Cavayas et al. (OR 1.55; ELSO data) and the meta-analysis by Thomas-Rüddel et al. [1, 7]. In our cohort, RRT was the strongest predictor of confirmed IFI (aOR 12.2), although the wide confidence intervals reflect the small number of events and the limited number of patients without RRT (only one patient in the confirmed IFI group did not receive RRT). The borderline association of VV-ECMO with confirmed IFI ($p = 0.053$) probably reflects the predominance of respiratory indications, the long duration of procedures, and severe pulmonary injury associated with the VV configuration [8].

The paradoxical negative association between viral pneumonia and confirmed IFI (aOR 0.14; $p = 0.002$) in our cohort requires very careful interpretation. This finding does not imply that viral lung injury is protective against fungal infection; rather, these patients were classified as having "possible mycosis"

based on clinical and radiological findings, without subsequent mycological confirmation. The lack of mycological confirmation was due to difficulties in obtaining samples and limited laboratory capacity during the "peak" of the COVID-19 pandemic. Among patients with viral pneumonia, the proportion of "possible" mycoses was higher than that of confirmed cases, whereas in patients with other types of lung pathology and a similar clinical presentation, microbiological or histological confirmation was more frequently obtained. A similar observation was noted in COVID-IA studies: during the COVID-19 pandemic, many patients with typical clinical and radiological signs did not undergo targeted mycological testing, particularly during the first wave. This resulted in an excess of "possible" cases, leading to overestimation of COVID-IA frequency in some studies and underestimation in others [17, 19, 20]. Thus, the negative adjusted OR for viral pneumonia should be interpreted as an artifact of the diagnostic classification, and it emphasizes the need for targeted mycological diagnosis specifically in patients with severe viral lung damage [11, 12, 14, 15].

Confirmed IFI and empirical antifungal therapy: analysis of potential contributing factors

A notable finding of this study is the diagnostic gap between the number of patients with clinical suspicion of IFI and/or empirical antifungal therapy and the number with microbiologically or histologically confirmed IFI. In 87 of 235 patients (37.0%), the ECMO team considered a diagnosis of invasive mycosis, yet only 29 cases (12.3%) were confirmed – a threefold difference. Of the 58 patients with clinical suspicion of IFI without mycological confirmation ("possible" mycosis), 55 (94.8%) received antifungal therapy – mainly polyenes – without subsequent confirmation. In one patient, the diagnosis was formally ruled out after further work-up.

This empirically treated group was the most severely ill across most parameters, including ECMO duration, RRT requirement, immunosuppressive therapy, systemic inflammatory markers, and thrombocytopenia (Table 3). The in-hospital mortality rate in this group was 89.7%, significantly higher than in the confirmed IFI group (58.6%; $p = 0.002$). Thus, empirical antifungals were given to the sickest patients with the highest mortality. Whether this therapy improved outcomes cannot be determined from this study design. Some of these patients died before a mycological diagnosis could be established; in others, clinical and radiological findings suggestive of possible aspergillosis or candidiasis likely reflected viral ARDS and/or bacterial superinfection. A similar pattern of COVID-IA "overdiagnosis" was documented in the prospective multicentre MSG-017 study, where twice as many patients met the ECMM/ISHAM criteria as met the MSGERC criteria; however, the estimated probability of true invasive aspergillosis in these overclassified cases was only 1–8% [17].

The clinical, pharmacoeconomic, and environmental consequences of widespread empirical antifungal prescribing during ECMO are unfavorable. Amphotericin B (both conventional and lipid formulations), which accounted for more than two-thirds of empirical prescriptions in our cohort, has substantial toxicity (nephrotoxicity, hypokalemia, hypomagnesemia, and infusion-related reactions) [26–28]. Alternative azoles (voriconazole, isavuconazole, fluconazole) have a significant potential for drug

interactions, including with sedatives, antiarrhythmics, anticoagulants, and immunosuppressants commonly used in ECMO patients. Voriconazole can cause QT prolongation, hepatotoxicity, and neurotoxicity, necessitating therapeutic drug monitoring (target trough concentration 1–5.5 µg/mL), which is not widely available in Russian centres [26, 28, 30]. It should be noted that pharmacokinetic alterations during critical illness and drug sequestration in the ECMO circuit often prevent attainment of target pharmacokinetic parameters with standard antifungal dosing [28–32]. The use of antifungal agents without adequate mycological diagnostics precludes identification of the pathogen and its susceptibility profile, which is particularly important given the spread of *C. auris* [24], *non-albicans Candida* species [22, 23], and moulds. Empirical therapy should not replace microbiological diagnostics, as emphasized in recent Russian [11, 14, 15] and international ECMM/ISHAM and FUNDICU guidelines [5, 10], which recommend testing for galactomannan in BAL, mannan/anti-mannan antibodies, and (1→3)-β-D-glucan before or concurrently with the initiation of antifungal therapy.

Comparing our data with registry studies, much of the variation in reported IFI incidence during ECMO is explained not by true epidemiological differences, but by differences in the patient categories included in the primary outcome. The ELSO registry, which relies on coded diagnoses, mainly captures proven and, to some extent, probable cases, thus yielding the lowest estimates [1]. Single-centre studies defining the outcome as any clinical diagnosis or antifungal prescription report the highest estimates. Routine application of consensus criteria (EORTC/MSGERC and FUNDICU), with separate reporting of possible, probable, and proven cases and transparent documentation of microbiological verification, would greatly improve comparability across studies. This approach has been partially adopted in recent prospective studies – APICOVID [16], MSG-017 [17], and the two-centre Wuhan/Nanjing study [18] – which report confirmed and suspected cases separately.

It is noteworthy that the EORTC/MSGERC 2019/2020 and FUNDICU 2024 criteria were largely complementary in our cohort: 21 patients met the formal EORTC criteria, and FUNDICU identified an additional 6 patients without classical host risk factors (a 28.6% increase). This demonstrates that in ECMO-treated ICU cohorts—where patients without haematological disease but with critical illness-associated immunosuppression predominate—the FUNDICU criteria complement rather than replace EORTC/MSGERC [5]. Two patients with histologically proven invasive aspergillosis at autopsy did not meet the formal criteria of either classification system during life, underscoring the limitations of current definitions in the ECMO setting and the need for further validation in this population. A similar problem is described in MSG-017. The authors proposed an additional conceptual filter for "putative" COVID-IA to distinguish between formally classified cases and true invasive aspergillosis [17].

A prospective multicentre study with a standardised diagnostic protocol is needed in Russian ECMO centres to better define diagnostic and therapeutic strategies for IFI.

Limitations

The retrospective design may introduce inherent biases. Serum galactomannan, mannan/anti-mannan antibodies, and (1→3)-β-D-glucan were not routinely measured in the study patients, which may have

reduced the sensitivity for detecting IFI and likely contributed to the low number of confirmed aspergillosis cases. The study cohort was rather heterogeneous—for example, it included only one case each of cryptococcosis and haematological disease, which precludes any subgroup analysis or conclusions for these conditions. The small number of events in the multivariable model for confirmed IFI resulted in wide confidence intervals.

Conclusions

In adult patients on ECMO for > 48 hours, confirmed IFI (proven or probable by EORTC/MSGERC or FUNDICU criteria) occurred in 12.3%, with invasive candidiasis and candidemia predominating. Independent predictors of confirmed IFI were prolonged lymphocytopenia and the need for renal replacement therapy; VV-ECMO showed a borderline association. The FUNDICU 2024 criteria complement, but do not replace, the EORTC/MSGERC 2019/2020 criteria.

A notable finding of this study is the diagnostic gap between clinical suspicion of IFI and/or empirical antifungal therapy (87 patients, 37.0%) and confirmed cases (29 patients, 12.3%). Patients who received empirical antifungal therapy without mycological confirmation were the most severely ill, had the longest ECMO duration, and the highest in-hospital mortality (89.7%). Thus, managing patients on long-term ECMO requires both clinical vigilance for IFI — particularly in those with prolonged lymphocytopenia or requiring RRT — and rigorous microbiological investigation, including repeated blood cultures, BAL galactomannan testing, mannan/anti-mannan antibody assays, and (1→3)-β-D-glucan detection. These findings support the need for prospective studies in Russian ECMO centres and the adoption of standardised diagnostic and therapeutic algorithms for antifungal therapy.

Declarations

Ethical expertise and funding

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the local Ethics Committee of MKNIC Hospital 52 (Protocol No. 08/0825, August 27, 2025). Given the retrospective nature of the study, subsequent database updates, anonymisation of data, and the absence of active patient enrolment, the Ethics Committee waived the requirement for informed consent. The authors declare that they have no competing interests and no external funding.

Availability of data and materials: We affirm that we had full access to all the study's data. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: not applicable

Funding: This study was sponsored by the ANO "Moscow Center for Innovative Healthcare Technologies"

Authors' contributions

S.S.A. - the idea and design of the study, definition of intellectual content, manuscript editing and manuscript review.

M.V.K. - the idea and design of the study, academic literature search, manuscript editing and manuscript review.

P.O.N. – collection of data, data analysis

K.D.S. - collection of data, data analysis

R.N.T. - definition of intellectual content, manuscript editing and manuscript review

T.K.I. - data acquisition, data analysis, manuscript preparation, manuscript editing

P.V.T. - academic literature search, manuscript editing and manuscript review

M.A.L. - supervised the study, revision of the manuscript.

I.V.D. - data analysis, manuscript preparation, manuscript editing and manuscript review.

All authors reviewed and approved the final manuscript.

Acknowledgements: The authors gratefully acknowledge the technical support provided by the ANO "Moscow Center for Innovative Healthcare Technologies" for the preparing of this article.

Information about the authors:

Corresponding author: **Sergey S. Andreev** – Candidate of Medical Sciences (PhD), Head of the Department of Clinical Pharmacology, MKNIC Hospital 52, Moscow Department of Health; Leading Specialist, Department of Clinical Pharmacology Organisation and Methodology, Research Institute for Healthcare Organisation and Medical Management (NIIOZMM), Moscow Department of Health; ORCID: <https://orcid.org/0000-0002-9147-4636> ; e-mail: nerowolf@mail.ru

Mikhail V. Ketskalo – PhD, Director, National Medical Research Center for Anesthesiology and Intensive Care for Pregnant Women, National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov", Ministry of Health of the Russian Federation, Russia, 117997, Moscow, Akademika Oparina St., 4, ORCID: <https://orcid.org/0000-0001-6569-2106>

Polina O. Narusova – clinical pharmacologist at MKNIC Hospital 52 DZM; ORCID: <https://orcid.org/0000-0002-2960-5236>

Darya S. Kuznetsova – clinical pharmacologist at MKNIC Hospital 52 DZM; ORCID: <https://orcid.org/0009-0003-7192-8738>

Teymur K. Isaev — MD, Doctor of Urology at MKNIC Hospital 52 DZM; ORCID: <https://orcid.org/0000-0003-3462-8616>

Ruslan N. Trushkin — MD, Head of the Urology Department at MKNIC Hospital 52 DZM; Professor of the Department of Urology and Operative Nephrology with a course in Oncourology at Patrice Lumumba Peoples' Friendship University of Russia; ORCID: <https://orcid.org/0000-0002-3108-0539>

Pavel V. Troshin — researcher at the National Research Medical Center for Anesthesiology and Intensive Care for Pregnant Women, Federal State Budgetary Institution National Medical Research Center of Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov" of the Ministry of Health of the Russian Federation, Russia 117997, Moscow, Akademika Oparina St., 4; ORCID: <https://orcid.org/0000-0002-4904-7913>.

Maryana A. Lysenko — MD, Director of MKNIC Hospital 52 DZM; Professor of the Department of General Therapy at the Faculty of Additional Professional Education of the Russian National Research Medical University named after N.I. Pirogov", Ministry of Health of Russia; ORCID: <https://orcid.org/0000-0001-6010-7975>

Ilya V. Dmitriev — MD, Head of the Department, Leading Researcher at the Department of Kidney and Pancreas Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Department of Health, Associate Professor of the Department of Transplantology and Artificial Organs of the FDPO INOPR, Pirogov University, Ministry of Health of the Russian Federation, ORCID: <https://orcid.org/0000-0002-5731-3310>; e-mail: dr.ildmi@gmail.com

References

1. Cavayas YA, Yusuff H, Porter R. Fungal infections in adult patients on extracorporeal life support. Crit Care. 2018;22(1):98. 10.1186/s13054-018-2023-z.
2. Mongardon N, Constant O, Taccone FS, Levesque E. Appraisal of fungal infections during ECMO therapy. Crit Care. 2018;22(1):145. 10.1186/s13054-018-2082-1.
3. Poth JM, Schmandt M, Schewe JC, et al. Prevalence and prognostic relevance of invasive fungal disease during veno-arterial ECMO: a retrospective single-center study. J Crit Care. 2024;83:154831. 10.1016/j.jcrc.2024.154831.
4. Donnelly PJ, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis. 2020;71:1367–76. 10.1093/CID/CIZ1008.
5. Bassetti M, Giacobbe DR, Agvald-Ohman C, et al. Invasive Fungal Diseases in Adult Patients in Intensive Care Unit (FUNDICU): 2024 consensus definitions from ESGCIP, EFISG, ESICM, ECMM, MSGERC, ISAC, and ISHAM. Intensive Care Med. 2024;50(4):502–15.

6. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med*. 2020;8(11):1121–31. 10.1016/S2213-2600(20)30328-3.
7. Thomas-Rüddel DO, Schlattmann P, Pletz M, Kurzai O, Bloos F. Risk Factors for Invasive Candida Infection in Critically Ill Patients: A Systematic Review and Meta-analysis. *Chest*. 2022;161(2):345–55. 10.1016/j.chest.2021.08.081.
8. Rodriguez-Goncer I, Thomas S, Foden P, et al. Invasive pulmonary aspergillosis is associated with adverse clinical outcomes in critically ill patients receiving veno-venous extracorporeal membrane oxygenation. *Eur J Clin Microbiol Infect Dis*. 2018;37(7):1251–7. 10.1007/s10096-018-3241-7.
9. Blot SI, Van den Taccone FS, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. *Am J Respir Crit Care Med*. 2012;186(1):56–64. 10.1164/rccm.201111-19780C.
10. Koehler P, Bassetti M, Chakrabarti A, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis*. 2021;21(6):e149–62. 10.1016/S1473-3099(20)30847-1.
11. Hostelidi SN, Kozlova OP, Shadrivova OV. and other. Invasive mycoses in intensive care units (registry data analysis and literature review). *Problems of Medical Mycology*. 2024; 26 (1): 3–21. (In Russ). 10.24412/1999-6780-2024-1-3-21
12. Klimko NN, editor. 2nd ed. additional and revised. M.: Pharmtek, 2015; 96 p. (In Russ).
13. Yakovlev SV, Briko NI, Sidorenko SV, Procenko DN, editors. Programma SKAT (Strategiya Kontrolya Antimikrobnoy Terapii) pri okazanii stacionarnoj medicinskoj pomoshchi. Rossijskie klinicheskie rekomendacii [SCAT Program (Antimicrobial Stewardship Strategy) in inpatient medical care. Russian clinical guidelines]. Moscow: Pero; 2018.
14. Klimko NN, Shadrivova OV. Invasive aspergillosis in severe respiratory viral infections (influenza and COVID-19). *Jurnal infektologii*. 2021;13(4):14–22. 10.22625/2072-6732-2021-13-4-14-24. (In Russ).
15. Ministry of Health of the Russian Federation. [The Temporary Guidelines: Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)]. Version 19 (in Russian).
16. Desmedt L, Raymond M, Le Thuaut A, et al. COVID-19-associated pulmonary aspergillosis in mechanically ventilated patients: incidence and outcome in a French multicenter observational cohort (APICOVID). *Ann Intensive Care*. 2024;14(1):17. 10.1186/s13613-023-01229-3.
17. Nguyen MH, Leal SM, Ostrosky-Zeichner L, et al. COVID-19-associated Pulmonary Aspergillosis in Mechanically Ventilated Patients at 7 US Hospitals: Epidemiology and Estimated Likelihood of Invasive Pulmonary Aspergillosis — Results of the Prospective MSG-017 Study. *Open Forum Infect Dis*. 2025;12(7):ofaf331. 10.1093/ofid/ofaf331.
18. Zhong A, Jiang W, Yang Y, et al. High mortality and mechanical ventilation in COVID-19-associated pulmonary aspergillosis: insights from a two-center retrospective cohort study. *Front Public Health*. 2026;13:1702502. 10.3389/fpubh.2025.1702502.

19. Hurt W, Youngs J, Ball J, et al. COVID-19-associated pulmonary aspergillosis in mechanically ventilated patients: a prospective, multicentre UK study. *Thorax*. 2024;79(1):75–82. 10.1136/thorax-2023-220002.
20. Feys S, Almyroudi MP, Braspenning R, et al. A Visual and Comprehensive Review on COVID-19-Associated Pulmonary Aspergillosis (CAPA). *J Fungi (Basel)*. 2021;7(12):1067. 10.3390/jof7121067.
21. Gioia F, Walti L, Orchanian-Cheff A, et al. Risk factors for COVID-19-associated pulmonary aspergillosis: a systematic review and meta-analysis. *Lancet Respiratory Med*. 2024;12:207–16. 10.1016/S2213-2600(23)00408-3.
22. Veselov AV, Mulikin NV, Klyasova GA, Tarasova GV, Agapova ED, Rebrova EV, et al. Epidemiology of candidiasis causative agents and their susceptibility to azoles: results of ARTEMIS disk study in Russia. *Clin Microbiol Antimicrob Chemother*. 2005;7(1):68–76. Russian.
23. Kim HY, Nguyen TA, Kidd S, Chambers J, Alastruey-Izquierdo A, Shin JH, et al. *Candida auris* — a systematic review to inform the World Health Organization fungal priority pathogens list. *Med Mycol*. 2024;62(6):myae042. 10.1093/mmy/myae042.
24. Chen J, Tian S, Han X, Chu Y, Wang Q, Zhou B, Shang H. Is the superbug fungus really so scary? A systematic review and meta-analysis of global epidemiology and mortality of *Candida auris*. *BMC Infect Dis*. 2020;20(1):827. 10.1186/s12879-020-05543-0.
25. Dushkin AD, Narusova PO, Andreev SS, Iskhakov RT, Chernov AA, Dukhanina OD, Akmalova KA, Lysenko MA. Risk factors for adverse outcome in invasive candidiasis. *Infekc bolezni (Infectious Diseases)*. 2025;23(1):65–72. 10.20953/1729-9225-2025-1-65-72. (In Russian).
26. Khostelidi SN, Mitrofanov BYV, Nikolaeva VS, Vasilieva NG. Chronic pulmonary aspergillosis, features of diagnosis and treatment (literature review). *Probl Med Mycol*. 2026;28(1):3–18. 10.24412/1999-6780-2026-1-3-18. (In Russ).
27. Lyster H, Shekar K, Watt K, Reed A, Roberts JA, Abdul-Aziz MH. Antifungal Dosing in Critically Ill Patients on Extracorporeal Membrane Oxygenation. *Clin Pharmacokinet*. 2023;62(7):931–42. 10.1007/s40262-023-01264-0.
28. Dzierba AL, Liang YH, Lyster H. Antimicrobial pharmacokinetics and stewardship in critically ill adult patients receiving ECMO: Challenges, evidence, and future directions. *JHLT Open*. 2025;11:100438. 10.1016/j.jhlto.2025.100438.
29. Rocha-Romero A, Chaverri-Fernández JM, Chaves-Fernández F, Zavaleta-Monestel E. Optimizing Drug Therapy in ECMO-Supported Critically Ill Adults: A Narrative Review and Clinical Guide. *Pharmacy*. 2025;13(6):151. 10.3390/pharmacy13060151.
30. Ronda M, Llop-Talaveron JM, Fuset M, Leiva E, Shaw E, et al. Voriconazole Pharmacokinetics in Critically Ill Patients and Extracorporeal Membrane Oxygenation Support: A Retrospective Comparative Case-Control Study. *Antibiot (Basel)*. 2023;12(7):1100. 10.3390/antibiotics12071100.
31. Abdul-Aziz MH, Diehl A, Liu X, Cheng V, Corley A, et al. Population pharmacokinetics of caspofungin in critically ill patients receiving extracorporeal membrane oxygenation — an ASAP ECMO study. *Antimicrob Agents Chemother*. 2025;69(2):e01435–24. 10.1128/aac.01435-24.

32. Zhang Y, Hu H, Zhang Q, Ou Q, Zhou H, et al. Effects of ex vivo Extracorporeal Membrane Oxygenation Circuits on Sequestration of Antimicrobial Agents. *Front Med (Lausanne)*. 2021;8:748769. 10.3389/fmed.2021.748769.

Figures

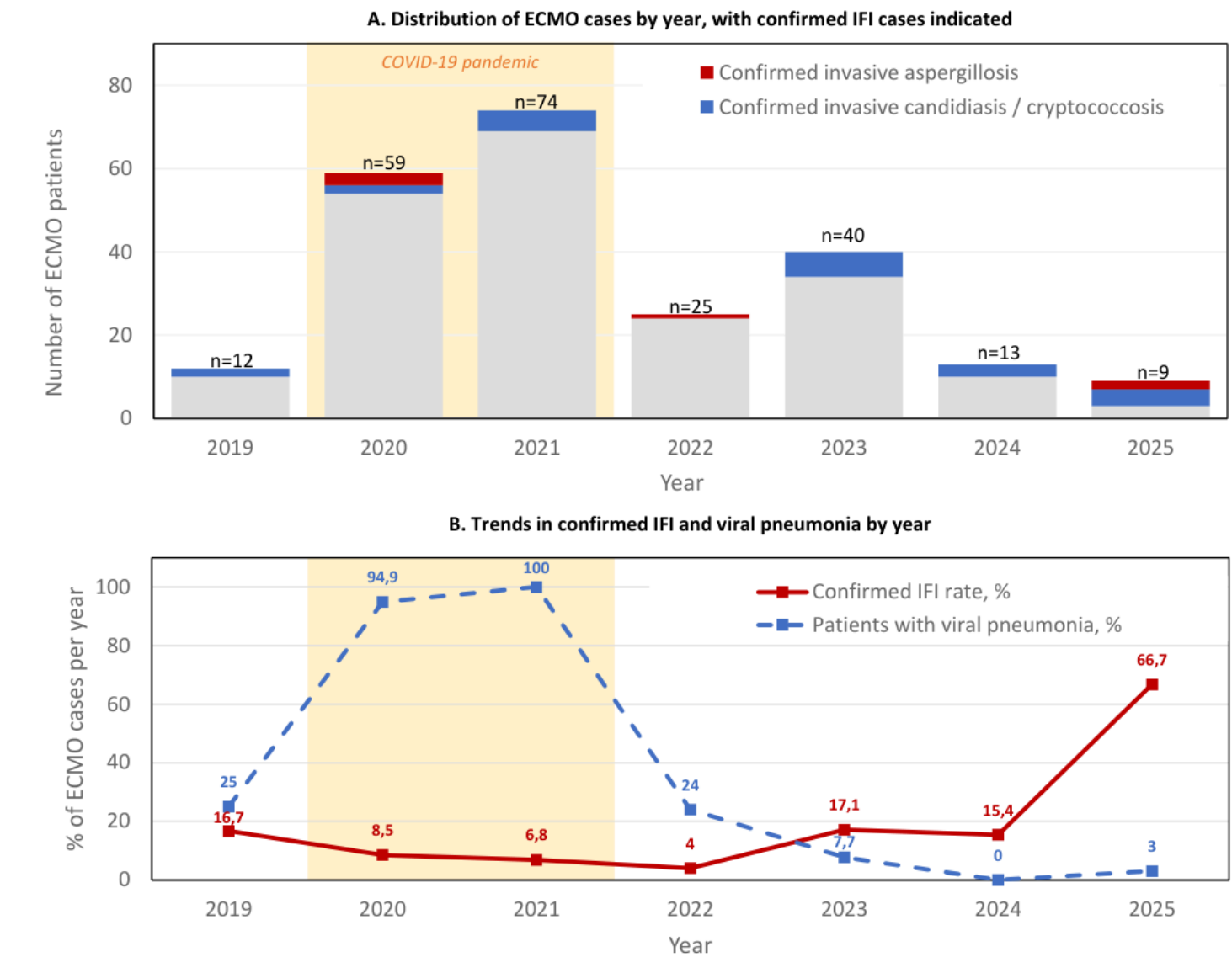


Figure 1

Distribution of ECMO cases and confirmed IFI by year (2019–2025). (a) Absolute numbers of ECMO patients per year, stratified by no IFI, confirmed invasive aspergillosis, and confirmed invasive candidiasis/cryptococcosis. (b) Frequency of confirmed IFI (solid red line) and proportion of patients with viral pneumonia (blue dotted line), % of ECMO cases per year. Orange shading indicates the peak of the COVID-19 pandemic (2020–2021). The single patient treated in 2026 was excluded from the temporal analysis.