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A retrospective Italian analysis on the characteristics of invasive fungal infections in the intensive care unit setting: CHARTER-IFI study

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Abstract

Background: Invasive fungal infections (IFI), prevalent in critically ill ICU patients, have gained attention due to post-COVID-19 epidemiological shifts. Notably, COVID-19-associated aspergillosis and candidiasis pose significant risks. WHO recognises key fungal pathogens, emphasising the need for enhanced research and interventions.

Methods: The CHARTER-IFI study retrospectively examines 186,310 individuals admitted to ICUs in Italy from 01/01/2012–01/09/2023, utilising administrative databases covering around 10 million inhabitants. Adult patients were included having at least one ICU discharge diagnosis of IFI at their first IFI-related hospitalisation and having at least 12 months of available data prior to this hospitalisation.

Results: A total of 746 IFI patients discharged from ICU (incidence of 4.0 per 1000 ICU-hospitalised patients), were included. Median age was 68 years, 63% were males, and the overall Charlson Comorbidity Index was 2.2. The top three diagnoses were candidiasis ($N = 501$, 2.7/1000 ICU-hospitalised patients), aspergillosis ($N = 71$, 0.4/1000), and pneumocystosis ($N = 55$, 0.3/1000). The evaluation of the comorbidity profile in IFI patients revealed the presence of hypertension (60.5%), use of systemic GC/antibacterials (45.3% during 12 months before and 18.6% during 3 months before hospital admission), cancer (23.1%), diabetes (24.3%) and cardiovascular diseases (23.9%). The mean (±SD) length of hospitalisation in ICU was 19.9 ± 24.1 days (median 11 days), and deaths occurred in 36.1% of IFI patients (within 30 days from discharge).

Conclusions: This retrospective analysis among ICU-hospitalised patients described the burden of IFI in ICU, and its understanding could be crucial to strengthen surveillance, investments in research, and public health interventions as required by WHO.

KEYWORDS
aspergillosis, candidiasis, COVID-19, intensive care units, invasive fungal infections, pneumocystosis

1 | INTRODUCTION

Invasive fungal infections (IFI) are severe infections that may affect critically ill patients in intensive care units (ICU),[1] patients undergoing invasive medical procedures and receiving broad-spectrum antibiotics and those taking immune-suppressing drugs.[2] Admission to the ICU implies the exposure of patients to several risk factors for the development of nosocomial infections, such as invasive mechanical ventilation, central venous catheters, sedation and surgical procedures, immune suppression (e.g. cancer patients and solid organ transplant recipients), surgical site infection, and large use of broad-spectrum antimicrobial agents. This link has been corroborated by the recent experience with the COVID-19 pandemic, which showed how bacterial and fungal co-infections are considerably common in patients admitted to the ICU.[3] Although the epidemiology of IFIs is generally characterised by geographical and temporal variability, it has been noticed that, over the past decade, the rate of candidaemia has increased in some settings by up to 50% with an incidence of 5.1/1000 ICU admissions.[3]

Therefore, IFIs represent a current clinical challenge that has gained even more interest in view of the relevant epidemiological changes in the post-COVID-19 era.[4,5] Among them, COVID-19 associated pulmonary aspergillosis (CAPA) and influenza associated pulmonary aspergillosis (IAPA) are of increasing concern.[6]

As fungal pathogens and infections are a growing global public health concern, World Health Organisation (WHO) has recently developed the first list of fungal priority pathogens (WHO FPPL), the first global effort to systematically prioritise fungal pathogens, considering their unmet research and development needs and perceived public health importance.[7] In this list, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Candida albicans* and *Candida auris* have been ascribed as "critical priority groups" highlighting the urgency for public health interventions to contain these infections.

In Europe, epidemiological and clinical data on IFI in ICU are scarce and largely variable according to geographical areas. Invasive candidiasis, including candidemia, is the most common IFI in the hospital setting, with around 700,000 cases of invasive candidiasis occurring worldwide per year,[2] and 7.07 episodes per 1000 ICU admissions in Europe.[8] In a recent observational cohort study, with 64 participating hospitals located in 20 European countries, overall 90-day mortality was 43% (265/617). Furthermore, increasing age, admission to the ICU, high Charlson comorbidity index score and *Candida* tropicalis as causative pathogen were identified as independent predictors of mortality in Cox regression analysis.[6]

The incidence of invasive aspergillosis in critically ill ICU patients is between 0.7% and 15%, with significant variations in rates reported from different geographic regions.[9] The mortality rate associated with invasive aspergillosis remains high, ranging from 30% to 90%, and is highly dependent on the degree or reversibility of the underlying host immune dysfunction, the severity of infection, and the time to receive targeted antifungal therapy.[9]

Furthermore, IFI often occurs in patients with influenza admitted to the ICU, with several studies describing IAPA. A multicenter Dutch–Belgian study, collecting data from patients admitted to the ICU between 1 January 2009, and 30 June 2016, reports that of 432 patients admitted with influenza 83 (19%) were diagnosed with IAPA, with a median of 3 days after admission to the ICU. 90-day mortality was 51% in patients in the IAPA cohort and 28% in the cohort without IAPA ($p = 0.0001$).[10]

CAPA is a life-threatening fungal infection that can affect critically ill COVID-19 patients. Since the beginning of the pandemic, numerous retrospective and prospective studies have been performed to get evidence of *Aspergillus* co-infection in this patient population.

A recent qualitative review summarised data from 48 studies and reported that the incidence of CAPA generally ranges between 10% and 15% of critically ill COVID-19 patients. Moreover, this co-infection resulted to be associated with increased length of hospital stay and/or mortality; specifically all-cause mortality was assessed at 55.2% in 728 patients with CAPA included in observational studies with available mortality data.[11] In Italy, the incidence and prevalence of IFIs are not clearly reported for both the general healthy population and specific at-risk groups.[12]

Despite growing concern, fungal infections receive very little attention and resources, leading to a paucity of quality data on the distribution of fungal diseases and antifungal resistance patterns.[7] In order to estimate the burden of IFIs in the Italian ICU setting and thus improving diagnosis and management in critically ill patients, the aim of our analysis is to describe demographic and clinical characteristics of IFI patients, ICU length of stay and mortality according to the type of IFI. Additionally, we also explored the prevalence of IAPA, CAPA and *Candida* infections. Lastly, we investigate the trends of epidemiological and ecological evolution of the fungal infections over time with respect to pre- and during COVID-19 pandemic were also evaluated.

2 | METHODS

2.1 | Data source

A retrospective observational analysis was carried out on data collected from the administrative flows of a pool of local health units (LHU) geographically distributed throughout the Italian territory and covering approximately 10 million health-assisted residents (approximately 16.7% of the Italian population). For the study purposes, the administrative databases were browsed to collect all data regarding the healthcare resources/services provided and reimbursed by the Italian National Healthcare Service (INHS), specifically: (1) beneficiaries' database to collect demographics such as age, gender and date of death; (2) pharmaceutical database for information on drug prescriptions, including the anatomical therapeutic chemical (ATC) code, number of packages, number of units per package, costs and prescription date; (3) hospitalisation database for information on discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Diagnosis Related Group (DRG) and DRG-related charge; (4)

outpatient specialist services database, to trace the delivery of diagnostic/laboratory tests and specialist visits; (5) exemption database, to gather active exemption codes by which patients are waived from paying services/treatments in case of specific disease diagnoses.

An anonymous univocal numeric code (patient ID) was assigned to each patient by the LHUs, in order to allow the electronic linkage between the databases. The anonymous code of the patient guarantees the anonymity of the extracted data in full compliance with UE Data Privacy Regulation 2016/679 ("GDPR") and Italian D.lgs. n. 196/2003, as amended by D.lgs. n. 101/2018. All the results of the present analysis are provided in aggregated form so that they cannot be linked, either directly or indirectly, to individual patients. In the case of subgroups of less than four patients, results were referred to as "not issuable" (NI) for data privacy since they were potentially reconductable to single patients, along with the Italian code for protection of personal data ("Codice in materia di protezione dei dati personali"). Informed consent was waived according to the pronouncement of the Data Privacy Guarantor Authority (general authorization for personal data treatment for scientific research purposes—no. 9/2014, 11 December 2014, published on the Official Gazette n. 301 of 30 December 2014), which was established that data treatment is authorised without patients' informed consent when their collection is impossible for organisational reasons. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the local Ethics Committee of the participating LHUs.

2.2 | Design of the analysis and study population

From January 2012 to September 2023, patients were selected if they met all the following inclusion criteria: (i) at least one record of hospitalisation discharge diagnosis (at any level) for IFI in the ICU setting during the inclusion period; (ii) age ≥18 years during the calendar year of inclusion (first IFI hospitalisation); (iii) at least 12 months of data availability before the date of the first IFI-related hospitalisation discharge. The date of the first IFI hospitalisation (at any level) in the ICU setting throughout the inclusion period was considered as an index-date. Patients' previous history was investigated during all available periods (of at least 12 months) before the index-date (characterisation period).

The hospital diagnoses of IFI were identified by the ICD-9-CM codes (detailed in Table S1 of the Supplementary materials) to capture the following: systemic candidiasis, including disseminated candidiasis, candidiasis of lung, candidiasis of other specified sites; aspergillosis [comprising influenza-associated pulmonary aspergillosis (IAPA: concurrent diagnosis of influenza due to identified novel H1N1 influenza virus) and COVID-19-associated pulmonary aspergillosis (CAPA: concurrent diagnosis of COVID-19)]; cryptococcosis, mucormycosis, pneumocystosis. Other mould infections were identified considering the ICD-9-CM code referring to ventilator associated pneumonia, associated with a fungal ICD-9-CM 11x.xx, excluding those above mentioned. The ICU hospitalisation was identified by code 49, which does not include coronary ICUs (UTIC). Using administrative databases, we could not differentiate between surgical and medical ICUs due to varying and inconsistent coding across hospitals. Thus, reliable differentiation between ICU types was not possible in this analysis.

2.3 | Evaluation of patient comorbidities and previous treatments

All included patients were characterised at baseline for their demographics, age at index-date and gender distribution (expressed as percentage of males) and comorbidities features. Patients' general comorbidity profile during the year prior to IFI hospitalisation was evaluated by the Charlson comorbidity index (CCI), a scoring system to predict mortality risk in the presence of 19 comorbidities weighted according to their severity. Then, the occurrence before inclusion of the following conditions previously described as predictors of IFI risk and prognosis[8,12-15], was also proxied and assessed through hospitalisation codes (during all available characterisation period) and/or specific drug prescriptions (during the 1-year period before the index-date): bone disorders/trauma, burns, cancer (comprising solid tumours and haematological malignancies), chronic kidney disease (CKD), cardiovascular disease (CVD), diabetes, dyslipidemia, hypertension, liver disease, HIV infection, chronic obstructive pulmonary disease (COPD), asthma, obesity, sepsis/septic shock, haematopoietic stem cell transplantation (HSCT)/solid organ transplantation, use of glucocorticoids/antibacterials, use of immunosuppressant, neutropenia. The codes used for the identification of the listed comorbid conditions are provided in Table S2 of the Supplementary materials.

2.4 | Statistical analysis

All the analyses were descriptive. Continuous variables are reported as mean ± standard deviation, categorical variables as numbers and percentages. All the analyses were performed using Stata SE version 17.0 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Baseline characteristics of ICU-hospitalised IFI patients

From a catchment area of 10 million health-assisted Italian residents followed in the LHUs involved in the analysis, 186,310 hospitalised patients in the ICU were identified: among them, a total of 746 patients (corresponding to 4.0 per 1000 ICU-hospitalised patients) with one hospitalisation discharge diagnosis for IFI (IFI–ICU patients) were included in the analysis (Figure 1). In this subset of 746 patients, the mean ± SD age at discharge date was 66.3 ± 15.1 years

FIGURE 1 Retrospective administrative database analysis. IFI, invasive fungal infection.

TABLE 1 Baseline characteristics of the included patients with distribution of IFI-related ICU admissions by etiologic agent (type of infection).

	Patients with IFI (*N* = 746)
Age, mean (SD) at index-date	66.3 (15.1)
Age, median	68
Male, *N* (%)	472 (63.3)
CCI, mean (SD)	2.2 (2.2)
Type of infection	
Candidiasis, *n* (%)	501 (67)
Disseminated candidiasis[a]	303 (41)
Aspergillosis, *n* (%)	71 (10)
Pneumocystosis, *n* (%)	55 (7)
Cryptococcosis, *n* (%)	6 (1)
Mucormycosis, *n* (%)	<4 (<1)
More than one diagnosis, *n* (%)	111 (15)

Abbreviations: CCI, Charlson Comorbidity Index; ICU intensive care units; IFI, invasive fungal infection; SD, standard deviation.

[a]Disseminated candidiasis has been identified using only code ICD-9-CM 112.5.

(median age of 68 years), 63.3% were males, and the CCI was averaged 2.2, indicating a mild-to-severe comorbidity profile. The most frequent fungal infections encountered in patients admitted to the ICU were due to candidiasis, accounting for 67% of patients (2.7/1000 hospitalised ICU patients), and in particular, disseminated candidiasis accounted for 41% of IFI-ICU patients (1.6/1000 ICU patients). Aspergillosis was observed in 10% of IFI patients (0.4/1000 ICU patients) and pneumocystosis in 7% of patients (Table 1). In detail among the 71 cases of aspergillosis, none with IAPA was identified, while of the 39 patients included during the COVID-19 pandemic period (March 2020–2022), 11 (corresponding to 15.5% of total aspergillosis cases and 28% of those included during the pandemic outbreak) experienced CAPA.

The clinical status of the 746 included patients was evaluated by analysing the pattern of the most common drug prescriptions during the 3-month period prior to the ICU admission. As Table 2 shows, 44.9% of patients received drugs for acid-related disorders, 41.6% with antibacterials for systemic use, 24.4% with systemic corticosteroids, 18.8% with drugs for obstructive airway diseases, and 2.5% were under systemic antimycotics.

Replicating the same analysis in the patients stratified by IFI etiologic agent, the results were generally comparable, with antiacids, antibiotics and systemic corticosteroids as the most commonly prescribed drugs in all subgroups. However, a peak in the use of antibacterials for systemic use was noticed among the patients with pneumocystosis (53.5%) and aspergillosis (54.5%); moreover, patients with pneumocystosis received more frequently systemic corticosteroids (47.3%), whereas patients with aspergillosis received more systemic antimycotics (8.5%) (Table 2).

The pattern of the 18 concomitant conditions/treatments plausibly associated with IFI[8,12,14] was assessed in the overall population and patients subgrouped by causal pathogen, during all available characterisation period for diseases, and 1 year before the index-date for medications. Among the overall population (Figure 2A), the most represented conditions were hypertension (60.5%), use of glucocorticoids and/or antibacterials (45.3%), cancer (23.1%), diabetes (24.3%) and CVD (21.8%). Considering the 3 months prior to the ICU admission, 18.6% of patients were prescribed with (GCs) and/or antibacterials. In the subset of patients with candidiasis, 64.5% had hypertension, 42.1% were users of GCs and/or antibacterials, 20.8% experienced cancer, 23.0% COPD (Figure 2B); in those with aspergillosis 62.0% were users of GCs and/or antibacterials, 35.2% experienced cancer, 19.7% COPD (Figure 2C); and in those with pneumocystosis, 60.0% were users of GCs and/or antibacterials, 21.8% were cancer patients, 18.2% were HIV patients (Figure 2D).

3.2 | Clinical outcomes

As shown in Table 3, among the entire IFI population included, the length of hospitalisation (covering the ordinary and ICU settings) was on average 45.5 days (median 38 days), and the mean length duration of ICU stay was averaged 19.9 days (median 11). The overall rate of deaths within 30 days from discharge was 36.1%. Analysing the patients stratified by pathogen, cryptococcosis was associated with the longest stay in ICU (on average 43.2 days) and the highest mortality within 1 month after discharge (66.7%).

3.3 | Epidemiological evolution trend

Epidemiological evolution trend in overall IFI patients by type of hospitalisation was then comparatively analysed in 34 months before and after the start of COVID-19. As the WHO declared COVID-19 on 11 March 2020,[22] the time intervals considered to evaluate the IFI epidemiological course pre- and during COVID-19

TABLE 2 Most frequent drug prescriptions (3-month period before index-date) in the included patients. Data were reported as absolute frequency and (percentage).

ATC code	Drug classes	Patients with IFI (*N* = 357)	Patients with candidiasis (*N* = 501)	Patients with aspergillosis (*N* = 71)	Patients with pneumocystosis (*N* = 55)
A02	Drugs for acid-related disorders	335 (44.9)	227 (45.3)	32 (45.1)	227 (45.3)
J01	Antibacterials for systemic use	310 (41.6)	194 (38.7)	38 (53.5)	194 (38.7)
B01	Antithrombotic agents	266 (35.7)	193 (38.5)	23 (32.4)	193 (38.5)
C09	Agents acting on the RAS system	234 (31.4)	169 (33.7)	21 (29.6)	169 (33.7)
C07	Beta blockers	200 (26.8)	145 (28.9)	19 (26.8)	145 (28.9)
H02	Corticosteroids for systemic use	182 (24.4)	98 (19.6)	28 (39.4)	98 (19.6)
C03	Diuretics	166 (22.3)	120 (24)	12 (16.9)	120 (24)
C10	Lipid modifying agents	140 (18.8)	91 (18.2)	15 (21.1)	91 (18.2)
R03	Drugs for obstructive airway diseases	49 (6.6)	31 (6.2)	7 (9.9)	31 (6.2)
R03BA	Inhaled glucocorticoids	136 (18.2)	94 (18.8)	17 (23.9)	94 (18.8)
A10	Drugs used in diabetes	128 (17.2)	93 (18.6)	11 (15.5)	93 (18.6)
J02	Antimycotics for systemic use	19 (2.5)	7 (1.4)	6 (8.5)	7 (1.4)

Abbreviations: ATC, anatomical therapeutic chemical; IFI, invasive fungal infection, RAS, renin-angiotensin system.

were May 2017–February 2020 and March 2020–December 2022, respectively. Moreover, the period was selected to guarantee complete data availability across all the LHUs included in the analysis. In total, 557 patients underwent IFI-related ICU hospitalisation from May 2017 to December 2022, of whom 224 (40.2%) in the pre-COVID-19 and 333 (59.8%) in the COVID-19 period, resulting in an increase of +33% after the pandemic outbreak (Figure 3A). Dividing the sample by fungal pathogen, it was only possible to analyse the subgroups with IFI due to candidiasis and aspergillosis, since the others had too low numerosity. IFIs due to aspergillosis were found in 22 (11.7%) patients before COVID-19 and 36 (13.1%) after COVID, confirming the upward trend (+1.9%) after the start of the pandemic. On the contrary, *candida*-related IFIs were observed in 152 (80.9%) patients pre-COVID-19 and 213 (77.5%) COVID, with a decrease of 3.4%.

Overall IFI and those due to candidiasis and aspergillosis showed a parallel trend over time (Figure 3B). It was not possible to analyse IFI caused by other fungal infections due to the small sample size.

3.4 | Ecological evolution trend

The pattern of the more impactive concomitant conditions/treatments plausibly associated with IFI[8,12,14] was evaluated in patients included before and after COVID-19 pandemic period, and from 2017 to 2022. As reported in Figure 4 and Table 4, the trend of comorbidities was reported. These data should be confirmed by increasing the sample size.

4 | DISCUSSION

This analysis was carried out to characterise a sample of the Italian population of IFI patients discharged from the ICU, focusing on their demographic and clinical characteristics, type of causal pathogen, length of ICU stays and mortality, by using real-world data. In total, 746 patients met the inclusion criteria corresponding to an incidence of 4.0 per 1000 ICU-hospitalised patients. Baseline characteristics revealed that the median age was 68 years, a slight male predominance (63.3%), and a mild-to-severe CCI of 2.2. These findings are largely consistent with the results from the Italian survey AURORA that described a median age of IFI the patients of 60 (44.5–71) years, with 63.8% males, and almost half of the patients older than 60 years.[5]

In the population analysed, the most common infections were candidiasis, accounting for 67% of IFI patients in ICU setting, followed by aspergillosis (10%). The high prevalence of *Candida* species, as the primary cause of IFIs in ICU admitted patients, is well-documented worldwide. Thus, this is an unsurprising finding in line with the Italian survey data mentioned above.[6] The EUCANDICU project investigated the incidence and outcomes of invasive candidiasis in 23 ICUs from nine European countries, reporting a cumulative incidence of 7.07 episodes per 1000 ICU admissions and crude 30-day mortality of 42%.[3] The incidence of IPA (invasive pulmonary aspergillosis) and ventilator-acquired invasive pulmonary aspergillosis in the ICU is unclear, ranging from 0.3% to 19% because of the difficulties of diagnosis.[7,8] Here, we found that among 39 patients with aspergillosis during the COVID-19 pandemic outbreak (2020–2022), approximately one third were identified as CAPA (28%), in line with

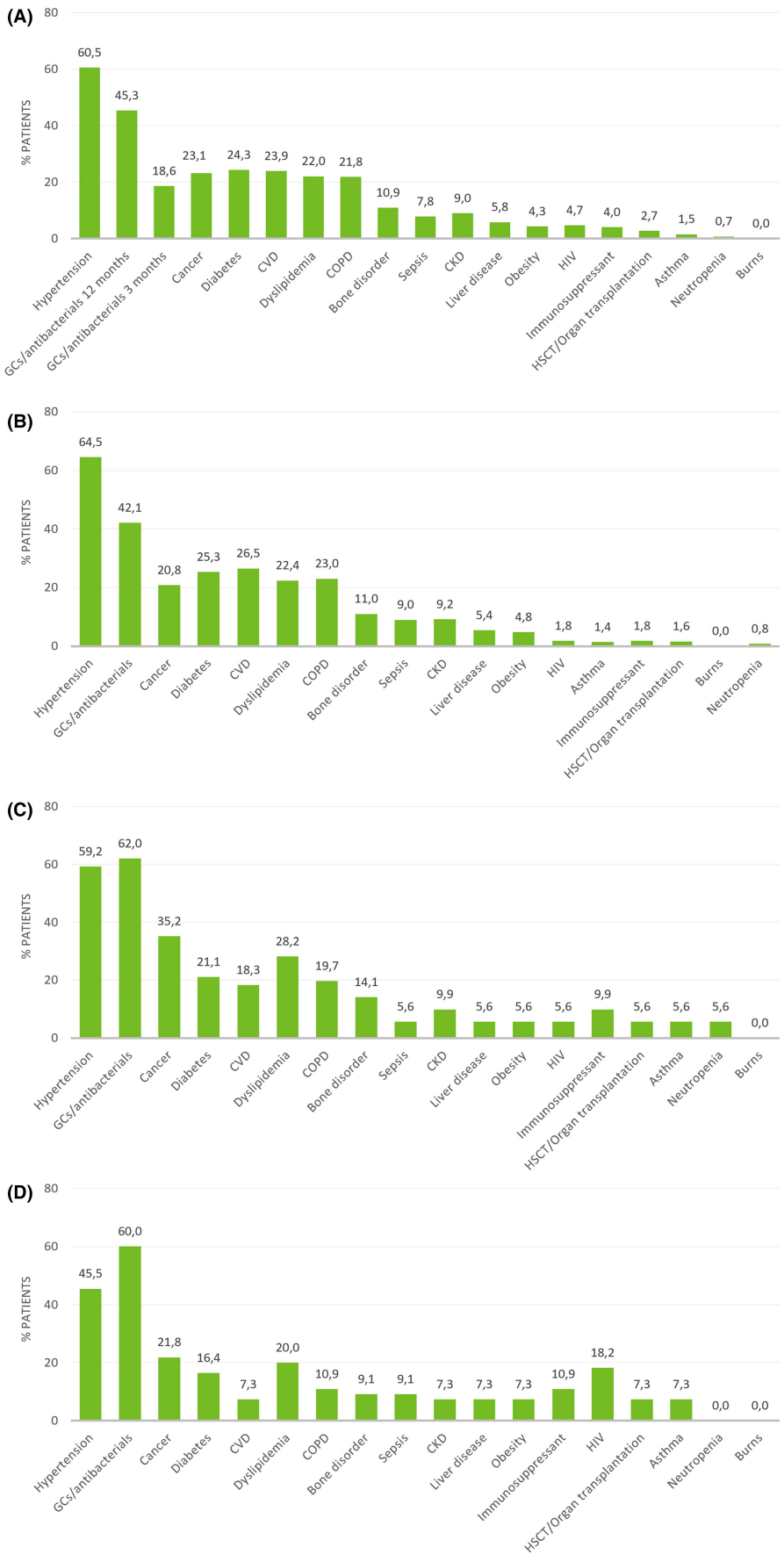

FIGURE 2 Frequency (%) of 18 concomitant conditions and treatments plausibly associated with IFI assessed before inclusion. Panel (A) shows data for the overall population, panel (B) for patients with candidiasis, panel (C) for patients with aspergillosis, and panel (D) for patients with pneumocystosis. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GC, glucocorticoids; HIV, human immunodeficiency virus; HSCT, hemopoietic stem cells transplantation.

TABLE 3 Length of hospitalizations and mortality within 1 month from discharge in the overall included patients and stratified by pathogen. Data are reported as median or mean and standard deviation (SD).

	Overall	Candidiasis	Aspergillosis	Cryptococcosis	Pneumocystosis
Number of patients	746	501	71	6	55
Hospital length of stay in days, mean (SD)	45.5 (36.2)	47.3 (35.0)	38.2 (25.1)	92.2 (77.0)	31.7 (28.4)
ICU length of stay in days, mean (SD)	19.9 (24.1)	21.0 (24.8)	17.3 (16.3)	43.2 (52.9)	18.3 (25.9)
ICU length of stay in days, Median	11	11	15	7	10
Deaths (within 30 days from ICU discharge), N (%)	269 (36.1)	178 (35.5)	20 (28.2)	4 (66.7)	23 (41.8)

Abbreviations: ICU, intensive care units, SD, standard deviation.

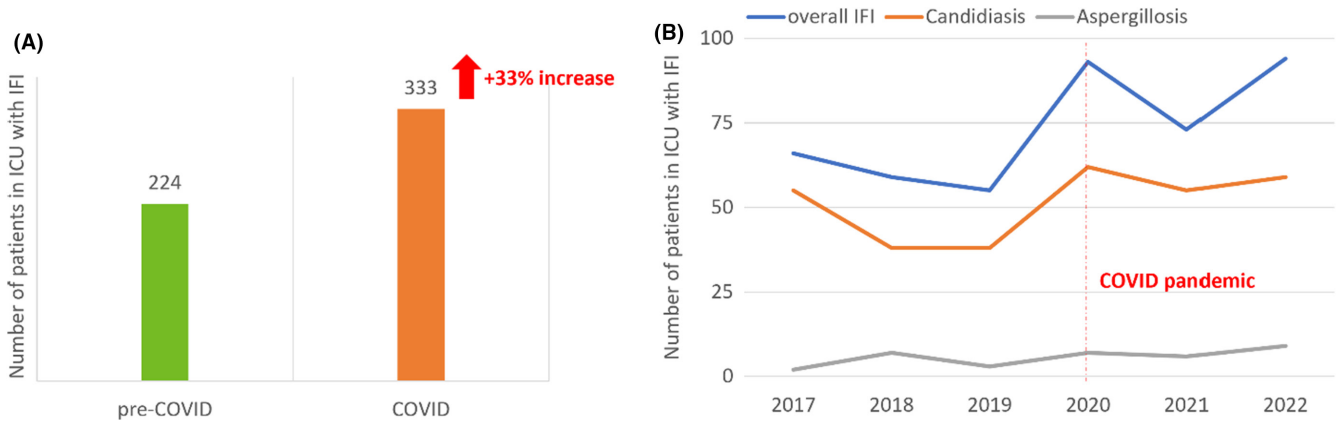

FIGURE 3 Epidemiological trends of invasive fungal infections (IFI) in intensive care units (ICUs). Panel (A) shows the evolution of IFI during the pre-COVID-19 period (in green) and the COVID-19 period (in orange). Panel (B) depicts the trends over time from 2016 to 2021 for the overall IFI population (in blue), and the subgroups of candidiasis (in orange) and aspergillosis patients (in grey).

a previous prospective multicentre Italian study by Bartoletti et al. that described CAPA occurring in 27.7% of intubated patients.[9]

Then, we analysed the proportion of patients who carried a risky condition among the 17 previously identified as potentially predictive of IFI susceptibility and prognosis.[8,12,14-21] Both in the overall population or patients subgrouped by causal fungal pathogen, the most common conditions were hypertension, use of glucocorticosteroids and/or antibacterials, cancer, diabetes and CVD. These data are largely in agreement with the results of the EUCANDICU project, which reported diabetes, CKD, solid tumours and the use of antibacterials as the most frequent observations among patients with invasive candidiasis.[3]

The analysis of clinical outcomes among the entire IFI population showed that the mean length of hospitalisation in the ICU was nearly 3 weeks and the mortality rate within 30 days from discharge was 36.1%, confirming the severity of these invasive infections. It has been reported that mortality associated to IFIs in ICU is very elevated, but highly variable from 5% to 70%.[10,11] The mortality in the candidiasis subcohort was 35.5%, thus below that of the EUCANDICU study of 42%, but this discrepancy might be explained by the different study population, design and different time of inclusion.[3]

The analysis of IFI epidemiological evolution as compared to the start of COVID-19 pandemic, confirmed the zenith in IFI cases observed during 2020, that was mirrored when considering invasive candidiasis alone. The increased incidence of IFIs in the COVID-19 period, especially during the early waves of the pandemic, might be feasibly explicated by the urgent need to have access to the ICU for most severe SARS-CoV-2 cases that in turn required a markedly increased use of invasive ventilation, thus exposing patients to more frequent nosocomial infections.[12]

The main limitations of the present study are related to the strategy of using administrative databases that might lack detailed clinical information. All concomitant diseases, either those included in the calculation of CCI, or those associated with IFI, were retrieved using hospitalisation codes and drug prescriptions as a proxy for diagnosis. For instance, the occurrence of CKD might be underestimated since it was not evaluated by eGFR values. Moreover, the consumption of medications during the hospital stay could not be fully evaluated, because the standard databases used here only trace high-cost drugs. Furthermore, the inability to differentiate between surgical and medical ICUs due to varying and inconsistent coding across hospitals is another limitation. Another limitation is related to the inclusion of different types of

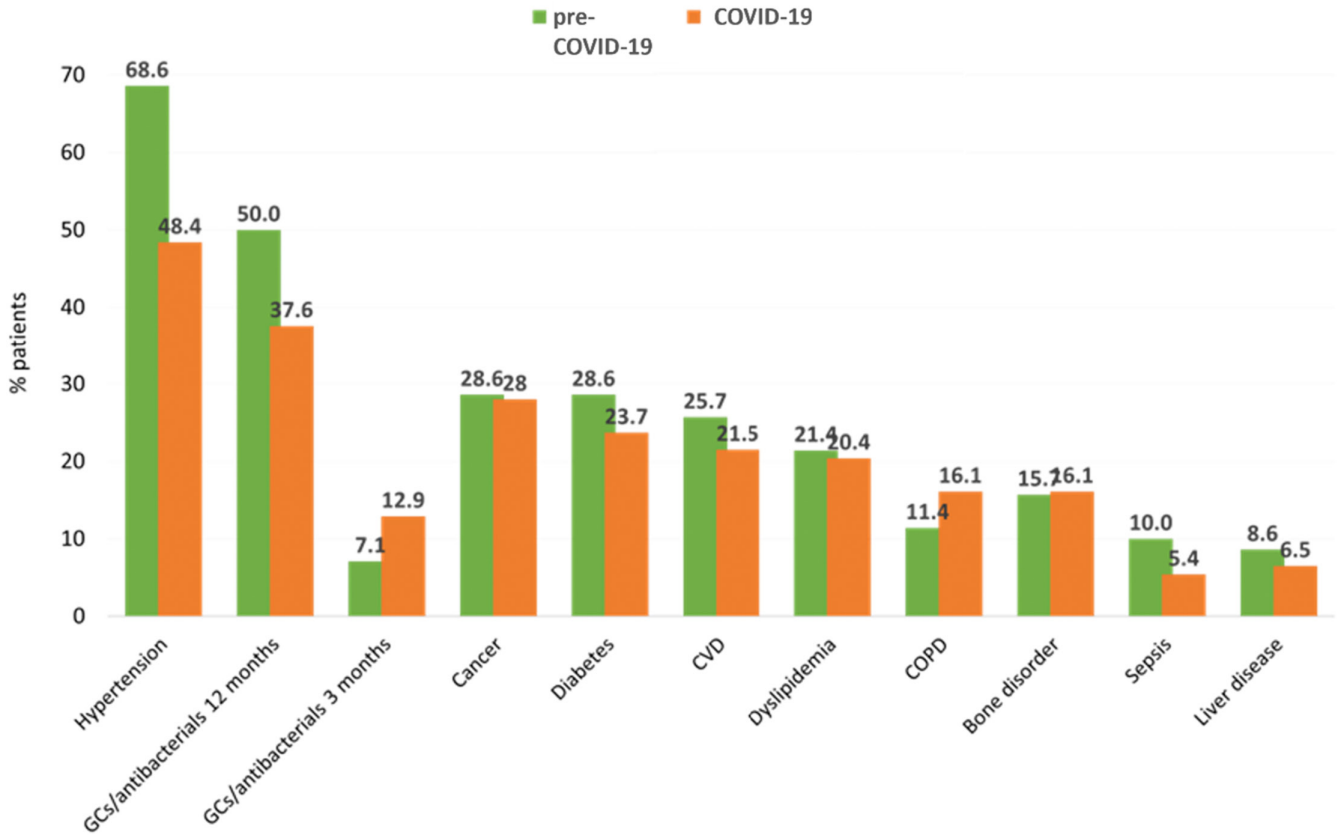

FIGURE 4 Invasive fungal infection (IFI) ecological evolution during the pre-COVID-19 and COVID-19 period in overall IFI population hospitalised in intensive care units. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; GC, glucocorticoids.

TABLE 4 Invasive fungal infection (IFI) ecological evolution across 2017–2021 in overall IFI population hospitalised in intensive care units.

	2017 (*N* = 66)	2018 (*N* = 59)	2019 (*N* = 55)	2020 (*N* = 93)	2021 (*N* = 73)	2022 (*N* = 94)
Hypertension, *N* (%)	40 (60.6)	33 (55.9)	41 (74.5)	59 (63.4)	44 (60.3)	49 (52.1)
Use of glucocorticoids/antibacterials (12 months)[a], *N* (%)	28 (42.4)	30 (50.8)	30 (54.5)	42 (45.2)	29 (39.7)	39 (41.5)
Use of glucocorticoids/antibacterials (3 months)[a], *N* (%)	15 (22.7)	7 (11.9)	10 (18.2)	21 (22.6)	12 (16.4)	15 (16.0)
Cancer, *N* (%)	13 (19.7)	11 (18.6)	12 (21.8)	25 (26.9)	12 (16.4)	18 (19.1)
Diabetes, *N* (%)	13 (19.7)	17 (28.8)	21 (38.2)	21 (22.6)	21 (28.8)	19 (20.2)
CVD, *N* (%)	12 (18.2)	16 (27.1)	16 (29.1)	18 (19.4)	22 (30.1)	26 (27.7)
Dyslipidemia, *N* (%)	11 (16.7)	11 (18.6)	10 (18.2)	20 (21.5)	18 (24.7)	23 (24.5)
COPD, N (%)	17 (25.8)	9 (15.3)	12 (21.8)	21 (22.6)	17 (23.3)	22 (23.4)

Abbreviations: CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease.

[a]Before hospital admission.

IFI. The use of ICD-9 codes might not fully capture all cases, especially for less common mould infections like lomentosporosis, scedosporosis, and fusariosis, leading to potential underestimation. Finally, LHUs registry data may primarily reflect individuals receiving care within the public health system, potentially underrepresenting those receiving care in private facilities or those without regular access to healthcare services. Variations in healthcare-seeking behaviour and diagnostic practises across different regions or demographic groups within Italy could also influence the characteristics of the study population. These factors should be considered when interpreting the results and extrapolating them to the entire Italian population.

In conclusion, this retrospective analysis among ICU-hospitalised patients confirmed that, consistent with international data, the most frequent IFI was candidiasis followed by aspergillosis. Comedications and comorbidities were frequently detected. The clinical emergence related to IFI was confirmed by the long duration of ICU hospitalisation and the elevated mortality, especially in patients with aspergillosis, including CAPA. Understanding the burden of IFI in critical care units could be crucial to strengthening surveillance, investments in research and public health interventions as required by the WHO.

AUTHOR CONTRIBUTIONS

Pier Luigi Viale: Conceptualization; methodology; supervision; validation; formal analysis; investigation; data curation; resources; writing – review and editing; visualization. **Silvia Mirandola:** Methodology; supervision; funding acquisition; validation; formal analysis; investigation; data curation; resources; writing – review and editing; visualization. **Ciro Natalini:** Conceptualization; methodology; funding acquisition; validation; formal analysis; investigation; data curation; resources; visualization; writing – review and editing. **Luca Degli Esposti:** Writing – original draft; validation; formal analysis; investigation; software; data curation; resources. **Melania Dovizio:** Methodology; software; writing – original draft; supervision; validation; formal analysis; investigation; data curation; resources; writing – review and editing; visualization. **Chiara Veronesi:** Software; writing – original draft; validation; formal analysis; investigation; data curation; resources; writing – review and editing; visualization. **Gabriele Forcina:** Conceptualization; methodology; supervision; funding acquisition; validation; formal analysis; investigation; data curation; resources; writing – review and editing; visualization. **Paolo Navalesi:** Conceptualization; methodology; supervision; validation; investigation; data curation; resources; writing – review and editing; visualization. **Annalisa Boscolo:** Methodology; validation; formal analysis; investigation; data curation; resources; writing – review and editing; visualization.

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CONFLICT OF INTEREST STATEMENT

SM, CN and GF report employment and being stockholders with Gilead Sciences during the conduct of the study and they contributed to the design of the study; to data collection, analysis or interpretation; to the revision of the manuscript and to the decision to publish the results. LDE, MD, CV report funding for the study and medical writing to their institution (CliCon) from Gilead Sciences during the conduct of the study and they contributed to the design of the study; to data collection, analysis, or interpretation; to the writing of the manuscript and to the decision to publish the results. PLV received research grants from Shionogi, Gilead and MSD, and sat on advisory boards for Pfizer, Gilead, MSD, Mundipharm, Viatris, bioMérieux and Astrazeneca. PN received research grants from Gilead and sat on advisory boards for Gilead. AB received a research grant from Gilead. PLV, PN and AB contributed to the design of the study; to data collection, analysis, or interpretation; to the revision of the manuscript and to the decision to publish the results.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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