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Secondary Invasive Fungal Infection in Hospitalized Patients with COVID-19 in the United States

Running title (50/50 characters): Invasive fungal infection in COVID-19 patients from the US

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Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions

Study design: GT, MM, ES, JJ, TK, KD, GG

Data acquisition: TK, GG

Data analysis: ES, JJ, TK, KD, GG

Interpretation of results: GT, MM, ES, JJ, TK, KD, GG

Disclosures

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ES, JJ are employees of Astellas Pharma Global Development Inc.

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Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available. Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at

www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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ABSTRACT (250/250)

Background: Invasive fungal infections (IFIs) have been identified as a complication in patients with Coronavirus disease 2019 (COVID-19). To date, there are few US studies examining the excess humanistic and economic burden of IFIs on hospitalized COVID-19 patients.

Objectives: This study investigated the incidence, risk factors, clinical and economic burden of IFIs in patients hospitalized with COVID-19 in the US.

Patients/Methods: Data from adult patients hospitalized with COVID-19 during 01 April 2020–31 March 2021 were extracted retrospectively from the Premier Healthcare Database. IFI was defined either by diagnosis or microbiology findings plus systemic antifungal use. Disease burden attributable to IFI was estimated using time-dependent propensity score matching.

Results: Overall, 515,391 COVID-19 patients were included (male 51.7%, median age 66 years); IFI incidence was 0.35/1000 patient-days. Most patients did not have traditional host factors for IFI such as hematologic malignancies; COVID-19 treatments including mechanical ventilation and systemic corticosteroid use were identified as risk factors. Excess mortality attributable to IFI was estimated at 18.4%, and attributable excess hospital costs were $16,100.

Conclusions: IFI incidence was lower than previously reported, possibly due to a conservative definition of IFI. Typical COVID-19 treatments were among the risk factors identified. Furthermore, diagnosis of IFIs in COVID-19 patients may be complicated because of the several non-specific shared symptoms, leading to underestimation of the true incidence rate. The healthcare burden of IFIs was significant among COVID-19 patients, including higher mortality and greater cost.

Keywords: Invasive fungal infection; hospitalization; COVID-19; healthcare; burden of disease; disease management; risk assessment; mortality

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INTRODUCTION

Invasive fungal infections (IFIs) caused by opportunistic pathogens such as *Candida*, *Aspergillus,* and *Cryptococcus* can result in significant morbidity and mortality for patients, especially in immunosuppressed patients and those with severe respiratory viral diseases.[1] Globally, it has been estimated that serious fungal infections affect over 300 million people per year[2] and lead to more than 1.5 million deaths.[3] Early and accurate diagnosis of IFIs is essential to improving clinical outcomes and reducing the associated socioeconomic burden of these diseases.[4] Recently, IFIs have been identified as a complication in patients with Coronavirus disease 2019 (COVID-19),[5–11] which, despite improvements in population immunity against the SARS-CoV-2 infection, remains an ongoing global issue associated with a significant clinical and economic burden.[12–14]

As with other viral respiratory diseases (e.g. influenza[15]), IFIs are believed to develop as a consequence of severe lung damage and the immunological deficits associated with the COVID-19 SARS-CoV-2 infection or its treatment. However, understanding the risk factors associated with IFI in COVID-19 patients may be important for early IFI diagnosis and treatment, as IFIs have been shown to increase the risk of death and other poor outcomes in COVID-19 patients.[5,16] Therefore, further evaluation of risk factors specific to secondary IFIs is particularly important in COVID-19 patients.

The epidemiology and mycology of IFIs have been previously shown in COVID-19 patients;[17] however, data regarding the incidence of IFIs are widely variable due to heterogeneity in patient populations, surveillance protocols, and definitions used for classification of fungal infections.[17,18] Therefore, we sought to investigate the incidence, risk factors, and healthcare burden (including excess mortality, days to

discharge, and cost) of IFI for hospitalized patients with COVID-19 in the US population.

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PATIENTS AND METHODS

Study design and participants

A retrospective analysis was performed on patients aged ≥18 years hospitalized with COVID-19 and who were discharged (or died) between 1 April 2020 and 31 March 2021 (the Main cohort), using the Premier Healthcare Database, a hospital-based database capturing ~25% of annual inpatients in the US.[19] In cases where a patient was hospitalized ≥2 times with COVID-19, the first hospitalization was used as the index encounter. Patients with IFIs at admission (the Prevalent IFI cohort) were excluded from the Main cohort. Patients requiring ICU admission, who did not have IFI before ICU admission, were categorized into the ICU sub-group of the Main cohort. The Incident IFI cohort included patients from the main cohort who developed IFI during their hospital stay.

IFIs were defined by International Classification of Diseases 10th revision (ICD-10) diagnosis codes (**Table S1**) and/or microbiology positive findings from otherwise sterile sites, plus systemic antifungal therapy use (defined as ≥5 days for discharged patients and ≥1 day for deceased patients, in line with a previous study[20]). Prevalent IFI cases were defined as those with IFI diagnosis (with a "present on admission" flag) and/or those with systemic antifungals at admission date. Details of IFI diagnosis, including the use of microbiology findings and antifungal treatments, are summarized in **Supplemental Information**. Microbiology data were only available for approximately 10% of hospitals in the database. *Candida* species identified from lower respiratory sites were not classified as IFIs but as *Candida* colonization, if no IFI diagnosis or microbiology findings from any other sterile sites (such as blood) were reported. IFI date was defined as anti-fungal therapy initiation date.

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Given the retrospective nature of this study, institutional review board approval was not deemed necessary. In accordance with the HIPAA Privacy Rule, disclosed Premier Healthcare Database data are considered deidentified per 45 CFR 164.506(d)(2)(ii)(B) through the "Expert Determination" method. This study was conducted in compliance with national requirements for noninterventional studies using deidentified data.

Statistical analysis

Patient characteristics at index date and time-dependent variables (collected between the admission date and the matching IFI date), including definitions for all traditional host factors for IFI, are summarized in the **Supplemental Information**. Patients were followed from the admission date to death, discharge, or transfer to another hospital.

IFI incidence

In the Main cohort and ICU subgroup, incidence of IFI was estimated as the overall proportion (%), the number of patients with IFI per 1000 patient-days, and as a cumulative incidence considering in-hospital death as a competing risk (censoring transfer to other hospital).

Risk factor analysis

Risk factors for IFI were assessed in the Main cohort. As a univariate analysis, IFI incidence per patient characteristic was estimated (e.g., males vs females). The quantitative impacts of typical COVID-19 treatments on IFI incidence were also

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assessed as a function of days in ICU and days on mechanical ventilation (MV), by separating those without these treatments and then by stratifying them in quartiles. In addition, the effects of corticosteroid (CS) daily dose (20 mg/day increment) and number of days on CS (weekly increment) on IFI incidence were assessed. Regarding multivariate analysis, a counting process type dataset was developed to analyze status change of time-dependent variables (of which the status can change only from No to Yes). The hazard ratio was estimated using Cox proportional hazard model; variables that did not achieve proportional hazard assumptions were excluded from this analysis.

Excess burden attributable to IFI

Excess burden due to IFI in COVID-19 patients was assessed by matching IFI cases with non-IFI cases, using time-dependent propensity scores. Propensity scores were estimated including all baseline factors and time-dependent variables as of IFI date. Each incident IFI patient was matched to three non-IFI patients who stayed at hospital at least to the IFI date using the derived propensity scores without replacement. Only data on or after the IFI date (or matching date) were used to account for immortal time bias.[21] Patient severity of illness and risk of mortality were quantified in four stages (Mild, Moderate, Major and Extreme) in line with the 3M® All Patients Refined-Diagnosis Related Groups (APRDRG) classification system.[22]

Excess mortality attributable to IFI was estimated as the difference in in-hospital mortality (%) between the matched groups. Days to hospital death was estimated using Kaplan–Meier (KM) methods. Excess days to discharge attributable to IFI was estimated as the difference in median days from matching to discharge using KM

methods, using two models. The first model considered discharge alive as an event (with hospital death and transfer to other hospital as censoring events), and the second model considered discharge dead or alive as an event (with transfer to other hospital censored), both dissociating matched pairs. Excess hospital costs attributable to IFI were estimated as a median difference in all-cause hospital costs after the matching date between IFI and non-IFI matched pairs. All statistical analyses were performed in SAS Studio version 9.4.

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RESULTS

Study population

A total of 516,249 patients diagnosed with COVID-19 were included. Of these, 858 (0.2%) had IFI at admission. The remaining patients (n= 515,391) were included in the Main cohort; with 143,021 (27.7%) patients in the Main cohort sub-categorized to the ICU subgroup. Baseline characteristics of patients included in each cohort are shown in **Table 1** and **Table S2**. Overall, there were similar proportions of males and females in the Main cohort, with median age (interquartile range [IQR]) of 66 (53–77) years. In-hospital mortality occurred in 13.0% of patients in this cohort, and the median (IQR) length of stay (LoS) was 5 (3–10) days (**Table S3**). The median (IQR) LoS was doubled in patients who died (10 [5–17] days). The numbers of patients with traditional host factors for IFI were low, including hematologic malignancies (1.4%), hematopoietic stem cell transplantation (HSCT) (0.0%), solid organ transplant (0.9%), and neutropenia (0.6%) (**Table 1**).

IFI incidence

In the Main cohort, 1442 (0.28%) patients had IFI during their hospital stay: the estimated incidence was 0.35/1000 patient-days (95% confidence interval [CI]: 0.33–0.36) (**Table 2**). IFI incidence was higher in the ICU subgroup 0.87%, 0.76/1,000 patient days (95% CI: 0.72–0.80). Overall, the cumulative incidence of IFI in the Main cohort (considering the competing risk of death) also gradually increased from admission to day 60. A similar trend was observed in the ICU subgroup (**Fig. S1**).

Antifungal use

In most of the prevalent IFI cases, antifungal therapy was initiated on admission date; antifungal initiation for incident IFI cases peaked at the second and third weeks from admission (**Fig. 1**, median 16 days). Days on antifungal therapy during the hospital stay largely varied in incident IFI cases (**Fig. 2**): median days on antifungal therapy was 9 days (IQR: 5–16) overall, 14 days (IQR: 8–20) in patients discharged alive, and 7 days (IQR: 3–13) in deceased patients. Overall, the most frequently prescribed antifungal for IFIs was micafungin (405/642, 63%), followed by fluconazole (323/642, 50%) for incident candidiasis cases, and voriconazole (195/262, 74%) for incident aspergillosis cases.

Diagnosis tests and specimen sources

Of incident IFI cases (N=1442), 643 (44.6%) had positive microbiology findings. Fungi were identified mostly from blood, followed by the lower respiratory tract, and the most prevalent fungal disease was invasive candidiasis (44.5%, 642/1442). The most frequently performed laboratory test with positive fungal results was bacterial culture (65.8%, 766/1164), followed by fungal culture (16.6%, 193/1164) (**Fig. S2**).

Risk factors for IFI

To evaluate the risk factors associated with IFI, the incidence of IFI was assessed descriptively for each baseline characteristic and time-dependent variable (**Fig. S3**). Notable findings included higher IFI incidences for patients with traditional host factors (e.g. HSCT), Elixhauser comorbidities (e.g. liver disease), and certain time-dependent variables (e.g. MV use) (**Fig. S3C–E**). Additionally, patient age was not linearly associated with IFI: incidence was lower in the youngest (18–29 years) and

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oldest (85+ years) age groups, and peaked at ages 65–74 years (**Fig S3A**). Male patients also showed higher IFI incidence compared with female patients (**Fig. S3A**).

In addition, the quantitative impacts of typical COVID-19 treatments on IFI incidence were assessed. The incidence of IFIs increased with the number of days on CS and with increasing daily dose (**Fig. 3**); incidence was highest in patients who received CS for longer than 2 weeks, and in those who received CS for 7–13 days with a daily dose >80 mg. Regarding MV, IFI incidence was much higher among patients with any days of MV use compared with no MV use, although there was no clear length dependency (**Fig. S4**). Regarding days in ICU, IFI incidence was also much higher among patients who spent any days in ICU compared with those who were not admitted to ICU. IFI incidence progressively increased among patients with 3–5 and 6–11 days in ICU, compared with 1–2 days in ICU; however, the IFI incidence was not length-dependent after 12+ days of ICU stay (**Fig. S4**).

Multivariate risk factor analysis demonstrated that MV use was associated with the highest risk of IFI (hazard ratio [HR] = 6.7 [95% CI: 5.37–8.25]), even after adjusting for all other factors (**Fig. 4A–C**). Compared to the youngest age group (18–29 years), patients aged 65–74 years showed a higher risk of IFI (HR = 1.8 [1.02–3.12]) (**Fig. S5**). Traditional host factors, including hematologic malignancy, acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV), solid organ transplant, and diabetes with complications, were also associated with a higher IFI risk (**Fig. 4A**). Patients with HSCT also demonstrated a higher IFI risk; however, this difference was not statistically significant (**Fig. 4A**).

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Among the Elixhauser comorbidities, pulmonary circulation disorders and alcohol abuse were associated with a higher IFI risk, and hypertension, obesity and psychoses were associated with a lower IFI risk. Most of the time-dependent variables were associated with higher IFI risks, including ICU, MV, extracorporeal membrane oxygenation (ECMO), CS use, total parenteral nutrition, chemotherapy, dialysis, *Candida* colonization, neutropenia, lymphocytopenia, leukocytosis, and tocilizumab use.

Excess burden due to IFI in COVID-19 patients

Before matching, patients with IFI were predominantly male (63% in IFI group vs 52% in non-IFI group); White (58% vs 64%); had higher percentages of traditional host factors (including solid organ transplant, diabetes with complications, and *Candida* colonization); and required more intensive treatments (including ICU admission, MV, systemic CS, ECMO, and tocilizumab) (**Table 1**). Patients with IFI were also primarily categorized into the "Extreme" category of APR-DRG scoring system for severity of illness (96.7% of patients with IFI vs 43.5% of patients without IFI) and risk of mortality (94.2% vs 41.6%). Higher hospital mortality (62.8% in the IFI group vs 12.9% in the non-IFI group) and longer median LoS (29 days vs 5 days) were observed among patients with IFI, while median hospital costs were almost 10 times higher in the IFI group ($115,200 vs $11,800).

As patients with poorer health can be at increased risk of developing IFI, matching was then performed to assess the excess burden attributable to IFI. Following matching, all baseline factors were well balanced (**Table 1**). The excess mortality attributable to IFI was estimated at 18.4% (62.7% vs 44.3%), and the median days to

hospital death was 3 days shorter in the IFI group (16 days) compared to the non-IFI group (19 days) (**Table 3**). Notably, the excess days to discharge alive attributable to IFI was 16 days and the excess hospital costs attributable to IFI were $16,100 (**Table 3**). Kaplan–Meier analyses of overall survival and time to discharge alive are presented in **Fig. 5A** and **5B**.

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DISCUSSION

In this retrospective, database study the burden of IFI in hospitalized patients with COVID-19 in the US was analyzed. Data were extracted from the US hospital-based Premier Healthcare Database, which captures 20–25% of inpatients in the US primarily from geographically diverse, non-profit, non-governmental, community, and teaching hospitals and health systems from both rural and urban areas.

Overall, incidence of IFI was relatively low. In addition to established risk factors, several non-typical risk factors were found to be associated with increased risk of developing IFIs (including typical COVID-19 treatments). Furthermore, the excess hospital mortality rates, excess days to discharge alive, and cost of inpatient hospital stay attributable to IFIs were found to be substantial. Assessment of these clinical and economic outcomes associated with secondary IFIs in COVID-19 patients can inform the treatment of associated Elixhauser comorbidities, fungal co-infections and secondary bacterial infections, as well as the treatment of potential subsequent COVID-19 waves.

Findings from our study showed a lower incidence of IFI in hospitalized patients with COVID-19 than in previous studies globally.[18,23–26] The global incidence remains uncertain, with previous reports ranging from 1 to 33%;[18] this range is likely a consequence of the heterogeneity in patient populations, surveillance protocols, and definitions used for classification of fungal infections.[18] In addition, as COVID-19 shares several non-specific symptoms with IFIs (e.g. fever, cough),[27,28] which further complicates early diagnosis and treatment as IFI may not be suspected, leading to an underestimation of the true incidence rate. While the incidence in this study was

low overall, patients admitted to the ICU had twice the incidence as those in the Main cohort; this is consistent with the increased susceptibility for IFIs associated with critically ill patients admitted to the ICU.[15,29]

Regarding risk factors for IFIs, in addition to the lung damage and immunological deficits associated with COVID-19,[25] other factors typically associated with development of IFIs may also be involved. Several established risk factors for IFIs in general[30] and in the ICU populations[31] were also confirmed as risk factors for IFI in this study, including neutropenia, AIDS/HIV, solid organ transplant, and diabetes with complications.

Compounding the challenge of treating these comorbid patients, typical treatments for COVID-19, including ICU admission, MV use, or systemic CS administration, were identified as risk factors for IFI. Further conditions, such as pulmonary circulation disorders, were also found to be associated with a higher risk of IFI. These are not established risk factors for IFI and may be confounding factors that resulted in increased MV usage. Since COVID-19 treatment approaches may put patients at risk of IFI, monitoring patients with established and emergent risk factors to diagnose fungal infection and initiate antifungal treatment is a priority.

Regarding laboratory tests to monitor fungal infection, positive fungal results were predominantly found in bacterial cultures (from blood and respiratory tract), rather than specific fungal culture orders. This highlights the utility of bacterial cultures for IFI monitoring purposes, since diagnosis of IFIs may be influenced by the presentation of non-specific symptoms shared between IFIs and COVID-19.

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Our study observed similar median costs for COVID-19 inpatient hospital stay/admission ($11,900) with those estimated from other Premier Healthcare Database studies (approximately $12,000).[34,35] Clinical outcomes were worse in patients with IFIs, with substantial increases in hospital costs. By matching IFI and non-IFI groups, this study showed that the excess costs attributable to IFI was estimated at $16,100. Further, the clinical burden due to IFI was substantial, with an excess hospital mortality rate of 18.4% and median excess days to discharge alive of 16.0 days.

There are several strengths and limitations to this study. As this study uses a US hospital-based database, it potentially has high degree of generalizability for the US population. Although the lack of federal or university hospitals in the Premier database may affect the generalizability of the data for such institutions, the database offers a broad view of healthcare to the general US population, particularly to support studies performed at tertiary-care referral hospitals. Additionally, only a small proportion of patients had traditional host factors for IFI, which makes this study unique from previous IFI reports. It should be noted that our definition of IFI (diagnosis codes [ICD-10] and/or microbiology findings plus antifungal therapy use) differs from the definition criteria described by EORTC/MSGERC, AspICU, and/or ECMM/ISHAM. Owing to the lack of necessary clinical information (e.g. clinical factors), we cannot directly compare these definitions; consequently our definition of IFI may be conservative. Microbiology evaluation was available for only 10% of hospitals in the Premier Healthcare Database, and fewer than half (44.6%) of all incident IFI cases in this study population reported positive microbiology findings.

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While we recognize that these missing data limits further clarification/categorization of IFI diagnosis, microbiology evaluation and/or mycologic evidence is often not available in other contexts, such as clinical trials; a previous global registrational phase 3 study (SECURE) showed that 64% of patients had mycological evidence available.[36]

We acknowledge that IFI patients may go undiagnosed and therefore may not always have IFI-specific diagnosis codes, may not always have positive microbiology findings, and are not always treated with antifungal therapy; consequently, the true IFI incidence in the US is likely to be underestimated. This is further complicated, as treatment versus prophylactic use of antifungal therapies cannot be distinguished in Premier data. As such, diagnosis codes for IFI may have been recorded for the prophylactic use of antifungal treatments, leading to misidentification and overestimation of treatment cases included in this study. This is particularly notable, as antifungal therapy as prophylaxis for IFIs has recently been shown to be high in patients with COVID-19 in the ICU.[37] As the true IFI onset dates were unknown, the antifungal treatment initiation dates were used instead. The IFI onset date may have been earlier than the antifungal treatment initiation date, so some of the time-dependent variables may be misclassified. For example, the impact of ICU admission that we ascribe to IFI risk may be due to IFI itself. Finally, medical history or medications outside of the index hospital are not captured.

The findings from this study have the potential to inform infectious disease and critical care communities on the epidemiology and outcomes of IFI in COVID-19 inpatients in the US. The identification of non-traditional factors associated with higher risks of IFI in this study suggests additional areas for close observation and

potential disease management. Our study also highlights the excess healthcare burden of IFIs among COVID-19 patients, including very lengthy stays and significantly higher IFI-attributable inpatient costs. Overall, these findings describe the severe impact of IFIs on COVID-19 patients and the increased challenge for hospitals to manage.

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TABLES

Table 1. Patient baseline characteristics and time-dependent variables, before and after matching

	Main cohort (N=515,391)	Before matching			After matching		
		With IFI (N=1,442)	Without IFI (N=513,949)	SMD	With IFI (N=1,441)	Without IFI (N=4,323)	SMD
Age, years							
Mean (SD)	63.5 (17.22)	64.4 (12.66)	63.5 (17.23)	0.0587	64.4 (12.67)	64.1 (12.88)	0.0225
Median (Q1–Q3)	66.0 (53.0–77.0)	66.0 (57.0–73.0)	66.0 (53.0–77.0)		66.0 (57.0–73.0)	66.0 (57.0–73.0)	
Range (min–max†)	18–89	22–89	18–89		22–89	18–89	
Gender, n (%)							
Male	266,548 (51.7)	905 (62.8)	265,643 (51.7)	0.2252	904 (62.7)	2,689 (62.2)	0.0110
Female	248,843 (48.3)	537 (37.2)	248,306 (48.3)		537 (37.3)	1,634 (37.8)	
Race							
White	329,674 (64.0)	829 (57.5)	328,845 (64.0)	0.1333	828 (57.5)	2,448 (56.6)	0.0168
Black	91,759 (17.8)	263 (18.2)	91,496 (17.8)	0.0113	263 (18.3)	794 (18.4)	0.0030
Asian	13,190 (2.6)	47 (3.3)	13,143 (2.6)	0.0418	47 (3.3)	135 (3.1)	0.0079
Other	56,042 (10.9)	213 (14.8)	55,829 (10.9)	0.1171	213 (14.8)	672 (15.5)	0.0213
Unable to determine	24,726 (4.8)	90 (6.2)	24,636 (4.8)	0.0634	90 (6.2)	274 (6.3)	0.0038
Baseline conditions							
Hematologic malignancies	7,373 (1.4)	41 (2.8)	7,332 (1.4)	0.0981	40 (2.8)	123 (2.8)	0.0042

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	Main cohort (N=515,391)	Before matching			After matching		
		With IFI (N=1,442)	Without IFI (N=513,949)	SMD	With IFI (N=1,441)	Without IFI (N=4,323)	SMD
AIDS/HIV	1,431 (0.3)	11 (0.8)	1,420 (0.3)	0.0677	11 (0.8)	32 (0.7)	0.0027
HSCT	215 (0.0)	5 (0.3)	210 (0.0)	0.0696	4 (0.3)	14 (0.3)	0.0084
Solid organ transplant	4,632 (0.9)	44 (3.1)	4,588 (0.9)	0.1557	43 (3.0)	125 (2.9)	0.0055
GVHD	84 (0.0)	3 (0.2)	81 (0.0)	0.0575	2 (0.1)	3 (0.1)	0.0215
Aplastic anemia	10,704 (2.1)	45 (3.1)	10,659 (2.1)	0.0658	45 (3.1)	143 (3.3)	0.0105
Leukocytosis	7,779 (1.5)	28 (1.9)	7,751 (1.5)	0.0333	28 (1.9)	135 (3.1)	0.0751
Neutropenia	3,113 (0.6)	14 (1.0)	3,099 (0.6)	0.0416	14 (1.0)	34 (0.8)	0.0198
Lymphocytopenia	13,395 (2.6)	36 (2.5)	13,359 (2.6)	0.0065	36 (2.5)	203 (4.7)	0.1182
Reticuloendothelial /immunity disorders	8,343 (1.6)	46 (3.2)	8,297 (1.6)	0.1030	45 (3.1)	139 (3.2)	0.0053
Diabetes, uncomplicated	65,062 (12.6)	130 (9.0)	64,932 (12.6)	0.1167	130 (9.0)	397 (9.2)	0.0056
Diabetes, complicated	144,904 (28.1)	654 (45.4)	144,250 (28.1)	0.3645	653 (45.3)	1,970 (45.6)	0.0051
Chronic respiratory airway abnormality	81,095 (15.7)	265 (18.4)	80,830 (15.7)	0.0705	264 (18.3)	842 (19.5)	0.0295
Other specified viral pneumonia‡	729 (0.1)	1 (0.1)	728 (0.1)	0.0223	1 (0.1)	5 (0.1)	0.0152
Impaired gut wall integrity	10,992 (2.1)	56 (3.9)	10,936 (2.1)	0.1030	56 (3.9)	167 (3.9)	0.0012
Candida colonization	5,207 (1.0)	59 (4.1)	5,148 (1.0)	0.1971	59 (4.1)	144 (3.3)	0.0404
Cannabis dependence	5,396 (1.0)	13 (0.9)	5,383 (1.0)	0.0148	13 (0.9)	40 (0.9)	0.0024
Nicotine dependence	40,871 (7.9)	100 (6.9)	40,771 (7.9)	0.0381	100 (6.9)	298 (6.9)	0.0018
Time dependent variables§							

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	Main cohort (N=515,391)	Before matching			After matching		
		With IFI (N=1,442)	Without IFI (N=513,949)	SMD	With IFI (N=1,441)	Without IFI (N=4,323)	SMD
ICU							
N (%)	143,102 (27.8)	1,329 (92.2)	141,773 (27.6)	1.7512	1,247 (86.5)	3,862 (89.3)	0.0860
Days in ICU							
Mean (SD)	8.3 (9.64)	25.8 (17.23)	8.2 (9.39)	1.2683	11.3 (9.56)	11.1 (9.45)	0.0204
Median (Q1–Q3)	5.0 (2.0–11.0)	22.0 (14.0–34.0)	5.0 (2.0–11.0)		10.0 (4.0–16.0)	10.0 (4.0–16.0)	
Range (min–max)	1–211	1–139	1–211		0–67	0–102	
MV							
N (%)	65,743 (12.8)	1,332 (92.4)	64,411 (12.5)	2.6607	1,172 (81.3)	3,589 (83.0)	0.0441
Days on MV							
Mean (SD)	10.6 (10.91)	21.9 (16.78)	10.3 (10.63)	0.8266	8.4 (8.33)	8.4 (8.53)	0.0015
Median (Q1–Q3)	7.0 (3.0–14.0)	18.0 (10.0–29.0)	7.0 (3.0–14.0)		7.0 (1.0–12.0)	6.0 (2.0–12.0)	
Range (min–max)	1–177	1–134	1–177		0–81	0–95	
ECMO							
N (%)	1,014 (0.2)	55 (3.8)	959 (0.2)	0.2613	41 (2.8)	111 (2.6)	0.0171
Days on ECMO							
Mean (SD)	9.5 (15.02)	13.5 (23.58)	9.3 (14.36)	0.2185	0.2 (1.51)	0.2 (2.42)	0.0356
Median (Q1–Q3)	1.0 (1.0–13.0)	1.0 (1.0–20.0)	1.0 (1.0–13.0)		0.0 (0.0–0.0)	0.0 (0.0–0.0)	
Range (min–max)	1–123	1–123	1–105		0–29	0–62	
Systemic CS							
N (%)	371,251 (72.0)	1,367 (94.8)	369,884 (72.0)	0.6444	1,307 (90.7)	3,954 (91.5)	0.0268

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	Main cohort (N=515,391)	Before matching			After matching		
		With IFI (N=1,442)	Without IFI (N=513,949)	SMD	With IFI (N=1,441)	Without IFI (N=4,323)	SMD
Days on systemic CS							
Mean (SD)	7.1 (6.01)	19.4 (13.00)	7.1 (5.92)	1.2263	11.2 (8.17)	10.3 (7.62)	0.1061
Median (Q1–Q3)	6.0 (3.0–9.0)	16.0 (10.0–26.0)	6.0 (3.0–9.0)		10.0 (6.0–15.0)	10.0 (5.0–14.0)	
Range (min–max)	1–139	1–87	1–139		0–58	0–83	
Tocilizumab							
N (%)	20,939 (4.1)	279 (19.3)	20,660 (4.0)	0.4914	264 (18.3)	761 (17.6)	0.0187
Days on tocilizumab							
Mean (SD)	1.2 (0.47)	1.3 (0.53)	1.2 (0.47)	0.1927	0.2 (0.54)	0.2 (0.52)	0.0328
Median (Q1–Q3)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	1.0 (1.0–1.0)		0.0 (0.0–0.0)	0.0 (0.0–0.0)	
Range (min–max)	1–7	1–4	1–7		0–3	0–4	
Baricitinib							
N (%)	929 (0.2)	7 (0.5)	922 (0.2)	0.0532	7 (0.5)	23 (0.5)	0.0065
Days on baricitinib							
Mean (SD)	6.5 (4.17)	10.1 (3.48)	6.5 (4.16)	0.9506	0.0 (0.71)	0.0 (0.54)	0.0227
Median (Q1–Q3)	6.0 (3.0–9.0)	11.0 (6.0–14.0)	6.0 (3.0–9.0)		0.0 (0.0–0.0)	0.0 (0.0–0.0)	
Range (min–max)	1–28	6–14	1–28		0–14	0–14	

†In the Premier Healthcare Database (using the PINC AI™ software platform), age 90+ are summarized as age 89; ‡Includes influenza, adenoviral, respiratory syncytial virus, parainfluenza, human metapneumovirus; §Before matching, from admission to discharge. After matching, from admission to (matching day - 1).

ECMO, extracorporeal membrane oxygenation; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; IFI, invasive fungal infection; MV, mechanical ventilation; Q, quartile; SD, standard deviation; SMD, standardized mean difference.

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Table 2. IFI incidence in the main cohort (N=515,391) and ICU subgroup (N=143,021)

	n	% (95% CI)	Incidence/1000 patient–days (95% CI)
Main cohort, total incidence	1,442	0.28 (0.27–0.29)	0.35 (0.33–0.36)
Invasive candidiasis	642	0.12 (0.11–0.13)	0.15 (0.14–0.17)
Invasive aspergillosis	262	0.05 (0.04–0.06)	0.06 (0.06–0.07)
Other IFI	561	0.11 (0.10–0.12)	0.13 (0.12–0.15)
Coccidioidomycosis	15	0 (0.00–0.00)	0 (0.00–0.01)
Histoplasmosis	2	0 (0.00–0.00)	0 (0.00–0.00)
Blastomycosis	1	0 (0.00–0.00)	0 (0.00–0.00)
Cryptococcosis	33	0.01 (0.00–0.01)	0.01 (0.00–0.01)
Mucormycosis	2	0 (0.00–0.00)	0 (0.00–0.00)
Pneumocystis	12	0 (0.00–0.00)	0 (0.00–0.01)
Other specified mycoses*	266	0.05 (0.05–0.06)	0.06 (0.06–0.07)
Unspecified mycosis†	341	0.07 (0.06–0.07)	0.08 (0.07–0.09)
ICU subgroup, total incidence	1,248	0.87 (0.82–0.92)	0.76 (0.72–0.80)

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Invasive candidiasis	564	0.39 (0.36–0.43)	0.34 (0.31–0.37)
Invasive aspergillosis	222	0.16 (0.13–0.18)	0.13 (0.12–0.15)
Other IFI	483	0.34 (0.31–0.37)	0.29 (0.27–0.32)
Coccidioidomycosis	9	0.01 (0.00–0.01)	0.01 (0.00–0.01)
Histoplasmosis	2	0 (0.00–0.00)	0 (0.00–0.00)
Blastomycosis	1	0 (0.00–0.00)	0 (0.00–0.00)
Cryptococcosis	28	0.02 (0.01–0.03)	0.02 (0.00–0.02)
Mucormycosis	2	0 (0.00–0.00)	0 (0.00–0.00)
Pneumocystis	10	0.01 (0.00–0.01)	0.01 (0.00–0.01)
Other specified mycoses*	232	0.16 (0.14–0.18)	0.14 (0.12–0.16)
Unspecified mycosis†	298	0.21 (0.18–0.23)	0.18 (0.16–0.20)

One patient can have multiple diagnoses

* Other specified mycoses include ICD10 = B48.8 (other specified mycoses), or microbiology findings for Cladophialophora, Fusarium, S. cerevisiae or unspecified yeast.

† Unspecified mycosis includes ICD10 = B49 (unspecified mycosis) or microbiology findings for unspecified pathogen (e.g., fungi).

CI, confidence interval; ICU, intensive care unit; IFI, invasive fungal infection.

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Table 3. Excess mortality, days to discharge, and hospital costs attributable to IFI

	With IFI (N=1,441)	Without IFI (N=4,323)	Excess burden due to IFI
Hospital death, n (%)	904 (62.7)	1,917 (44.3)	
Excess mortality, % (95% CI)			18.4 (16.4, 20.4)
Days to death			
Median (Q1, Q3)	16 (6, 51)	19 (7, 59)	–3 days
Days to discharge alive†			
Median (Q1–Q3)	33 (18–52)	17 (8–31)	16 days
Days to discharge dead or alive‡			
Median (Q1–Q3)	12 (5–24)	9 (4–18)	3 days
Excess hospital costs, 1,000 USD			
Mean (SD)	88.3 (119.67)	49.9 (75.92)	
Median (Q1–Q3)	48.5 (21.6–107.4)	26.5 (11.0–60.6)	16.1 (14.46–18.39)
Range (min–max)	0–1553	0–1436	

Excess mortality was estimated as the difference in mortality rate between the groups.

Excess days to death and discharge from matching day was estimated as the difference in median Kaplan–Meier estimates between the groups while disassociating matched pairs.

†Event is discharge alive, censoring events are death and transfer to other hospital.

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‡Event is discharge dead or alive, and censoring event is transfer to other hospital.

CI, confidence interval; IFI, invasive fungal infection; Q, quartile; SD, standard deviation; USD, United States dollar.

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FIGURE LEGENDS

Figure 1. Days from admission to antifungal therapy initiation in incident and prevalent IFI cases

Patients discharged alive and <5 days on antifungal therapy were considered as non–IFI cases.
IFI, invasive fungal infection.

Figure 2. Days of antifungal therapy among incident IFI cases by discharge status

IFI, invasive fungal infection

Figure 3. IFI incidence by daily dose and days on corticosteroid

In this analysis, corticosteroid users without dosage info (N = 3,395) were excluded.
CS, corticosteroid; IFI, Invasive fungal infection.

Figure 4. Multivariate risk factor forest plots: A) Baseline conditions; B) Elixhauser comorbidities†; C. Time–dependent variables.

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AIDS, acquired immunodeficiency syndrome; CS, corticosteroid; ECMO, extracorporeal membrane oxygenation; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LCL, lower confidence limit; MV, mechanical ventilation; UCL, upper confidence limit.

[†]Some additional variables, primarily Elixhauser conditions, were excluded from the Cox regression model due to deviation from the proportional hazard assumption (**Supplemental Information**).

Figure 5. A) Overall survival and B) time to discharge alive after time-dependent propensity score matching

Log–rank p-value was 0.0009 for overall survival and <0.0001 for time to discharge.
IFI, invasive fungal infection.

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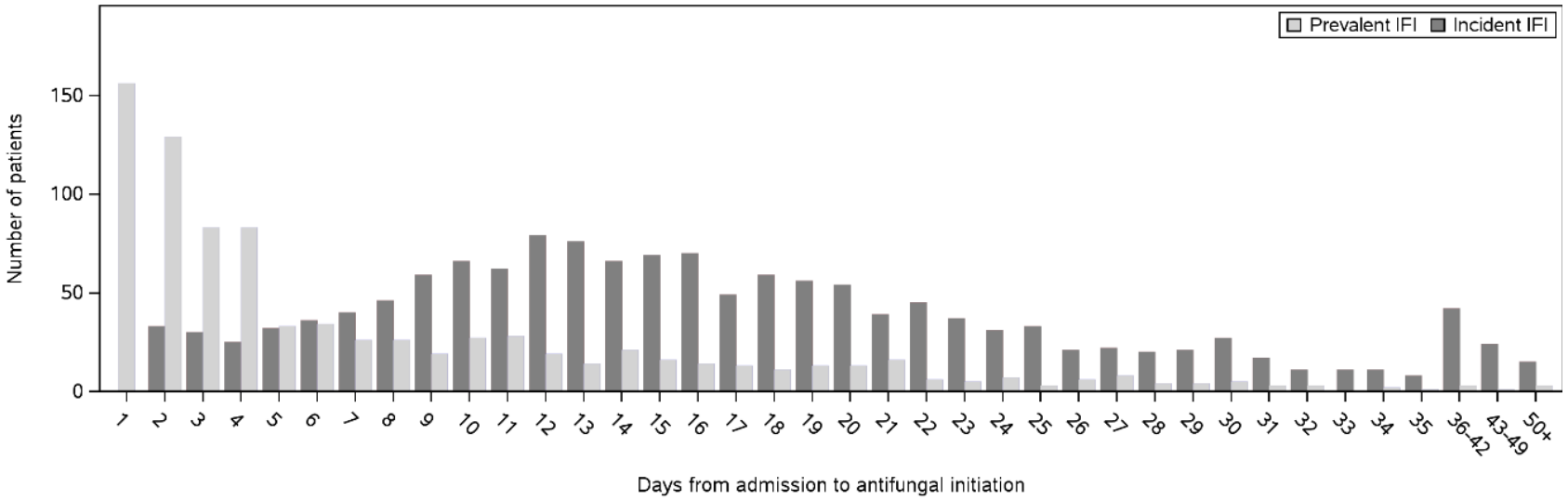
FIGURES

Figure 1. Days from admission to antifungal therapy initiation in incident and prevalent IFI cases



Patients discharged alive and <5 days on antifungal therapy were considered as non–IFI cases.

IFI, invasive fungal infection.

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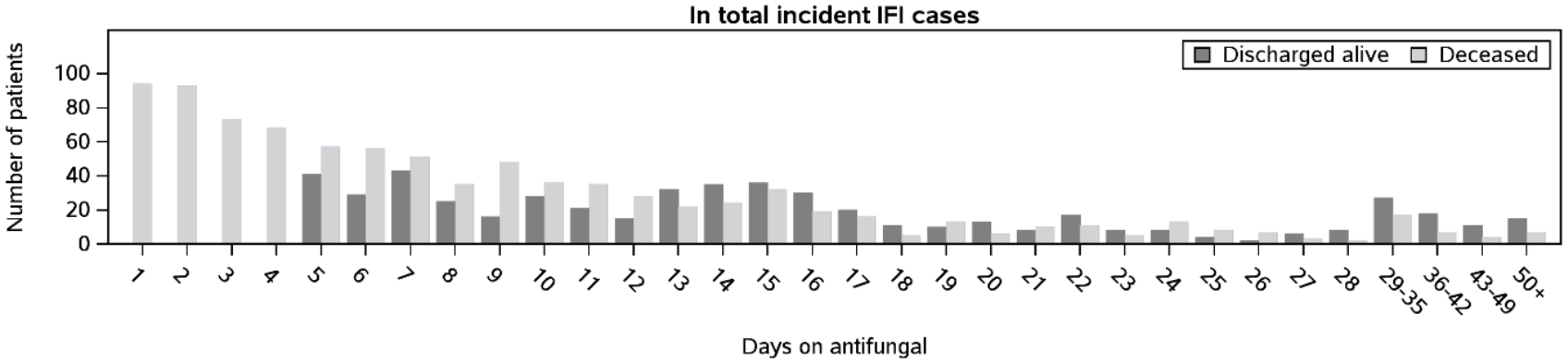
Figure 2. Days of antifungal therapy among incident IFI cases by discharge status



IFI, invasive fungal infection

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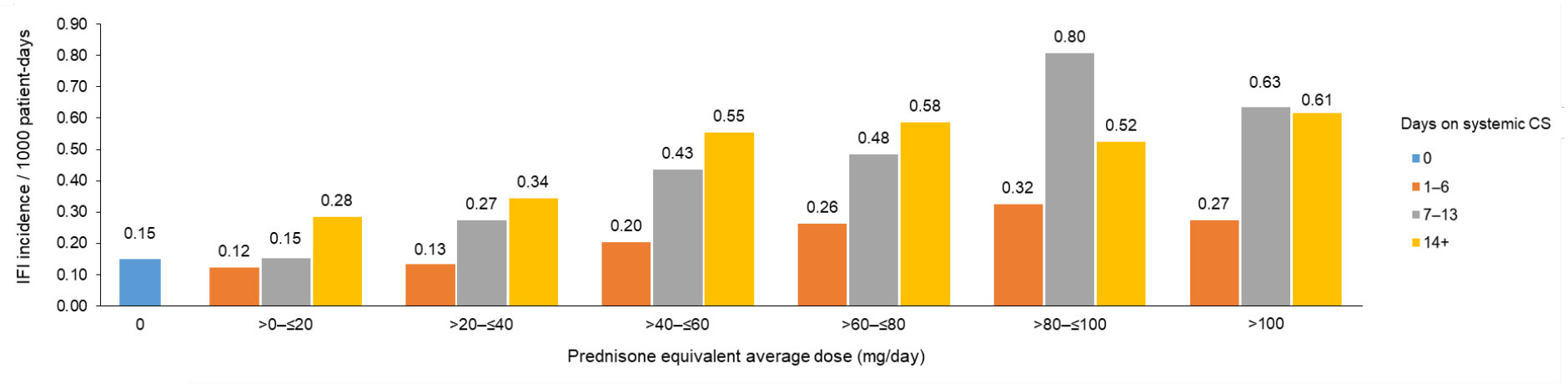
Figure 3. IFI incidence by daily dose and days on corticosteroid



In this analysis, corticosteroid users without dosage info (N = 3,395) were excluded.

CS, corticosteroid; IFI, Invasive fungal infection.

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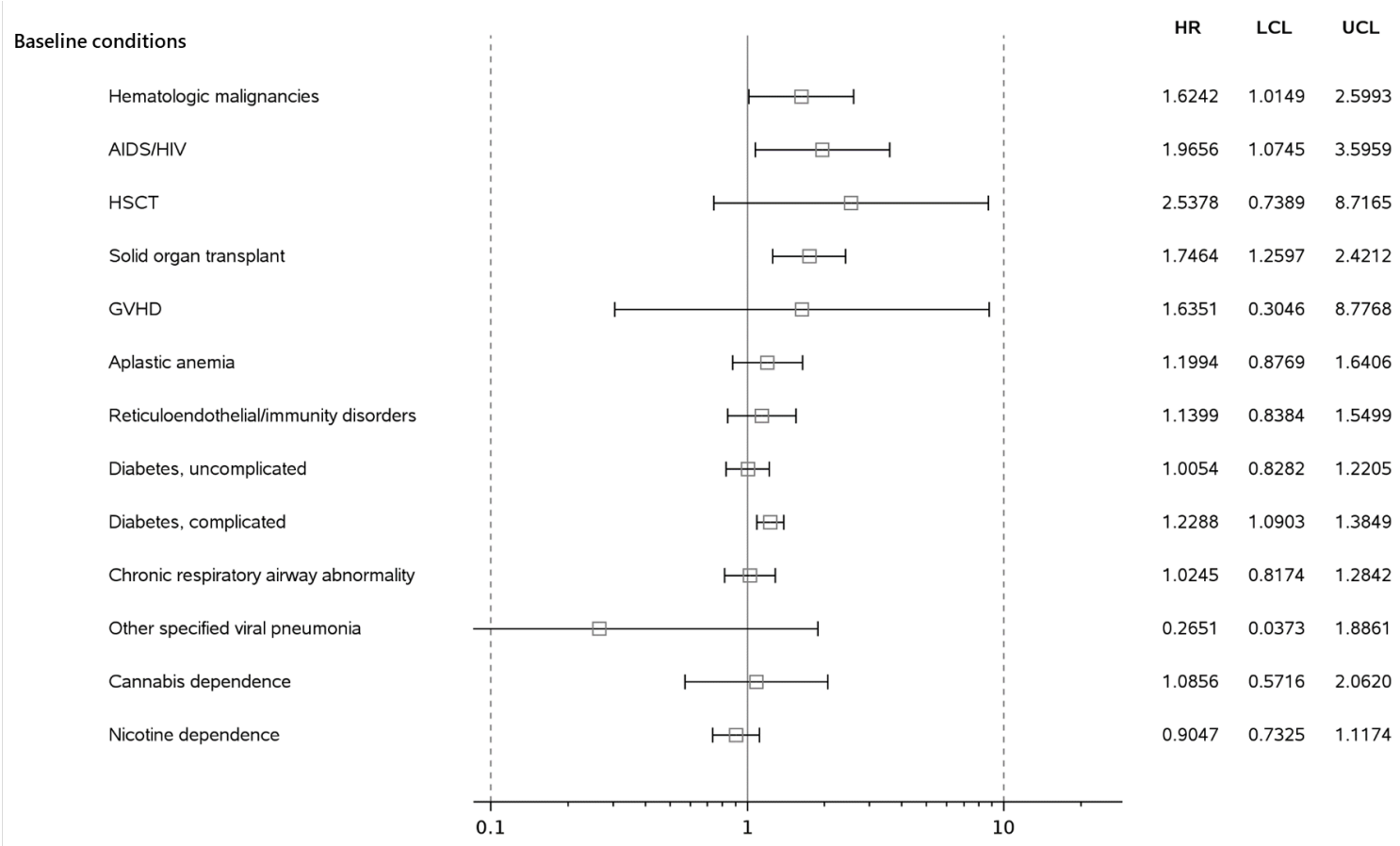
Figure 4. Multivariate risk factor forest plots: A) Baseline conditions; B) Elixhauser comorbidities†; C. Time–dependent variables.

A.



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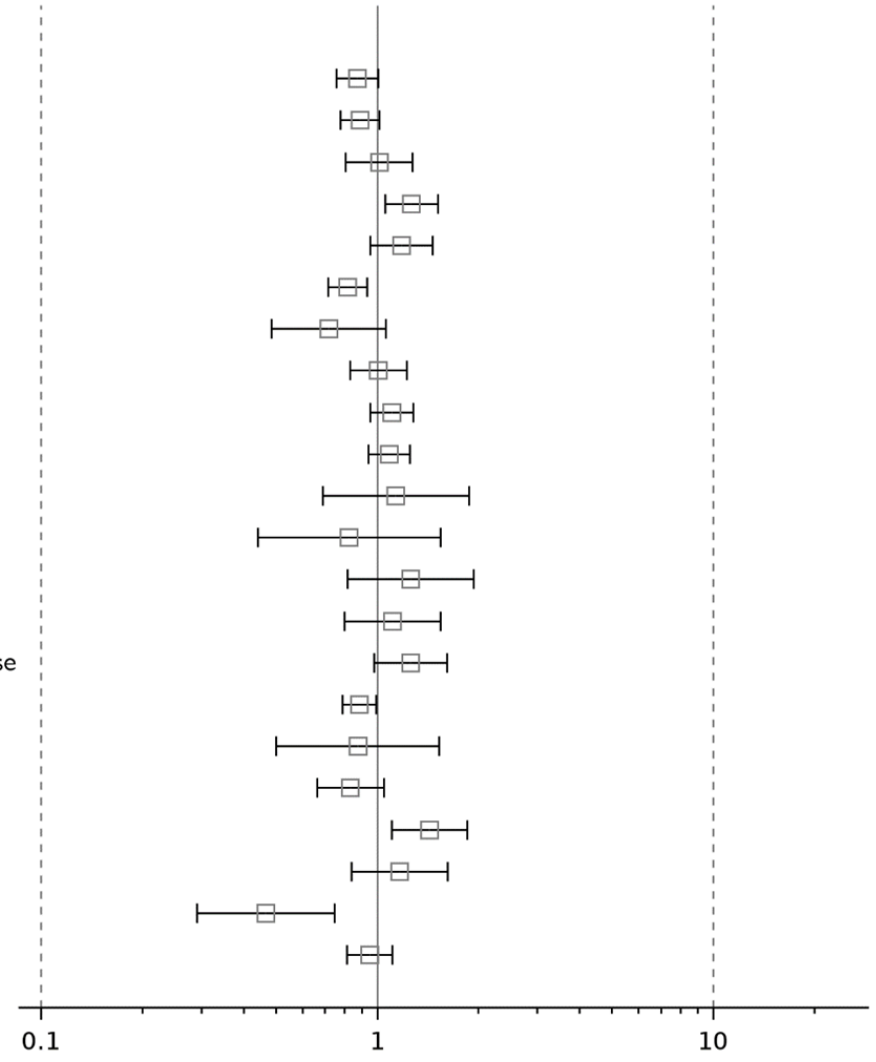

Elixhauser comorbidities	HR	LCL	UCL
Congestive heart failure	0.8727	0.7570	1.0060
Cardiac arrhythmias	0.8878	0.7777	1.0135
Valvular disease	1.0147	0.8069	1.2761
Pulmonary circulation disorders	1.2642	1.0556	1.5140
Peripheral vascular disorders	1.1809	0.9549	1.4605
Hypertension	0.8156	0.7132	0.9325
Paralysis	0.7170	0.4852	1.0595
Chronic pulmonary disease	1.0087	0.8303	1.2253
Hypothyroidism	1.1036	0.9530	1.2780
Renal failure	1.0863	0.9409	1.2541
Peptic ulcer disease, no bleeding	1.1375	0.6886	1.8789
Lymphoma	0.8254	0.4420	1.5413
Metastatic cancer	1.2582	0.8185	1.9342
Solid tumor without metastasis	1.1109	0.7984	1.5457
Rheumatic disease/collagen vascular disease	1.2592	0.9819	1.6147
Obesity	0.8850	0.7877	0.9944
Blood loss anemia	0.8750	0.5006	1.5293
Deficiency anemia	0.8326	0.6614	1.0481
Alcohol abuse	1.4304	1.1060	1.8498
Drug abuse	1.1655	0.8390	1.6190
Psychoses	0.4655	0.2904	0.7462
Depression	0.9489	0.8115	1.1095

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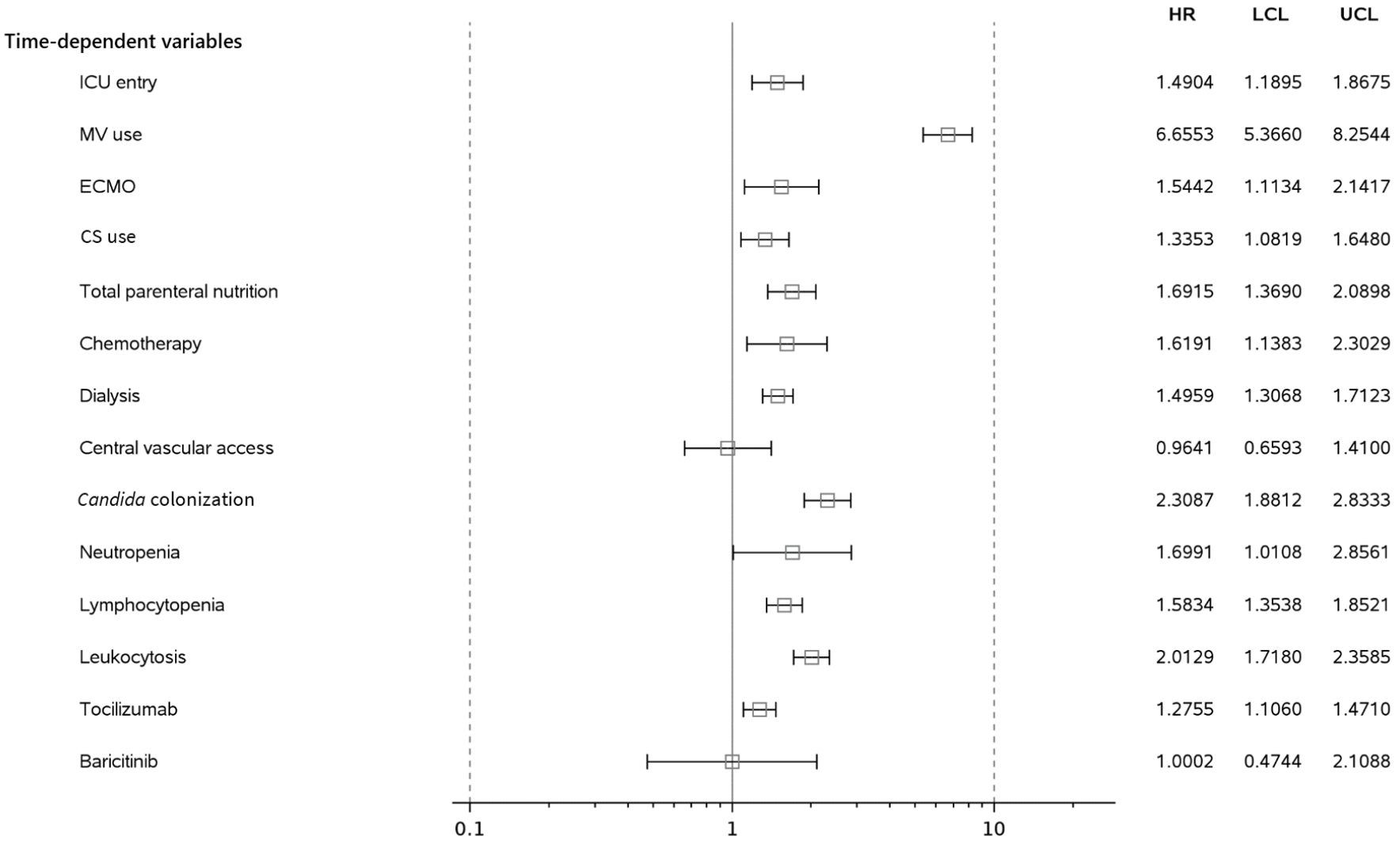
C.



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AIDS, acquired immunodeficiency syndrome; CS, corticosteroid; ECMO, extracorporeal membrane oxygenation; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LCL, lower confidence limit; MV, mechanical ventilation; UCL, upper confidence limit.

[†]Some additional variables, primarily Elixhauser conditions, were excluded from the Cox regression model due to deviation from the proportional hazard assumption (**Supplemental Information**).

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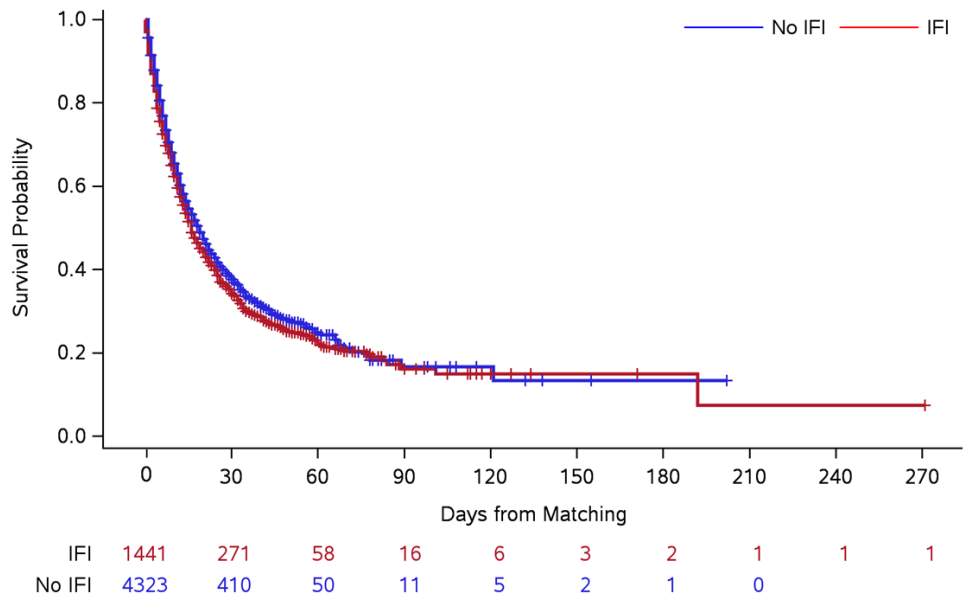
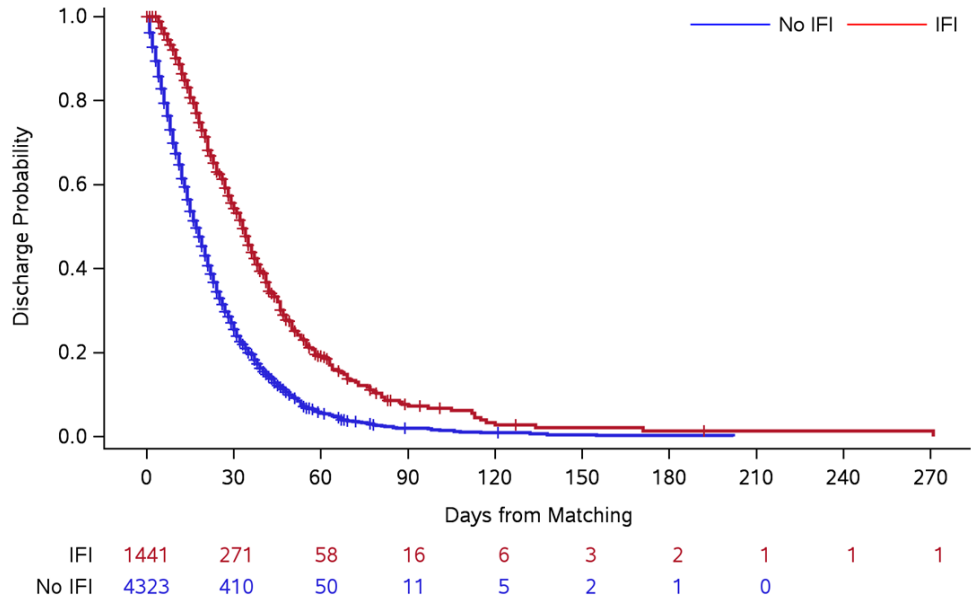
Figure 5. A) Overall survival and B) time to discharge alive after time-dependent propensity score matching

A.



B.



Log–rank p-value was 0.0009 for overall survival and <0.0001 for time to discharge.
IFI, invasive fungal infection.

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SUPPLEMENTAL INFORMATION

Baseline characteristics and time-dependent variables

Baseline characteristics

At admission

- Age (years old)
- Gender (male/female)
- Race (White, Black, Asian, others, unable to determine)
- Payor type (Medicare, Medicaid, Commercial, Self–Pay, Others)
- Calendar month of admission
- Hospital characteristics (geographic region, teaching/non–teaching, rural/urban, number of beds)
- Point of origin (home, transfer from other facilities, ambulatory care, SNF [Skilled Nursing Facility]/ICF [Intermediate Care Facility], other, unknown)
- Traditional host factors for IFI (category #1), defined basically with diagnosis codes with Present on Admission [PoA] flag
    - Hematologic malignancies
    - Neutropenia: diagnosis codes with PoA and/or lab results at admission date (<500/mm^3)
    - Lymphocytopenia: diagnosis codes with PoA and/or lab results at admission date (<1000/mm^3)
    - Leukocytosis: diagnosis codes with PoA and/or lab results at admission date (>10000/mm^3)
    - Other specified viral pneumonia (including influenza, parainfluenza, adenovirus, human metapneumovirus, respiratory syncytial virus)
    - *Candida* colonization:
        - diagnosis codes with PoA and/or
        - microbiological *Candida* findings
            - recovery of *Candida* species in cultures obtained from non–sterile sites (respiratory tract secretions, stool, skin, wound sites, urine, and drains), and
            - collected on 2 or more separate days, and

- without *Candida* findings from sterile site on the same collection date

Within 180 days prior to the admission, plus diagnosis at admission (with Present on Admission [PoA] flag)

- Elixhauser comorbidity index (30 conditions)
- Elixhauser comorbidity weighted score
- Traditional host factors for IFI (category #2)
    - AIDS/HIV
    - HSCT: diagnosis with PoA flag and/or procedure codes and billing data within 180 days prior to admission (not including the admission date)
    - GVHD
    - Aplastic anemia
    - Reticuloendothelial/immunity disorders (except for autoimmune disease not elsewhere classified)
    - Diabetes, uncomplicated (identical to the one in the Elixhauser comorbidity index)
    - Diabetes, complicated (identical to the one in the Elixhauser comorbidity index)
    - Chronic respiratory airway abnormality (identical to the one in the Elixhauser comorbidity index)
    - Impaired gut wall integrity
    - Cannabis dependence
    - Nicotine dependence

During entire history in the Premier Database

- Traditional host factors for IFI (category #3)
    - Solid organ transplant: defined by ICD-10 and ICD-9 diagnosis codes, ICD-10 and ICD-9 procedure codes, CPT and HCPCS procedure codes, and/or systemic tacrolimus billing codes

Time–dependent variables

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The following events were collected between the admission day (inclusive) and IFI (in incident IFI cases) or matching date (in non-IFI cases) (exclusive) and summarized as binary variable (yes/no).

- ICU admission
- MV use
- ECMO
- CS use
- Neutropenia
- Lymphocytopenia
- Leukocytosis
- Total parenteral nutrition (TPN)
- Abdominal surgeries
- Chemotherapy
- Central vascular access (CVA) procedure
- Hemodialysis
- *Candida* colonization
- Tocilizumab use
- Baricitinib use

Variables included in the Cox proportional hazard model for risk factor analysis

The final model for risk factor analysis included all baseline variables and time-dependent variables. However, the following variables that did not achieve proportional hazard assumptions were excluded from the final model: impaired gut wall integrity, neurological disorders (Elixhauser), liver disease (Elixhauser), coagulopathy (Elixhauser), weight loss (Elixhauser), fluid and electrolyte disorders (Elixhauser), and point of origin. In addition, admission year and month were summarized by quarterly basis, and the number of beds categories (<200, 200–399, 400+) and geographic regions (Midwest, Northeast, South and West) were replaced with a new variable combining these categories.

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