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Invasive pulmonary aspergillosis real-world outcomes: Clinical features and risk factors associated with increased mortality

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Abstract

Invasive pulmonary aspergillosis (IPA) is a severe fungal infection that primarily affects immunocompromised patients and is associated with high mortality. Contemporary clinical characteristics of IPA and "real-world" estimates and predictors of associated mortality are inadequate. TriNetX, a global research network, was queried to identify adult patients with IPA diagnoses based on the ICD-10 code B44.0. We performed a propensity score-matched analysis comparing clinical characteristics among patients who survived versus non-survivors at 1 year. We identified 4371 patients with IPA. We found neoplasms, solid organ transplant recipients, hematologic malignancies, and aplastic anemia as the most predominant risk factors. The overall 1-year mortality was 32% for IPA. 1-year mortality was highest for patients with COVID-19 in the ICU, followed by those with acute myeloid leukemia and aplastic anemia (54%, 50%, and 39%, respectively). After propensity score matching, severe sepsis, pleural effusion, and candidiasis were mortality contributors within a year after diagnosis. Liver injury, systemic glucocorticoid exposure over the previous 6 months, lower lymphocyte and CD4 counts, elevated ferritin, LDH, thrombocytopenia, anemia, or elevated glycosylated hemoglobin (HbA1c) were independent predictors of mortality at 1 year. Voriconazole was the most common treatment (67%). The annual incidence of IPA was 0.001%, increasing to 0.02% among critically ill patients in the ICU. IPA continues to have a very high mortality. We encourage prospective studies to validate and refine the identified clinical markers linked to increased mortality.

Lay summary

Invasive pulmonary aspergillosis (IPA) is common among immunocompromised patients. Analyzing a global research network, we found 32% of patients with IPA died a year after diagnosis. We identified the primary underlying conditions, contributors, and predictors of mortality.

Key words: *Aspergillus*, invasive pulmonary aspergillosis, mortality, drug therapy.

Introduction

Invasive pulmonary aspergillosis (IPA) is a severe fungal infection that primarily affects immunocompromised patients, including those with hematologic malignancies, solid organ transplantation, and critically ill patients in intensive care units (ICUs).[1] Additional host factors include severe and prolonged neutropenia, use of high-dose glucocorticoids, and other conditions affecting the cellular immune response.[2] *Aspergillus* species are ubiquitous in the environment and can be found in soil, water, and decaying organic matter, and humans are constantly exposed to the *Aspergillus* spores. *Aspergillus fumigatus*, *A. flavus*, and *A. terreus* are the most common species causing invasive aspergillosis.[3]

A recent systematic review and meta-analysis found the incidence of IPA in patients with hematologic malignancies varies from 5% to 25%, depending on the type of cancer and the intensity of chemotherapy.[4] Similarly, invasive aspergillosis in solid organ transplant recipients ranges from 0.5% to 10%, with the highest rates reported in lung transplant recipients.[5] In critically ill ICU patients, a well-known population at risk for invasive aspergillosis, the incidence is between 0.7% and 15%, with significant variations in rates reported from different geographic regions.[6]

The mortality rate associated with invasive aspergillosis remains high, ranging from 30% to 90%, and is highly dependent upon the degree or reversibility of underlying host immune dysfunction, the infection's severity, and the time to receipt of effective antifungal therapy.[7]

Diagnosing IPA is challenging, and the mortality rate remains high despite advances in antifungal therapy. Recognizing the contemporary and emerging risk factors for IPA and implementing appropriate preventive and diagnostic strategies in high-risk patient populations is essential. There are insufficient contemporary clinical characteristics of IPA and "real-world" estimates of associated mortality. We aim to characterize the clinical features of IPA and its factors related to 1-year mortality using an international global health network database.

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Methods

Global federated research network

The TriNetX global research network database (https://trinetx.com/) was queried to identify adult patients with IPA diagnosis based on the ICD-10 code (B44.0) ($n = 4371$) in February 2023. TriNetX datasets include clinical patient data, such as demographics, diagnoses, procedures, laboratories, and medications—commonly referred to as real-world data. TriNetX has global data for approximately 100 million patients from more than 80 medical centers in the US, Canada, Europe, Australia, Indonesia, and other countries. [8,9] TriNetX, limited liability company (LLC) complies with the Health Insurance Portability and Accountability Act (HIPAA), the US federal law protecting healthcare data's privacy and security, and any additional data privacy regulations applicable to the contributing healthcare organization (HCO). Each HCO delivers electronic medical record (EMR) systems data collected to provide care to patients. Received data is either structured or unstructured data processed by Natural Language Processing Technology. Most participating HCOs are large academic medical institutions with inpatient and outpatient facilities. The data they provide represent the entire patient population at the HCO. Most give an average of 7 years of historical data. TriNetX receives data directly from an HCO research repository into the TriNetX environment, or the HCO sends TriNetX data extracts in the form of comma-separated values (CSV) files coded in the TriNetX Data Dictionary. HCO and other data providers update their data at various times, with over 80% refreshing in 1-, 2-, or 4-week frequency intervals. The average lag time for an HCO's source data to refresh is 1 month. TriNetX maps the data to a standard, controlled set of clinical terminologies and transforms it into a proprietary data model. This transformation process includes extensive data quality assessment that includes data cleaning that rejects records that do not meet the TriNetX quality standards.

TriNetX is certified by the International Organization for Standardization (ISO) 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX platform in aggregate form, or any patient-level data provided in a data set generated by the TriNetX platform, only contains de-identified data as per the de-identification standard defined in Section 164.514(a) of the HIPAA Privacy Rule. The process of de-identifying data is attested to a formal determination by a qualified expert as defined in Section 164.514(b)[1] of the HIPAA Privacy Rule. Geographic reporting at the regional level prevents potential re-identification through the localization of patients or HCOs.

Study design and population

The analysis compared clinical characteristics among IPA patients who survived ($n = 2714$) versus non-survivors ($n = 1657$) 1 year after the index event (diagnosis). The query criteria for each cohort were based on ICD-10-CM codes and laboratory results (Supplementary Tables S1–S4). In patients with multiple encounters, the earliest encounter for IPA was identified as the index event. Demographic characteristics, diagnoses, procedures, medications, complications, and measurements (e.g., laboratory test results; see Supplementary data) were captured 6 months before the index event (IPA diagnosis). Comorbidities were selected based on frequency and clinical importance. Results were reported before and after propensity score matching. Propensity score matching was performed to control for differences between survivors versus non-survivors based on age, gender, ethnicity, and comorbidities linked to increasing mortality (human immunodeficiency virus (HIV) infection, aplastic anemia and other bone marrow failure syndromes, chronic kidney disease, solid neoplasms, lymphoid malignancy, diabetes mellitus, and solid or bone marrow transplant status).

Global federated research network outcome measures

We captured mortality as the primary outcome following the diagnosis of IPA at 30 days, 10 weeks, and 1 year. The secondary outcomes included the proportion of patients with IPA who required emergency department visits, hospitalization, ICU care, or developed intracranial abscesses or granulomas (ICD-10, G06) within 1 year after the index event (Supplementary Table S4).

Treatment pathway

We captured the treatment pathways within the TriNetX platform for all patients diagnosed with IPA (B44.0). Treatment was recorded within 3 months after the index event. Antifungals were grouped into eight different categories based on RxNorm codes (Supplementary Table S3): voriconazole, fluconazole, voriconazole plus amphotericin B, posaconazole, voriconazole plus an echinocandin, isavuconazole, itraconazole, and amphotericin B. A line of treatment was defined as taking the same medication within 3 days from the index event, and it was considered completed once absent from the patient's record for 3 consecutive days.

Incidence/prevalence analysis

The incidence and prevalence analysis was performed in the TriNetX platform. We used all visits within the system for individuals $\geq$ 18 years of age. We designed a query with adult patients with immunodeficiency based on the presence of aplastic anemia, solid neoplasm, lymphoid malignancies, transplant status, or inflammatory bowel disease, and for adults under ICU care. We queried from January 1, 2020, through December 31, 2022.

Statistical analysis

We completed the statistical analyses of the global federated research network on the TriNetX platform. Descriptive statistics were presented as means and standard deviations for continuous variables and as frequency and proportions for categorical variables. Continuous data were compared using independent t tests, whereas categorical data were compared using χ^2 or Fisher's exact test, as appropriate. Propensity score matching was performed using a 1:1 greedy nearest-neighbor algorithm. Graphs were designed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, CA, USA (www.graphpad.com).

Data access

The corresponding author had full access to data in the study and had final responsibility for the decision to submit the manuscript for publication. The aggregated datasets

generated and analyzed in the current study are available from the TriNetX platform with a subscription or through the corresponding author per a formal request.

Ethics statement

Research utilizing TriNetX does not require ethical approval because patient-identifiable information is not accessible to users. The current project is in HIPAA compliance, according to the Colorado Multiple Institutional Review Board (COMIRB) at the University of Colorado Denver.

Results

Clinical characteristics of patients with IPA

We identified 4371 patients with IPA by ICD-10 coding (B44.0). The average age at diagnosis was 58 years. The majority (64%) were White men. A total of 13% were Black/African–American individuals, and 7% were Hispanic individuals. Before the presentation, the most common ICD-based symptoms included dyspnea (39%), cough (28%), malaise and fatigue (26%), chest pain (23%), fever (23%), and diarrhea (20%). Other less commonly recorded symptoms were hemoptysis (16%), lymphadenopathy (11%), and headaches (12%). Hematologic underlying conditions, malignant neoplasms of the lymphoid tissue (lymphoid and myeloid leukemia) (27%), and aplastic anemias (21%) were common. Neoplasms (46%), chronic lower respiratory diseases (38%), diabetes mellitus (24%), solid organ transplant recipients (22%), and chronic kidney disease (20%) were also common. The most frequent complications seen during IPA diagnosis included severe sepsis (18%), candidiasis (12%), and pleural effusions (16%). The mean laboratory results displayed leukocytosis—lymphocytic predominant—normal range neutrophil count, borderline low clusters of differentiation-4 (CD4) cell counts, mild anemia, elevated creatinine, and inflammatory markers (c-reactive protein (CRP) and ferritin levels). Mean 1,3 beta-D-glucan levels were elevated (58 ± 98). *Aspergillus* PCR testing data was not available. Glucocorticoids, antineoplastics, and immunosuppressants were common among patients with IPA (Table 1).

Outcomes measures for patients with IPA

Of all 4371 patients with an ICD-10 code for IPA, 19% required hospital admission within 1 year of diagnosis (14% within the first month). At 1 year, 22% of patients needed critical care, 12% had an emergency room visit, 0.5% developed intracranial abscesses or granulomas, and 32% died. At 30 days and 10 weeks, the mortality was 12% and 19%, respectively. For patients with malignant lymphoma (ICD-10 codes: C81–C96), acute myeloid leukemia, and aplastic anemia, the mortality reached 50% in 1 year. Patients with a history of neoplasm had a 1-year mortality of 39% compared to 30% in patients with chronic lower respiratory diseases. Among patients with COVID-19 in the ICU, the 1-year mortality of IPA reached 54% and was most pronounced within the first 60 days (Fig. 1).

Clinical features associated with 1-year mortality

Before balancing, we found 2714 survivors and 1657 non-survivors 1 year after the index event. Unmatched patients who died were older and predominantly white men (Supplementary Table S5). Symptoms and comorbid conditions were more frequent in the non-survivor group except for HIV, liver transplant status, and systemic lupus erythematosus (SLE). Antineoplastics, immunosuppressive medications, and glucocorticoids were more frequent in those who died. All laboratory markers and oxygen saturation were worse among the non-survivors.

After balancing the cohorts for the selected covariates, TriNetX matched 1185 patients in each group (survivors versus non-survivors within 1 year of the index event) (Table 1). Symptoms related to more significant lung compromise, increased systemic infection, or underlying disease involvement were linked to increased mortality (Table 1). Dyspnea before or during IPA diagnosis was captured in half of the patients who died. Most comorbidities remained balanced between the two groups. Kidney transplant recipient status was slightly linked to increased survival. Conversely, pulmonary fibrosis, systemic connective tissue diseases, and inflammatory bowel disease were higher in the non-survivors group. All peri-diagnosis complications—pleural effusion, pneumothorax, candidiasis, and cytomegalovirus (CMV) disease—were significantly higher in the group that died. Liver injury, lower lymphocyte, CD4 counts, and worse anemia or glycosylated hemoglobin were predictors of mortality at 1 year. Elevated ferritin, lactate dehydrogenase (LDH), and lower platelet count were independent mortality predictors (Fig. 2). Galactomannan levels were slightly higher in the non-survivor group, although not statistically significant. The rates of immunosuppressants and antineoplastics were similar in both groups. Patients who died were more likely to be on glucocorticoids, most commonly prednisone or methylprednisolone.

Treatment pathways for patients with IPA

Within 3 months after the index event, most patients received voriconazole (67%), followed by fluconazole (15%), posaconazole (9%), and combination therapy of voriconazole plus an echinocandin (6%) (Fig. 3). The duration of treatment was variable but lasted approximately 2 months for voriconazole, posaconazole, and itraconazole (Table 2). Death rates among different medication groups ranged between 2% and 17%. The shortest time before death was in patients on amphotericin B.

Overall annual incidence and prevalence of IPA

Within approximately 90 million adult visits in the TriNetX platform, we found an annual incidence of IPA of 0.001% and a prevalence of 0.004% during the last 3 years (2020–2022). Incidence and prevalence were highest among 65–69 years old (0.002% and 0.008%, respectively) and persons identifying as Native Hawaiian or Other Pacific Islanders (0.03%). There were no differences in sex. Among immunocompromised patients (aplastic anemia, neoplasm, lymphoid malignancies, transplant status, or inflammatory bowel disease), IPA's annual incidence and prevalence increased to 0.003% and 0.02%, respectively. The overall yearly incidence and prevalence among critically ill patients in the ICU were 0.02% and 0.06%

Discussion

We found neoplasms, solid organ transplant recipients, hematologic malignancies, and aplastic anemia as the most

Table 1. Invasive pulmonary aspergillosis patient clinical characteristics categorized by post propensity score matching survival status.

Variable Mean ± SD, *N* (%)	Non-survivors *N* = 1185[π]	Survivors *N* = 1185[π]	*P*-value
Demographics			
Age (years)	58 ± 17	58 ± 15	.659
Men	716 (60%)	738 (62%)	.353
White	828 (70%)	818 (69%)	.656
Black	171 (14%)	164 (14%)	.68
Hispanic	76 (6%)	100 (8%)	.06
Symptoms			
Dyspnea	625 (53%)	475 (40%)	< .0001
Cough	372 (31%)	369 (31%)	.894
Malaise and fatigue	457 (39%)	359 (30%)	< .0001
Chest pain	353 (30%)	301 (25%)	.017
Fever, unspecified	398 (34%)	305 (26%)	< .0001
Hemoptysis	288 (24%)	172 (15%)	< .0001
Lymphadenopathy	170 (14%)	146 (12%)	.147
Cachexia	138 (12%)	41 (3%)	< .0001
Comorbidities			
Aplastic anemia	474 (40%)	367 (31%)	< .0001
Neoplasms	718 (61%)	729 (62%)	.643
Chronic lower respiratory Dx	508 (43%)	464 (39%)	.066
Lymphoid malignancies	441 (37%)	443 (37%)	.932
• Myeloid leukemia	245 (21%)	228 (19%)	.382
• Lymphoid Leukemia	117 (10%)	127 (11%)	.499
Diabetes mellitus	348 (29%)	356 (30%)	.719
Transplanted organ and tissue	332 (28%)	332 (28%)	1
• Kidney transplant	60 (5%)	84 (7%)	.039
• Heart transplant	32 (3%)	46 (4%)	.107
• Lung transplant	89 (8%)	68 (6%)	.083
• Liver transplant	36 (3%)	47 (4%)	.248
• Heart-Lung transplant	10 (< 1%)	10 (< 1%)	1
Neutropenia	533 (45%)	438 (37%)	< .0001
Chronic kidney disease	301 (25%)	305 (26%)	.851
Crohn's disease and UC	281 (24%)	199 (17%)	< .0001
Pulmonary fibrosis	151 (13%)	93 (8%)	< .0001
Bone marrow transplant	98 (8%)	95 (8%)	.822
Systemic connective tissue Dx	104 (9%)	67 (6%)	.003
Influenza	83 (7%)	47 (4%)	.003
COVID-19	59 (5%)	71 (6%)	.269
Sarcoidosis	20 (2%)	23 (2%)	.644
HIV	25 (2%)	31 (3%)	.417
Complications			
Severe Sepsis	467 (39%)	121 (10%)	< .0001
Pleural effusion	292 (25%)	197 (17%)	< .0001
Candidiasis	233 (20%)	147 (12%)	< .0001
Pneumothorax	183 (15%)	93 (8%)	< .0001
CMV disease	124 (10%)	80 (7%)	.001
Laboratory parameter			
Creatinine (mg/dl)	1 ± 1	1 ± 1	.507
Aspartate aminotransferase (AST) (IU/ml)	114 ± 531	36 ± 132	< .0001
Leukocytes (10^3/μl)	20 ± 162	36 ± 329	.177
Lymphocytes (10^3/μl)	1.6 ± 2.2	2.2 ± 2.1	< .0001
Neutrophils (10^3/μl)	4.9 ± 2.8	2.9 ± 1.7	.065
Hemoglobin (mg/dl)	9 ± 2	10 ± 2	< .0001
Hemoglobin A1c (%)	7 ± 2	6 ± 2	.035
CD4 count (cells/μl)	167 ± 216	330 ± 363	.002
1,3 beta-D-glucan (pcg/ml)	73 ± 120	62 ± 103	.617
Galactomannan	1.3 ± 2.5	.8 ± 1.2	.148
Medications			
Antineoplastics	395 (33%)	368 (31%)	.235
Glucocorticoids	917 (77%)	832 (70%)	< .0001
Prednisone	555 (47%)	506 (43%)	.043
Dexamethasone	475 (40%)	390 (33%)	< .0001
Methylprednisolone	481 (41%)	377 (32%)	< .0001
Immunosuppressants[**]	307 (26%)	337 (28%)	.166
Tacrolimus	229 (19%)	264 (22%)	.077
Mycophenolate	138 (12%)	183 (15%)	.007

Table 1. Continued

Variable Mean ± SD, *N* (%)	Non-survivors $N = 1185^{\pi}$	Survivors $N = 1185^{\pi}$	*P*-value
Cyclosporine	73 (6%)	50 (4%)	.033
Rituximab	63 (5%)	45 (4%)	.076
Sirolimus	42 (4%)	33 (3%)	.291
Infliximab	10 (1%)	10 (1%)	1
Etanercept	10 (1%)	0 (0%)	.002

*includes all patients before propensity score matching.
**Includes Tacrolimus, Mycophenolate mofetil, Mycophenolic acid, Cyclosporine, Azathioprine, Sirolimus, Infliximab, Basiliximab, Belatacept, Omalizumab, Siltuximab, Belumosudil, and Ustekinumab. Π: After propensity matching. BM, bone marrow failure; Dx, diseases; CS, corticosteroids; MSK, musculoskeletal; and UC, ulcerative colitis.

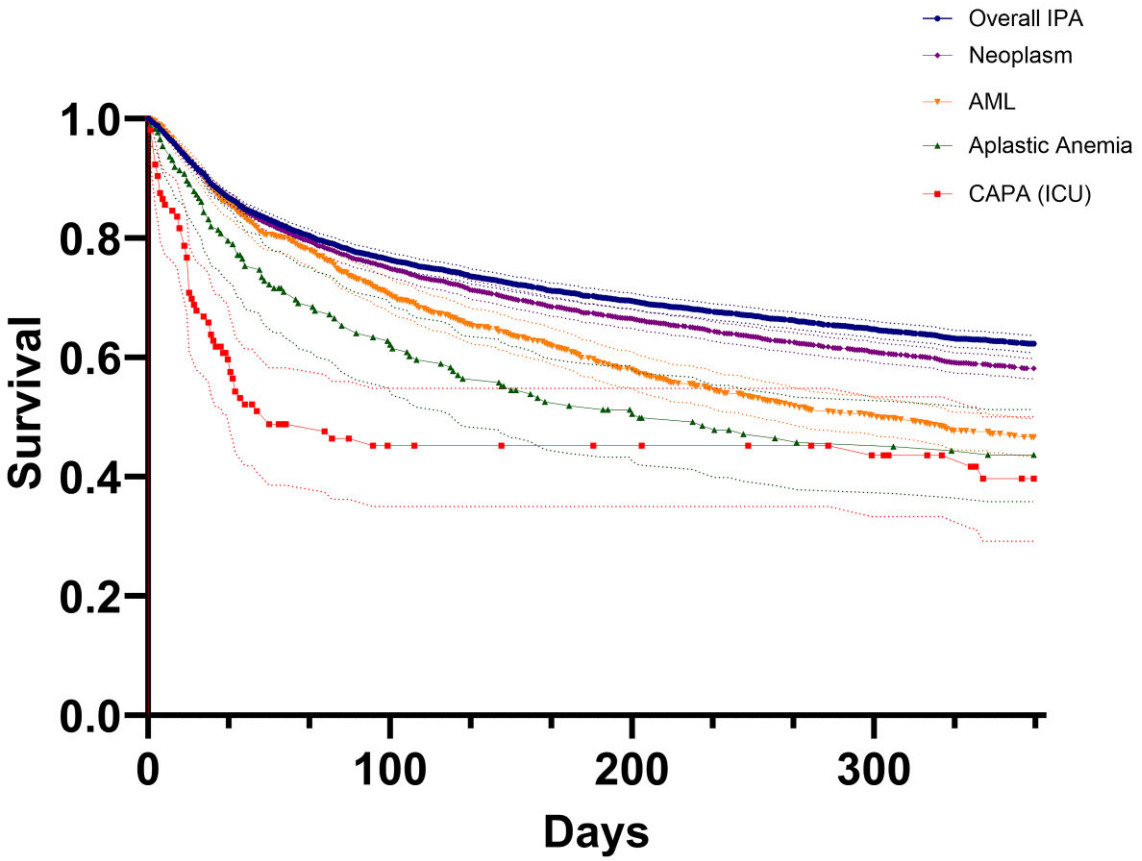

Figure 1. Kaplan–Mieir survival analysis for IPA by underlying conditions. IPA, invasive pulmonary aspergillosis; AML, acute myeloid leukemia; CAPA, COVID-19 associated pulmonary aspergillosis.

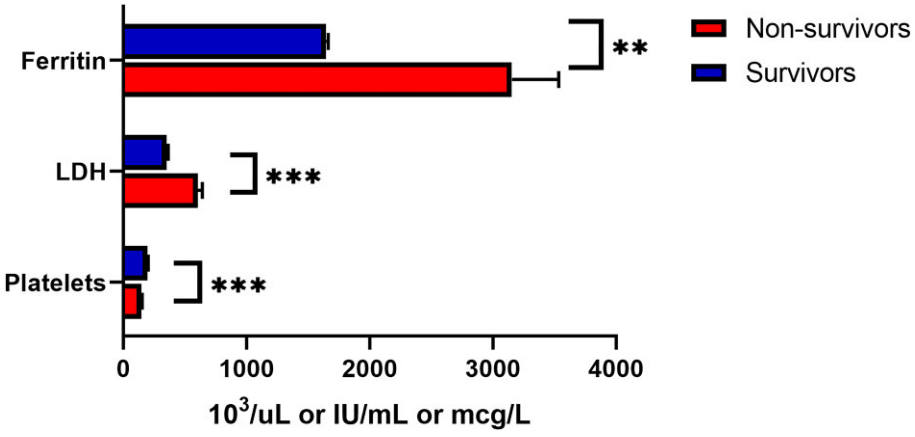

Figure 2. Selected additional laboratory findings of invasive pulmonary aspergillosis after propensity score matching comparing survivors versus non-survivors. The upper bars represent the standard deviation. NS: non-significant *P*-value, * *P*-value < .05, ** *P*-value < .01, and *** *P*-value < .001.

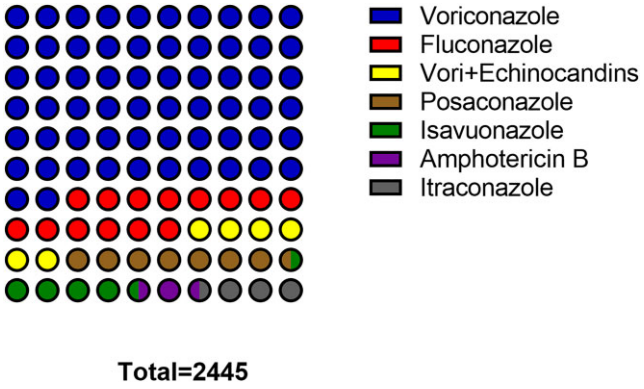

Figure 3. Distribution of initial antifungal choice to treat invasive aspergillosis.

predominant risk factors among patients with IPA. Chronic diseases affecting the lungs were also common. Previously, the most frequently reported risk factors have been prolonged neutropenia, glucocorticoid therapy, hematologic malignancies, and solid organ and hematopoietic stem cell transplantation, mirroring risk factors identified in the present study.[10] Additional risk factors such as critically ill patients, patients with chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS), severe COVID-19 treated with immunomodulatory therapies, and patients on TNF-α inhibitors are relevant as well.[10] Based on our findings, assessing patients with aplastic anemia for the risk of IPA is critical.

The pulmonary and systemic symptoms described in our study reinforce those previously reported.[11] Dyspnea, fever, malaise and fatigue, chest pain, pleural effusions, cachexia, and hemoptysis could be surrogates of an increased fungal burden, advanced lung invasion, or worse underlying immune function, each associated with increased mortality. Severe sepsis and candidiasis were common complications during IPA, which can contribute to increased mortality due to their frequency among critically ill patients requiring ICU care. [12,13] Liver injury, systemic glucocorticoid exposure over the previous 6 months, lower lymphocyte count including CD4, and worse anemia or hemoglobin A1c were independent predictors of mortality at 1 year. IPA increases mortality in patients with liver disease.[14] We have previously reported anemia, uncontrolled diabetes, and glucocorticoid use with worsening outcomes for other invasive fungal infections. [8,15,16] Additionally, organ injury, more severe baseline hematologic disease, worse cell-mediated immunosuppression, and possible increased fungal burden with prior glucocorticoid use may explain these findings mechanistically.

Voriconazole remained the most frequent therapeutic choice for patients with IPA. It is reassuring that voriconazole is the most common antifungal used, as the Infectious Diseases Society of America (IDSA) guidelines recommend.[1] However, recent clinical trials have found posaconazole and isavuconazole non-inferior compared to voriconazole. [17,18] Combination therapy of echinocandins and other antifungals with voriconazole was relatively common (close to 20%), which can be a surrogate for worse disease since adding more active agents is not uncommon for sicker patients in clinical practice. Our data lacked additional details needed to conduct an efficacy analysis for the different treatment pathways.

We also found a 19% risk of hospitalization and 32% mortality within 1 year after diagnosis. A previous report found a 1-year mortality of nearly 50% among 301 patients with *Aspergillus* species.[19] The reported 1-year mortality among hematopoietic stem cell transplant recipients (HSCT) in a prospective cohort was 25%.[20] As described, the 1-year mortality can vary significantly per the underlying primary risk factor, highest for hematologic malignancies and solid organ cancers and lowest for patients with chronic lower respiratory diseases. Interestingly, we found identical COVID-19-related mortality among critically ill patients of 54% to the one in a meta-analysis.[21] The overall lower mortality could be a decreased uptake of hospitalization if they were done outside the TriNetX network or mislabeled ICD coding from other forms of aspergillosis.

We found an annual incidence of IPA of 0.001%, increasing to 0.02% among critically ill patients in the ICU. A smaller study found a slightly higher mean incidence of 2.4 cases/100 000 (0.002%) patients for invasive aspergillosis.[19] A previous population-based laboratory active surveillance study from the 1990s in San Francisco found an identical incidence of 0.001% of *Aspergillus*.[22] In contrast, an HSCT study reported a cumulative incidence of invasive aspergillosis of 1.6%.[20]

Our study has several limitations. The retrospective nature of the follow-up cohort can introduce selection bias. Diagnosis of IPA was made through ICD code, which can be subject to code errors and capture patients not meeting diagnostic criteria. We did not have access to microbiologic or histology data to confirm cases clinically, identify the *Aspergillus* species, or determine antifungal susceptibility. Also, missing data may impair the strength of the association. The platform also limited us from running a subgroup analysis by participating centers. Non-survivors may have additional comorbidities which were not documented that could confound the mortality findings.

Table 2. Treatment pathways.

Treatment N (%); Mean ± SD	*N* = 2245*	Duration (days)	Switches	Deaths	Death in days
Voriconazole	1514 (67%)	55 ± 35	355 (23%)	204 (14%)	26 ± 23
Fluconazole	342 (15%)	9 ± 17	71 (31%)	38 (17%)	28 ± 26
Voriconazole dual**	244 (11%)	–	–	–	–
Posaconazole	190 (9%)	49 ± 36	72 (38%)	20 (11%)	30 ± 31
Vori + Echinocandin	144 (6%)	21 ± 26	115 (80%)	8 (6%)	16 ± 17
Isavuconazole	125 (6%)	7 ± 14	42 (34%)	16 (13%)	33 ± 27
Itraconazole	88 (4%)	61 ± 34	25 (28%)	5 (6%)	25 ± 24
Amphotericin B	42 (2%)	24 ± 27	35 (83%)	1 (2%)	7 ± 0

*Patients in the cohort with a documented pathway.
**Voriconazole plus amphotericin B.

However, this is one of the most extensive IPA studies ever analyzed, with nearly 5000 subjects. We performed a specific adjustment of comorbidities and other mortality risk factors and ran a robust validation analysis.

Conclusions

Overall 1-year mortality was 32% for patients with IPA. Hematologic and solid malignancies and aplastic anemia were common among patients who did not survive. Symptoms related to more significant lung compromise, increased systemic infection, or underlying disease involvement were linked to increased mortality. Severe sepsis and candidiasis can also contribuite to mortality. The annual incidence of IPA was 0.001%, rising to 0.02% among critically ill patients in the ICU.

Supplementary material

Supplementary material is available at *Medical Mycology* online.

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None

Author contributions

Andrés F. Henao-Martínez (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing), Michaele F. Corbisiero (Project administration, Writing – review & editing), Ixchel Salter (Project administration, Writing – review & editing), Daniel B. Chastain (Data curation, Investigation, Project administration, Writing – review & editing), and George R. Thompson (Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing).

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Conflicts of interest

None

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