ORIGINAL ARTICLE

Opportunistic invasive fungal disease in patients with type 2 diabetes mellitus from Southern China: Clinical features and associated factors

Minxi Lao[1], Chen Li[1], Jin Li[1,2], Dubo Chen[3], Meilin Ding[1], Yingying Gong[1,2,*] iD

[1]Department of Geriatrics, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [2]Department of Endocrinology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, and [3]Department of Laboratory Medicine, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

ABSTRACT

Aims/Introduction: A retrospective study was carried out to investigate the clinical characteristics and associated factors for invasive fungal disease in patients with type 2 diabetes mellitus.

Materials and Methods: Demographic and clinical data were recorded. Associated factors were analyzed by logistic regression analysis.

Results: Invasive fungal disease was diagnosed in 120 patients with type 2 diabetes mellitus (prevalence, 0.4%). Yeast infection (56/120, 46.7%), including candidiasis (31/56, 55.4%) and cryptococcosis (25/56, 44.6%), was the most common. The urinary tract was mainly involved in candidiasis (12/31, 38.7%). More than half of the cryptococcosis (16/25, 64.0%) presented as pneumonia. Mold infection accounted for 40.8% of the cases, and predominantly involved the lung (34/49, 69.4%). A total of 15 (12.5%) patients had mixed fungal infection. *Candida albicans* (24/111, 21.6%), *Cryptococcus neoformans* (19/111, 17.1%) and *Aspergillus fumigatus* (14/111, 12.6%) were the leading agents. Co-infection occurred in 58 (48.3%) patients, mainly presenting as pneumonia caused by Gram-negative bacteria. The inpatient mortality rate of invasive fungal disease was 23.3% (28/120). Glycated hemoglobin levels were higher in non-survivors than survivors (8.8 ± 2.5 vs 7.7 ± 2.1%, $P = 0.02$). Anemia (adjusted odds ratio, 3.50, 95% confidence interval 1.95–6.27, $P < 0.001$), hypoalbuminemia (adjusted odds ratio, 5.42, 95% confidence interval 3.14–9.36, $P < 0.001$) and elevated serum creatinine (adjusted odds ratio, 2.08, 95% confidence interval 1.07–4.04, $P = 0.03$) were associated with invasive fungal disease in type 2 diabetes mellitus patients.

Conclusions: Invasive fungal disease is a life-threatening complication in type 2 diabetes mellitus patients. *C. a albicans*, *C. neoformans*, and *A. fumigatus* are the leading agents. Prolonged hyperglycemia results in unfavorable outcomes. Correction of anemia and hypoalbuminemia might improve prognosis.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by high blood glucose levels over a prolonged period. Patients with diabetes are susceptible to infection and usually require more hospitalization, compared with the general population[1,2]. With the productive management of diabetic complications, the proportional mortality due to vasculopathy has declined, offset by non-vascular causes, including infection, during the past three decades[3]. In developing countries, infection is one of the three leading causes of deaths in patients with diabetes, and increases the excess risk to fourfold[4].

Invasive fungal disease (IFD) is a life-threatening infection with high mortality. The attributable mortality of invasive candidiasis is considered to range from 10 to 15%, and that of

invasive aspergillosis is 42–64%[5] in critically ill patients. IFD in diabetes patients presents different characteristics. Diabetes patients are vulnerable to fungal infection. The risk of mycoses increases 1.38-fold in patients with diabetes[6], and diabetes is widely recognized as a risk factor for invasive pulmonary aspergillosis[5]. Uncontrolled hyperglycemia contributes to a poor prognosis of type 2 diabetes patients with cryptococcosis[7]. Diabetes is a potential risk factor for IFD caused by unusual fungi, such as *Histoplasma capsulatum*[8]. Fungi in patients with diabetes present increasing drug resistance. Biofilm is a major physical barrier to reducing the absorption of antifungals, leading to antifungal tolerance[9–11]. *Candida* spp. isolated from the oral cavity from type 2 diabetes patients are more likely to form biofilm than those in non-diabetic individuals[12,13].

China has the largest burden of diabetes[14]. China is also an epidemic region for IFD[15]. To determine the epidemiology and clinical features of IFD in Chinese diabetes patients, early recognition and treatment is required. Herein, we carried out a retrospective study, aiming to investigate the clinical characteristics and associated factors of IFD in adult patients with type 2 diabetes from Southern China.

METHODS

Study design

A retrospective study was carried out with inpatients aged ≥14 years from the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, from 1 January 2013 to 31 December 2018. The International Classification of Diseases 10th revision coding of discharged diagnoses was used to identify patients with type 2 diabetes and IFD (Appendix 1). One episode of IFD from each patient was collected. A total of 30,984 patients with type 2 diabetes were screened, and 122 of them had IFD. The 122 records were re-evaluated by two physicians (Minxi Lao and Yingying Gong) using the diagnostic criteria shown in Appendix 2. One patient was excluded, because IFD was diagnosed before type 2 diabetes diagnosis. One patient was excluded for incomplete data. Finally, 120 patients with type 2 diabetes and IFD were included. The enrolling patients were subcategorized by comorbidities. The average age and duration of type 2 diabetes were calculated within groups. Patients with type 2 diabetes, but no infection during the same period of hospitalization, were chosen and classified by comorbidities. In each subgroup, controls with age between the age of cases ± 5 years and disease duration between duration of cases ± 1 year were selected. Then, we re-selected the control patients randomly from age and disease duration-matching subgroups with different comorbidities. The total number of controls were set as twice the number of the cases (Figure 1). The ethics committee of the First Affiliated Hospital of Sun Yat-sen University approved the research (approval number: 2019422), waiving written informed consent for deidentified patient data. This work was carried out according to the provisions of the Declaration of Helsinki[16].

Definition of cases

Diabetes mellitus was defined according to Chinese guidelines for type 2 diabetes[17]. Diabetic nephropathy was diagnosed based on the measurement of abnormal levels of urinary albumin (≥30 mg/24 h) in a diabetes patient coupled with exclusion of other causes of albuminuria[18].

The diagnostic criteria for IFD are shown in Appendix 2. IFD was designated as proven, probable or possible according to the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) Guidelines[19,20], and Chinese expert consensus on diagnosis and treatment of candidiasis[21]. Nosocomial infection was defined as infection acquired in a hospital or infection that originates in a hospital, but shows symptoms after discharge. Accordingly, infection initiating 48 h after admission was considered nosocomial infection. Disseminated IFD was defined in the case of fungemia or IFD that involved two or more non-consecutive organs. Fungal infection only involving skin, genitalia and the oral cavity was considered as a superficial fungal infection, and was excluded. No patient with type 2 diabetes and histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis or infection due to *Talaromyces marneffei* was found in our database.

Co-infection with bacteria was considered as proven or probable according to etiology evidence. Proven infection was confirmed if pathogens were identified by microscopy or culture. Probable infection was diagnosed on the basis of clinical symptoms, radiographic imaging, indirect laboratory data and treatment response to antibiotics. Superficial fungi infection was defined as fungi infection that occurred in the oral cavity, skin/mucosa or genitalia with culture evidence. Acute viral infection was diagnosed on the basis of clinical and radiographic manifestations, positivity for antiviral immunoglobulin (Ig) M antibodies and subsequent specific IgG antibodies, and replication of the virus was confirmed by molecular methods, such as polymerase chain reaction.

Demographical and clinical data

Demographic and clinical data were collected from the medical records. Clinical characteristics included diabetic complications, potential risk factors, and invasive procedures within the 3 months before IFD. Accumulated dose of glucocorticoid (GC) during the 3 months before IFD was summed and converted to equivalent prednisolone using the following equation: 1 mg of prednisone = 0.8 mg of methylprednisolone = 0.15 mg of dexamethasone. Clinical characteristics of IFD included symptoms and signs, sites of infection, and antifungi treatment. Laboratory data included routine blood tests, blood glucose level and glycated hemoglobin (HbA1c). Hypoalbuminemia was defined as serum albumin level <3.5 g/dL. β-D-glucan detection and galactomannan antigen test were carried out according to the manufacturer's type 2 diabetes instructions. Cryptococcal capsule polyglycan antigens were detected by latex agglutination test. Microbial culture and biopsy findings were recorded if available.
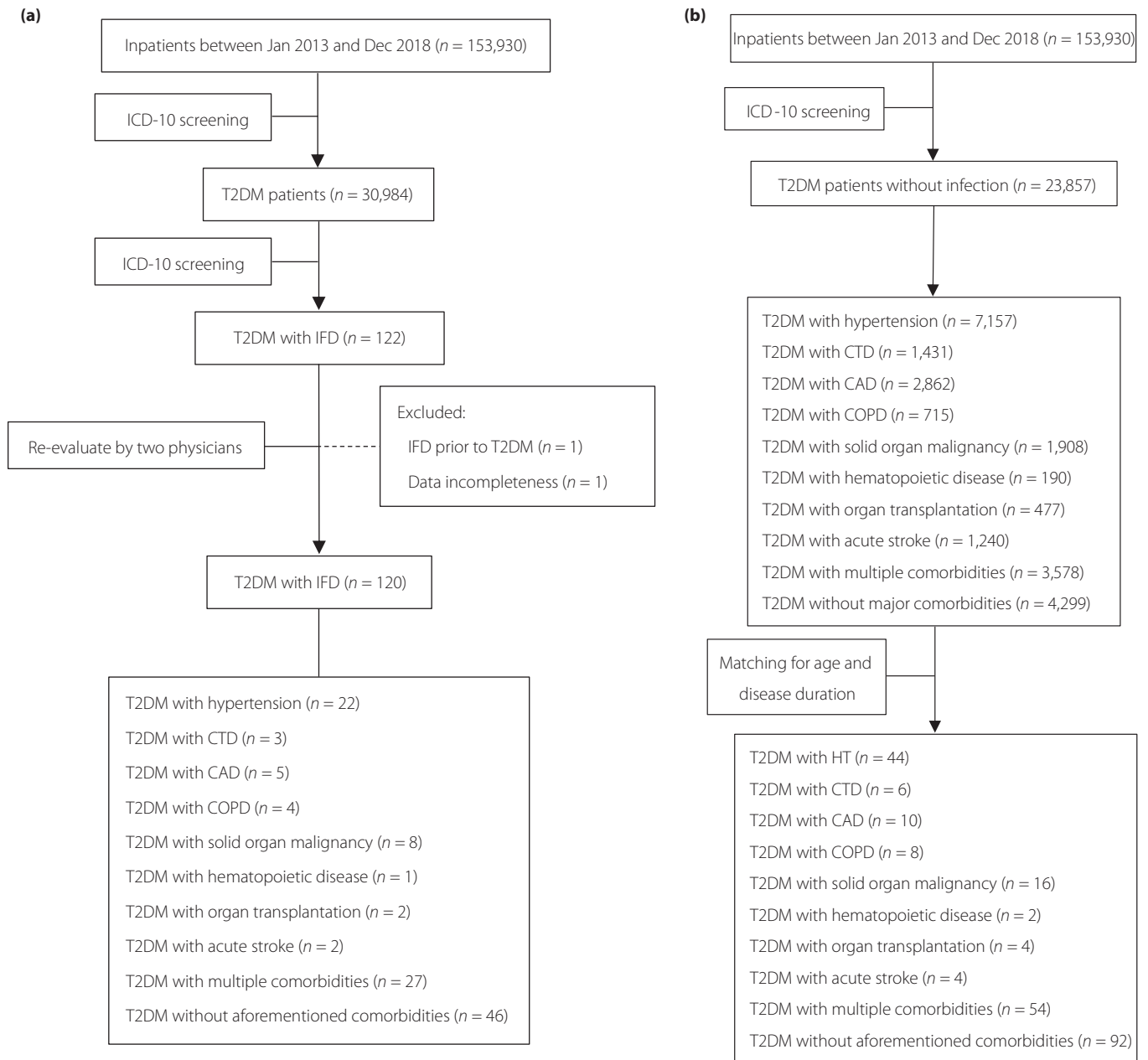
(a)

Inpatients between Jan 2013 and Dec 2018 ($n = 153,930$)

ICD-10 screening

T2DM patients ($n = 30,984$)

ICD-10 screening

T2DM with IFD ($n = 122$)

Re-evaluate by two physicians

Excluded:
IFD prior to T2DM ($n = 1$)
Data incompleteness ($n = 1$)

T2DM with IFD ($n = 120$)

T2DM with hypertension ($n = 22$)

T2DM with CTD ($n = 3$)

T2DM with CAD ($n = 5$)

T2DM with COPD ($n = 4$)

T2DM with solid organ malignancy ($n = 8$)

T2DM with hematopoietic disease ($n = 1$)

T2DM with organ transplantation ($n = 2$)

T2DM with acute stroke ($n = 2$)

T2DM with multiple comorbidities ($n = 27$)

T2DM without aforementioned comorbidities ($n = 46$)

(b)

Inpatients between Jan 2013 and Dec 2018 ($n = 153,930$)

ICD-10 screening

T2DM patients without infection ($n = 23,857$)

T2DM with hypertension ($n = 7,157$)

T2DM with CTD ($n = 1,431$)

T2DM with CAD ($n = 2,862$)

T2DM with COPD ($n = 715$)

T2DM with solid organ malignancy ($n = 1,908$)

T2DM with hematopoietic disease ($n = 190$)

T2DM with organ transplantation ($n = 477$)

T2DM with acute stroke ($n = 1,240$)

T2DM with multiple comorbidities ($n = 3,578$)

T2DM without major comorbidities ($n = 4,299$)

Matching for age and disease duration

T2DM with HT ($n = 44$)

T2DM with CTD ($n = 6$)

T2DM with CAD ($n = 10$)

T2DM with COPD ($n = 8$)

T2DM with solid organ malignancy ($n = 16$)

T2DM with hematopoietic disease ($n = 2$)

T2DM with organ transplantation ($n = 4$)

T2DM with acute stroke ($n = 4$)

T2DM with multiple comorbidities ($n = 54$)

T2DM without aforementioned comorbidities ($n = 92$)

Figure 1 | Screening algorithm. (a) The screening algorithm for patients with type 2 diabetes (T2DM) and invasive fungal disease (IFD). (b) The screening algorithm for control cases. CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; HT, hypertension; ICD, International Classification of Diseases.

Statistical analysis

Quantitative variables are expressed as the mean ± standard deviation or median (interquartile range), and qualitative variables as absolute numbers and percentages. Proportions were compared using Fisher's exact test or Pearson's χ^2-test. According to the study design, controls were not strictly matched to cases by 2:1. Therefore, between-group comparison was evaluated using Student's t-test for continuous variables with normal distribution or Mann–Whitney U-test for continuous variables with non-normal distribution. The odds ratio (OR) and corresponding 95% confidence interval (CI) of clinically significant variables with a $P < 0.1$ in between-group comparison was adjusted by multivariate logistic regression analysis to identify the associated factors of infection. The forward procedure was applied in the multivariate logistic regression analysis. The two-sided level of significance was set at $P < 0.05$. All statistical

analysis was carried out with the SPSS 19 statistical package (IBM Corporation, Armonk, NY, USA).

RESULTS

Demographics

A total of 120 patients (73 men, 47 women) with type 2 diabetes were included. The mean (standard deviation) age was 60.5 ± 11.7 years (range 15–88 years). The median (interquartile range) duration of type 2 diabetes at IFD onset was 54 months (5.5–120 months). Diabetic nephropathy was diagnosed in 36 (30.0%) patients. No patient was infected with human immunodeficiency virus. The prevalence of IFD in type 2 diabetes inpatients was 0.4% (120/30,984). By contrast, the prevalence of IFD in non-diabetes inpatients from the same institution was 0.2% (249/119,255). Proven cases accounted for 51.7% (62/120), probable cases for 30.8% (37/120) and possible cases for 17.5% (21/120). Nosocomial infection accounted for 33.3% (40/120). A total fo 81 (67.5%) patients were receiving treatment for type 2 diabetes before IFD onset. Insulin alone was prescribed to 34 (42.0%) patients, oral antidiabetic drugs to 40 (49.4%), and combined therapy of insulin and oral antidiabetic drugs to seven (8.6%) patients. The average (stabndard deviation) HbA1c level was 8.0 ± 2.2%.

Characteristics of yeast infection

A total of 56 (46.7%) patients had yeast infection, among which 31 (55.4%) developed candidiasis and 25 (44.6%) developed cryptococcosis. The characteristics of candidiasis are shown in Table 1. The urinary tract was the most commonly involved (12/31, 38.7%), followed by the abdominal cavity (10/31, 32.3%; Figure 2a). All the patients developing intraabdominal candidiasis (IAC) received gastrointestinal operation before IFD. The positive rate of β-D-glucan detection in candidal infection was 47.4% (9/19).

Cryptococcosis was diagnosed in 25 patients (Table 1). Four (16.0%) patients were complicated with connective tissue disease (CTD), and one fifth (5/25) were taking GC before IFD. More than half of cryptococcosis (16/25, 64.0%) developed in the lung, and 16% (4/25) occurred in meninges (Figure 2b). Serum cryptococcal capsule polyglycan antigen was positive in 16 out of 20 patients (80.0%).

Characteristics of mold infection

A total of 49 (40.8%) patients with type 2 diabetes developed mold infection (Table 1). The lung (34/49, 69.4%) was the most frequently involved, followed by sinus (13/49, 26.5%; Figure 2c). Positivity of serum galactomannan antigen test and bronchoalveolar lavage fluid galactomannan antigen test was 41.2% (14/34) and 73.3% (11/15), respectively.

Characteristics of mixed fungal infection

Mixed fungal infection developed in 15 (12.5%) patients with type 2 diabetes (Table 1). The proportions of patients having CTD (3/15, 20%) or organ transplantation (2/15, 13.3%) were

the highest in this group. Similarly, the largest number of patients who received GC (4/15, 26.7%) or immunosuppressants (5/15, 33.3%) was observed. The lung (8/15, 53.3%) was the most frequently involved, followed by the abdominal cavity (2/15, 13.3%; Figure 2d).

Characteristics of IFD in type 2 diabetes patients under specific conditions

The characteristics of community-acquired and nosocomial IFD are shown in Table 2. Patients with nosocomial IFD were older (aged 63.8 ± 12.9 vs 58.9 ± 10.7 years, P = 0.03), having longer disease duration (82 vs 36 months, P = 0.003) and higher proportion of diabetic nephropathy (47.5% vs 21.3%, P = 0.003). Candidiasis is the major infectious pattern in nosocomial IFD (55.0% vs 11.3%, P < 0.001).

Seven type 2 diabetes patients received chemotherapy before IFD onset. Three (42.9%) of them developed mold infection, two (28.6%) developed candidiasis and two (28.6%) developed mixed fungal infection. Two type 2 diabetes patients were complicated with hematopoietic disease, including one with acute lymphocytic leukemia and one with myelodysplastic syndrome. These two patients developed pulmonary aspergillosis and sinus mucormycosis, respectively. A total of 20 cases of IFD occurred postoperation. There was a trend toward candidiasis (11/20, 55.0%), followed by mixed fungal infection (6/20, 30.0%). The abdominal cavity was the predominant infective site (8/20, 40.0%). A total of 30 type 2 diabetes patients received central venous catheterization, and three (10.0%) of them developed fungemia. A total of 22 type 2 diabetes patients received indwelling urinary catheterization, and four (18.2%) of them developed a fungal urinary tract infection. IFD secondary to bacterial infection occurred in 31 (25.8%) patients. Aspergillosis (12/31, 38.7%) and candidiasis (11/31, 35.5%) were comparable. The lung (12/12, 100%) and urinary tract (6/11, 54.5%) were commonly affected.

Distribution of causative fungi

Causative fungi were isolated from sputum (n = 20), ascitic fluid (n = 16), urine (n = 16), bronchoalveolar lavage fluid (n = 10), blood (n = 6), cerebrospinal fluid (n = 5), esophageal brushing sample (n = 3), bile (n = 1), drain from a brain hematoma (n = 1) and drain from the renal pelvis (n = 1). Fungi were found in biopsied tissue or operative specimens from 34 patients. A total of 111 strains of fungi, including 64 (57.7%) strains of yeasts and 47 (42.3%) strains of mold, were identified (Table 3). *Candida albicans* (24/111, 21.6%) was the most common agent in yeast infection, followed by *Cryptococcus neoformans* (19/111, 17.1%). *Aspergillus fumigatus* was the major causative mold, accounting for 12.6% (14/111) of the cases. Data of antifungal susceptibility tests were available in 17 strains of *C. albicans*, eight strains of *C. glabrata*, seven strains of *C. tropicalis* and four strains of *C. parapsilosis*. The resistance rates of *C. albicans* against itraconazole, flucytosine and fluconazole were 11.8% (2/17), 5.9% (1/17) and 5.9% (1/17),

Table 1 | Characteristics of type 2 diabetes patients with invasive fungal disease

	Yeast infection (n = 56)		Mold infection (n = 49)	Mixed fungal infection (n = 15)
	Candidiasis (n = 31)	Cryptococcosis (n = 25)		
Demographic characteristics				
Sex (male:female)	20:11	14:11	30:19	9:6
Age, years (mean ± SD)	60.5 ± 15.3	61.0 ± 7.5	61.6 ± 10.5	56.2 ± 12.7
BMI, kg/m^2 (mean ± SD)	22.4 ± 3.2	22.3 ± 2.9	20.6 ± 3.1	22.8 ± 3.6
Smoker, n (%)	13 (41.9)	3 (12.0)	20 (40.8)	4 (26.7)
Comorbidities				
Hypertension, n (%)	13 (41.9)	13 (52.0)	15 (30.6)	5 (33.3)
CTD, n (%)	1 (3.2)	4 (16.0)	4 (8.2)	3 (20.0)
CAD, n (%)	5 (16.1)	4 (16.0)	4 (8.2)	2 (13.3)
COPD, n (%)	1 (3.2)	0 (0)	5 (10.2)	0 (0)
Solid organ malignancy, n (%)	6 (19.4)	2 (8.0)	3 (6.1)	2 (13.3)
Hematopoietic disease, n (%)	0 (0)	0 (0)	2 (4.1)	0 (0)
Organ transplantation, n (%)	2 (6.5)	0 (0)	2 (4.1)	2 (13.3)
Acute stroke, n (%)	0 (0)	1 (4.0)	2 (4.1)	0 (0)
Characteristics of T2DM				
Median duration of T2DM, months (IQR)	84 (24-120)	48 (3-120)	48 (6-120)	24 (2.5-84)
Diabetic ketoacidosis, n (%)	0 (0)	0 (0)	1 (2.0)	2 (13.3)
Diabetic nephropathy, n (%)	16 (51.6)	4 (16.0)	10 (20.4)	6 (40.0)
HbA1c, % (mean ± SD)	7.4 ± 2.0	7.7 ± 1.9	8.5 ± 2.3	7.7 ± 2.7
Risk factors				
ICU admission, n (%)	4 (12.9)	2 (8.0)	7 (14.3)	7 (46.7)
Use of broad-spectrum antibiotics, n (%)	21 (67.7)	3 (12.0)	18 (36.7)	11 (73.3)
Use of GC, n (%)	1 (3.2)	5 (20.0)	3 (6.1)	4 (26.7)
Immunosuppressants/chemotherapy, n (%)	3 (9.7)	2 (8.0)	4 (8.2)	5 (33.3)
Operation, n (%)	11 (35.5)	0 (0)	3 (6.1)	6 (40.0)
Dialysis-dependent, n (%)	3 (9.7)	0 (0)	4 (8.2)	0 (0)
Indwelling urinary catheter, n (%)	6 (19.4)	0 (0)	9 (18.4)	7 (46.7)
Central venous catheter, n (%)	11 (35.5)	2 (8.0)	8 (16.3)	9 (60.0)
Total parenteral nutrition, n (%)	5 (16.1)	0 (0)	0 (0)	2 (13.3)
Inpatient mortality, n (%)	7 (22.6)	3 (12.0)	10 (20.4)	8 (53.3)

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; GC, glucocorticoid; ICU, intensive care unit; IFD, invasive fungal disease; IQR, interquartile range; SD, standard deviation; T2DM, type 2 diabetes mellitus.

respectively. Three (37.5%) strains of *C. glabrata* were resistant to itraconazole. The resistance rates of *C. tropicalis* against fluconazole, voriconazole and itraconazole were 28.6% (2/7), 14.3% (1/7) and 14.3% (1/7), respectively. Of note, one strain of *C. tropicalis* was resistant against fluconazole, voriconazole and itraconazole simultaneously.

Co-infection in diabetes patients with IFD

Co-infection with other agents was diagnosed in 58 (48.3%) patients. The lung was frequently involved (30/58, 51.7%). Most of the patients (54/58, 93.1%) were co-infected with bacteria. Among 92 strains of bacteria isolated from 43 patients, 67 (72.8%) strains were Gram-negative bacteria, and 25 (27.2%) strains were Gram-positive bacteria. One (1/58, 1.7%) patient was co-infected with active tuberculosis. Viral infection included pneumonia caused by influenza virus (n = 1), pneumonia caused by cytomegalovirus (n = 1) and viral meningitis (n = 1).

Treatment and outcomes of IFD

Antifungal treatment was documented in 108 (90.0%) patients. A total of 90 (83.3%) patients received antifungal medications, 12 (11.1%) patients underwent operation alone, and six (5.6%) patients were treated with operation and subsequent antifungal medications. The median follow-up period was 0.9 months (interquartile range0.5–2.7 months). A majority of patients (92/108, 85.2%) showed disease improvement. The inpatient mortality rate was 23.3% (28/120). Septic shock was the primary cause (22/28, 78.6%), followed by acute stroke (2/28, 7.1%), heart failure (2/28, 7.1%), pleural hemorrhage (1/28, 3.6%) and asphyxia (1/28, 3.6%). The mortality was the highest in patients with mixed fungal infection (8/15, 53.3%), followed by mold infection (10/49, 20.4%) and yeast infection (10/56, 17.9%).

A comparison between survivors and non-survivors was carried out (Table 4). Patients with poor prognosis were more likely to have diabetic nephropathy (50.0% vs 23.9%, *P* = 0.01),
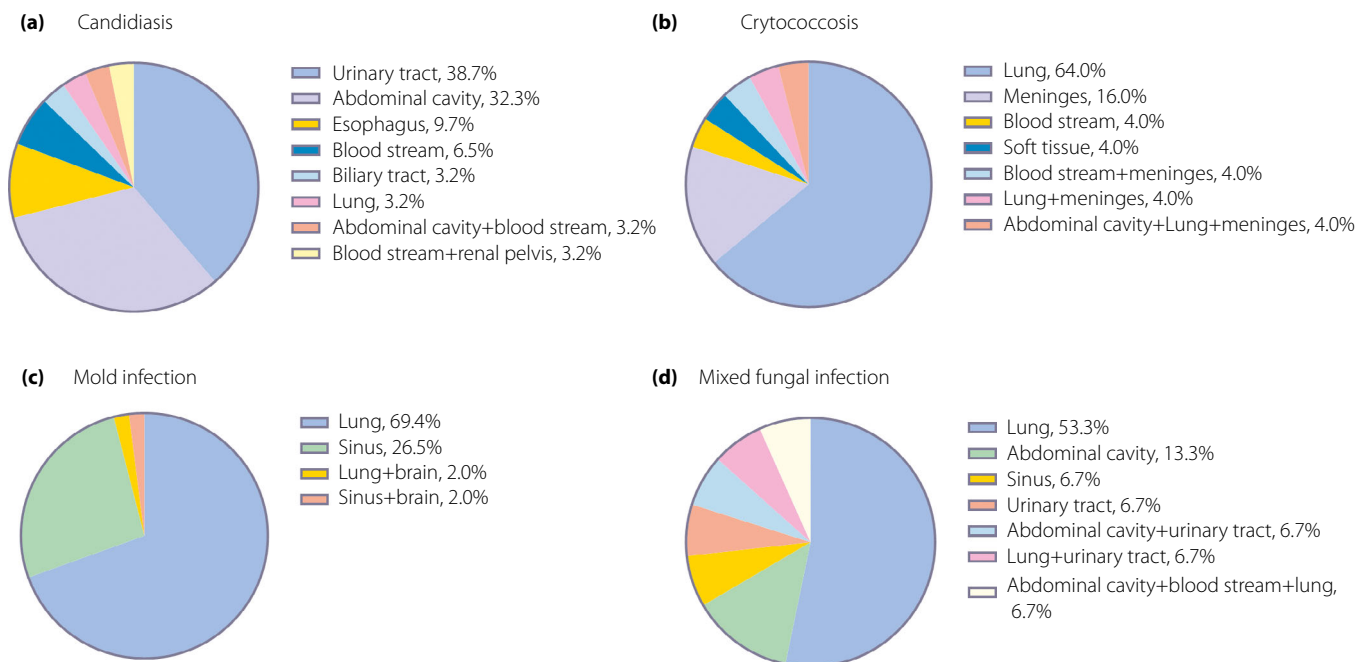
(a) Candidiasis

- Urinary tract, 38.7%
- Abdominal cavity, 32.3%
- Esophagus, 9.7%
- Blood stream, 6.5%
- Biliary tract, 3.2%
- Lung, 3.2%
- Abdominal cavity+blood stream, 3.2%
- Blood stream+renal pelvis, 3.2%

(b) Crytococcosis

- Lung, 64.0%
- Meninges, 16.0%
- Blood stream, 4.0%
- Soft tissue, 4.0%
- Blood stream+meninges, 4.0%
- Lung+meninges, 4.0%
- Abdominal cavity+Lung+meninges, 4.0%

(c) Mold infection

- Lung, 69.4%
- Sinus, 26.5%
- Lung+brain, 2.0%
- Sinus+brain, 2.0%

(d) Mixed fungal infection

- Lung, 53.3%
- Abdominal cavity, 13.3%
- Sinus, 6.7%
- Urinary tract, 6.7%
- Abdominal cavity+urinary tract, 6.7%
- Lung+urinary tract, 6.7%
- Abdominal cavity+blood stream+lung, 6.7%

Figure 2 | Anatomic sites of invasive fungal disease (IFD) in patients with type 2 diabetes. (a) Infected sites of candidiasis. (b) Infected sites of cryptococcosis. (c) Infected sites of mold infection. (d) Infected sites of mixed fungal infection.

mixed fungal infection (28.6% vs 7.6%, $P = 0.01$), disseminated IFD (25.0% vs 6.5%, $P = 0.01$) and co-infection (92.9% vs 34.8%, $P < 0.001$). Lymphopenia was more predominant in deceased patients (57.1% vs 21.7%, $P < 0.001$). HbA1c level was higher in non-survivors (8.8 ± 2.5 vs 7.7 ± 2.1%, $P = 0.02$).

Comparison between type 2 diabetes patients with and without IFD

A comparison between diabetes patients with and without IFD is shown in Table 5. Diabetic nephropathy (30.0% vs 15.8%, $P = 0.002$) was more prevalent in the IFD group. Patients with IFD were more likely to have lymphopenia (30.0% vs 8.3%, $P < 0.001$), anemia (56.7% vs 15.0%, $P < 0.001$) and hypoalbuminemia (62.5% vs 16.3%, $P < 0.001$). Serum creatinine levels elevated remarkably in diabetes patients with IFD (36.7% vs 10.8%, $P < 0.001$).

Multivariate regression analysis showed that anemia (adjusted OR 3.50, 95% CI 1.95–6.27, $P < 0.001$), hypoalbuminemia (adjusted OR 5.42, 95% CI 3.14–9.36, $P < 0.001$) and elevated serum creatinine (adjusted OR 2.08, 95% CI 1.07–4.04, $P = 0.03$) were associated factors for IFD in patients with type 2 diabetes (Table 6).

DISCUSSION

In the present study, IFD was a life-threatening complication in diabetes patients. *C. albicans*, *C. neoformans* and *A. fumigatus* were the major pathogens. Uncontrolled diabetes led to

unfavorable outcomes. Anemia, hypoalbuminemia and elevated serum creatinine were associated with IFD in type 2 diabetes patients.

Yeast infection was the major infectious pattern in the present study. Diabetes, especially uncontrolled diabetes, provides a favorable environment for gas-forming organisms, such as *Candida* spp., to grow[22]. Candiduria is the most common. A previous study showed that *Candida* spp. ranked second in the pathogens isolated in diabetes patients with urinary tract infection, after *Escherichia coli*[23]. IAC is also frequently found. All the IAC occurred after gastrointestinal operation. Aside from the invasive procedure, patients with diabetes might bear a higher burden of intestinal *C. albicans* colonization[24]. It was found that the gut colony forming units of *C. albicans* in patients with type 1 diabetes is 2.7-fold higher than their healthy counterparts[25]. Although frequently diagnosed, candidiasis was not the first ranking in the present study, which contradicts with previous report[26]. One of the explanations could be the exclusion of oral candidiasis, which is the most common[27], vulvovaginal candidiasis and cutaneous candidiasis. Additionally, the variable definition of pulmonary candidiasis might yield different results. *Candida* spp. are part of the normal respiratory microflora[28]. Until recently, the diagnostic criteria for pulmonary candidiasis were obscure. In order to capture the real case, we applied a relatively strict inclusion criteria and only one patient with pathological evidence was diagnosed as pulmonary candidiasis. Therefore, the present results highlighted candiduria and IAC as the main infectious patterns of

Table 2 | Comparison between community-acquired and nosocomial invasive fungal disease in patients with type 2 diabetes mellitus

	Community-acquired (n = 80)	Nosocomial (n = 40)	P-value
Demographic characteristics			
Sex (male : female)	49:31	24:16	0.89
Age, years (mean ± SD)	58.9 ± 10.7	63.8 ± 12.9	0.03*
BMI, kg/m^2 (mean ± SD)	21.7 ± 3.5	21.7 ± 2.7	0.94
Smoker, n (%)	23 (28.8)	17 (42.5)	0.10
Comorbidities			
Hypertension, n (%)	28 (35.0)	18 (45.0)	0.29
CTD, n (%)	12 (15.0)	0 (0)	0.01*
CAD, n (%)	6 (7.5)	9 (22.5)	0.02*
COPD, n (%)	4 (5.0)	2 (5.0)	1.00
Solid organ malignancy, n (%)	7 (8.8)	6 (15.0)	0.001*
Hematopoietic disease, n (%)	2 (2.5)	0 (0)	0.31
Organ transplantation, n (%)	2 (2.5)	4 (10.0)	0.08
Acute stroke, n (%)	2 (2.5)	1 (2.5)	1.00
Characteristics of T2DM			
Median duration of T2DM, months (IQR)	36 (2–120)	82 (36–180)	0.003*
Diabetic ketoacidosis, n (%)	2 (2.5)	1 (2.5)	1.00
Diabetic nephropathy, n (%)	17 (21.3)	19 (47.5)	0.003*
HbA1c, % (mean ± SD)	8.0 ± 2.2	7.8 ± 2.3	0.56
Risk factors			
Use of GC, n (%)	11 (13.8)	2 (5.0)	0.15
Median accumulated dose of PSL, mg (IQR)	1,417.5 (487.5–2,952.5)	457 (453.5–460.5)	0.36
Immunosuppressants/chemotherapy, n (%)	10 (12.5)	4 (10.0)	0.69
Operation, n (%)	1 (1.3)	19 (47.5)	<0.001*
Dialysis-dependent, n (%)	1 (1.3)	6 (15.0)	0.002*
Indwelling urinary catheter, n (%)	6 (7.5)	16 (40.0)	<0.001*
Central venous catheter, n (%)	10 (12.5)	20 (50.0)	<0.001*
Total parenteral nutrition, n (%)	0 (0)	7 (17.5)	0.001*
Infective sites			
Lung, n (%)	48 (60.0)	11 (27.5)	0.001*
Sinus, n (%)	13 (16.3)	1 (2.5)	0.03*
CNS, n (%)	4 (5.0)	0 (0)	0.15
Abdominal cavity, n (%)	3 (3.8)	9 (22.5)	0.001*
Esophagus, n (%)	2 (2.5)	1 (2.5)	1.00
Urinary tract, n (%)	1 (1.3)	12 (30.0)	<0.001*
Soft tissue, n (%)	1 (1.3)	0 (0)	0.21
Biliary tract, n (%)	0 (0)	1 (2.5)	0.01*
Disseminated, n (%)	8 (10.0)	5 (12.5)	0.81
Infective patterns			
Candidiasis, n (%)	9 (11.3)	22 (55.0)	<0.001*
Cryptococcosis, n (%)	25 (31.3)	0 (0)	0.02*
Mold infection, n (%)	37 (46.3)	12 (30.0)	0.13
Mixed fungal infection, n (%)	9 (11.3)	6 (15.0)	0.63
Inpatient mortality, n (%)	12 (15.0)	16 (40.0)	<0.001*

*P < 0.05. BMI, body mass index; CAD, coronary artery disease; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; GC, glucocorticoid; IFD, invasive fungal disease; IQR, interquartile range; PSL, prednisolone; SD, standard deviation; T2DM, type 2 diabetes mellitus.

invasive candidiasis in patients with type 2 diabetes. Poor blood glucose control could worsen the situation.

Antifungal drug resistance is a matter of concern[29]. In the current study, the drug with the highest resistance rate was itraconazole, and more than one-third of the *C. glabrata* was not

sensitive to it. As the most frequently used drug, fluconazole is effective to treat most of the candidiasis, except *C. tropicalis*, whose resistance rate was 28.6%, similar to other reports (0–26.8%)[30]. In line with previous findings[31,32], amphotericin B or voriconazole resistance was very low in the present study. In

Table 3 | Distribution of isolated fungi

Isolated fungi	n (%)
Total	111
Yeast	64 (57.7)
Candida albicans	24 (21.6)
Candida glabrata	9 (8.1)
Candida tropicalis	8 (7.2)
Candida parapsilosis	4 (3.6)
Candida krusei	0 (0)
Cryptococcus neoformans	19 (17.1)
Mold	47 (42.3)
Aspergillus fumigatus	14 (12.6)
Aspergillus flavus	6 (5.4)
Aspergillus niger	2 (1.8)
Aspergillus versicolor	1 (0.9)
Aspergillus unclassified	14 (12.6)
Mucor spp.	8 (7.2)
Rhizopus spp.	1 (0.9)
Fusarium spp.	1 (0.9)

the case of severe candidiasis, such as candidemia, amphotericin B or voriconazole is still recommended as the first-line therapy[21]. Of note, the liposomal formulation of amphotericin B is found to be more effective in the eradication of the biofilm cells for all the *Candida* spp. than deoxycholate formulation[33]. Echinocandin tolerance was not detected in the present study. Echinocandin resistance is considered unusual. However, that of *C. glabrata* seemed to increase from 0% to 12.3% during the past two decades[34,35]. In addition, caspofungin shows a higher biomass reduction capacity compared with micafungin, implying that caspofungin might be superior to micafungin in treating biofilm-forming fungi[36].

A high infective rate of cryptococcosis was observed in the present study. Diabetes was present in 8.5–33% of cryptococcosis cases in reported series[37–39]. Our results showed 16% of the type 2 diabetes patients with cryptococcosis had CTD. Cryptococcosis is a critical issue in patients with CTD. The incidence rate of cryptococcal meningitis in patients with systemic lupus erythematosus is 0.5%[40]. Approximately 0.2% of the patients with rheumatoid arthritis are complicated with cryptococcosis[41]. In addition, prolonged use of GC increases the risk of cryptococcosis[42]. Consistent with this, 20% of the type 2 diabetes patients with cryptococcosis received long-term GC treatment in the present study, compared with 3.2% and 6.2% of patients with candidiasis and aspergillosis. Therefore, CTD and prolonged use of GC contribute to the high infective rate of cryptococcosis in type 2 diabetes.

Pulmonary mold infection is another major infectious pattern in type 2 diabetes patients. Different from previous findings[43], mucormycosis was not common in the present study. The overall incidence of zygomycosis tends to decrease in patients with diabetes[44]. In addition, the involvement of diabetes in mucormycosis shows a large geographical variation.

In Mexico, 72% of the patients with mucormycosis had diabetes[44], but the number dropped to 17% in central Europe and Asia[45]. Furthermore, mucormycosis is likely to develop in patients with diabetic ketoacidosis, but just three patients with diabetic ketoacidosis were enrolled in our study[45]. Alternatively, *Aspergillus* spp. appeared to be the predominant pathogens. Antimicrobial susceptibility of *Aspergillus* spp. was not tested in our center. In previous research, the triazole resistance of *A. fumigatus* ranged from 0.6% to 29.6%[30], and some isolates of *A. flavus* and *A. ustus* were resistant to amphotericin B[46–48]. The present results suggest that aspergillosis is common in type 2 diabetes patients without diabetic ketoacidosis, and drug resistance of *Aspergillus* spp. requires increasing attention.

Nosocomial IFD differs from community-acquired IFD. Patients developing nosocomial IFD tended to be older and had longer disease duration. Candidiasis is common in nosocomial IFD, and this could be largely attributed to invasive procedures. Given that only a small number of patients had other underlying conditions, further analysis was not carried out. More information could be obtained in previous studies focusing on particular subpopulations[49–51].

The present study was the first to explore co-infection in diabetes patients with IFD. Nearly 48.3% of the patients had co-infection, and mainly presented as pneumonia caused by Gram-negative bacteria. Physicians should be vigilant against co-infection in diabetes patients, even though IFD is established. Timely empiric coverage for Gram-negative bacteria could improve the prognosis.

Several factors, including steroid use, neutropenia and immunosuppressants, are established risk factors for IFD. After adjusting these variables in multivariate logistic regression, we found anemia, hypoalbuminemia and elevated serum creatinine were associated with IFD in patients with type 2 diabetes. Anemia leads to poor outcomes in diabetes patients[52]. Half of the patients with IFD in the present study were aged >60 years. Age per se is a contributor to anemia, because the function of hematopoietic stem cells becomes inferior during aging[53]. Prolonged hyperglycemia, advanced glycated end-products and the complication of diabetic nephropathy result in decreased production and/or impaired function of erythropoietin. In addition, chronic inflammation induced by hyperglycemia increases the consumption of hematopoietic materials[54]. Hypoalbuminemia is associated with infection and increases mortality[55]. Diabetes decreases the synthetic rate of serum albumin, and increases the transcapillary escape of albumin from the vascular to the interstitial compartment[56,57]. Acute inflammation caused by infection suppresses the synthesis of albumin, and diabetic nephropathy increases albumin leakage through urine[58]. Therefore, early intervention of anemia and hypoalbuminemia is important to reduce the risk of IFD in patients with type 2 diabetes.

Inadequate blood glucose control is an independent risk factor for infection in diabetes patients[59,60]. HbA1c levels

Table 4 | Comparison between survivors and non-survivors with invasive fungal disease

	Survivors (*n* = 92)	Non-survivors (*n* = 28)	*P*-value
Demographic characteristics			
Sex (male : female)	54:38	19:9	0.38
Age, years (mean ± SD)	60.3 ± 11.1	61.0 ± 13.6	0.79
BMI, kg/m^2 (mean ± SD)	21.6 ± 3.2	22.1 ± 3.2	0.49
Smoker, *n* (%)	27 (29.3)	13 (46.4)	0.09
Risk factors			
ICU admission, *n* (%)	1 (1.1)	19 (67.9)	<0.001*
Use of broad-spectrum antibiotics, *n* (%)	30 (32.6)	23 (82.1)	<0.001*
Use of GC, *n* (%)	10 (10.9)	3 (10.7)	0.98
Median accumulated dose of PSL, mg (IQR)	875 (453.5–2,461.3)	1,740 (1,095–2,385)	0.56
Immunosuppressants/chemotherapy, *n* (%)	9 (9.8)	5 (17.9)	0.24
Operation, *n* (%)	8 (8.7)	12 (42.9)	<0.001*
Dialysis-dependent, *n* (%)	6 (6.5)	1 (3.6)	0.56
Indwelling urinary catheter, *n* (%)	4 (4.3)	18 (64.3)	<0.001*
Central venous catheter, *n* (%)	7 (7.6)	23 (82.1)	<0.001*
Total parenteral nutrition, *n* (%)	5 (5.4)	2 (7.1)	0.74
Characteristics of T2DM			
Median duration of T2DM, months (IQR)	48 (3.8–120)	60 (12–168)	0.13
Diabetic ketoacidosis, *n* (%)	0 (0)	3 (10.7)	0.001*
Diabetic nephropathy, *n* (%)	22 (23.9)	14 (50.0)	0.01*
Characteristics of IFD			
Agents			
Yeast, *n* (%)	46 (50.0)	10 (35.7)	0.07
Mold, *n* (%)	39 (42.4)	10 (35.7)	0.91
Mixed fungi, *n* (%)	7 (7.6)	8 (28.6)	0.01*
Disseminated IFD, *n* (%)	6 (6.5)	7 (25.0)	0.01*
Co-infection, *n* (%)	32 (34.8)	26 (92.9)	<0.001*
Laboratory data			
Leukopenia, *n* (%)	3 (3.3)	2 (7.1)	0.56
Lymphopenia, *n* (%)	20 (21.7)	16 (57.1)	<0.001*
Anemia, *n* (%)	48 (52.2)	20 (71.4)	0.07
Hypoalbuminemia, *n* (%)	54 (58.7)	21 (75.0)	0.12
Elevated serum creatinine, *n* (%)	29 (31.5)	15 (53.6)	0.03*
HbA1c, % (mean ± SD)	7.7 ± 2.1	8.8 ± 2.5	0.02*

*P < 0.05. BMI, body mass index; GC, glucocorticoid; ICU, intensive care unit; IFD, invasive fungal disease; IQR, interquartile range; PSL, prednisolone; SD, standard deviation; T2DM, type 2 diabetes mellitus.

were significantly higher in the deceased patients than survivors in the present study. However, as patients who require hospitalization usually have severe complications or suffer from uncontrolled blood glucose, the HbA1c levels did not differ between patients with and without IFD. The present results suggested that prolonged hyperglycemia leads to poor outcomes of IFD. Strict blood glucose control is still of great importance.

The present study had certain limitations. Data originated from one tertiary hospital in China. The generalization of the results to the type 2 diabetes population needs to be cautious. In addition, only type 2 diabetes patients were included. Whether the trends of IFD extend to patients with other diabetes subtypes remains to be elucidated. Additionally, although we tried to match some confounding factors, such as comorbidities between patients with and without IFD, no direct parameters, such as CD4$^+$ lymphocyte count, were available to evaluate the immune status. Given the small number of patients involved in these medical backgrounds, we suggest studies on particular subpopulations would be more informative.

The present study provides an overview of IFD in patients with type 2 diabetes. Urinary candidiasis, pulmonary aspergillosis and pulmonary cryptococcosis are the main patterns. Aside from the traditional risk factors, anemia, hypoalbuminemia and elevated serum creatinine are associated with IFD in diabetes patients.

Table 5 | Comparison between type 2 diabetes patients with and without invasive fungal disease

Characteristics	Case ($n = 120$)	Control ($n = 240$)	P-value
Demographic characteristics			
Sex (male : female)	73:47	150:90	0.76
Age, year (mean ± SD)	60.5 ± 11.7	61.1 ± 9.3	0.62
BMI, kg/m^2 (mean ± SD)	21.7 ± 3.2	23.0 ± 3.1	<0.001*
Smokers, *n* (%)	40 (33.3)	73 (30.4)	0.57
Risk factors			
Use of GC, *n* (%)	13 (10.8)	21 (8.8)	0.52
Median accumulated dose of PSL, mg (IQR)	875.0 (450.0–2,797.5)	900 (450.0–1,350.0)	0.27
Immunosuppressants/chemotherapy, *n* (%)	14 (11.7)	23 (9.6)	0.54
Dialysis-dependent, *n* (%)	7 (5.8)	5 (2.7)	0.16
Comorbidities			
Hypertension, *n* (%)	46 (38.3)	105 (43.8)	0.33
CTD, *n* (%)	12 (10.0)	24 (10.0)	1.00
CAD, *n* (%)	15 (12.5)	41 (17.1)	0.26
COPD, *n* (%)	6 (5.0)	16 (6.7)	0.53
Solid organ malignancy, *n* (%)	13 (10.8)	33 (13.8)	0.43
Hematopoietic disease, *n* (%)	2 (1.7)	4 (1.7)	1.00
Organ transplantation, *n* (%)	6 (5.0)	12 (5.0)	1.00
Stroke, *n* (%)	3 (2.5)	16 (6.7)	0.10
Characteristics of T2DM			
Median duration of T2DM, months (IQR)	54 (5.5–120)	60 (15.5–120)	0.55
Diabetic ketoacidosis, *n* (%)	3 (2.5)	2 (0.9)	0.24
Diabetic nephropathy, *n* (%)	36 (30.0)	38 (15.8)	0.002*
Laboratory data			
Leukopenia, *n* (%)	5 (4.2)	15 (6.3)	0.42
Lymphopenia, *n* (%)	36 (30.0)	20 (8.3)	<0.001*
Anemia, *n* (%)	68 (56.7)	36 (15.0)	<0.001*
Hypoalbuminemia, *n* (%)	75 (62.5)	39 (16.3)	<0.001*
Elevated serum creatinine, *n* (%)	44 (36.7)	26 (10.8)	<0.001*
HbA1c, % (mean ± SD_	8.0 ± 2.2	8.3 ± 2.8	0.27

*$P < 0.05$. BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; GC, glucocorticoid; IFD, invasive fungal disease; IQR, interquartile range; PSL, prednisolone; SD, standard deviation, T2DM, type 2 diabetes mellitus.

Table 6 | Factors associated with invasive fungal disease in type 2 diabetes patients

Characteristics	Univariate logistic regression			Multivariate logistic regression		
	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
BMI (kg/m^2)	0.87	0.80–0.94	<0.001*	–	–	–
Diabetic nephropathy	2.39	1.42–4.03	0.001*	–	–	–
Lymphopenia	4.93	2.70–8.99	<0.001*	–	–	–
Anemia	7.53	4.56–12.44	<0.001*	3.50	1.95–6.27	<0.001*
Hypoalbuminemia	9.02	5.45–14.92	<0.001*	5.42	3.14–9.36	<0.001*
Elevated serum creatinine	4.78	2.77–8.25	<0.001*	2.08	1.07–4.04	0.03*

*$P < 0.05$. BMI, body mass index; CI, confidence interval; IFD, invasive fungal disease; OR, odds ratio; T2DM, type 2 diabetes mellitus.

DISCLOSURE
The authors declare no conflict of interest.

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APPENDIX 1

INTERNATIONAL CLASSIFICATION OF DISEASES 10TH REVISION CODING OF TYPE 2 DIABETES AND INVASIVE FUNGAL DISEASE

Disease	ICD-10 coding
T2DM	E11.900, E11.800, E11.201+N08.3*, O24.300, E11.503, E11.301+H36.0*, E11.401+G63.2*, E13.900, E11.101, E11.406+G99.0*, E11.501+I79.2*, E11.302+H28.0*, E11.002, E11.601+M14.2*, E11.001, E11.505, E11.303+H22.1*, E11.405+G73.0*, E11.504, E11.603+L99.8*, E11.102, E11.403+G63.2*, E11.404+G99.0*, E11.103, E11.003, E11.502+I79.2*, E11.402+G99.0*, E11.700, E11.000, E11.600, E11.200, E11.400, E11.100, E11.300, E11.604, E13.800, E14.900, E14.800, E13.700, E14.000, E13.000, E14.600, E13.600, E14.200, E13.200, E14.400, E13.400, E14.100, E13.100, E14.300, E13.300, E14.500, E13.500, O24.100
Aspergillosis	B44.051+, B44.101+, B44.102+, B44.103+, B44.151, B44.751, B44.752, B44.801, B44.901
Blastomycosis	B40, B40.051+, B40.151+, B40.201+, B40.751, B40.752, B40.851, B40.901
Candidiasis	B37.101+, B37.401+, B37.551+, B37.601+, B37.751, B37.801, B37.802, B37.803, B37.804, B37.805, B37.806+, B37.81, B37.852
Coccidioidomycosis	B38, B38.051+, B38.052+, B38.151+, B38.201+, B38.451+, B38.751, B38.752, B38.851, B38.901, B38.051+
Cryptococcosis	B45.001+, B45.101+, B45.102+, B45.103+, B45.351+, B45.751, B45.752, B45.851, B45.901
Fungal disease	B49.X51
Histoplasmosis	B39.051+, B39.151+, B39.201+, B39.251+, B39.352+, B39.353, B39.451, B39.901
Mucormycosis	B46.001+, B46.151+, B46.251+, B46.451, B46.452, B46.501
Mycosis	B48.751, B49.XO1, B49.XO2, B49.XO4+, B49.XO5, B49.XO6 B49.XO7+, B49.XO9+, B49.X10+, B49.X11, B49.X12+, B49.X13+, B49.X14+, B49.X15, B49.X16+
Paracoccidioidomycosis	B41.700, B41.900, B41.800, B41.000
Penicilliosis	B48.451
Sporotrichosis	B42, B42.151, B42.751, B42.152, B42.851, B42.901
Zygomycosis	B46.952

ICD, International Classification of Diseases; IFD, invasive fungal disease; T2DM, type 2 diabetes mellitus.

APPENDIX 2

CRITERIA FOR DIAGNOSIS OF INTERNATIONAL CLASSIFICATION OF DISEASES IN PATIENTS WITH TYPE 2 DIABETES

Category	Criteria
Proven	Histopathological examination reveals fungal infection in normally sterile sites, or recovery of a mold/yeast from samples obtained by a sterile procedure, or blood culture yielding a mold/yeast (*Aspergillus* spp. excluded)
Probable	Patients with DM satisfying the following clinical and mycological criteria were considered to have probable mold infection.
Mold infection	a. Clinical criteria Lung infection: pulmonary CT scan showed (i) dense, well-circumscribed lesions with or without a halo sign, or (ii) air-crescent sign, or (iii) cavity; or bronchoscopy found tracheobronchial ulceration, nodule, pseudomembrane, plaque or escha. Sinonasal infection: imaging suggesting sinusitis with (i) acute localized pain, and/or (ii) evidence of bone erosion, and/or (iii) nasal ulcer with black eschar revealed by nasal endoscopy CNS infection: imaging showing focal lesions or meningeal enhancement b. Mycological criteria: satisfying at least one of the following criteria (i) Mold in sputum, BALF, bronchial brush or sinus aspirate samples (ii) Positive GM antigen detection in plasma, serum, BALF or CSF (for aspergillosis only).
Cryptococcosis	Patients with DM showing one of the aforementioned radiographic manifestation along with (i) *Cryptococcus* spp. isolated in sputum, BALF, bronchial brush; or (ii) positivie CrAg detection in serum or CSF.
Possible	

Appendix 2 (*Continued*)

Category	Criteria
Mold infection/ cryptococcosis Yeast infection	Patients with DM satisfying the aforementioned clinical criteria, but without mycological evidence were considered to have possible mold infection/cryptococcosis.
	a. Lung infection: patients with DM satisfying all the following criteria were considered to have possible pulmonary candidiasis: (i) clinical symptoms suggesting lung infection and CT scan showing new onset bronchopneumonia or micronodules or diffused infiltrates, (ii) positive twice in microscopic examination showing fungal hyphae/pseudohyphae and recovery twice of the same yeast in sputum/BALF culture, (iii) positive twice in serum G-test, (iv) excluded other possible pathogens
	b. UTI: patients with DM satisfying all the following criteria were considered to have possible urinary candidiasis: (i) clinical symptoms indicating urinary infection, (ii) increased leukocytes in clean-catch midstream urine, (iii) positive twice in urine culture for the same yeast, (iv) excluded other possible pathogens
	c. Esophageal infection: patients with DM satisfying all the following criteria were considered to have possible esophageal candidiasis: (i) white plaques found in endoscopic examination, (ii) fungal hyphae, pseudohyphae or spores found in esophageal brushing sample

BALF, bronchoalveolar lavage fluid; CNS, central nervous system; CrAg, cryptococcal capsule polyglycan antigen; CSF, cerebrospinal fluid; CT, computed tomography; DM, diabetes mellitus; G-test, β-D-glucan detection; GM, galactomannan; IFD, invasive fungal disease; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.