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## Case Control Study

# Invasive aspergillosis in liver transplant recipients, an infectious complication with low incidence but significant mortality

Azam Farahani, Fereshteh Ghiasvand, Setareh Davoudi, Zahra Ahmadinejad

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## Abstract

### BACKGROUND

Infections, including invasive fungal infections (IFIs), are among the leading causes of mortality in liver transplant recipients during the first year post-transplantation.

### AIM

To investigate the epidemiology, clinical manifestations, risk factors, treatment outcomes, and mortality rate of post-liver transplantation invasive aspergillosis (IA).

### METHODS

In this case-control study, 22 patients with IA were identified by reviewing the archived and electronic medical records of 850 patients who received liver transplants at the Imam Khomeini Hospital complex in Tehran, Iran, between 2014 and 2019. The control group comprised 38 patients without IA infection matched for age and sex. The information obtained included the baseline characteristics of liver transplant patients, operative reports, post-transplantation characteristics of both groups and information about the fungal infection of the patient group.

### RESULTS

The prevalence rate of IA among liver transplant recipients at Imam Khomeini Hospital was 2.7%. The risk factors of IA among studied patients included high serum creatinine levels before and post-transplant, renal replacement therapy, antithymocyte globulin induction therapy, post-transplant bile leakage, post-transplant hepatic artery thrombosis, repeated surgery within 30 d after the

transplant, bacterial pneumonia before the aspergillosis diagnosis, receiving systemic antibiotics before the aspergillus infection, cytomegalovirus infection, and duration of post-transplant hospitalization in the intensive care unit. The most prevalent form of infection was invasive pulmonary aspergillosis, and the most common chest computed tomography scan findings were nodules, pleural effusion, and the halo sign. In the case group, prophylactic antifungal therapy was administered more frequently than in the control group. The antifungal therapy response rate at 12 wk was 63.7%. The 3- and 12- mo mortality rates of the patients with IA were 36.4% and 45.4%, respectively (compared with the mortality rate of the control group in 12 mo, which was zero).

## CONCLUSION

In this study, the prevalence of IA among liver transplant recipients was relatively low. However, it was one of the leading causes of mortality following liver transplantation. Targeted antifungal therapy may be a factor in the low incidence of infections at our facility. Identifying the risk factors of IFIs, maintaining an elevated level of clinical suspicion, and initiating early antifungal treatment may significantly improve the prognosis and reduce the mortality rate of liver transplant recipients.

**Key Words:** Aspergillosis; Cytomegalovirus infection; Immunosuppression therapy; Liver transplantation; Risk factors; Fungal infections; Fungal pneumonia

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**Core Tip:** In our center, invasive aspergillosis had a low incidence but a high mortality rate among liver transplant recipients. Invasive pulmonary aspergillosis was the most prevalent form of infection. Nodules, pleural effusion, and halo signs were the most commonly observed findings on chest computed tomography scans. Antifungal prophylaxis was more prevalent in the case group than in the control group. At week 6 of antifungal treatment, more than 60% of patients experienced complete recovery or relative response to therapy.

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## INTRODUCTION

Invasive aspergillosis (IA) is one of the most common invasive fungal infections (IFIs) following solid organ transplants (SOT) and the leading cause of mortality and morbidity among transplant recipients. Several studies have reported rates of IA in organ transplant recipients between 1% and 15% [1-4]. In the TRANSNET study, an extensive cohort study on the prevalence of IFI in SOT recipients, the annual incidence rate of IA was 0.65%, second only to candidiasis [5].

IA typically develops 1 to 3 mo after a transplant [6]. However, delayed IA (6 mo after transplant) has recently been reported [7]. In a Swiss Transplant cohort study, the incidence of IA among liver transplant recipients was significantly lower than among recipients of other organ transplants [8]. In immunocompromised hosts, *Aspergillus* can infect every organ; however, sinopulmonary involvements are more common. Involvement of the central nervous system (CNS) and multiple organs is more prevalent in liver transplants than in other SOT [9].

The mortality rate of IA among recipients of liver transplants has not fallen over the past 15 years (compared with other SOTs). The 90-day mortality rate of liver transplant recipients with IA is higher than that of recipients of other organ transplants (85.7% vs 15.9%) [8,10].

Early diagnosis and proper treatment of IA are associated with a more favorable prognosis. Noninvasive modalities (such as imaging and antigen detection) aid in antifungal treatment initiation and duration. However, aggressive diagnostic approaches, such as bronchoalveolar lavage (BAL), should be considered for patients with imaging findings suggestive of IA [11,12].

Investigations revealed that BAL culture has a sensitivity of 50% in focal pulmonary lesions [13]. In such instances, a definitive diagnosis necessitates aggressive procedures, such as a thoracoscopic biopsy. Invasive diseases are strongly predicted by isolating *Aspergillus* species from sputum or BAL samples [14]. In the early stages of IA, single or multiple nodules are the most frequent finding on computed tomography (CT) scans [15]. Halo sign with peri-nodular haziness is a reliable indicator of IA [16]. In serial CT scan studies, the halo sign decreases during the first week, while the air crescent sign (another radiologic marker of pulmonary IA) increases [17]. Despite the clinical response to antifungal therapy, pulmonary lesions increase in size during the first week of treatment.

Positive serum and BAL galactomannan (GM), in conjunction with IA predisposing factors of the host, clinical and imaging findings consistent with IA, eliminate the need for invasive procedures in diagnosing IA [18]. The GM sensitivity decreases in the case of simultaneous use of active antimold agents [19]. Historically, Piperacillin-Tazobactam has been

linked to false positive GM results[20]. Blood[21,22] and BAL[23,24] *Aspergillus* PCR are used for initial IA diagnosis. However, further prospective studies are required to investigate the combination of diagnostic modalities in the early IA stages.

Voriconazole is more effective than amphotericin B in the early treatment of IA and significantly improves survival (71% vs 58%)[25]. Voriconazole improved the prognosis of CNS involvements[26], which in most cases resulted in high mortality rates[27]. Accordingly, it is recommended as the treatment of choice for IA. There are no clinical trials involving echinocandins as a first-line treatment for IA. Recent attention has been drawn to a combination of echinocandin and amphotericin B or azoles, and *in vitro*, studies have confirmed the synergistic effect of this combination[28,29].

In probable *aspergillus* cases, a combination of echinocandin with amphotericin B was associated with 40%-60% prognosis improvement[30,31]. Marr *et al*[32] reported survival improvement by combining voriconazole and echinocandin (compared with voriconazole alone). However, further studies are required to investigate the advantages of combination therapy in IA. Patients who recovered a single episode of IA are at higher risk of re-infection during immunosuppressive therapy. Therefore, effective antifungal prophylaxis is recommended, particularly in the hematopoietic stem cell transplant (HSCT) group[33,34].

This study examined the prevalence, epidemiology, clinical manifestations, risk factors, antifungal therapy response, and prognosis of IA infection in liver transplant recipients.

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## MATERIALS AND METHODS

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The study population consisted of liver transplant recipients in the Imam Khomeini Hospital complex between 2014 and 2019. This hospital is a major referral and educational hospital and the second-largest center of liver transplants in Iran, with over 100 transplants per year.

### Inclusion criteria

The study included all patients who received a liver transplant between 2014 and 2019 and were diagnosed with probable/proven IA.

### Exclusion criteria

Multi-organ transplant recipients were excluded from the study.

### Control group

Patients without IFI after the liver transplant. The following formula was utilized to determine the sample size of the control group:

Z tests-Correlations: Two independent Pearson  $r$ 's; Analysis: A priori: Compute required sample size; Input: Tail (s) = One; Effect size  $q = 0.84$ ;  $\alpha$  err probability = 0.05; Power (1- $\beta$  err probability) = 0.90; Allocation ratio  $N2/N1 = 2$ .

### Output

Critical  $z = 1.6448536$ ; Sample size group 1 (case) = 21; Sample size group 2 (control) = 42; Total sample size = 63; Actual power = 0.9037178.

A questionnaire containing the necessary information was created and filled out using data from liver transplant recipients' electronic and non-electronic medical records. The pre-transplant information included: Age, sex, underlying diseases, the Model for End-Stage Liver Disease (MELD) score, intensive care unit (ICU) hospitalization before the transplant, ventilator support during the week before the transplant, fungal colonization or infection within three months before the transplant, dialysis within the month before the transplant, diabetes mellitus, bacteremia within a month before the transplant, bacterial peritonitis before the transplant, cytomegalovirus (CMV) serology, and creatinine level before the transplant.

The peri-transplant information included: The date of transplant, transplant type (from deceased or living donor), type of anastomosis (duct to duct or Roux-en-Y), cold ischemia time (measured by minutes), and the number of transfused blood units (packed cells) during the operation.

The post-transplant information of the patients included: Induction therapy, type of antifungal prophylaxis after transplant, repeated surgery within 30 d after the transplant, ICU admission duration, mechanical ventilation after the transplant, bacteremia and pneumonia within 2 wk before IA diagnosis, creatinine level at the time of diagnosis, CMV viremia or disease within one month before the diagnosis, transplant rejection requiring treatment within three months before the diagnosis of IA.

*Aspergillus* information included: The time of infection, proven or probable diagnosis, the involved organ, the result of fungus culture, GM, pathology, PCR, radiologic findings, type of antifungal treatment, response to treatment at weeks 6 and 12, death within 12 mo of diagnosis, repeated transplant within 3 mo of diagnosis, and transplant rejection requiring treatment within three months of diagnosis. Proven and probable diagnoses of IA were defined according to the European Organisation for Research and Treatment of Cancer (EORTC) criteria[35].

The surgical methods, preventative measures, and immunosuppressive regimen utilized at our center are described in another article[36]. However, since 2018, the antifungal prophylaxis method has been changed from universal to targeted prophylaxis, and since 2020, the diagnosis of CMV infection has been based on PCR rather than CMVPP65 Ag detection.

### Ethical considerations

The Institutional Review Board of the Tehran University of Medical Sciences approved the study with the file number (IR.TUMS.MEDICINE.REC.1399.874). The patients' information was registered anonymously in questionnaires. Due to the study's retrospective nature, no written consent was obtained from the patients.

### Data analysis

The data was analyzed using SPSS version 26. The data was expressed as mean  $\pm$  standard deviation (SD) to present quantitative variables with normal distribution and frequency (%) for qualitative variables. The qualitative variables were analyzed by chi-squared test, and continuous quantitative variables with normal distribution were analyzed with Student's *t*-test. *P* values  $< 0.05$  were considered statistically significant. Multiple logistic regression analyses (both multivariate and bivariate) were performed.

## RESULTS

Between 2014 and 2019, 850 patients received a liver transplant at the Imam Khomeini Hospital Complex in Tehran, Iran. Investigations of these patients' medical records revealed 22 cases of IA. To examine the risk factors of IA, 38 liver transplant recipients without a history of IA who matched the case group regarding age and sex were selected as the control group and enrolled in the study. **Table 1** summarizes both groups' demographic and pretransplant information (cases and controls).

Of 22 patients with IA infection, 18 (81.8%) were male, and 4 (18.2%) were female. The mean  $\pm$  SD age of the patients was  $45.27 \pm 14.85$  years. In the control group, 31 (81.6%) were male, and the mean age of the control group was  $47.21$  (SD = 12.03). The mean number of MELD scores in the case and control groups was similar (21.05 *vs* 20.24). The blood creatinine level in the case group before the transplant was significantly higher than in the control group [ $1.74$  mg/dL *vs*  $1.22$  mg/dL, *P* value 0.04, odds ratio (OR): 0.34; confidence interval (CI): 0.13-0.87]. There were no statistically significant differences between the proportions of fulminant hepatic failure (FHF) patients in the patient and control groups [*P* value = 0.18; 27.3% (*n* = 6) and 5.3% (*n* = 2), respectively]. A higher percentage of IA patients were re-transplants [22.7% (*n* = 5) *vs* 7.9% (*n* = 3), *P* = 0.13], but the difference was not statistically significant. The mean time between liver transplantation and occurrence of IA was  $313 \pm 337.64$  d (range 15-1350 d).

The most prevalent symptom of IA was pulmonary aspergillosis. Of the 22 cases of IA, nine patients had confirmed IA, and 13 had probable IA. Amphotericin B was the primary antifungal treatment (empirical therapy) for 72.6% of the patients. Nodular lesions and halo signs were the most common radiographic findings among the patients (50% and 45.5%, respectively). At week 6 of antifungal therapy, complete recovery and response to treatment were observed in 10 patients (45.5%), and relative response to treatment was observed in 4 patients (18.2%). The mortality rate after the study period was 36.4%. (8 patients). **Table 2** presents the patients' information regarding IA.

Among the variables related to the peritransplant period, four variables, including induction therapy with antithymocyte globulin (ATG) [case no = 8 (36.4%), control no = 6 (15.8%), *P* value  $< 0.001$ , OR: 0.08, CI: 0.02-0.41] biliary leakage (case no = 9 [40.9%], control no = 0, *P* value  $< 0.001$ ), reoperation within 30 d of the transplant [case no = 12 (54.5%), control no = 5 (13.2%), *P* value  $< 0.001$ , OR = 7.92, CI: 2.25-27.94], and hepatic artery thrombosis [case no = 8 (36.4%), control no = 1 (2.6%), OR = 21.14, CI: 2.42-184.79], were significantly higher among patients with IA (**Table 3**).

Within 2 wk before the IA diagnosis, the immunosuppressive regimen included tacrolimus and mycophenolate in over 80% of patients and the control group. Nineteen patients in the case group (86.4%) and 18 patients in the control group (47.4%) received antifungal prophylaxis (40.9% of the patients' group and 13.1% of the control group received voriconazole). Bacterial pneumonia was diagnosed in 13 individuals in the case group (59.1%) and four individuals in the control group (10.5%) within 2 wk of the fungal infection diagnosis (*P* value  $< 0.001$ ).

During the 2 wk preceding the infection, 16 patients (72.7%) received antibiotics, whereas 39% (no = 15) of patients in the control group received antibiotics during the same period (*P* value  $< 0.01$ ). The maximum creatinine level at the time of IA diagnosis was  $1.87$  mg/dL (SD = 1.1) in the case group *vs*  $1.21$  (SD = 1.43) in the control group. CMV viremia was significantly higher in IA patients [case no = 9 (40.9%), control no = 4 (10.5%), *P* value=0.009]. Transplant rejection requiring treatment within 3 mo before the IA diagnosis occurred in 13 patients in the case group (59.1%) and 10 patients in the control group (26.3%) (*P* value = 0.01; OR: 4.04; CI: 1.33-12.34).

The mean lengths of stay in the ICU at the time of transplantation were 4.1 d for the case group and 1.8 d for the control group (*P* value = 0.008). The number of patients in the IA group who underwent dialysis was greater [7 (31.8%) cases *vs* 4 (10.5%) controls; *P* value = 0.08], but the difference was not statistically significant. The results pertaining to post-transplant factors are summarized in **Tables 4** and **5**.

The case group had a significantly lower 12-month survival rate than the control group (56.4% *vs* 100%) (*P* value  $< 0.001$ ) (**Tables 1** and **2**).

## DISCUSSION

The epidemiology of IFIs (including aspergillosis) among transplant recipients has changed during the last two decades. The incidence rate of IA has significantly reduced (from 40% to less than 10%), and most cases now occur more than 90 d after the transplant[37].

**Table 1 Demographic information and background factors before transplantation of the study population**

Covariate	Case	Control	P value	OR (95%CI)
Gender (Male)	18 (81.8%)	31 (81.6%)	0.9	-
Gender (Female)	4 (18.2%)	7 (18.4%)	0.9	-
Age mean (SD)	45.27 (14.85)	47.21 (12.03)	0.58	-
MELD score (SD)	21.05 (6.78)	20.24 (5.54)	0.62	-
Pretransplant ICU stay	1.95 (0.22)	1.97 (0.16)	0.9	-
Duration of pretransplant ICU stay	2 (1)	1 (0)	0.27	-
Pretransplant creatinine	1.74 (1.03)	1.22 (0.47)	0.04	0.34 (0.13-0.87)
Pretransplant ventilator within 1 wk	-	1 (2.6%)	0.9	-
Pretransplant dialysis within 1 mo	-	1 (2.6%)	0.9	-
Pretransplant diabetes mellitus	12 (54.5%)	15 (39.5%)	0.26	-
Fulminant hepatic failure	6 (27.3%)	2 (5.3%)	0.18	-
Immunosuppressive agents (steroids)	2 (9.1%)	6 (15.8%)	0.08	-
Immunosuppressive agent (antimetabolites)	1 (4.5%)	1 (2.6%)	0.08	-
Immunosuppressive agent (steroids & antimetabolites)	1 (4.5%)	0	0.08	-
Immunosuppressive agent (steroids & calcineurin inhibitors)	1 (4.5%)	0	0.08	-
Immunosuppressive agent (no)	12 (54.5%)	31 (81.6%)	0.08	-
The pretransplant episode of documented bacterial peritonitis	3 (13.6%)	5 (13.2%)	0.9	-
Previous systemic antibiotic use of more than 14 consecutive days	5 (22.7%)	6 (15.8%)	0.51	-
Re transplantation	5 (22.7%)	3 (7.9%)	0.13	-

CI: Confidence interval; ICU: Intensive care unit; OR: Odds ratio; SD: Standard deviation.

The prevalence of IA in liver transplant recipients was 2.7% in the present study. Other studies have reported incidence rates between 1% and 8% [4,38]. The lower incidence of IA is attributable to several factors, including improvements in surgical techniques, immunosuppressive regimens, and targeted antifungal prophylaxis in patients at moderate to high risk for fungal infection [37]. There was no significant difference between the two groups' underlying liver disease and MELD scores (case and control groups). In earlier studies, however, a MELD score greater than 30 was associated with an increased risk of fungal infection [38].

Several studies have investigated the risk factors associated with IA in transplant recipients. Among the identified risk factors are longer duration of surgery, severe blood loss during the operation, reoperation, steroid-resistant rejection, renal failure (especially when dialysis is required), CMV infection, diabetes, and long-term use of broad-spectrum antibiotics [39-41]. Fortún *et al* [40] (2002) found that positive GM, in addition to reoperation and post-transplant dialysis, was a risk factor for aspergillus infection in 13 patients with IA and 38 patients without IA (control group).

Due to epidemiological changes in IFIs among liver transplant recipients, antifungal prophylaxis for the low-risk group is no longer recommended. The American Society of Transplantation and Infectious Diseases Society of America (IDSA) reserves antifungal prophylaxis against candidiasis in moderate-risk patients (patients with complicated surgeries, anastomosis of choledochojejunostomy and candida colonization before transplantation), and anti-mold prophylaxis for high-risk patients (repeated liver transplant, repeating the surgery, and post-transplant renal replacement therapy) [42-44].

Our facility has also implemented a targeted prevention strategy since 2018. In our study, over 80% of patients with IA received antifungal prophylaxis, compared to less than 50% of patients in the control group.

ATG induction therapy was more common among patients with IA than the control group. Given that administering this medication as induction therapy in our facility is primarily reserved for patients with renal dysfunction, renal function may influence this relationship. However, the immunosuppressive therapy type is a known risk factor for IA [45, 46]. CMV reactivation, an additional risk factor for delayed IA, is one of the most common side effects of anti-thymocyte globulin therapy. In addition, an increased dose of immunosuppressives for the treatment of rejection episodes (such as administration of corticosteroid pulses) was more prevalent in the case group than in the control group (59.1% vs 26.3%) [46-49].

In the case group, post-transplant ICU stays were significantly longer than in the control group (4.1 vs 1.8). This statistically significant difference in ICU admission length reflects the critical illness of the case group (which requires intensive care) and their increased susceptibility to opportunistic infections [45].

**Table 2 Clinical and laboratory information of patients with invasive aspergillus infection<sup>1</sup>**

Covariate	Number (percent)
Diagnosis (proven)	9 (40.9%)
Diagnosis (probable)	13 (59.1%)
Site of diagnosis (isolated pulmonary)	19 (86.4%)
Site of diagnosis (isolated sinusitis)	2 (9.1%)
Site of diagnosis (peritonitis)	1 (4.5%)
Positive galactomannan (serum)	5 (22.7%)
Positive galactomannan (BAL)	8 (36.4%)
Positive galactomannan (N/A)	9 (40.9%)
PCR (positive)	8 (36.4%)
PCR (negative)	3 (13.6%)
PCR (N/A)	11 (50%)
Pathology (positive)	2 (9.1%)
Pathology (negative)	4 (18.2%)
Pathology (N/A)	16 (72.7%)
Fungal culture (positive)	10 (45.5%)
Fungal culture (negative)	2 (9.1%)
Fungal culture (N/A)	10 (45.5%)
Site of positive culture (sputum)	2 (9.1%)
Site of positive culture (BAL)	6 (27.3%)
Site of positive culture (sinus biopsy)	4 (18.2%)
Site of positive culture (pulmonary biopsy)	1 (4.5%)
Site of positive culture (peritonitis)	1 (4.5%)
CT scan findings (nodules)	11 (50%)
CT scan findings (ground glass opacity)	2 (9.1%)
CT scan findings (halo sign)	10 (45.5%)
CT scan findings (consolidation)	5 (22.7%)
CT scan findings (cavity)	3 (13.6%)
CT scan findings (pleural effusion)	7 (31.8%)
Treatment response at 6 & 12 wk (cure)	10 (45.5%)
Treatment response at 6 & 12 wk (partial response)	4 (18.2%)
Treatment response at 6 & 12 wk (stable)	-
Treatment response at 6 & 12 wk (progression)	-
Treatment response at 6 & 12 wk (death)	8 (36.4%)
12- month mortality	10 (4.45%)

<sup>1</sup>Cases information are attached.

BAL: Bronchoalveolar lavage; CT: Computed tomography; PCR: Polymerase chain reaction; N/A: Not applicable.

A creatinine level equal to or higher than 2 mg/dL is suggested as a risk factor for IA[5]. Renal dysfunction, renal replacement therapy, and dialysis after transplantation are known factors associated with the incidence of IFIs in organ transplant recipients[2,8,40,46]. In the current study, most patients with IA underwent dialysis; however, the difference was not statistically significant, which may be due to the low sample size and lower mean creatinine level before IA diagnosis.

**Table 3 Comparison of factors related to the transplant of the study population**

Covariate	Case	Control	P value	OR (95%CI)
Type of anastomosis (duct to duct)	16 (72.7%)	30 (78.9%)	0.53	-
Type of anastomosis (Roux-en-Y)	6 (27.3%)	8 (21.1%)	0.53	-
Cold ischemic time (h)	283.95 (66.58)	300.37 (58.39)	0.32	-
Underlying disease (NASH)	6 (27.3%)	6 (15.8%)	0.74	-
Underlying disease (PSC)	3 (13.6%)	8 (21.1%)	0.74	-
Underlying disease (HBV)	3 (13.6%)	5 (13.2%)	0.74	-
Underlying disease (HCV)	2 (9.1%)	1 (2.6%)	0.74	-
Underlying disease (AIH)	1 (4.5%)	3 (7.9%)	0.74	-
Underlying disease (AIH & HCC)	1 (4.5%)	1 (2.6%)	0.74	-
Underlying disease (HCV & NASH)	1 (4.5%)	-	0.74	-
Underlying disease (PBC)	1 (4.5%)	-	0.74	-
Underlying disease (Others)	4 (18.1%)	5 (13.2%)	0.74	-
Underlying disease (ASH)	-	2 (5.3%)	0.74	-
Underlying disease (HCV & HCC)	-	2 (5.3%)	0.74	-
Underlying disease (NASH & HCC)	-	2 (5.3%)	0.74	-
Underlying disease (NASH & PSC)	-	1 (2.6%)	-	-
Underlying disease (HBV & HCC)	-	1 (2.6%)	-	-
Underlying disease (Wilson)	-	1 (2.6%)	-	-
Intraoperative blood transfusion	3.45 (3.05)	2.5 (2.57)	0.2	-
Induction therapy (ATG)	8 (36.4%)	6 (15.8%)	< 0.001	0.08 (0.02-0.41)
Induction therapy (methyl prednisolon)	14 (63.6%)	32 (84.2%)	< 0.001	0.05 (0.01-0.25)
Biliary leak post-transplant	9 (40.9%)	-	< 0.001	-
Reoperation within 30 d of transplant	12 (54.5%)	5 (13.2%)	< 0.001	7.92 (2.25-27.94)
Hepatic artery thrombosis post-transplant	8 (36.4%)	1 (2.6%)	< 0.001	21.14 (2.42-184.79)

AIH: Autoimmune Hepatitis; ASH: Alcoholic Steatohepatitis; ATG: Antithymocyte Globulin; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; NASH: Nonalcoholic Steatohepatitis; PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis; CI: Confidence interval; OR: Odds ratio.

According to previous studies[8,46] and the current investigation, any local or systemic infection requiring IV antibiotics for more than 3-14 d is associated with further disruption of the normal microbial flora, the predominance of opportunistic pathogens, and an increased risk of IA. The incidence of bacterial pneumonia was significantly higher in IA cases two weeks before diagnosis (59.1% in the case group compared with 10.5% in the control group). The proportion of IA patients receiving systemic antibiotics two weeks before diagnosis was also greater than that of the control group ( $P = 0.01$ ).

CMV is one of the immunosuppressive viruses known to cause various complications in organ transplant recipients due to cytokine dysregulation. CMV infection has been associated with increased susceptibility to IFIs due to dysfunction of the host's neutrophils and macrophages, which play a crucial role in aspergillosis defense. According to our study, CMV viremia was four times higher in IA patients than in the control group (40.9% *vs* 10.5%). Previous research shows CMV viremia is one of the most prominent predictors of IA (mostly the late form of IA)[10,40].

According to previous studies[47,49,50], type of anastomosis (Roux-en-y choledochojejunostomy), repeated transplant, FHF, antibiotics, and immunosuppressive medications before the transplant are among the reported risk factors for post-liver transplant aspergillosis. However, our study did not observe a significant difference between the two groups regarding these factors, which may be due to the low sample size of the present study.

In the past two decades, the rate of late IA (more than 90 d after transplant) has increased with intervals ranging from 22 to 1117 d[9,10,40,46]. An average of 313 d elapsed between the time of liver transplantation and the occurrence of IA, according to the present study (range 15-810 d). This shift in the onset of IA infection may be attributable to improvements in the early management of high-risk patients, advances in surgical techniques, or delayed risk factors (including CMV infection).

**Table 4 Comparison of the post-transplant factors in the study population**

Covariate	Case	Control	P value	OR (95%CI)
Antifungal prophylaxis after transplant (Fluconazole)	10 (45.5%)	13 (34.2%)	0.003	0.20 (0.05-0.85)
Antifungal prophylaxis after transplant (voriconazole)	9 (40.9%)	5 (13.1%)		0.08 (0.02-0.43)
Antifungal prophylaxis after transplant (no)	3 (13.6%)	20 (52.7%)		-
Bacteremia within 2 wk before diagnosis	3 (13.6%)	4 (10.5%)	0.70	-
Pneumonia within 2 wk before diagnosis	13 (59.1%)	4 (10.5%)	< 0.001	0.08 (0.02-0.31)
Systemic antibacterial within 2 wk before diagnosis	16 (72.7%)	15 (39.5%)	< 0.001	4.09 (1.31-12.81)
Dialysis requirement	7 (31.8%)	4 (10.5%)	0.08	
CMV viremia before diagnosis	9 (40.9%)	4 (10.5%)	0.009	5.89 (1.54-22.47)
CMV diseases before diagnosis	3 (13.6%)	2 (5.3%)	0.35	
Length of ICU stay at the time of transplant	4.05 (3.59)	1.75 (1.20)	0.008	0.56 (0.38-0.82)
Duration of mechanical ventilation at the time of transplant	1.25 (0.55)	1.12 (0.41)	0.34	
Creatinine at the day of diagnosis (highest value)	1/87 (SD:1/1)	1/21 (SD:1/43)	-	-

CI: Confidence interval; CMV: Cytomegalovirus; ICU: Intensive care unit; OR: Odds ratio; SD: Standard deviation.

**Table 5 Rejection before and after diagnosis of invasive aspergillosis**

Covariate	Case	Control	P value	OR (95%CI)
Rejection requiring treatment within 3 mo before diagnosis	13 (59.1%)	10 (26.3%)	0.01	4.04 (1.33-12.34)
Rejection required treatment after diagnosis	4 (18.2%)	4 (10.5%)	0.45	-

CI: Confidence interval; OR: Odds ratio.

Statistically significant differences were also observed between patients with IA and controls regarding biliary leakage after transplant (40.9% *vs* 0%) and hepatic artery thrombosis (36.4% *vs* 2.6%). It is necessary to consider these factors when determining the risk of IFIs. However, no similar findings were reported in the published literature.

Lungs were this study's most common site of IA (86.4%). This finding was consistent with other studies, which indicated that pulmonary aspergillosis (66% to 79%) was the most prevalent form of IA[4,46]. Environmental exposure to *Aspergillus* and inhalation of spores will result in airway colonization, which can progress to infection and disease development following transplant-induced immunodeficiency[4,46]. Elevated GM levels at any time after transplantation are an independent factor associated with aspergillosis, which may be a suitable predictor of IA prognosis[40]. In addition to a positive culture or positive PCR of secretions, GM serum antigen > 0.5 or BAL GM > 1 with a sensitivity of 22% and specificity of 84% aids in the diagnosis of IA[51].

In our study, GM was detected in 59.1% of cases, most of which were in the BAL. This finding is consistent with previous research indicating that BAL GM is more sensitive[18,52]. Due to the absence of GM measurement in the control group, the sensitivity and specificity of this test for IA diagnosis cannot be calculated.

In the present study, the most common CT scan findings were lung nodules (50%), halo sign (45.5%), and pleural effusion (31.8%). According to previous research, imaging-specific findings are ground glass opacities, cavities, and the nodule (with or without a halo sign)[15-17]. Halo sign, a typical and early finding of IA in HSCT and neutropenic patients, is rarely observed in SOT patients[53,54]. The high frequency of halo signs in the present study may be due to early diagnosis of this infection and conducting lung CT scan in our center as a primary diagnostic action for each patient with changes in general conditions, with or without pulmonary symptoms.

According to the most recent IDSA guidelines, voriconazole is the drug of choice for IA[55]. Isavuconazole and liposomal amphotericin B are alternatives. In our study, liposomal amphotericin B was administered to most patients with a high probability of fungal infection. After the diagnosis was confirmed, the treatment was changed to voriconazole. Those who received voriconazole had a higher recovery and survival rate than those who received amphotericin B[25]. In our study, the response to treatment, defined as complete and partial recovery within 12 wk of initiating antifungal treatment, was 45.5% and 18.2%, respectively. The overall treatment response rate of 63.7% was consistent with previous studies[9,42].

Overall, 16.9% of the mortality during the first year post-transplant is due to IA. The highest mortality rate is observed in CNS involvements and disseminated aspergillosis[10]. However, due to the increased rate of late-onset IA, the mortality has been reduced from 65%-92% to 22% (the higher mortality rate was related to the studies before 2000)[56].

Nevertheless, the mortality rate of IA in liver transplant patients remains high[8]. According to our study, the 12-week mortality rate was 36.4%. A study by Nagao *et al*[7] (2016) on five IA patients reported a mortality rate of 80%. The one-year survival rate of aspergillosis patients in this study was 54.6%. In contrast, the entire control group population survived one year after the transplant. A study by Barchiesi *et al*[4] revealed a 35% one-year survival rate. After the year 2000, the survival of patients who received voriconazole improved in the absence of renal failure.

Considering the study's retrospective nature, it was impossible to investigate several factors (including the role of GM and  $\beta$ -d-glucan in the IA diagnosis). In addition, due to the absence of invasive diagnostic procedures, most IA patients were not diagnosed.

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## CONCLUSION

Despite the significant decline in the incidence of IA at our center, this disease has a negative impact on the survival of transplant recipients. Early diagnosis based on clinical symptoms and imaging modalities, as well as identification of factors related to the incidence of IA, is of significant importance. The imaging findings of aspergillosis, including nodule and halo signs, continue to play a crucial role in diagnosing this lethal invasive infection.

Furthermore, according to our study, the level of creatinine before the transplant, the creatinine level after the transplant, or patients who require renal replacement therapies after transplantation, induction therapy with ATG, ICU length of stay after the transplant, pneumonia 2 wk before the IA diagnosis, CMV viremia within one month before the IA diagnosis, receiving systemic antibiotics more than three days within the two weeks before the IA diagnosis, treatment-required transplant rejection within three months before the IA diagnosis, repeated surgery within 30 d after the transplant were the risk factors associated with increased risk of IA. We also hypothesize that biliary leakage and hepatic artery thrombosis after the transplant are two potential risk factors for IA.

## ARTICLE HIGHLIGHTS

### **Research background**

During the past two decades, the incidence rate and onset time of invasive fungal infections (IFIs), such as aspergillosis, have changed in liver transplant recipients.

### **Research motivation**

Determining the new risk factors and treatment outcomes of early and late-onset invasive aspergillosis (IA) in high-volume centers for liver transplants is essential. It may have a key role in improving the prognosis of these patients.

### **Research objectives**

This study sought to determine the prevalence, risk factors, treatment outcomes, and prognosis of IA infection among liver transplant recipients at our institution. We also investigated the study patients' major clinical, laboratory, and radiologic manifestations of IA.

### **Research methods**

To determine the prevalence of IA, we analyzed the data of 850 patients who received a liver transplant at the Imam Khomeini Hospital Complex in Tehran, Iran, between 2014 and 2019, and recorded the study variables for patients with an IA diagnosis. In addition, we devised a case-control study to identify the risk factors for IA and compare the prognoses of patients with and without IA.

### **Research results**

Our center's IA rate was 2.7%. Pulmonary aspergillosis was the most common presentation of the patients with IA. In most of our patients, imaging findings indicative of aspergillosis, including nodule and halo signs, were detected. The high level of creatinine before and after the transplant, renal replacement therapy after transplantation, induction therapy with antithymocyte globulin, longer duration of intensive care unit admission after the transplant, pneumonia 2 wk before the IA diagnosis, cytomegalovirus viremia within 1 mo before the IA diagnosis, receiving systemic antibiotics for more than three days within the 2 wk before the IA diagnosis, treatment-required transplant rejection within three months before the IA diagnosis, receiving systemic antibiotics for longer than three months before the IA diagnosis, repeated surgery within 30 d after the transplant, biliary leakage after the transplant and hepatic artery thrombosis were the risk factors associated with increased risk of IA.

### **Research conclusions**

In this study, the prevalence of IA among liver transplant recipients was relatively low. However, it was one of the leading causes of mortality following liver transplantation. Identifying and addressing risk factors for IA, early diagnosis and prompt treatment of this fatal disease may improve the prognosis and decrease the mortality rate of liver transplant recipients.

### Research perspectives

The primary risk factors of IA in liver transplant recipients should be determined through a large, multicenter study. Moreover, we must investigate the role of noninvasive and rapid diagnostic tests in diagnosing patients suspected of IFI early.

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**Author contributions:** Ahmadinejad Z designed the research study, translate the article into English and revised the manuscript according to the reviewer comments; Farahani A performed the research, analyzed the data and prepared the draft of manuscript in Persian language; Ghiasvand F and Davoudi S scientifically and grammatically edit the translated manuscript; All authors have read and approve the final manuscript.

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