Delayed-onset chest infections in liver transplant recipients: a prospective study

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Objectives Liver transplant recipients are liable to many infectious and noninfectious chest complications, especially post-transplant pneumonia, which is the major cause of morbidity and mortality. Many studies have evaluated post-liver-transplant early-onset pneumonia. The aim of this study was to evaluate delayed-onset chest infections following liver transplantation.

Materials and methods This prospective study was carried out on 50 adult living donor liver transplant recipients (mean age: 49.68±6.4 years; 44 men and six women). Delayed-onset chest infections that developed after the first month after transplant until the end of the first year were evaluated to determine their frequency, causative microorganisms, associated risk factors, and effect on mortality.

Results Delayed-onset chest infections were detected in six patients (12%) and were complicated, with a 50% mortality rate. The causative organisms were carbapenemase-producing *Enterobacteriaceae* spp., multidrug-resistant *Pseudomonas* aeruginosa, and methicillin-resistant *Staphylococcus aureus* and *Streptococcus pneumoniae*. Only one case was diagnosed as pleural tuberculosis in the late period of 6–12 months post liver transplantation. The mortality rate was significantly higher in patients who developed chest infections than among those who developed graft- related complications (P=0.009). Persistent moderate-to-large post-transplant transudative pleural effusion and the use of tacrolimus were associated with increased frequency of post-transplant delayed-onset chest infections (P=0.029 and 0.021, respectively).

Conclusion Despite the relatively low incidence of post-transplant delayed-onset pulmonary infections, they are a major cause of morbidity and mortality in liver transplant recipients. Tuberculosis should be considered as a cause of post-transplant delayed-onset chest infections.

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Introduction

Liver transplantation (LT) is an accepted therapy for patients with end-stage liver disease. Pulmonary morbidity and mortality are major concerns for LT recipients [1]. The goal of immunosuppressive regimens used in LT recipients is to optimize graft function by prevention of rejection with minimal side effects, especially opportunistic infections. Immunosuppressive agents are associated with opportunistic infections. However, there is individual variation in and difficulty in evaluation of the susceptibility of LT recipients to infections [2]. Many researchers have focused their studies on post-transplant early-onset pneumonia without evaluation of delayed-onset pneumonia because of the highest incidence of infections during this period being associated with initial intensive immunosuppression [1,3–5]. The aim of this study was to analyze delayed-onset pulmonary infections as regards frequency, timing, causative microbial agent(s), associated risk factors, and associated mortality.

Materials and methods

Patients

This prospective descriptive study included 50 living donor LT (LDLT) recipients. It was carried out at the Department of Chest Medicine, Gastroenterology Center, Mansoura University Hospitals, between August 2013 and July 2014. All LT operations were performed after obtaining informed consent from the patients and approval from the Liver Transplantation Committee of Mansoura University. After LT, patient follow-up included one visit per week during the second month, one visit every 2 weeks until the end of the fifth month, and then one visit every 3 weeks until the end of the first year. All LT recipients who developed chest infections or graft-related

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complications were hospitalized. The protocol of this study was approved by the institutional research board of the Faculty of Medicine, Mansoura University, Egypt, and was in accordance with the Helsinki Declaration of 1975.

The following data were collected from all patients in this study:

(1) Demographic information (age and sex).
(2) Information on underlying liver disease.
(3) Pretransplant Child–Pugh classification [6] and Model for End-Stage Liver Disease score, which was calculated as $9.57\times\log_e$ [creatinine (mg/dl)] $+3.78\times\log_e$ [total bilirubin (mg/dl)]$+11.2\times\log_e$ (INR)+6.43 according to Wiesner *et al.* [7].

Immunosuppressive regimen

All patients received one of the calcineurin inhibitors (tacrolimus and cyclosporine) or everolimus (either as monotherapy or in combination with a low dose of one of the calcineurin inhibitors) with mycophenolate mofetil. Steroids were added on a rejection episode, which was pathologically diagnosed by liver biopsy.

Pneumonia diagnosis

Pneumonia was diagnosed in patients with a new infiltrate on lung imaging, cough, dyspnea, and at least two of these three clinical features: fever>38°C, leukocytosis or leukopenia, and purulent secretions [8]. Microbiological diagnosis was performed using blood and respiratory samples, either sputum (in spontaneously breathing patients) or bronchoalvealar lavage (BAL) cultures (in patients on mechanical ventilation). BAL samples were obtained via fiberoptic bronchoscopy (Olympus BF-1T20D fiberoptic bronchoscopy; Olympus, Tokyo, Japan) under aseptic conditions. BAL samples were obtained from the lobe or segment with the most radiological abnormality or from the lingula or middle lobe in cases of diffuse infiltration [9,10]. All respiratory samples were subjected to Gram staining, aerobic bacterial culture, drug sensitivity testing, *Mycobacterium tuberculosis* (TB) assessment by Ziehl–Neelsen staining for acid-fast bacilli, nucleic acid amplification by PCR and culture on Lowenstein–Jensen medium, and fungal assessment by wet mount staining and culture on Sabouraud dextrose agar slants.

Complications of pneumonia

Patients were diagnosed as having acute respiratory distress syndrome (ARDS) if they developed the following: (i) acute respiratory failure that was not fully explained by cardiac failure or fluid overload; (ii) bilateral opacities consistent with pulmonary edema on the chest radiograph or computed tomography scan and (iii) worsening respiratory symptoms [11]. Severe sepsis was diagnosed in the presence of septic shock or sepsis-induced organ hypoperfusion (decreased urine output, rising serum creatinine levels, hyperbilirubinemia, thrombocytopenia, or coagulopathy) [12].

Pleural effusion

Pleural effusion was diagnosed by chest radiography, ultrasonography (US), and computed tomography of the chest. Pleural effusions were classified as minimal (blunting of the costophrenic angle), small (less than one-third of the hemithorax), moderate (from one-third of the hemithorax to less than 50%), and large (occupying >50 % of the hemithorax) [13]. Pleural aspiration was guided by chest US. Pleural fluid analysis was carried out according to Abbreviated Light's criteria to differentiate exudative from transudative effusion [14]. Pleural fluid samples were subjected to microbiological and cytological examination of the exudative type. Microbiological pleural study included aerobic bacterial culture, Ziehl–Neelsen staining, and fungal culture on Sabouraud dextrose agar. Pleural fluid adenosine deaminase was requested in lymphocytic effusion according to Perez-Rodriguez and Light [15]. Pleural biopsy was taken in patients with undiagnosed lymphocytic effusion. Closed pleural biopsy using Abrams needle was performed first according to the standardized technique, and if not diagnostic, we proceeded with thoracoscopic biopsy (KARL STORZ thoracoscope, Tuttlingen, Germany), which was carried out following the standardized technique [16,17]. Pleural TB was diagnosed by demonstration of caseating granuloma on histological examination of pleural biopsy specimens [15].

Biliary tract complications

Biliary complications were diagnosed by abdominal Doppler US, which revealed the presence of dilated bile ducts or bile collection (biloma). In cases in which US did not show evidence of bile-duct dilatation despite progressive jaundice, the next step was magnetic resonance cholangiopancreatography to diagnose biliary stricture. Endoscopic retrograde cholangiopancreatography was done for biliary stricture balloon dilatation and stent placement.

Intra-abdominal infections

Cholangitis associated with biliary stricture was diagnosed by the presence of fever, abdominal pain, and progressive jaundice, with elevated C-reactive

protein levels and leukocytosis or leukopenia. Infected biloma was diagnosed by a positive bacterial culture of a US-guided percutaneous aspirate. Bacterial peritonitis was diagnosed by the presence of an ascitic fluid neutrophil count of at least 250 cells/ml, with positive culture of percutaneous drainage, or an ascitic fluid neutrophil count greater than 500 cells/ml, with negative culture of percutaneous drainage [18].

Renal function evaluation

Serum creatinine was evaluated at every follow-up visit throughout the first year post LT. Acute renal dysfunction was diagnosed according to the Risk, Injury, Failure, Loss, and End-stage kidney disease classification [19].

Statistical analysis

Data were analyzed with SPSS version 21 (SPSS Inc., Chicago, Illinois, USA). The normality of the data was first tested with a one-sample Kolmogorov–Smirnov test. Qualitative data were described using numbers and percentages. Continuous variables were presented as mean±SD for parametric data and median (min–max) for nonparametric data. The two groups (patients with and those without delayed-onset pulmonary infections) were compared using Student's *t*-test (parametric data), the Mann–Whitney test (nonparametric data), and the χ^2-test or Fisher's exact test (categorical variables). Statistical significance is considered when the probability of error is less than 5% ($P \leq 0.05$).

Results

This prospective descriptive study included all patients who underwent LDLT at the Gastroenterology Center of Mansoura University between August 2013 and July 2014. These included 44 (88%) men and six (12%) women, with a mean age of 49.68±6.4 years (range 28–60 years). The follow-up period was divided into two periods: the first period (intermediate period) was from the second month post LT until the end of the fifth month, and the second period (late period) was from the sixth month until the end of the first year post transplantation. The primary indications for LT were post hepatitis C virus (HCV) cirrhosis [*n*=30 (60%)], hepatocellular carcinoma [*n*=18 (36%)], and other indications, including Budd–Chiari syndrome and cryptogenic cirrhosis [*n*=2 (4%)]. As regards the severity of the underlying liver disease before transplantation, the majority of the patients were of Child class C [*n*=28 (56%)]. The mean Model for End-Stage Liver Disease score was 15.34±3.88, ranging from 6 to 22 (Table 1).

The post-transplant delayed-onset chest infections in the studied cases are shown in (Fig. 1). Six patients (12%) developed chest infections [pneumonia (*n*=3 (6%)), pneumonia with parapneumonic effusion (*n*=2 (4%)), and pleural TB (*n*=1 (2%))]. Five patients developed chest infections within the intermediate period and one patient, within the late period.

Microbiologic cultures of the sputum, pleural fluid, blood, and BAL fluid isolated seven causative organisms of delayed-onset chest infections in the studied cases (Table 2). In the intermediate period, the frequency of bacterial pneumonia [*n*=6 (85.8%)] was higher than that of fungal pneumonia [*n*=1 (14.3%)]. Among the gram-negative bacilli, carbapenemase-producing *Enterobacteriaceae* spp. (CRE) [*n*=2 (28.6%)] was more frequent than multidrug-resistant (MDR) *Pseudomonas aeruginosa* [*n*=1 (14.3%)]. Among the gram-positive bacilli, the frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) [*n*=2 (28.6%)] was higher than that of *Streptococcus pneumoniae* [*n*=1 (14.3%)]. Only one episode of pleural TB occurred within the late period of 6–12 months post LT.

Table 3 shows the course of the six cases of post-transplant chest infections. Three patients (50%) showed complete resolution. Severe sepsis complicated the course of chest infections in three patients (50%). Three patients (50%) developed respiratory failure necessitating mechanical ventilation [one patient (16.7%) developed ARDS]. For patients with post-transplant delayed-onset chest infections, the length of ICU stay and duration of

Table 1 Criteria of the studied patients

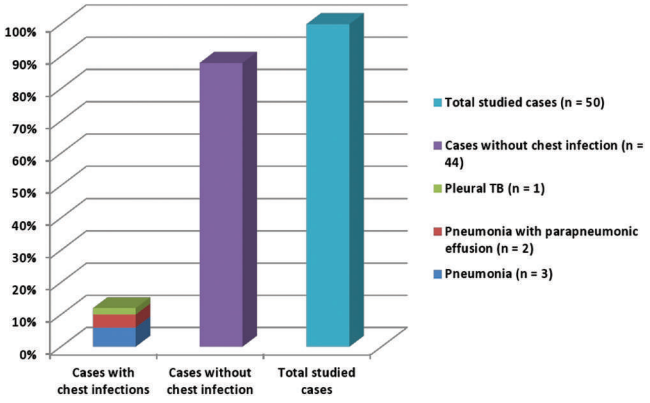
Total studied cases	*n*=50
Age (years)	
Mean±SD	49.68±6.4
Min–max	28–60
Sex [*n* (%)]	
Male	44 (88)
Female	6 (12)
Indications for liver transplantation [*n* (%)]	
Post HCV cirrhosis	30 (60)
HCC	18 (36)
Other indications	2 (4)
Child Pugh Score [*n* (%)]	
Child B	22 (44)
Child C	28 (56)
MELD score	
Mean±SD	15.34±3.88
Min–max	6–22

mechanical ventilation were significantly longer in comparison to those in patients who did not develop chest infections (P=0.001). There was a statistically significant association between post-transplant chest infections and acute renal dysfunction (P=0.009). Patients who developed chest infections had a significantly higher mortality rate than those who developed graft-related complications (P=0.009; Table 4).

Thirty patients developed post-transplant graft complications (Table 5): 17 (56.7%) patients developed cellular rejection; 14 (46.7%) developed intra-abdominal infections; 13 (43.3%) developed biliary complications, biliary strictures in 11 patients and biloma in two patients; and one patient (3.3%) developed recurrent hepatocellular carcinoma.

Figure 2 shows the Kaplan–Meier survival curve of the studied LT recipients. Five patients died during the follow-up period. As regards chest infection-related mortality, one patient died at the second month post LT and two patients died at the third month. For graft complication-related mortality, one patient died at the eighth month post LT and the other died at the 12th month.

Fig. 1



Post-transplant chest infections in the studied cases.

Table 2 Causative organisms of delayed-onset chest infections in the studied cases

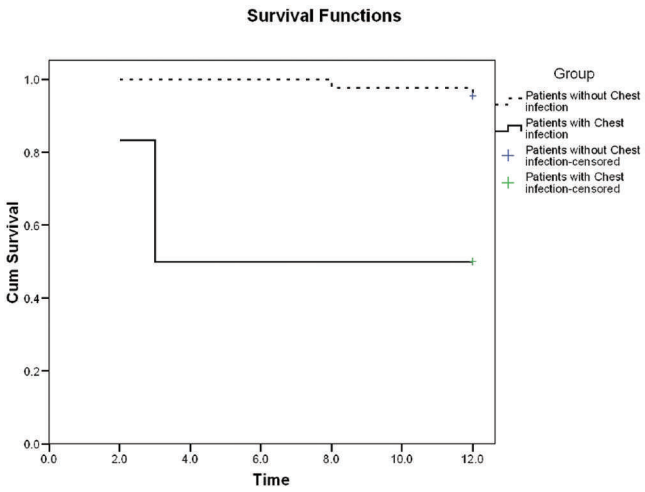
Causative organisms	n=7	100%
Gram-negative bacilli	3	42.9
CRE	2	28.6
MDR *Pseudomonas aeruginosa*	1	14.3
Gram-positive cocci	3	42.9
MRSA	2	28.6
Streptococcus pneumoniae	1	14.3
Fungal	1	14.3
Candida albicans	1	14.3

The post-transplant predictors of delayed-onset chest infections are shown in Table 6. Univariate analysis showed that the rates of persistent moderate-to-large post-transplant transudative pleural effusion (P=0.029) and the use of tacrolimus (P=0.021) were significantly higher for patients with post-transplant delayed-onset chest infections versus patients without chest infections. However, there was no statistically significant association between post-transplant delayed-onset chest infections and the use of cyclosporine and everolimus (P=0.378 and 0.297, respectively). In addition, there was no statistically significant association between post-transplant delayed-onset chest infections and the occurrence of cellular rejection and intra-abdominal infections (P=0.378 and 1, respectively).

Discussion

LT is now an accepted therapy for patients with terminal liver disease. LT recipients are liable to many infectious and noninfectious complications, especially post-transplant pneumonia because of its negative impact on the outcome of LT [20]. Hence, the aim of this study was to analyze delayed-onset chest

Fig. 2



Kaplan–Meier survival curve of the studied LT recipients. LT, liver transplant.

Table 3 Course of post-transplant chest infections in the studied cases

Patients with chest infections[a]	n=6	100%
Resolved	3	50
Mortality	3	50
Severe sepsis	3	50
Respiratory failure + mechanical ventilation	3	50
ARDS	1	16.7

Table 4 Outcomes of post-transplant delayed-onset chest infections

	Patients with chest infections (*n*=6)	Patients without chest infections (*n*=44)	*P*-value
Ward stay [median (min–max)]	27 (9–50)	16 (0–34)	*Z*=1.95, *P*=0.052
ICU stay [median (min–max)]	14 (0–40)	0 (0–6)	*Z*=4.2, *P*=0.001
MV duration [median (min–max)]	10 (0–32)	0 (0–6)	*Z*=3.25, *P*=0.001
Acute renal dysfunction [*n* (%)]	3 (50)	2 (4.5)	*P*=0.009*
Mortality [*n* (%)]	3 (50)	2 (4.5)	*P*=0.009*

Table 5 Graft complications in the studied cases

Studied cases with graft complications[a]	(*n*=30)	100%
Cellular rejection	17	56.7
Intra-abdominal infections	14	46.7
Biliary complications (biliary stricture and biloma)	13	43.3
Recurrent HCC	1	3.3
Mortality	2	6.7

infections that developed after the first month post transplantation until the end of the first year to determine their frequencies, causative microorganisms, associated risk factors, and effects on mortality.

The results of this study revealed that the majority of the studied patients (60%) indicated for LT had post-HCV cirrhosis, and 36% had well-differentiated HCC. Similarly, Weiss *et al.* [4] showed that the underlying liver diseases in their recipients were viral hepatitis-related cirrhosis [*n*=57 (38.5%)], alcoholic liver disease [*n*=50 (33.8%)], and biliary cirrhosis [*n*=18 (12.2%)]. However, Lin *et al.* [1] reported that the primary indications for LT were post-HBV cirrhosis (*n*=59), primary liver cancer with cirrhosis (*n*=41), Wilson's disease with cirrhosis (*n*=3), proximal hepatic cholangiocarcinoma (*n*=2), and alcoholic cirrhosis (*n*=2). The difference in the results can be attributed to the fact that Egypt has the highest HCV prevalence in the world, proved by The Egyptian Demographic Health Survey, a cross-sectional survey including HCV biomarkers that was conducted in 2008 on a large nationally representative sample and estimated HCV prevalence among the 15–59-year age group to be 14.7% [21]. However, the estimated prevalence of HCV infection in the USA was 1.0% (95% confidence interval, 0.8–1.2%), corresponding to 2.7 million chronically infected individuals [22].

The results of this study reported the development of delayed-onset chest infections in six patients (12%), which corresponds to that reported by Chen and colleagues, who performed a retrospective analysis of 68 LT recipients. They showed the anatomical sites of the bacterial infections during the intermediate and late periods; the biliary tract was the most common site (16 episodes, 32%), followed by the blood stream (six episodes, 12%), liver (abscesses, three episodes, 6%), and lungs (pneumonia, two episodes, 4%) [23]. In addition, Golfieri *et al.* [24] reported that nine among the 300 LT recipients developed intermediate and late pneumonia; in six patients pneumonia occurred during the second month, and three had late-onset pneumonia. Similarly, a study conducted on 251 LDLT recipients in Ain Shams University Specialized Hospital and Egypt Air Specialized Hospital reported pneumonia in 8.9% of patients [25]. Other studies showed that up to 95% of the post-transplant pneumonia episodes occurred within the first 6 months, with the highest incidence during the first month [26,27].

The results of this study showed that seven pathogens were found for these six episodes of chest infections; one episode was polymicrobial. Bacterial pneumonia was more frequent than fungal pneumonia [gram-negative bacilli and gram-positive bacilli had the same frequencies (each 42.9%), and the frequency of fungal infection was 14.3%]. Bronchoscopy with BAL was performed in three patients, sputum microbiology was studied in two patients, and pleural fluid cultures were performed in two patients. One patient underwent thoracoscopic biopsy, which revealed caseating granuloma, consistent with pleural TB. The detected microorganisms were CRE, MRSA, MDR *P. aeruginosa*, *S. pneumoniae*, and *Candida albicans*. These results were in agreement with those of the Ain Shams study, which showed that pneumonia was commonly caused by bacterial infection, mainly by gram-negative organisms (70%), whereas gram-positive bacterial infection, fungal infection, and viral

Table 6 Posttransplant predictors of delayed-onset chest infections

Variable	Patients with delayed-onset chest infections (*n*=6)	Patients without chest infections (*n*=44)	*P*-value
Demographic data			
Age (mean±SD)	50.8±5.7	49.52±6.53	*t*=0.467, *P*=0.643
Sex [*n* (%)]			
Male	4 (66.7)	40 (90.9)	χ^2=2.938, *P*=0.086
Female	2 (33.3)	4 (9.1)	
Persistent moderate-to-large post-transplant transudative pleural effusion [*n* (%)]	3 (50)	4 (9.1)	*P*=0.029*
Immunosuppressive therapy [*n* (%)]			
Tacrolimus	5 (83.3)	15 (34.1)	χ^2=5.335, *P*=0.021
Cyclosporine	3 (50)	30 (68.2)	χ^2=0.778, *P*=0.378
Everolimus	2 (33.3)	7 (15.9)	χ^2=1.086, *P*=0.297
Graft-related complications [*n* (%)]			
Cellular rejection	3 (50)	14 (31.8)	χ^2=0.778, *P*=0.378
Intra-abdominal infections	2 (33.3)	12 (27.3)	*P*=1*

*Fisher's exact test.

infection represented 18.2, 10.4, 1.3% of the pneumonia cases, respectively [25]. In addition, Zhong *et al.* conducted a retrospective cohort study including 217 LT patients and reported 67 isolates of multidrug-resistant gram-negative bacteria from 66 infected LT patients [28].

After LT, bacterial infections comprise the most frequent type of infection, followed by fungal infections. Reactivation of latent infections, including those caused by *Mycobacterium* spp., might occur [29]. Currently the emergence of multidrug-resistant bacteria is of great concern in LT patients. The prevalence of extended-spectrum β-lactamase-producing Enterobacteriaceae, CRE, MDR *Acinetobacter* spp., MDR *Pseudomonas* spp., MRSA, and vancomycin-resistant *Enterococci* spp. is increasing and related to higher rates of treatment failure [30,31].

This study revealed that 30 patients developed post-transplant graft complications, with reported mortality in only two cases (graft failure from cellular rejection in one case and recurrent multifocal HCC with graft cirrhosis in the other case). Consistent with the results of this study, Wadhawan *et al.* [32] reported an incidence of biliary complications of 19% (65 patients) among 338 LT recipients, with no statistically significant difference in survival between those with and those without biliary complications. Osorio *et al.* [33] reported that 34 of 248 LT recipients developed cellular rejection, with only two deaths (5.88%).

As regards the six patients with post-transplant chest infections in this study, 50% developed respiratory failure necessitating mechanical ventilation that was complicated by severe sepsis, and this resulted in significantly longer durations of ICU stay and mechanical ventilation in comparison to those in patients who did not develop chest infections (*P*=0.001). In addition, there was a statistically significant association between post-transplant chest infections and post-transplant acute renal dysfunction (*P*=0.009). Hence, patients who developed delayed-onset chest infections had a significantly higher mortality (50%) than those who developed graft-related complications (4.5%) (*P*=0.009). Similarly, Golfieri *et al.* [24] reported mortality in five of nine patients who developed intermediate and late pneumonia (all cases of mortality were within the second month). The Ain Shams study reported a 1-year mortality from post-transplant pneumonia of 10.8% [25].

As regards the risk factors associated with delayed-onset chest infections, univariate analysis showed that the rates of persistent moderate-to-large post-transplant transudative pleural effusion (*P*=0.029) and the use of tacrolimus (*P*=0.021) were significantly higher for patients with post-transplant delayed-onset chest infections than for those without

chest infections. In agreement with these results, Golfieri *et al.* [24] reported that persistent pleural effusion and atelectasis were the major independent predictors of post-transplant pneumonia (odds ratio=3.95, 95% confidence interval=2.16–7.25, $P \leq 0.001$). In addition, Valdez-Ortiz *et al.* [34] found an increase in the number of episodes of infection occurring during the early and late periods as a result of a shift in immunosuppressive therapy toward tacrolimus. Tacrolimus is 10–100 times more potent than cyclosporine and displays similar adverse effects to cyclosporine, with perhaps less hypertension and hypercholesterolemia but more neurotoxicity and diabetes and impaired glycemic control in diabetic patients [35,36].

However, this study revealed that post-transplant intra-abdominal infections were not associated with increased risk for post-transplant chest infections ($P=1$). In addition, there was no statistically significant association between post-transplant delayed-onset chest infections and the use of cyclosporine or everolimus ($P=0.378$ and 0.297, respectively). Consistent with the results of this study, Valdez-Ortiz *et al.* [34] reported that there was no statistically significant association between post-transplant infections and the use of cyclosporine or everolimus.

In agreement with the results of this study, which revealed no statistically significant association between post-transplant delayed-onset chest infections and the occurrence of cellular rejection (50 vs. 31.8%, $P=0.378$), Golfieri *et al.* reported that the occurrence of rejection did not represent a statistically significant risk factor for pneumonia ($P=0.177$) [24]. In addition, Chen *et al.* [23] reported that there was no statistically significant association between the occurrence of rejection and development of infections within 1 year post transplantation ($P=0.68$).

Conclusion

Although post-transplant chest infections have a lower incidence than other types of infections, they are major causes of morbidity and mortality in LT recipients. *M. tuberculosis* should be considered within the differential diagnosis of post-transplant delayed-onset chest infections. Early investigation by chest imaging of LT recipients presenting with any respiratory symptom, even only cough, during their regular follow-up visits to the transplant clinic is mandatory because the presentation of chest infections are usually nonspecific or subtle in these immunosuppressed patients, and early diagnosis and management may improve the outcome.

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Conflicts of interest

Author contributions: Mohammad Khairy El-Badrawy contributed to the concept and design of study; Rehab Ahmad Elmorsey contributed to the acquisition of data; Dr Raed El-Metwaly Ali and Amr Mohamad Yassen contributed to the analysis and interpretation of data; Mohammad Khairy El-Badrawy, Dr Raed El-Metwaly Ali, Mohammad Ahmad Abou Elela, and Rehab Ahmad Elmorsey contributed to drafting of the article. Mohammad Khairy El-Badrawy and Dr Raed El-Metwaly Ali contributed to revising the article critically for important intellectual content. All authors provided final approval for the version to be published.

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