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RESEARCH ARTICLE

The frequency and clinical features of post-transplant pneumonia in solid-organ transplantation recipients: A transplant center experience

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ABSTRACT

The frequency and clinical features of post-transplant pneumonia in solid-organ transplantation recipients: A transplant center experience

Introduction: In solid-organ transplant (SOT) recipients, while survival rates have improved with immunosuppressive therapies, the risk of opportunistic infections has also increased. This study aimed to evaluate the frequency of pneumonia, identify microbiological factors, investigate diagnostic methods, and analyse prognosis.

Materials and Methods: A retrospective study was conducted to identify adult SOT recipients referred to the pulmonary diseases department with a preliminary pneumonia diagnosis between 2011 and 2019. Data on demographics, clinical and transplantation characteristics, pneumonia frequency, microbiological sampling methods, pathogens, radiological findings, and prognosis were collected. Confirmed pneumonia was defined as symptoms consistent with pneumonia alongside microbiological confirmation.

Results: We conducted 426 pulmonary consultations involving 168 patients (86 kidney; 82 liver transplant recipients) with a preliminary pneumonia diagnosis. Pneumonia was diagnosed in 87% of the cases, with common findings including multiple symptoms, glucocorticoid use, focal or multilobar infiltrations, and diffuse ground-glass nodules. Pneumonia frequency was higher during the first, sixth, and twelfth months for liver transplants and after twelve months for kidney transplants. Diagnostic sampling was conducted for

128 patients, with a success rate of 63.3%. Of 476 respiratory samples, 32.6% yielded diagnoses, with bacterial growth detected in 42.9%, predominantly *Pseudomonas aeruginosa*. Microbiological agents were isolated by 18.4% using non-invasive methods, 15.5% using invasive methods. Non-invasive methods primarily isolated gram-positive and gram-negative bacteria, *Acinetobacter* spp., *Klebsiella* spp., *Haemophilus* spp., whereas invasive methods were more effective for *Candida* spp. *Acinetobacter* spp. was more prevalent in liver transplant patients and fungal species in kidney transplant patients. Intensive care unit admission occurred in 36.3% of the patients, 19% died.

Conclusion: While pneumonia was common among SOT recipients, the associated mortality rate was relatively low. Over half the patients were diagnosed through microbiological sampling. Invasive sampling is valuable for non-bacterial agents. Due to high gram-negative bacteria frequency and early post-transplant pneumonia, increased attention is needed for hospital-acquired agents.

Key words: Solid-organ transplantation; pneumonia; microbiological factors

ÖZ

Solid organ nakli alıcılarında post-transplant pnömoni sıklığı ve klinik özellikleri: Bir transplant merkezi deneyimi

Giriş: Solid organ nakli alıcılarında, bağışıklık baskılayıcı tedavilerle sağkalım oranları artarken aynı zamanda fırsatçı enfeksiyon riski de yükselmektedir. Bu çalışmada, merkezimizde takip edilen böbrek ve karaciğer nakli alıcılarında pnömoni sıklığını, mikrobiyolojik etkenleri, tanı yöntemlerini ve prognozu değerlendirmek amaçlanmıştır.

Materyal ve Metod: 2011-2019 yılları arasında pnömoni ön tanısı ile göğüs hastalıkları bölümüne danışılan yetişkin solid organ nakli alıcıları geriye dönük olarak incelendi. Demografik veriler, klinik ve nakil özellikleri, pnömoni sıklığı, mikrobiyolojik örnekleme yöntemleri, patojenler, radyolojik bulgular ve prognoz ile ilgili veriler toplandı. Mikrobiyolojik testlerle doğrulanan ve semptom ile bulguları uyumlu olan vakalar pnömoni olarak kabul edildi.

Bulgular: Göğüs hastalıklarına yapılan 426 konsültasyon doğrultusunda 168 hasta (86 böbrek; 82 karaciğer nakli alıcısı) pnömoni ön tanısı ile değerlendirilmiştir. Hastaların %87'sinde pnömoni tanısı düşünülmüş; çoklu semptomlar, glukokortikoid kullanımı, fokal veya multilobar infiltrasyon ile yaygın buzlu cam nodülleri daha sık saptanmıştır. Karaciğer nakli alıcılarında pnömoni sıklığı ilk bir ay, ilk altı ay ve ilk 12 ayda, böbrek nakli alıcılarında ise ilk 12 aydan sonra daha yüksekti. Yüz yirmi sekiz hastadan örnekleme yapıldı ve %63,3'ünde tanısız sonuçlar elde edildi. Toplam 476 solunum yolu örneğinden %32,6'sı tanı sağladı; %42,9'unda, çoğunlukla *Pseudomonas aeruginosa* olmak üzere, bakteriyel üreme tespit edildi. Mikrobiyolojik etkenler, %18,4 ile non-invaziv, %15,5 ile invaziv yöntemlerle izole edildi. Non-invaziv yöntemlerle genellikle gram-pozitif ve gram-negatif bakteriler, *Acinetobacter* spp., *Klebsiella* spp., *Haemophilus* spp. tanısı konulurken; invaziv yöntemlerle *Candida* spp. daha üstün şekilde elde edildi. *Acinetobacter* spp. karaciğer nakli alıcılarında, mantar türleri ise böbrek nakli alıcılarında daha sık görüldü. Yoğun bakım ünitesi yatışı %36,3 oranında gerçekleşti, %19'u hayatını kaybetti.

Sonuç: Solid organ nakli alıcılarında pnömoni sıklığı yüksek, ancak mortalite nispeten düşüktü. Mikrobiyolojik örnekleme ile hastaların yarısından fazlasında tanı konulabildi. Bakteri dışı etkenler için invaziv örnekleme değer taşımaktadır. Gram-negatif bakteri sıklığı ve nakil sonrası erken dönemde pnömoni göz önünde bulundurulduğunda hastane kaynaklı etkenlere karşı daha dikkatli olunmalıdır.

Anahtar kelimeler: Solid organ nakli; pnömoni; mikrobiyolojik etkenler

INTRODUCTION

Pneumonia is a common infectious complication of solid-organ transplantation (SOT) (1). Its differential diagnosis depends on various non-specific factors, including age, transplanted organ type, post-transplantation duration, immunosuppression status, environmental exposures, pneumonia development site (community, hospital), and radiological infiltrative pattern (2). The incidence of pneumonia in this population varies by type of transplant (2-4). Studies have shown that it is the second most frequent infectious complication after liver transplantation and less frequent in kidney transplantation (5,6).

Numerous microorganisms can cause pneumonia in the SOT recipients, making it a significant cause of morbidity and mortality, with an incidence of 19.4 episodes per 1000 population on follow-up per year (7).

Pneumonia often occurs early after transplantation and affects both graft and recipient survival, as well as increasing the healthcare cost for SOT recipients (8). Despite historically high mortality rates, recent data suggest a possible decline (9). Hospital-acquired and fungal infections are particularly prevalent during the first month post-transplant. Between first and sixth months, infections by *Aspergillus* and *Pneumocystis jirovecii* are prominent. Especially high-dose steroid use may lead to *Nocardia* infections.

Diagnosis in an immunocompromised patient requires a combination of clinical history, physical and radiological examinations, and microbiological or pathological examination of respiratory tract samples obtained by invasive or non-invasive methods is important. Diagnostic evaluation should be guided

by clinical radiological features. However, the diagnostic approach to pneumonia in SOT recipients is not standardized, and recent guidelines lack specific recommendations for this population (10).

Since 1992, a total of 1.042 solid organ transplants (primarily kidney and liver) have been performed in the transplant unit of our tertiary care university hospital. These patients, along with others who had undergone transplants at different centres, have been followed by our transplant team since then. After 2011, a multidisciplinary approach was established, enabling regular evaluations by specialized consultants, including pulmonary specialists.

A comprehensive evaluation of pneumonia in this patient group was planned at our centre. This study aimed to investigate the frequency of pneumonia, microbiological factors, diagnostic methods, and prognosis in kidney transplant (KT) and liver transplant (LT) recipients followed at our centre between January 2011 and December 2019.

MATERIALS and METHODS

This study was approved by the local ethics committee (Decision No: 2020/27-20) and conducted in full accordance with the ethical guidelines of the Declaration of Helsinki (1975). Given its retrospective nature, the requirement for informed consent was waived. The analysis was based on data obtained from the hospital's electronic medical records, including demographic, clinical, laboratory-microbiological, and radiological characteristics, following necessary permissions.

This retrospective, observational, descriptive study included KT and LT recipients followed in our centre, aged ≥ 18 years who were consulted to our pulmonary diseases department with a preliminary diagnosis of pneumonia between January 1, 2011, and December 31, 2019. Patients were screened with ICD codes (Z94, Z94.0, Z94.4, Z94.8, Z94.89, Z94.9) in the hospital database. Pneumonia was defined according to Centers for Disease Control and Prevention (CDC) criteria (11). A total of 168 SOT recipients met the inclusion criteria for this analysis.

Immunosuppressive Protocol and Antimicrobial Prophylaxis

The immunosuppressive protocol consisted of corticosteroids, mycophenolate mofetil (MMF), and cyclosporine (CsA) or tacrolimus (Tac). Antiviral and

antifungal prophylaxes were not routinely administered; however, KT recipients received trimethoprim-sulfamethoxazole prophylaxis for six months post-transplant.

Microbiological Examination

All samples collected under a preliminary diagnosis of pneumonia were microbiologically evaluated. Sputum, endotracheal aspirate (ETA), bronchial lavage (BL), and bronchoalveolar lavage (BAL) fluid samples were collected, carried out, and evaluated according to the criteria outlined by The Turkish Thoracic Society (TTS) Consensus Report on the Diagnosis and Treatment of Pneumonia in Immunocompromised Adults (12). The TTS Consensus Report on the Diagnosis and Treatment of Community-Acquired Pneumonia in Adults is used to explain the diagnostic and treatment criteria for community-acquired pneumonia (13). Microscopic detection of *P. jirovecii* was performed by ECIL guidelines (14).

Diagnostic Criteria

The diagnostic thresholds for quantitative culture results from lower respiratory secretions were as follows, 10^5 - 10^6 colony-forming units (CFU)/mL for sputum, ETA, BL, and 10^4 CFU/mL for BAL (15).

Statistical Analysis

Data were analysed using SPSS software version 26 (IBM Corp., Armonk, NY, USA). We used mean and standard deviation or median and 25th-75th percentiles according to the distribution of the data. For parametric evaluations, we used the Student's t-test; for non-parametric values, we used the Mann-Whitney U test. Categorical data were evaluated by chi-square or Fisher's exact test. $p < 0.05$ was considered significant.

RESULTS

Patients' Characteristics

Between January 1, 2011, and December 31, 2019, a total of 168 adult SOT recipients [86 (51.2%) KT, 82 (48.8%) LT] were consulted by the department of pulmonary diseases at least once for post-transplant pulmonary infections, resulting in 426 consultations [median: 2 (1-3) per patient]. Median age at consultation was 58 years (51-63) for LT and 53 years (43-59) for KT recipients. Majority of the patients were male (75.0%, $n = 126$). Additionally, 143 transplants (85.1%) were performed at our centre. Living donor

transplants were more frequent (57.1%, n= 96). Preoperatively, 17.3% of the patients did not receive any prophylaxis for *P. jirovecii* or latent tuberculosis infection (LTBI) and data on prophylaxis was unavailable for 66 patients (39.3%).

Median time to the first consultation for post-transplant pneumonia was 34.5 months (9-120). Clinical presentations included cough and sputum (27.4%), fever (13.7%), dyspnea and hypoxemia (11.9%), chest pain (0.6%), multiple symptoms (≥ 2 symptoms) (35.7%), and atypical symptoms (7.1%). Six patients (3.6%) had no symptoms.

Diagnostic Approach

A total of 476 respiratory tract samples were collected from 168 consulted patients, and 155 samples (32.6%) were diagnostic. Invasive sampling via fiberoptic bronchoscopy (FOB) was performed in 80 patients (47.6%), including BAL in 65 patients (38.7%). Additionally, a diagnostic tissue biopsy was carried out in one patient. At least one airway sampling method was used in 128 patients (76%), while two or more sampling methods were employed in 61 patients (36%), with a median of two methods per patient (1-4). Microbiological diagnosis was confirmed in 81 patients (63.3%). Non-invasive methods (sputum and ETA) identified microorganisms in 31 patients (18.4%), combined invasive and non-invasive methods in 32 patients (19.0%), and invasive methods (specifically FOB) alone in 26 patients (15.5%). Microbiological

cultures were positive in 88 patients (52.4%), and *P. jirovecii* was detected in one patient via polymerase chain reaction (PCR) test (Table 1).

Bacterial pathogens were isolated in 72 patients (42.9%). *Streptococcus pneumoniae* was the most common gram-positive bacterium (4.8%), while gram-negative bacteria were more prevalent overall, with 92 samples (52.0%) from 60 patients (35.7%) (Table 2). *Pseudomonas aeruginosa* was the most frequently detected gram-negative bacterium found in 19 patients (11.3%) with both gram-negative staining and positive culture results. Ziehl-Neelsen staining was positive in 17 patients, with *Mycobacterium tuberculosis complex* (MTC) growth observed in 9 (5.3%) and non-tuberculous mycobacteria (NTM) detected in the remainder. *Acinetobacter* spp. was more commonly identified in LT patients ($p= 0.047$), while fungal pathogens were more frequent in KT patients ($p= 0.022$). No other significant differences were observed in pathogen detection based on transplant type, underlying etiological factors, transplant centre, donation type, prophylaxis regimen, symptoms, or immunosuppressive therapy. Fungal examinations was conducted in 75 patients and fungal pathogens were isolated in 49 patients (29.2%) (Table 2). *P. jirovecii* was the most frequently detected fungal pathogen, identified in 24 cases, followed by *Candida* spp., *Aspergillus* spp.

Table 1. Diagnostic samples, sampling state and growth of cultures of the patients

		n (%)
Diagnostic sample methods	Sputum	40 (25.8)
	Endotracheal aspirate	28 (18.1)
	Bronchial lavage	43 (27.7)
	Bronchoalveolar lavage	43 (27.7)
	Tissue	1 (0.6)
	Total	155 (100.0) of the samples*
Growth state	Culture positivity	88 (52.4)
	No growth	26 (15.5)
	Mixed growth	12 (7.1)
	Unqualified sample	2 (1.2)
	Total	128 (76.2) of the patients [†]
	No sampling	40 (23.8)
Total		168 (100.0) patients

*Samples were not taken from all patients, and some of the patients sampled were diagnosed with more than one diagnostic method.
[†]The growth state is related to the general reproductive status of the patient.

Table 2. Distribution of microbiological pathogens obtained in the samples

Pathogens			Samples (n)	KT patients n= 86	LT patients n= 82
Bacteria	Gram (+) stain	<i>Streptococcus</i> spp.	8	2 (25.0)	6 (75.0)
		<i>Staphylococcus</i> spp.	2	1 (50.0)	1 (50.0)
		CoNS	2	2 (100.0)	0 (0.0)
		<i>Diphtheroid bacillus</i>	2	0 (0.0)	2 (100.0)
		<i>Nocardia</i> spp.	1	0 (0.0)	1 (100.0)
		<i>Enterococcus</i> spp.	1	0 (0.0)	1 (100.0)
	Gram (-) stain	<i>Pseudomonas</i> spp.	19	11 (57.9)	8 (42.1)
		<i>Acinetobacter</i> spp.	23	7 (30.4)	16 (69.6)
		<i>Klebsiella</i> spp.	15	6 (40.0)	9 (60.0)
		<i>Haemophilus</i> spp.	16	9 (56.3)	7 (43.8)
		<i>S. maltophilia</i>	10	5 (50.0)	5 (50.0)
		<i>Enterobacter</i> spp.	5	5 (100.0)	0 (0.0)
		<i>Moraxella catarrhalis</i>	4	1 (25.0)	4 (75.0)
		<i>Proteus</i> spp.	3	0 (0.0)	3 (100.0)
		<i>Escherichia coli</i>	2	2 (100.0)	0 (0.0)
		Unidentified	1	0 (0.0)	1 (100.0)
	MTC		9	4 (44.4)	5 (55.6)
	NTM	<i>Mycobacterium abscessus</i>	1	0 (0.0)	1 (100.0)
		<i>Mycobacterium fortuitum</i>	1	1 (100.0)	0 (0.0)
		Unidentified	6	3 (50.0)	3 (50.0)
Fungus		<i>P. jirovecii</i>	24	14 (58.3)	10 (41.7)
		<i>Candida</i> spp.	21	12 (57.1)	9 (42.9)
		Yeast-like fungi except <i>P. jirovecii</i>	6	4 (66.7)	2 (33.3)
		<i>Aspergillus</i> spp.	6	4 (66.7)	2 (33.3)
		<i>Penicillium</i> spp.	1	0 (0.0)	1 (100.0)
		<i>Trichosporon</i> spp.	2	1 (50.0)	1 (50.0)
Total			191		

Data are given as n (%) unless otherwise stated.
 CoNS: Coagulase-negative staphylococci, KT: Kidney transplant, LT: Liver transplant, MTC: *Mycobacterium tuberculosis* complex, NTM: non-tuberculous mycobacteria, *P. jirovecii*: *Pneumocystis jirovecii*, *S. maltophilia*: *Stenotrophomonas maltophilia*.

The growth of gram-positive bacteria ($p= 0.012$), gram-negative bacteria ($p= 0.030$), *Acinetobacter* spp. ($p= 0.013$), *Klebsiella* spp. ($p= 0.005$), and *Haemophilus* spp. ($p= 0.031$) was more frequent with non-invasive methods. In contrast, *Candida* spp. was more commonly detected using invasive methods ($p= 0.018$). Across transplant types, gram-positive bacteria ($p= 0.001$), *S. pneumoniae* ($p= 0.011$), *Klebsiella* spp. ($p= 0.005$), and *Haemophilus* spp. ($p< 0.001$) grew more frequently in sputum cultures, while gram-negative bacteria ($p< 0.001$) and *Acinetobacter* spp. ($p< 0.001$) were more common in

ETA samples. Culture positivity was higher in samples obtained via FOB ($p< 0.001$), and *Pseudomonas* spp. ($p< 0.001$), *P. jirovecii* ($p= 0.001$), *Aspergillus* spp. ($p= 0.016$), and other fungi (excluding *P. jirovecii*) ($p< 0.001$) were more found in BAL samples.

Pneumonia occurred at a median of 33 months (8-120) following transplantation. LT patients experienced pneumonia sooner, with a median onset of 12 months (4-45) compared to 91 months (23-132) in KT patients ($p< 0.001$). Pneumonia was more frequent in LT patients within the first month ($p= 0.002$),

Table 3. Thoracic CT findings of the patients and radiological pattern distribution within each group

Radiological patterns	All patients n= 168	KT patients n= 86	LT patients n= 82
Focal consolidation	59 (35.1)	26 (30.2)	33 (40.2)
Diffuse ground-glass nodules	35 (20.8)	19 (22.1)	16 (19.5)
Multilobar infiltration	33 (19.6)	23 (26.7)	10 (12.2)
Centrilobular nodules	18 (10.7)	12 (14.0)	6 (7.3)
Cavities	11 (6.5)	8 (9.3)	3 (3.7)
Mass or metastatic nodules	6 (3.6)	1 (1.2)	5 (6.1)
Pleural effusion	52 (31.0)	20 (23.3)	32 (39.0)
Mediastinal lymphadenopathy	3 (1.8)	0 (0.0)	3 (3.7)
No abnormality	13 (7.7)	6 (7.0)	7 (8.5)

Data are given as n (%) unless otherwise stated. Column percentages are given.
KT: Kidney transplant, LT: Liver transplant, CT: Computed tomography.

the first six months ($p < 0.001$), and the first 12 months ($p < 0.001$), whereas it predominantly occurred in KT patients after 12 months ($p < 0.001$). Pneumonia onset within the first six months was more common in patients receiving Tac ($p = 0.012$) and glucocorticosteroids (GCs) ($p = 0.017$), while patients receiving everolimus (EVE) had a lower incidence ($p = 0.026$). Bacterial infections occurred earlier, particularly, within the first month, six months, and 12 months, while MTC infections were observed in the first 12 months. Fungal infections, including *Candida* spp., yeast-like fungi, and *P. jirovecii* were identified after 12 months, although none of these differences were statistically significant.

The thoracic CT findings are presented in Table 3. Multilobar infiltration was observed more frequently in KT patients ($p = 0.018$), while pleural effusion was more common in LT patients ($p = 0.027$). Pleural effusion was significantly more prevalent in patients exhibiting symptoms of dyspnea and hypoxemia ($p = 0.003$). ETA was the most common diagnostic method employed for patients with focal and multilobar infiltration ($p = 0.006$; $p = 0.022$, respectively), centrilobular nodules ($p = 0.040$), and diffuse ground-glass nodules ($p = 0.021$). Focal infiltration was associated with a higher prevalence of bacterial growth ($p = 0.004$), particularly gram-negative bacteria ($p = 0.010$).

Among the evaluated patients, 146 (86.9%) required hospitalization, with 53 patients (36.3%) needing admission to an intensive care unit (ICU) during their hospitalization. ICU admissions were higher in patients with pneumonia during the first- and sixth months post-transplantation ($p < 0.001$; $p = 0.002$, respectively). Bacterial infections ($p < 0.001$), gram-

negative bacteria ($p < 0.001$), *Acinetobacter* spp. ($p < 0.001$), and *Klebsiella* spp. ($p = 0.002$) were more common in ICU admissions. Focal infiltration ($p = 0.001$) and pleural effusion ($p < 0.001$) were also more prevalent among ICU admissions.

Of the 168 patients, 135 (80.4%) were discharged with full recovery, one was lost to follow-up, and 32 (19%) died. Mortality was significantly higher among patients with pneumonia within the first six months post-transplant ($p = 0.042$). Non-surviving patients more frequently had bacterial infections ($p = 0.019$), especially gram-negative bacteria ($p = 0.010$), *Acinetobacter* spp. ($p = 0.001$), and *Klebsiella* spp. ($p = 0.021$). Additionally, ICU admissions were notably higher among patients who did not survive ($p < 0.001$).

DISCUSSION

This study provides a detailed analysis of post-transplant pulmonary infections in adult SOT recipients spanning approximately 10 years, offering key insights into the frequency, etiology, and clinical management of these infections. The median time to pneumonia development was significantly shorter in LT recipients. We found that both invasive and non-invasive diagnostic methods play important roles, emphasizing the need to optimize these processes for better clinical outcomes. Notably, 86.9% of patients required hospitalization, with 36.3% admitted to the ICU, primarily due to pneumonia within the first six months post-transplant. The presence of gram-negative bacteria, such as *Acinetobacter* spp. and *Klebsiella* spp., correlated with increased ICU admissions, highlighting the critical need for effective infection management strategies during the post-transplant period.

In line with previous studies, male patients were predominant among those developing pneumonia post-transplantation (16). Comparative studies in Italy and Spain have similarly reported a median age of 62 in SOT recipients with post-transplant pneumonia, likely reflecting the demographic composition of the older population in those regions (17). This may be related to the large elderly population in those countries. In another Turkish cohort, a 24-year follow-up revealed pneumonia in 20% of SOT recipients, with a mean age of 37.6 years and a predominance of male patients (72%) (18).

Notably, prophylaxis guidelines emphasize *P. jirovecii* prophylaxis for 3-6 months following KT or LT in Europe (19,20). Similarly, pre-transplant LTBI prophylaxis is advised for SOT recipients (21). In our centre, prophylaxes were provided to 28 (16.7%) SOT recipients for *P. jirovecii* and 15 (8.9%) for LTBI, with durations of six and nine months, respectively. Pulmonary consultations advised against LTBI prophylaxis in 17.8% of the cases due to a low perceived need, although retrospective review limited data from 67 patients. Neofytos et al. stated that the vast majority (2465, 86.7%) of SOT received primary *P. jirovecii* prophylaxis for a median duration of 176 days (22). In England, Periselneris et al. have reported out of 912 KT recipients that 243 (26.6%) received isoniazid for LTBI; however, 42 (4.6%) patients who needed prophylaxis did not (23). It is obvious that the number of recipients receiving LTBI will increase in our country, considering that the tuberculosis burden should be considered, and the processes are working according to the guidelines in our centre.

Our study revealed that the frequency of pneumonia was 87% (92% in KT patients, 82% in LT patients), out of the total patients consulted to the department of pulmonary diseases for a preliminary diagnosis of pneumonia. Prior studies have reported pneumonia incidence rates of 8-23% following LT and 25-30% after KT (24,25). The reason for the high prevalence of pneumonia in our study is thought to be that the study population consisted of patients who had already been consulted with pulmonary diseases with this preliminary diagnosis, that was, selected patients.

Clinical manifestations of pneumonia in SOT recipients are diverse, influenced by immunosuppression and the wide array of potential pathogens (26). While typical symptoms such as fever, cough, sputum production, dyspnea, and hypoxemia were common in

our study, a small proportion of patients (7.1%) presented with atypical symptoms, consistent with other reports from Türkiye (18). Duration and severity of symptoms can be important clinical clues. Acute-onset symptoms are often indicative of bacterial pneumonia, whereas a more gradual presentation may suggest fungal, mycobacterial, or *P. jirovecii* infections (26). Chronic cough, persistent fever, or unexplained hypoxemia may be the only clinical signs of infection in these patients. Also, we found a statistically significant association between fever symptoms and the detection of *Candida* spp. and MTC.

Diagnostic sampling played a critical role, with at least one airway sampling method used in 128 patients (76%) and two or more methods in 61 (36%). Microbiological diagnosis was achieved in 81 (63.3%) patients. These findings are comparable with previous reports, where etiological diagnoses were achieved in 60.7% of cases (17). Chang et al. stated that non-invasive and invasive procedures led to a diagnosis of pneumonia in 31.5% (n= 29) and 45.6% (n= 42) of patients, respectively. FOB was used in 64 patients and had a diagnostic yield in 38 cases (59.3%) (16). Microbiological agents were isolated in 18.4% of the patients by non-invasive methods (sputum, ETA), 15.5% by invasive methods (FOB), and 19.0% by both methods. Except that *Acinetobacter* spp. was more common in LT recipients and fungal culture growth was more prevalent in KT recipients, there was no significant difference between pathogens by transplant type.

In recent years, the management of opportunistic pathogens has improved, leading to a relative increase in the prevalence of conventional bacterial pathogens within transplant populations. Kara et al. conducted a retrospective review of medical records for all KT recipients from January 2010 to December 2014, identifying pneumonia in 18 patients (13.4%) out of 134 KT recipients (27). Bacterial infections were the most common cause of pneumonia (28%), followed by fungal infections (8%). Similarly, Hoyo et al. diagnosed pneumonia in 54 patients (8.8%) among 610 KT recipients, with bacterial infection accounting for the most frequent etiology (44%) (4). Our study similarly identified bacterial pathogens as the leading cause of pneumonia in 68.4% of cases. Furthermore, gram-negative bacteria represented 90% and 69% of bacterial pneumonia cases in LT and KT patients, respectively (3,16). In the current trial, gram-negative bacterial pathogens were identi-

fied as the most common pathogens, accounting for 35.7% of cases. This relatively low rate may be attributed to the limited use of additional diagnostic methods. Also, fungal infections were identified as a critical complication, which was crucial after bacterial isolation. These findings highlight the importance of considering fungal infections to ensure timely diagnosis and treatment.

A study conducted in Türkiye reported bacterial infections as the most prevalent cause of pneumonia in 55 patients (49.5%), consistent with our findings, especially involving *Haemophilus influenzae*, *Stenotrophomonas maltophilia*, and *P. aeruginosa* (18). Notably, 50.4% of the patients (n= 56) in that study showed no positive microbiological growth. In our study, the most commonly identified pathogens were *Pseudomonas* spp., *Acinetobacter* spp., *Klebsiella* spp., *H. influenzae*, and *S. maltophilia*, respectively. MTC was detected in nine patients (5.3%) and *Nocardia* in one.

During the first month post-transplantation, infections typically arise from surgical complications, donor-derived infections, pre-existing recipient infections, or nosocomial sources (28). The risk of infection is higher among LT recipients compared to KT recipients (29). In the current study, pneumonia was observed at a median of 33 months (8-120) post-transplantation, with most cases occurring after the sixth month. Similarly, in a study conducted by Giannella et al., the median time to pneumonia onset in 54 patients was 25 months (3-96), with most cases also after the sixth month (17). Pneumonia onset was significantly earlier in LT patients compared to KT patients with most in LT patients occurring within the first 12 months post-transplantation.

In the study by Fishman et al., more than 90% of the infections occurring within the first month post-transplantation were nosocomial, primarily involving bacterial or *Candida* infections at surgical sites, lungs, urinary tract, or vascular access devices (30). After the first month, the infection profile in transplant recipients shifts, and sustained immunosuppression predisposes patients to opportunistic infections, including *P. jirovecii*, *Aspergillus* spp., endemic fungi, MTC, NTM, *Listeria* spp., and various parasites, barring significant epidemiological risks. We investigated the relationship between the observed pathogens and the timing of their occurrence post-transplantation; *Acinetobacter* spp. infections were more prevalent within the first month and up to 12 months

post-transplantation. MTC infections were particularly common during the first 12 months, while fungal infections, including *Candida* spp., yeast-like fungi, *Aspergillus* spp., and *P. jirovecii*, were more frequently observed after 12 months, although none of these associations reached statistical significance.

In patients with compatible symptoms and physical examination findings, consolidation on chest radiographs, when present, is often sufficient to diagnose pneumonia. Microbiological diagnosis is crucial in guiding pneumonia treatment in immunocompromised patients, enabling the selection of targeted and effective antibiotics while reducing the risks of ineffective empirical regimens or unnecessary broad-spectrum antibiotics (31). However, obtaining a definitive diagnosis is often challenging, emphasizing the importance of determining the most appropriate sampling method based on clinical presentation and underlying risk factors. In a study by Ranzani et al., a median of three diagnostic methods (2-4) was applied to 200 hospital-acquired pneumonia patients in six ICUs in Barcelona, Spain (32). At least one respiratory sampling method was utilized in 93% of the patients, and two or more methods were employed in 40%, with microbiological diagnosis achieved in 50%. Similarly, in our study, microbiological diagnosis was obtained in 63% of the patients using one to four diagnostic methods employed.

According to the Pneumonia in Solid Organ Transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice, sputum culture for gram stain and bacterial culture is recommended in adults with sputum production, though evidence is weak and data quality is low (2). Additionally, the 2016 American Thoracic Society and the Infectious Diseases Society of America guidelines for hospital-acquired pneumonia recommend non-invasive respiratory sampling (31). In our study, regardless of transplantation type, gram-positive bacteria, gram-negative bacteria, *Acinetobacter* spp., *Klebsiella* spp., and *Haemophilus* spp. were more frequently identified by non-invasive methods. Among these, sputum cultures showed particularly higher growth rates for Gram-positive bacteria, *S. pneumoniae*, *Klebsiella* spp., and *Haemophilus* spp. while ETA cultures had significantly higher growth rates of gram-negative bacteria and *Acinetobacter* spp.

In certain cases, more invasive diagnostic procedures are required to achieve an accurate diagnosis (31).

The decision to perform such procedures should be carefully tailored to the individual patient, with a thorough clinician-led risk-benefit analysis. Invasive methods are particularly valuable for diagnosing fungal infections (33-35). Several studies highlight the utility of FOB in identifying bacterial pneumonia in SOT recipients. For instance, Ranzani et al., in a study of 200 patients with hospital-acquired pneumonia across six ICUs, observed significantly higher microbiological diagnosis rates in the invasive group (BL and BAL) compared to non-invasive methods (56% vs. 39%, $p=0.018$) (32). A study from Türkiye by Küpeli et al. utilized FOB to evaluate lung infiltrates in 61 LT and KT patients, yielding microorganism growth in 39.3% of cases with common isolates including MTC (10/24), *Staphylococcus aureus* (3/24), *Klebsiella pneumoniae* (2/24), *Escherichia coli* (2/24), and *S. pneumoniae* (1/24) (36). Similarly, Eyüboğlu et al., in a cohort of 90 LT and KT patients (including one heart transplant), found bacterial growth in 32 patients (35.5%), with pathogens such as *S. aureus* (4/32), *Moraxella catarrhalis* (4/32), *S. pneumoniae* (2/32), and *S. maltophilia* (1/32) (37). In our study, FOB yielded diagnostic results in 32.5% of cases, with *Candida* spp. more frequently detected via invasive methods. Notably, BL samples often revealed *S. maltophilia*, MTC, NTM, and *Candida* spp., while BAL samples, regardless of transplant type, commonly identified *Pseudomonas* spp., *P. jirovecii*, *Aspergillus* spp., and non-*P. jirovecii* fungi.

BAL is recommended for patients with diffuse or focal pulmonary infiltrates who do not respond to empirical antibacterial therapy and for whom a diagnosis could not be established through non-invasive methods (strong recommendation, moderate quality evidence) (2). Our findings indicate that ETA is the most frequently used diagnostic method for patients with focal infiltration, multilobar infiltration, centrilobular nodules, diffuse ground-glass opacities, and pleural effusion. The diagnostic specificity of quantitative cultures from ETA and BAL is comparable (38). While both methods have the potential to yield a diagnosis, the decision to proceed with further invasive procedures in a SOT recipient with pneumonia must carefully weigh the procedural risks against the potential diagnostic and therapeutic benefits.

CT imaging is the preferred modality for evaluating pneumonia in SOT recipients, as it often provides more accurate diagnostic information than chest X-rays, which may be insufficient for accurate assess-

ment. Bacterial pneumonia, including *Legionella*, may present as focal consolidation on CT scans (26). Additionally, CT can identify diffuse infiltrates associated with viral pneumonias or *P. jirovecii*. In a study involving 45 pneumonia cases, the most common CT findings included consolidation ($n=37$; 82%), ground-glass opacification ($n=34$; 76%), septal thickening ($n=33$; 73%), pleural effusion ($n=33$; 73%), as well as multiple ($n=25$; 56%) or single ($n=2$; 4%) nodules (39). Furthermore, no significant differences were observed in the prevalence of these findings among bacterial, viral, and fungal pneumonias.

In our study, thoracic CT findings included focal consolidation, diffuse ground-glass nodules, multilobar infiltration, centrilobular nodules, cavitation, and mass/metastatic nodules. Notably, focal infiltrates were more frequently associated with bacterial and gram-negative bacterial growth.

A multicentre study conducted across 35 centres (18 in Italy and 17 in Spain) examined 54 SOT patients with pneumonia and reported that 11.1% required ICU admission (17). Similarly, data from a transplant centre in Türkiye indicated that 51 out of 193 recipients (26.4%) who developed pneumonia post-transplant were managed in the ICU (40). In our study, 36.3% of the evaluated patients required ICU admission at some point during their hospitalization. Among the 168 patients consulted, 32 (19%) died. Of the surviving patients, 52.6% were KT recipients, though this observation did not reach statistical significance.

A recent retrospective study from our country further analysed 51 out of 193 post-transplant patients with pneumonia who required ICU care, documenting a mortality rate of 39.2%, with no significant mortality difference across transplant types (40). Chang et al. also reported a 29.3% mortality rate among 92 patients with pneumonia, accounting for 27 deaths (16).

Our study has several limitations. Galactomannan testing could not be performed due to intermittent technical issues, and as a result, this data could not be included in our study. This limitation may have impacted the ability to assess the full spectrum of infections, potentially leading to an underestimation of fungal-related complications. Additionally, the prognosis for all referred patients remains unknown, and the retrospective design presented certain challenges. Incomplete data, particularly regarding PCR for *P. jirovecii*, and the lack of evaluation of appropri-

ate treatment regimens and comorbidities limited our ability to establish a clear link between ICU admission and mortality outcomes.

CONCLUSION

Despite the limitations inherent to its retrospective nature, this study offers valuable insights to the existing literature, by analysing data collected over nine-year period of data from a transplant centre. Our findings highlight the high frequency of pneumonia among clinically suspected cases, with bacterial pathogens, particularly in the early post-transplant period, being predominant. This underscores the critical need for heightened attention to nosocomial agents, especially considering the inadequacy of prophylaxis against opportunistic infections both pre- and post-transplant. The diagnostic accuracy for both invasive and non-invasive methods was above average. Notably, ICU admission and mortality rates were lower than those typically reported for pneumonia in immunocompromised populations. Continuous monitoring of pneumonia epidemiology and its risk factors in SOT recipients remains essential for advancing preventive and therapeutic strategies.

Ethical Committee Approval: This study was approved by Dokuz Eylül University non-Interventional Clinical Research Ethics Committee (Decision Date: 09.11.2020, Decision No: 2020/27-20).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: SÇK, AÖA

Analysis/Interpretation: SÇK, AÖA

Data Acquisition: All of authors

Writing: SÇK, AÖA

Clinical Revision: SÇK, AÖA

Final Approval: All of authors

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