

Aetiology, management, and outcome of lower respiratory tract infection in renal allograft recipients - A report from a tropical country

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ABSTRACT

Introduction: Lower respiratory tract infections (LRTIs) among renal transplant recipients (RTRs) are a significant cause of morbidity and mortality. This study aimed to analyse the aetiology, outcome, and risk factors associated with mortality. **Methods:** We analysed baseline transplant characteristics, symptoms, hospital course, laboratory, serological and microbial results, and their association with the outcome of all RTRs between January 2011 and December 2019. **Results:** A total of 206 LRTI patients out of 1051 RTRs were analysed. The incidence proportion was nearly 22 episodes per 1000 patients per year. The mean age was 39.3 years, with male predominance. Bacterial was the most common aetiology (53%), and staphylococcus was the most common species. Among the fungal causes (14%), 68% had aspergillus infection. More than one-third RTRs died during the hospital course mainly because of bacterial causes (42.6%). The aspergillus infection was the most common fungus associated with 50% mortality. On multi-variate analysis, sepsis, septic shock, and the need for mechanical ventilation independently predicted mortality. **Conclusion:** Bacterial aetiology was the most common cause; though the fungal aetiology was seen less, it was associated with higher mortality. Mortality in RTR with LRTI was associated with sepsis, septic shock, and the need for mechanical ventilation.

KEY WORDS: Immuno-suppressed, lower respiratory tract infection, pneumonia, renal allograft recipient

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INTRODUCTION

Renal transplantation offers the best treatment for end-stage renal disease (ESRD) patients as it provides survival advantages, a better quality of life, and cost benefits compared to haemodialysis.^[1] Long-term renal

allograft survival advantage improvement is because of potent immuno-suppression, but the trade-off effects are a marked increase in infections, malignancy, and cardio-vascular events.

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The risk of infection in renal transplant recipients (RTRs) is determined primarily by balancing the pathogen's epidemiologic exposure and the net state of immuno-suppression.^[2] Around 40–80% of RTRs suffer infection after renal transplant, with high mortality.^[3,4] It is estimated that infections complicate the course of 50–70% of RTRs in developing countries, with mortality ranging from 20 to 60%^[5] affected by demographics of the hosts, and microorganisms.^[6] The most common infections are urinary tract infections (UTI) (61%), followed by respiratory tract infections (8%), intra-abdominal infections (6%), and cytomegalovirus (CMV) infection (6%).^[7] However, lower respiratory tract infection (LRTI) is the most common infection associated with the highest mortality.^[8] Unfortunately, there are limited data on the aetiology, course, and outcome of LRTI in RTR,^[6] more so from the developing world. Most of the data in the literature are before 2010.

This study aims to identify clinical and microbial spectrum [either the in-patient department (IPD) or intensive care unit (ICU)] with LRTI in RTR and their outcomes in hospitalized patients. This retrospective analysis would add to the literature regarding the spectrum of LRTI and its manifestation in RTR, especially in the modern immuno-suppression era from the developing world.

MATERIALS AND METHODS

Study design

This retrospective observational study was performed in North Indian renal transplant centre of a tertiary care medical institute after approval of institute ethics committee (IEC code 2020-317-IP-EXP-33 dated 18-11-2020). We analysed data of RTRs who underwent live donor-related renal transplant surgery between January 2011 and December 19. All donors were first-degree relatives or spousal.

Inclusion criteria

RTRs had an episode of LRTI and required admission as per CDC criteria.^[9]

Data collection

Baseline demographic data were collected from electronic hospital information systems and case sheets, as described in Table 1. The patients were analysed for variables related to their LRTI episode, as described in Tables 2 and 3. Data were taken for various bio-chemical and micro-biological parameters and outcomes, such as sepsis, septic shock, the need for vasopressors, sputum examination and culture, blood culture, requirement of bronchoalveolar lavage (BAL) antibiotic used, need and duration of non-invasive ventilation (NIV), mechanical ventilation, ICU admission, and ICU mortality.

Management of LRTI

Diagnosis: Pulmonary infection was defined by demonstrating an infiltrate on chest imaging in a patient

Table 1: Demographic and transplant-related characteristics of the study population

Parameter	RTR with LRTI (n=206)	RTR without LRTI (n=845)	P
Mean age in years	39.32±12.44	41.23±10.34	0.04
Gender			
Males	172 (83.4%)	669 (79.2%)	0.16
Females	34 (16.5%)	176 (20.8%)	0.16
Donors (Live)			
Parents	64 (31.06%)	283 (33.49%)	0.12
Siblings	46 (23.78%)	181 (21.42%)	0.31
Spousal	81 (39.32%)	345 (40.82%)	0.11
Offspring	15 (07.28%)	46 (05.44%)	0.35
Basic kidney disease			
Chronic glomerulonephritis	101 (49%)	382 (45.2%)	0.32
Diabetic nephropathy	53 (25.7%)	251 (29.8%)	0.12
Chronic interstitial nephritis	46 (22.3%)	163 (19.3)	0.16
Poly Cystic kidney disease	6 (2.9%)	49 (5.7%)	0.04
Induction			
Anti-Thymocyte Globulin	41 (19.9%)	106 (12.6%)	0.01
Basiliximab	145 (70.4%)	627 (74.3%)	0.13
No induction	20 (9.7%)	112 (13.2%)	0.08
CNI			
Tacrolimus based	171 (83.2%)	671 (79.4%)	0.12
Cyclosporine based	35 (16.8%)	174 (21.6%)	0.12
Anti-metabolite			
Mycophenolate	134 (65%)	590 (69.8%)	0.09
Azathioprine	63 (30.6%)	213 (25.3%)	0.05
None	9 (4.4%)	42 (05%)	0.35
Prior Rejection	48 (23.3%)	123 (14.6%)	0.01
CRAI	32 (12.6%)	65 (7.6%)	0.01

LRTI, lower respiratory tract infection; RTR, renal transplant recipients

with a clinically compatible syndrome (e.g., fever, dyspnoea, cough, and sputum production) with or without a positive culture of expectorated sputum or bronchial aspirate.

- Bacterial pulmonary infections were diagnosed when sputum or bronchoscopy specimens showed pathogenic bacteria on culture.
- CMV pneumonitis was considered when the elevated CMV DNA titers were noted in serum or bronchoalveolar lavage specimens or the presence of histopathological findings.
- Pneumocystis *jirovici* pneumonia was diagnosed by immuno-fluorescent stain with crystal violet or Giemsa stain.
- Fungal respiratory tract infection was diagnosed when (a) fungal hyphae were identified by cytopathologic or histopathologic evaluation of sputum or the bronchoalveolar lavage specimen; (b) positive culture findings were noted from sputum the bronchoalveolar lavage fluid or blood; (c) clinical and radiographic patterns were consistent with the diagnosis of fungal infection.

We would obtain computed tomography (CT) of the chest when LRTI is suspected based on clinical features despite a negative chest radiograph or in all patients unless they improved dramatically with empirical treatment.

Indications for admission

Upon presenting the RTR with respiratory symptoms suggestive of LRTI, they were analysed regarding the need

Table 2: Clinical features, aetiology, and complications associated with LRTI

Clinical presentation	n=206 (%)
Fever	169 (82%)
Cough	154 (74.7%)
Dyspnoea	126 (61.1%)
Chest pain	80 (38.8%)
Orthopnoea	74 (35.9%)
Haemoptysis	34 (16.5%)
Hypoxia	109 (52.9%)
Etiology	
Bacterial	111 (53.8%)
CMV pneumonitis	6 (2.9%)
Fungal	29 (14.1%)
Mycobacterial	16 (7.8%)
No microbiologic isolation	44 (21.4%)
Complications	
Median SOFA score at presentation	7 (3-14)
Sepsis	178 (86.4%)
Septic shock	94 (45.6%)
Non-invasive ventilation	76 (36.8%)
Mechanical ventilation	63 (30.5%)
Graft dysfunction	86 (41.7%)
Need of RRT	46 (22.3%)
Hospital stay in days (median)	19
Timeline of respiratory infections	
<1 month	32 (15.5%)
1 month to 6 months	31 (15.0%)
6 months to 1 year	27 (13.2%)
>1 year	116 (56.3%)

RRT - Renal Replacement Therapy, CMV - Cyto-megalo virus, SOFA - Sequential Organ Failure Assessment score, LRTI - Lower respiratory infection

Table 3: Comparison of immuno-suppressive medication and clinical presentation of renal allograft recipients with LRTI with and without mortality

	LRTI with mortality	LRTI without mortality	P
Number of patients	68	138	
Time from transplant	10±6 months	23±8 months	0.02
Induction			
ATG	20	12	0.03
IL-2 Blocker	46	99	0.09
Calcineurin inhibitor			
Tacrolimus	46	95	0.05
Cyclosporine A	22	43	0.35
Antimetabolite			
MMF	50	84	0.13
Azathioprine	20	43	0.08
Clinical presentation			
Fever	60	109	0.09
Cough	56	98	0.38
Dyspnoea	64	62	0.04
Chest pain	40	40	0.05
Orthopnoea	46	28	0.01
Hypoxia	58	51	0.03
Haemoptysis	20	14	0.07

RRT - Renal Replacement Therapy, MMF - Mycophenolate Mofetil, LRTI - lower respiratory tract infection, ATG - anti-thymocyte globulin, IL-2 blocker - interleukin - 2 blocker

for admission in IPD or ICU. Symptoms such as hypoxia at room air, dyspnoea NYHA grade 3 or 4, orthopnoea, chest pain, haemoptysis, non-resolving fever, and infiltrate on chest X-ray were used for admission. In addition, patients

were directly taken to the ICU if they fulfilled IDSA/AST criteria^[10] for severe community-acquired pneumonia or features suggestive of severe nosocomial LRTI.

Investigations

Laboratory tests were carried out as per standard care.

Pulmonary secretions and blood cultures were obtained and evaluated by direct smear examination by Grams stain, KOH stain for the fungal element, and Ziehl–Nelson stain (Z–N) acid-fast bacilli (AFB), and various culture media from all patients.

BAL was performed in stable patients and when there was no sputum production or inconclusive sputum studies or no clinical and radiographic improvement on empirical therapy or when there were multiple, bilateral, or diffuse pulmonary infiltrates. Samples were sent for microscopy, culture, and serologic tests.

Treatment: Empirical antibiotics were started after sending off expectorated sputum samples. Later, the management was changed as per the result of the investigations. Empirical anti-tubercular or anti-fungal medicines were used only if a patient failed to improve with anti-bacterial agents given for more than 2 weeks, and the clinical situation demanded the use of both or either of these drugs.

The response to therapy was assessed based on the symptoms and signs, improved arterial blood gas values, and radiological improvement. In the absence of isolation of a specific organism, response to therapy was taken as criteria for that infection, whether bacterial, fungal, viral, or tubercular in origin.

Aetiology: Antibiotics were down-titrated according to the culture sensitivity report, and the patient was followed for the signs of resolution. If there was no resolution of the infections with the antibiotics, additional pathology such as fungal or tubercular was suspected and managed with either empirical anti-fungals or ATT.

Immuno-suppression protocol at our centre

- Induction: Patients usually receive induction based on their risk assessment as per KDIGO guidelines.^[11] It usually consists of anti-thymocyte globulin or basiliximab.
- Maintenance Immuno-suppression Protocol: Triple drug immuno-suppression as per KDIGO guidelines^[11] consisting of tacrolimus/cyclosporine (CNI), mycophenolate mofetil (MMF), and prednisolone was used.
- Tacrolimus: Unless contraindicated, all renal allograft recipients start on tacrolimus at a dose of 0.05–0.1 mg/kg/day. Target levels are as per KDIGO guidelines.^[11]
- During episodes of LRTI, the decision to reduce or deduct immuno-suppressive therapy was individualised according to the patient’s clinical

status and haematological parameters. First, azathioprine or mycophenolate mofetil was stopped. Later, the calcineurin inhibitor was also tapered or gradually withdrawn if an infection was non-responsive or progressive even on treatment.

- Anti-microbial prophylaxis: Cotrimoxazole prophylaxis is used for 1 year and re-started for 6 months again if the patient is treated with augmented immuno-suppression for rejection episodes. In cases with ATG induction or received plasmapheresis for ABO-incompatible renal transplant or HLA desensitisation, the patient received oral valganciclovir for anti-viral prophylaxis. In addition, oral clotrimazole solution was used to prevent oral thrush.

Statistical techniques

Categorical variables were expressed as proportions and percentages. Continuous variables were defined as means with standard deviations.

Uni-variate and multi-variate analyses were performed to assess the predictors of mortality. The statistical analyses were performed using IBM SPSS software (Statistical Package for the Social Sciences, version 20.0, SSPS Inc., Chicago, IL).

RESULTS

Baseline demographics and transplant-related characteristics

A total of 206 out of 1051 renal allograft recipients had an episode of LRTI requiring admission, nearly 20% over 9 years. The incidence proportion was nearly 22 episodes per 1000 RTRs per year. Basic demographic features and baseline transplant-related characteristics have been summarised in Table 1. The majority of the population was male (n 172, 83.4%), and the median age of the patients was 39.32 ± 12.44 years (range 13–71 years). The post-transplant time interval ranged from immediate (<1 week) to more than 5 years. LRTI episodes most commonly occurred 1 year (56.3%), followed by <1 month (32, 15.5%), 1–6 months (31, 15%), and 6–12 months (27, 13.2%) after transplant [Table 2].

A history of rejections and chronic renal allograft injury (CRAI) at the time of presentation was noted in 48 (23.3%) and 32 (12.6%) patients, respectively, and all these patients received some form of heightened immuno-suppression, either a bolus dose of parenteral methylprednisolone or ATG. A history of CMV disease was present in 22 (10.6%) patients.

Clinical presentation and laboratory parameters of LRTI

Presenting clinical features [Table 2] included fever (82%), cough (74.7%), dyspnoea (61.1%), chest pain (38.8%), and orthopnoea (35.9%). Productive cough and haemoptysis were seen in 117 (56.7%) and 34 (16.5%) patients, respectively. Hypoxemia and the need for oxygen therapy were noted in 109 (52.9%) of patients at presentation.

In our study, around 144 (70%) required ICU admission. Non-invasive ventilation (NIV) and mechanical ventilation (MV) was needed in 76 (36.8%) and 63 patients (30.5%) [Table 2].

Sepsis was present in 86.4% (178 of 206) of the patients, which was higher among the mortality (94.1%) group compared to the recovery group (77.5%) patients. The need for vasopressors occurred in 94 (45.6%) patients [Table 2].

Graft dysfunction was seen in 86 (41.7%) patients at presentation, and 46 (22.3%) patients underwent haemodialysis. Among patients with graft dysfunction, 68 (79.0%) patients showed recovery in graft function, either complete or partial. Of 18 patients, ten suffered death censored graft loss, and the remaining eight were shifted on maintenance haemodialysis.

Chest radiography

Chest radiography was performed in all the patients and showed infiltrates in 80.09% of patients (165 of 206). In 108 (65.5%) and 57 (34.5%) patients, uni-lateral and bi-lateral infiltrates were noted, respectively. High-resolution computerised tomography (HRCT) thorax was performed in 129 patients; ground-glass opacities (GGOs) were the most common manifestation (92 cases, 71.3%), followed by consolidation (52 cases, 40.3%), broncho-vascular bundle thickening (49 cases, 37.9%), nodule (28 cases, 21.7%), tree-in-bud pattern (21 cases, 16.2%), reticular or linear shadow (13 cases, 10.1%), and cavity (14 cases, 10.8%).

Micro-biological data

Sputum/BAL culture was performed in 182 (88.3%) patients, and 56 (27.1%) underwent bronchoscopy to isolate respiratory tract infection in this cohort. Bacterial infections were the most common cause (111, 53.8%), followed by no micro-biological isolation (44, 21.3%) and fungal (29, 14.1%). Tubercular and CMV were not common aetiologies and were seen in 7.8% (16 of 206) and 2.9% (6 of 206) patients, respectively [Table 2].

Among the bacterial causes, the most common was staphylococcus species seen in 38% of patients, followed by Streptococcus (23%), Pseudomonas (17%), Klebsiella (14%), and Acinetobacter (8%).

Among the 29 fungal causes, species identification was possible in 25 patients, out of which 20 (68%) patients had Aspergillus infection. Mortality occurred in ten patients with Aspergillus infection, which accounted for around 35% of the total mortality cases and 70% of the mortality cases associated with fungal aetiology.

Patient outcome

Mortality was seen in 66 (33%) patients during illness. Most of these non-survivors had bacterial aetiology (29/68, 42.6%), followed by fungal (14/29, 48.2%) [Figure 1]. However, fungal aetiology did not constitute a significant part of the mortality population but was significantly associated with mortality ($p \leq 0.02$).

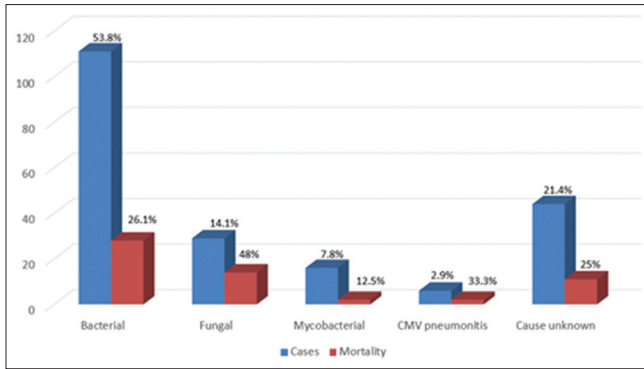


Figure 1: The effect of aetiology on mortality

Sepsis was present in 94.5% (64 of 68) and 78% (107 of 138) of non-survivor and recovery groups, respectively. Oxygenation was needed in 100% of patients in the non-survivor group.

Demographic features and clinical parameters on the presentation that were significantly associated with mortality were a shorter time from transplantation (<12 months) ($p \leq 0.02$), use of anti-thymocyte globulin (ATG) as an induction agent ($p \leq 0.03$), fungal aetiology ($p \leq 0.02$), high median SOFA score at presentation ($p \leq 0.01$), the presentation with sepsis ($p \leq 0.01$), hypoxemia ($p \leq 0.03$), dyspnoea ($p \leq 0.04$), and orthopnoea ($p \leq 0.01$) [Table 3].

Complications that were significantly found to be associated with mortality were the need for oxygenation ($p \leq 0.02$), non-invasive ventilation ($p \leq 0.02$), vasopressor requirement ($p \leq 0.03$), mechanical ventilation ($p \leq 0.04$), and dialysis requirement ($p \leq 0.03$) [Table 4].

Predictors of mortality

Upon uni-variate analysis of sepsis, hypoxemia, dyspnoea, orthopnoea, SOFA score, the need for non-invasive ventilation, vasopressor requirement, mechanical ventilation, and demand for dialysis predicted the mortality.

However, upon multi-variate analysis, sepsis (OR = 4.6%, CI: 3.2–6.8; $P \leq 0.01$), septic shock (OR = 3.9%, CI: 2.4–6.4; $P \leq 0.03$), and the need for mechanical ventilation (OR = 7.1%, CI: 3.8–13.7; $p \leq 0.04$) were independently associated with mortality [Figure 2].

DISCUSSION

We report the most extensive descriptive data to the best of our knowledge, addressing LRTI in RTRs. We observed that one-fifth of renal allograft recipients developed LRTI, mainly 1 year after transplant. Clinical presentation of LRTI was like the general population, but most of these patients were admitted to ICU and required assisted ventilation. Many of these patients developed sepsis, septic shock, and graft dysfunction during their course of illness. Bacterial infections were the most common aetiology, followed

Table 4: Comparison of aetiology and complications of renal allograft recipients with LRTI with and without mortality

Variables	With mortality <i>n</i> =68	Without mortality <i>n</i> =138	<i>P</i>
Aetiology			
Bacterial (<i>n</i> =111)	29	82	NS
Fungal (<i>n</i> =29)	14	15	0.02
CMV (<i>n</i> =6)	2	4	NS
Unknown (<i>n</i> =44)	11	33	NS
Tubercular (<i>n</i> =16)	2	14	NS
Complications			
Median SOFA score at presentation	11 (7-14)	4 (3-8)	0.01
Sepsis (<i>n</i> =178)	67	111	0.01
Oxygen demand (<i>n</i> =109)	78	31	0.02
NIV (<i>n</i> =76)	36	40	0.02
MV (<i>n</i> =63)	48	15	0.04
Graft dysfunction (<i>n</i> =86)	50	36	NS
Need for vasopressors (<i>n</i> =94)	60	34	0.03
Need for Dialysis (<i>n</i> =46)	26	20	0.03
Length of hospital stay in days (median)	20 (14-43)	21 (8-40)	0.02

LRTI - lower respiratory tract infection, CMV - cytomegalovirus, NIV - non-invasive ventilation, MV - mechanical ventilation.

*Antimicrobial susceptibility pattern of some significant isolates from renal allograft recipients is summarised in table 5

by fungus. Staphylococcus and Aspergillus were the most common bacterial and fungus species, respectively, causing LRTI. Nearly one-third of patients with LRTI had mortality during management.

Most of our cohort was young and male, and the cause of this gender and age deviation could be their dominant demographic representation in our RTR pool.

In the literature, the incidences of LRTI varied between 8% and 20%.^[12,13] We have observed similar findings in concordance with the literature.

A majority (>50%) of patients in our study had LRTI, 1-year post-transplant rather than in the immediate post-transplant period (13%, <1 month). This finding is supported by other literature studies,^[12,14] reporting LRTI 6 months post-transplant. This delay in presentation could be attributed to the widespread use of trimethoprim–sulfamethoxazole. In addition, the incidence of infections had declined during the initial phase of post-transplant but remained of concern when prophylaxis was discontinued.^[12,14]

The common finding on the HRCT chest was GGO, as reported by other studies.^[5,15]

In various studies, bacterial infections were the primary cause of post-transplant LRTI, constituting an incidence of 44%.^[5,16] In Indian studies,^[5,16,17] the incidence of bacterial infections has been found to range from 25 to 33.3%.^[16] Our study found bacteria to account for 68.5% (111 out of 162 organisms isolated) of all the organisms isolated in our patients. At the same time, of the total population, it was present in (53.8%) bacterial cause

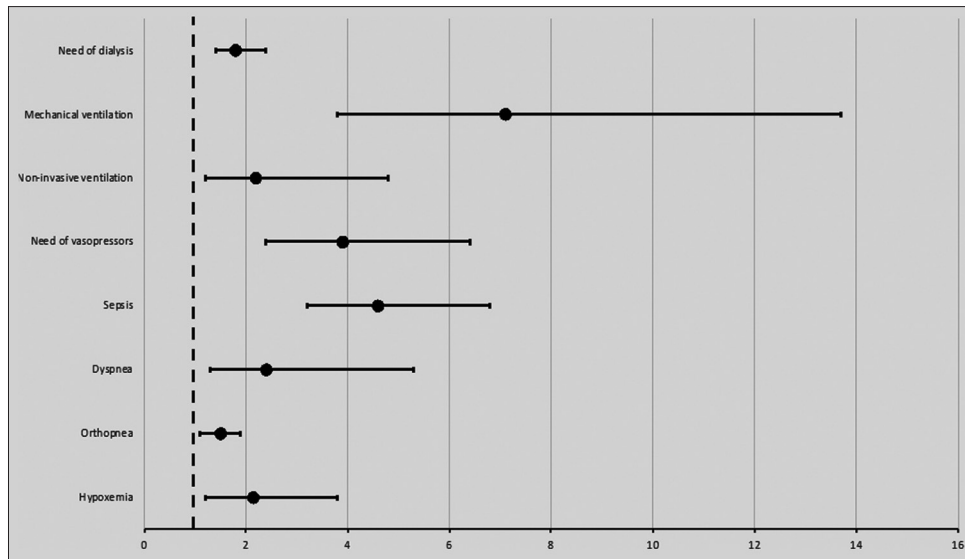


Figure 2: Effect of different variables on mortality in renal allograft recipients with LRTI

Table 5: Anti-microbial susceptibility pattern of some significant isolates from renal allograft recipients

Anti-microbial agents/Isolates sensitivity	<i>S. aureus</i> n=42	<i>Streptococcus</i> n=25	<i>Pseudomonas</i> n=18	<i>Klebsiella</i> n=16	<i>Acinetobacter</i> n=9	<i>Aspergillus</i> n=20
Ampicillin	15/42	25/25	-	-	0/9	-
Amoxicillin_clavulanate	15/42	25/25	-	-	0/9	-
Piperacillin_Tazobactam	-	25/25	-	-	3/9	-
Aztreonam	-	-	-	-	3/9	-
Cefoxitin	-	-	4/18	5/16	-	-
Ceftazidime	-	-	18/18	6/16	3/9	-
Ceftriaxone	-	-	12/18	-	-	-
Cefepime	-	-	15/18	-	-	-
Imipenem	-	-	12/18	7/16	-	-
Meropenem	-	-	12/18	7/16	-	-
Ciprofloxacin	28/42	25/25	6/18	-	-	-
Levofloxacin	25/42	25/25	9/18	5/16	-	-
Azithromycin	18/42	25/25	-	-	-	-
Clindamycin	-	25/25	-	-	-	-
Erythromycin	-	25/25	-	-	-	-
Gentamicin	-	-	11/18	-	-	-
Amikacin	-	-	11/18	-	-	-
Linezolid	42/42	25/25	-	-	-	-
Ticoplanin	42/42	25/25	-	-	-	-
Vancomycin	42/42	25/25	-	-	-	-
Tetracyclines	22/42	25/25	-	14/16	9/9	-
Trimethoprim-sulfamethoxazole	21/42	25/25	-	-	-	-
Colistin	-	-	-	16/16	9/9	-
Amphotericin B	-	-	-	-	-	20/20
Caspofungin	-	-	-	-	-	20/20
Voriconazole	-	-	-	-	-	20/20

was followed by no microbial isolation (21.4%) and then fungal (14.1%). The exact incidence of bacterial respiratory tract infections among RTRs is challenging to assess because broad-spectrum antibiotics are empirically started early upon or before admission. *Staphylococcus* was the most common species of all the bacteria infections, constituting 38% (42 of 111) of the total. Other studies show it as the most common causative organism of respiratory tract infection in RTRs.^[17] However, in a few studies, *pseudomonas*^[16] and *streptococcus*^[16] have been the primary cause of bacterial LRTI. The fungal cause

(14% of total), which is nearly like the incidence in various other studies (4–18%),^[12,17] had 68% *Aspergillus* infection.

More than two-third of our study population required ICU admission. The need for ventilation occurred in NIV and MV in 36.8% (76 of 206) and 30.5% (63 of 206), respectively, of the study population as per the literature, ranged 30–89%.^[12,18] Sepsis and septic shock were present in 86.4% and 45.6% of the study population, respectively. The incidence of sepsis in RTR with LRTI in other studies^[12] was around 25%, which was less than

our study, which might be because of the lesser sample size being used by them. However, the incidence of septic shock has not been validated in the currently available literature.

Graft dysfunction, followed by renal replacement therapy (RRT), was seen in 41.7% (86 of 206) and 22.3% (46 of 206) populations, respectively. A study in the literature^[16,18] also showed a nearly similar graft dysfunction incidence in most patients, and 25–30% of them required RRT in septicemic RTR. Of the patients with graft dysfunction, 68 (79.0%) patients showed recovery in graft function, either complete or partial. Of 18 patients, ten suffered death censored graft loss, and the remaining eight were shifted on maintenance haemodialysis.

Analysis of mortality in renal allograft recipients with LRTI

Nearly one-third of our study cohort suffered mortality, which is slightly higher than the study by Dizdar OS *et al.*, having a mortality of one-fourth of the population.^[19] Overall mortality in RTRs with LRTI was found to be between 21% and 35%; however, mortality because of nosocomial and community-acquired infection was 58% and 8%, respectively.^[12]

Mortality was significantly associated with a shorter post-transplant period (<12 months). LRTI of early onset (<12 months) was also seen as a risk factor by the study of G Tu *et al.*^[20] This could be because of a higher net state of immuno-suppression in the initial transplant phase, which predisposes to more infection.

ATG as the induction agent was significantly associated with mortality in this cohort, like other studies.^[18,21] In a survey by Hesse *et al.*,^[22] RTRs, who received azathioprine and ATG, had a higher frequency of LRTI and related mortality than patients who received cyclosporine. Our study found no correlation between the type of maintenance immuno-suppression and patients' mortality because of LRTI. However, in other studies, mycophenolate mofetil was a risk factor for infectious complications in RTRs.^[23]

A higher proportion of LRTI because of the fungal cause suffered mortality (50%) in comparison to the bacterial cause (42.6%) of LRTI in RTRs [Figure 1]. Various other studies found fungal aetiology to be a significant risk factor associated with mortality in RTR suffering from LRTI.^[23,24] Aspergillus infection was the most common fungal aetiology of LRTI; 50% of them suffered mortality, which accounts for around 70% of the total mortality from the fungal aetiology of LRTI. This finding was like other studies, showing high mortality associated with LRTI because of aspergillus infection, around 88%.^[4,25]

Various factors at presentation were found to be significantly associated with mortality, dyspnoea (61.1%),

orthopnoea (35.9%), hypoxia (52.9%), and need for oxygenation. The need for oxygenation was 100% among the mortality group. These factors were present significantly more in the mortality group compared to the recovery group. This comparison of clinical presentation with mortality among RTRs with LRTI has not been established in available studies.

Sepsis and septic shock were significantly associated with mortality among the patients suffering from LRTI in RTRs. Moreover, these factors were also associated with inferior graft and patient survival^[26,27] in other studies.

Graft dysfunction, followed by RRT's need, was significant among the mortality group compared to the recovery group. As per our study, various studies have shown that advanced graft dysfunction is significantly associated with mortality in RTR.^[27,28]

The non-invasive and mechanical ventilation requirement was significantly associated with mortality among the study population. In addition, studies showed that the need for ventilation or mechanical intubation was associated with mortality among infected RTRs.^[27,29]

Upon uni-variate analysis, a shorter duration from transplant (<12 months), ATG induction, fungal aetiology, sepsis, hypoxemia, dyspnoea, orthopnoea, SOFA score, and the need for non-invasive ventilation, vasopressors, mechanical ventilation, and need of dialysis all predicted mortality. Upon multi-variate analysis, sepsis, septic shock, and the need for mechanical ventilation predicted mortality.

Our study's major strength is that it is one of the most descriptive and relatively recent studies to analyse LRTI in RTR regarding microbiological, radiological, graft dysfunction, and mortality aspects in detail. Most of the studies on this topic in the literature are decades old.

Limitations of our study include its retrospective nature, and the risk factor for LRTI in renal allograft recipients was not analysed.

To conclude, bacterial aetiology was the most common cause; although fungal aetiology was seen less, it was associated with higher mortality. Mortality in RTRs with LRTI was associated with sepsis, septic shock, and the need for ventilation, either non-invasive or mechanical ventilation.

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Conflicts of interest

There are no conflicts of interest.

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