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ORIGINAL RESEARCH

PROSPECTIVE STUDY ON PULMONARY COMPLICATIONS IN RENAL TRANSPLANT RECIPIENTS: EPIDEMIOLOGY, CLINICAL SPECTRUM, AND RISK FACTORS

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ABSTRACT

Background: Pulmonary complications pose significant challenges in renal transplant recipients due to immunosuppression and diverse underlying renal diseases. Understanding their epidemiology, clinical presentation, microbial spectrum, and risk factors is crucial for optimal management.

Methods: We conducted a prospective observational study over 24 months, following 458 renal transplant recipients. Data on demographics, clinical presentation, underlying renal diseases, and microbial spectrum were collected. Risk factors influencing pulmonary complications were analyzed.

Results: Among the cohort, 45 incidents (9.8%) of pulmonary complications occurred, with fever (66.7%) being the most common symptom. The majority of complications (51%) occurred over six months post-transplantation, with infectious complications predominating (89%). Risk factors included leucopenia (24.4%), CMV infection (8.9%), HCV infection (8.9%), ART (20%), and NODAT (11.1%).

Conclusion: Early detection and targeted antimicrobial therapy are essential in managing pulmonary complications in renal transplant recipients. Multidisciplinary approaches are crucial for optimizing patient outcomes. Further research is needed to explore the long-term implications on graft function and survival.

Keywords: Renal transplant, pulmonary complications, immunosuppression, epidemiology, risk factors, antimicrobial therapy

INTRODUCTION

Renal transplantation stands as a definitive treatment for end-stage renal disease (ESRD), offering patients a chance at enhanced quality of life and improved survival rates compared to dialysis[1]. However, the success of renal transplantation is often shadowed by the potential for postoperative complications, notably those affecting the pulmonary system[2]. Pulmonary complications in renal transplant recipients present a multifaceted challenge, encompassing both infectious and non-infectious etiologies[2].

The introduction of tacrolimus-based triple immunosuppression regimens has revolutionized the field of organ transplantation, significantly reduced the incidence of acute rejection episodes and

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improved graft survival rates[3]. However, the impact of these potent immunosuppressive agents on pulmonary complications remains a topic of ongoing investigation and concern[3].

Pulmonary complications following renal transplantation represent a significant cause of morbidity and mortality among recipients[4]. While the precise incidence varies across studies, it is widely recognized that both infectious and non-infectious pulmonary complications contribute to adverse outcomes in this population[5]. Infectious pulmonary complications encompass a spectrum of pathogens, including bacteria, viruses, fungi, and opportunistic infections such as Pneumocystis jirovecii pneumonia (PCP) and cytomegalovirus (CMV) pneumonia[6]. Non-infectious pulmonary complications, on the other hand, encompass a diverse array of entities, including acute respiratory distress syndrome (ARDS), pulmonary edema, drug-induced lung injury, and bronchiolitis obliterans syndrome (BOS)[7]. These complications may manifest acutely in the immediate post-transplant period or develop gradually over time, posing diagnostic and therapeutic challenges to clinicians[5].

Tacrolimus, a calcineurin inhibitor, has become a cornerstone of immunosuppressive therapy in renal transplantation due to its potent anti-rejection properties and favorable pharmacokinetic profile[8]. When used in combination with other immunosuppressive agents such as mycophenolate mofetil (MMF) and corticosteroids, tacrolimus forms the backbone of most contemporary immunosuppression regimens[9].

While the benefits of tacrolimus-based triple therapy in preventing acute rejection are well-established, concerns persist regarding its potential for pulmonary toxicity and predisposition to infectious complications[8]. Tacrolimus-induced pulmonary toxicity, characterized by interstitial pneumonitis and fibrosis, represents a rare but potentially life-threatening adverse effect that necessitates prompt recognition and intervention. Furthermore, the profound immunosuppression achieved with tacrolimus-based regimens may predispose renal transplant recipients to opportunistic infections, particularly in the pulmonary tract[9].

Despite advances in surgical techniques, immunosuppressive regimens, and postoperative care, pulmonary complications continue to exert a significant toll on renal transplant recipients. The need for a comprehensive understanding of the spectrum, timing, and predictors of pulmonary complications in this population is underscored by their impact on both short-term and long-term outcomes[10]. By elucidating the epidemiology and risk factors associated with pulmonary complications, clinicians can optimize pre-transplant evaluation, perioperative management, and post-transplant surveillance strategies. Additionally, insights gained from this study may inform the development of targeted interventions aimed at reducing the incidence and severity of pulmonary complications, thereby improving overall transplant outcomes, and enhancing patient survival.

The primary objective of this study is to evaluate the spectrum and time of occurrence of both infectious and non-infectious pulmonary complications in renal transplant recipients receiving tacrolimus-based triple immunosuppression. By systematically analyzing the incidence, timing, and clinical characteristics of pulmonary complications, we aim to provide insights into their epidemiology and natural history in this population.

This study endeavors to shed light on the complex interplay between immunosuppression, pulmonary complications, and transplant outcomes in renal transplant recipients. By addressing critical knowledge gaps in this field, we aspire to enhance our understanding of pulmonary complications following renal transplantation and pave the way for targeted interventions aimed at improving patient care and outcomes.

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MATERIALS & METHOD

Study Setting: The study adopted a prospective observational design, with the aim of systematically observing and analyzing pulmonary complications among renal transplant recipients over a 24-month period from January 2017 to December 2018. Conducted at the Rajiv Gandhi Government General Hospital located in Park Town, Chennai, India, the study was situated within the renal transplant clinic of the Department of Nephrology.

Study Participants: Renal transplant recipients attending the post-transplant clinic of the Department of Nephrology within the specified timeframe constituted the study population. Inclusion criteria encompassed recipients on tacrolimus-based triple immunosuppression presenting with symptoms suggestive of pulmonary disease or radiological features indicative of complications post-transplantation by December 2017. Exclusion criteria included recipients on non-tacrolimus-based immunosuppression, those experiencing graft failure, pregnant women transitioning immunosuppression, recipients transplanted after December 2017, and those unwilling to participate.

Sampling Method: Consecutive sampling was employed, whereby renal transplant recipients attending the post-transplant clinic of the Department of Nephrology at Rajiv Gandhi Government General Hospital between January 2017 and December 2018 were included in the study.

Sample Size: A total of 458 renal transplant recipients meeting the inclusion criteria were followed up until December 2018 for the prospective evaluation of pulmonary complications. Among these, 37 patients developed 45 episodes of pulmonary complications, necessitating detailed pulmonary evaluation.

Study Procedure: All 458 renal transplant recipients fulfilling the inclusion criteria were regularly monitored at the transplant clinic of the nephrology department at Rajiv Gandhi Government General Hospital every fortnight. During each visit, patients were assessed for respiratory complaints. Those presenting with respiratory symptoms and radiological evidence of pulmonary infiltrates were admitted for thorough evaluation.

Data Collection: Data collection during hospitalization encompassed a comprehensive array of patient-related information aimed at providing a thorough understanding of the clinical context surrounding pulmonary complications in renal transplant recipients. Patient demographics, including name, age, sex, and address, were recorded to facilitate accurate patient identification and follow-up. Indication for renal transplantation, along with the waiting period for transplantation, offered insights into disease severity and urgency of transplant intervention. Additionally, the date and type of transplantation, whether from a deceased or live related donor, were documented to delineate transplantation specifics.

Furthermore, the induction agent used, and the immunosuppressive regimen employed were meticulously noted to understand the pharmacological milieu surrounding the transplant procedure and subsequent management. Histories of prior lung disease, cardiac disease, and rejection episodes were captured to elucidate potential predisposing factors and comorbidities influencing pulmonary outcomes. Pre-transplant pulmonary function tests served as baseline assessments, aiding in the interpretation of subsequent respiratory symptoms and complications post-transplantation.

Patient-reported presenting respiratory complaints and constitutional symptoms were documented to characterize the clinical manifestation of pulmonary complications comprehensively. The duration of symptoms and the interval between transplantation and the development of pulmonary complications provided temporal context, aiding in understanding the natural history of these events. Radiographic findings, including chest X-rays and CT scans, were carefully analyzed to delineate the anatomical and pathological characteristics of pulmonary infiltrates.

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In cases where CT findings suggested infection, patients underwent fiberoptic bronchoscopy with BAL, allowing for direct sampling of the lower respiratory tract. BAL samples underwent bacterial, fungal, and mycobacterial cultures, facilitating the identification of causative pathogens and guiding antibiotic therapy based on sensitivity patterns.

Risk factors influencing survival outcomes in renal transplant recipients with pulmonary complications were systematically evaluated. These included leukopenia, viral infections (e.g., CMV, hepatitis B, hepatitis C), history of anti-rejection treatment, prior ATT therapy, herpes zoster infection, fungal infections, urinary tract infections, surgical history, anemia, and graft dysfunction.

All 37 patients included in the study received a tacrolimus-based triple immunosuppression regimen, administered in conjunction with MMF or azathioprine and prednisolone. This standardized regimen ensured consistency in treatment and allowed for meaningful comparisons across patient cohorts. Finally, the final outcome of pulmonary complications was assessed based on patient survival following the episode, providing valuable insights into the clinical course and prognosis of these complications in renal transplant recipients.

Statistical Analysis: The data analysis was conducted using IBM SPSS version 25. Descriptive statistics were employed to summarize patient demographics and clinical characteristics.

Ethical Issues: The study protocol was approved by the institutional ethics committee, ensuring adherence to ethical principles and patient confidentiality. Informed consent was obtained from all participants prior to enrollment in the study.

RESULTS

A total of 458 patients who satisfied the inclusion and exclusion criteria were followed up throughout the study period. All the patients were followed up fortnightly. Among these patients 45 incidents (37 patients) of pulmonary complications were recorded. Incidence of pulmonary complications among the study group was 9.8%.

The age of the renal transplant recipients included in the study ranged from 16 to 55 years, with a mean age of 33 years. Among the 37 patients who developed pulmonary complications, 29 (78%) were males and 8 (22%) were females.

The clinical presentation of pulmonary complications in immunosuppressed renal transplant recipients varied, with fever being the most common symptom (66.7%). Other symptoms included cough with productive sputum (62.2%), dyspnea (53.3%), chest pain (26.7%), hemoptysis (8.9%), weight loss (6.7%), and leg swelling (2.2%).

The underlying renal diseases among the study participants were varied, with the majority having chronic kidney disease (CKD) of unknown cause (54%). Other prevalent underlying diseases included CKD secondary to hypertension (16%), CKD secondary to diabetes (11%), vesico-ureteric reflux (5%), IgA nephropathy (8%), Alport syndrome (3%), and steroid-resistant nephrotic syndrome (3%).

Table 1: Type of renal transplant and induction therapy among the study participants

Variables		Number	Percentage
Type of renal transplant	Live related	13	35
	Deceased donor	24	65
Induction therapy	Anti thymocyte globulin (ATG)	22	49
	Basiliximab	15	33
	No induction	8	18

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Graft function during pulmonary infection	Normal	28	62
	Impaired	17	38

Most pulmonary complications occurred more than 6 months post-transplantation, accounting for 51% of cases. About 27% of cases occurred within the first month post-transplantation, while 22% occurred between 1- and 6-months post-transplantation. The analysis revealed that infectious complications were predominant, constituting 89% of cases. Non-infectious complications accounted for only 11% of cases. The infectious pulmonary complications and spectrum of infections are illustrated in Figure 1 and Table 2 respectively.

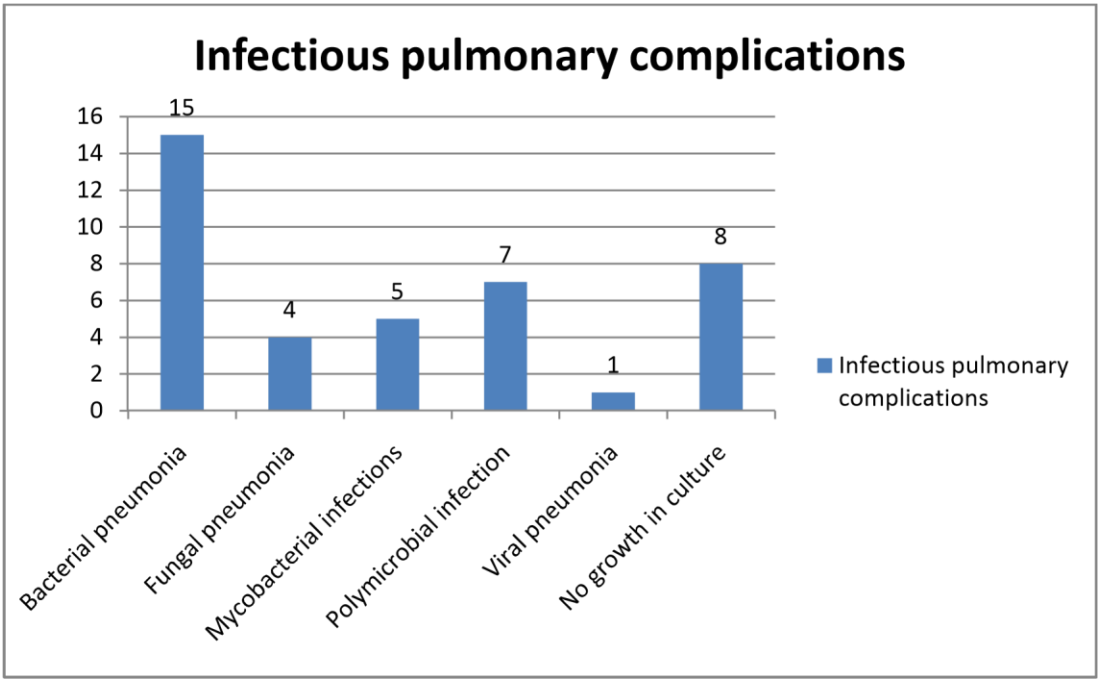

Figure 1: Infectious pulmonary complications

Table 2: Spectrum of micro-organisms isolated post transplantation

Time interval to complication	No of incidents (%)	Organisms grown	Day of presentation	Percentage
0 – 1 month post transplantation	11 (27.5%)	Acinetobacter (2)	19, 24	18.2%
		Klebsiellacapacea (1)	10	9.1%
		Pseudomonas (3)	5, 8, 10	27.3%
		Polymicrobial (1) (Candida fumata+Sphingomon as paucimobilis)	26	9.1%
		Escherchia coli (1)	2	9.1%
		Staphylococcus aureus (1)	10	9.1%
		Aspergillusflavus (1)	2	9.1%
		No Growth (1)	7	9.1%
>1month to	9 (22.5%)	Klebsiella pneumonia (2)	58, 125	22.2%

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<6month post transplantation		Mycobacterium tuberculosis (2)	107, 124	22.2%
		Candida (1)	132	11.1%
		Polymicrobial (Acinetobacter baumanni, Klebsiella pneumonia, Candida) (2)	92, 96	22.2%
		Klebsiellaoxytoca (1)	62	11.1%
		No growth (1)	68	11.1%
>6 months post transplantation	20 (50%)	Mycobacterial infection (4)	436, 1424, 223, 1747	20%
		Pseudomonas (1)	408	5%
		Cladosporidium (1)	222	5%
		Polymicrobial (4) Klebsiella pneumonia, Pseudomonas putida, Enterobacterclocae, Enterococcus Pneumocystis carnii cysts, Candida)	1817, 1066, 2924, 189	20%
		Klebsiella pneumonia (2)	363, 202	10%
		Klebsiellaoxytoca (1)	373	5%
		CMV (1)	346	5%
		Mucromycosis (1)	304	5%
		No growth (5)	1594, 650, 887, 1666 1726	25%

A comprehensive evaluation of risk factors among the entire cohort revealed various significant factors contributing to pulmonary complications in renal transplant recipients. These factors include leucopenia, observed in 11 cases (24.4%), CMV infection and HCV infection each affecting 4 cases (8.9%), ART in 9 cases (20%), and NODAT in 5 cases (11.1%).

DISCUSSION

Pulmonary complications pose significant challenges in renal transplant recipients due to their immunocompromised state and the multifactorial nature of these complications. Our study provides valuable insights into the epidemiology, clinical presentation, microbial spectrum, risk factors, and outcomes of pulmonary complications in this patient population.

The incidence of pulmonary complications in our cohort was 9.8%, consistent with previous studies reporting rates ranging from 5% to 20%[10-12]. This relatively high incidence underscores the importance of vigilant monitoring and early detection of respiratory symptoms in renal transplant recipients. The predominance of males in our study population aligns with existing literature suggesting a male predominance in renal transplant recipients[11].

Fever emerged as the most common symptom of pulmonary complications, followed by cough with productive sputum and dyspnea. These findings highlight the nonspecific nature of respiratory symptoms in immunocompromised individuals, making early diagnosis and intervention challenging. The diverse spectrum of underlying renal diseases among our study participants

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emphasizes the heterogeneity of this patient population and the need for tailored management approaches.

Our analysis revealed that infectious complications accounted for most pulmonary complications, with bacterial pneumonia being the most common type of infection. This finding underscores the importance of vigilant infection control measures, including prophylactic antimicrobial therapy and immunization, in renal transplant recipients. The identification of specific pathogens implicated in pulmonary infections, such as Acinetobacter, Pseudomonas, and Mycobacterium tuberculosis, informs targeted antimicrobial therapy and highlights the importance of microbial surveillance in this population[13].

The time interval to complication post-transplantation emerged as a significant determinant of infection type, with different pathogens predominating at different stages post-transplantation. Early post-transplantation complications were characterized by bacterial infections, whereas late complications were more commonly associated with fungal and mycobacterial infections. These findings highlight the dynamic nature of infectious risk in renal transplant recipients and underscore the importance of longitudinal surveillance and tailored antimicrobial prophylaxis strategies[14].

Risk factor analysis revealed several significant predictors of pulmonary complications in renal transplant recipients, including leucopenia, CMV infection, HCV infection, anti-rejection treatment (ART), and new-onset diabetes after transplantation (NODAT). These findings highlight the complex interplay between immunosuppression, infectious risk, and comorbidities in renal transplant recipients and highlight the need for multidisciplinary approaches to risk assessment and management in this population[15].

The favorable survival outcomes observed in our study population are encouraging and underscore the importance of early detection and timely intervention in mitigating the impact of pulmonary complications in renal transplant recipients[15]. However, further research is needed to elucidate the long-term implications of pulmonary complications on graft function, overall survival, and quality of life in this patient population.

Our study has several limitations that warrant acknowledgment. Firstly, the retrospective nature of the study may have introduced selection bias and limited the generalizability of our findings. Additionally, the relatively small sample size and single-center design may have limited the statistical power and external validity of our results. Future studies incorporating larger, multicenter cohorts and prospective study designs are needed to validate our findings and provide further insights into the epidemiology, risk factors, and outcomes of pulmonary complications in renal transplant recipients.

The study provides valuable insights into the epidemiology, clinical presentation, microbial spectrum, risk factors, and outcomes of pulmonary complications in renal transplant recipients. Despite advances in immunosuppression and antimicrobial therapy, pulmonary complications remain a significant cause of morbidity and mortality in this patient population. Vigilant monitoring, early detection, and targeted intervention are essential for optimizing patient outcomes and improving long-term graft and patient survival. Further research is needed to elucidate the complex pathophysiology of pulmonary complications in renal transplant recipients and inform evidence-based strategies for prevention, diagnosis, and management in this vulnerable patient population.

CONCLUSION

In conclusion, our study sheds light on the epidemiology, clinical presentation, microbial spectrum, and risk factors of pulmonary complications in renal transplant recipients. Despite the

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challenges posed by immunosuppression and diverse underlying renal diseases, our findings highlight the importance of early detection, targeted antimicrobial therapy, and multidisciplinary management approaches in optimizing patient outcomes. By addressing these gaps in knowledge, we can improve the quality of care for renal transplant recipients and ultimately enhance their long-term prognosis and quality of life.

REFERENCES

1. Abecassis M, Bartlett ST, Collins AJ, Davis CL, Delmonico FL, Friedewald JJ, Hays R, Howard A, Jones E, Leichtman AB, Merion RM, Metzger RA, Pradel F, Schweitzer EJ, Velez RL, Gaston RS. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. Clin J Am Soc Nephrol. 2008 Mar;3(2):471-80. doi: 10.2215/CJN.05021107.
2. Yoo KD, Kim CT, Kim MH, Noh J, Kim G, Kim H, An JN, Park JY, Cho H, Kim KH, Kim H, Ryu DR, Kim DK, Lim CS, Kim YS, Lee JP. Superior outcomes of kidney transplantation compared with dialysis: An optimal matched analysis of a national population-based cohort study between 2005 and 2008 in Korea. Medicine (Baltimore). 2016 Aug;95(33):e4352. doi: 10.1097/MD.0000000000004352.
3. Pazarlar BA, Egilmez CB, Erdogan MA, Erbas O. Immunosuppressant Tacrolimus Treatment Delays Acute Seizure Occurrence, Reduces Elevated Oxidative Stress, and Reverses PGF2α Burst in the Brain of PTZ-Treated Rats. Neurochem Res. 2023 Jun;48(6):1971-1980. doi: 10.1007/s11064-023-03885-0.
4. Pencheva VP, Petrova DS, Genov DK, Georgiev OB. Risk factors for lung diseases after renal transplantation. J Res Med Sci. 2015 Dec;20(12):1127-32. doi: 10.4103/1735-1995.172978.
5. Sommerer C, Schröter I, Gruneberg K, Schindler D, Behnisch R, Morath C, Renders L, Heemann U, Schnitzler P, Melk A, Della Penna A, Nadalin S, Heeg K, Meuer S, Zeier M, Giese T; Transplant Cohort of the German Center for Infection Research (DZIF Transplant Cohort) Consortium. Incidences of Infectious Events in a Renal Transplant Cohort of the German Center of Infectious Diseases (DZIF). Open Forum Infect Dis. 2022 May 13;9(7):ofac243. doi: 10.1093/ofid/ofac243.
6. van Delden C, Stampf S, Hirsch HH, Manuel O, Meylan P, Cusini A, Hirzel C, Khanna N, Weisser M, Garzoni C, Boggian K, Berger C, Nadal D, Koller M, Saccilotto R, Mueller NJ; Swiss Transplant Cohort Study. Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study. Clin Infect Dis. 2020 Oct 23;71(7):e159-e169. doi: 10.1093/cid/ciz1113.
7. Iliyasu G, Abdu A, Dayyab FM, Tiamiyu AB, Habib ZG, Adamu B, Habib AG. Post-renal transplant infections: single-center experience from Nigeria. Transpl Infect Dis. 2016 Aug;18(4):566-74. doi: 10.1111/tid.12548.
8. Shrestha BM. Two Decades of Tacrolimus in Renal Transplant: Basic Science and Clinical Evidences. Exp Clin Transplant. 2017 Feb;15(1):1-9. doi: 10.6002/ect.2016.0157.
9. Fatly ZA, Betjes MG, van Gestel J, Verschragen M, de Weerd AE. The Burden of Gastrointestinal Complaints in Kidney Transplant Recipients Using Tacrolimus With and Without Mycophenolate Mofetil: A Randomized Controlled Study. Front Nephrol. 2022 Jul 19;2:933954. doi: 10.3389/fneph.2022.933954.
10. Reyna-Sepúlveda F, Ponce-Escobedo A, Guevara-Charles A, Escobedo-Villarreal M, Pérez-Rodríguez E, Muñoz-Maldonado G, Hernández-Guedea M. Outcomes and Surgical Complications in Kidney Transplantation. Int J Organ Transplant Med. 2017;8(2):78-84.

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11. Chan S, Pascoe EM, Clayton PA, McDonald SP, Lim WH, Sypek MP, Palmer SC, Isbel NM, Francis RS, Campbell SB, Hawley CM, Johnson DW. Infection-Related Mortality in Recipients of a Kidney Transplant in Australia and New Zealand. Clin J Am Soc Nephrol. 2019 Oct 7;14(10):1484-1492. doi: 10.2215/CJN.03200319.
12. Zheng C, Teixeira-Pinto A, Hughes JT, Sinka V, van Zwieten A, Lim WH, Wong G. Acute Rejection, Overall Graft Loss, and Infection-related Deaths After Kidney Transplantation in Indigenous Australians. Kidney Int Rep. 2022 Sep 3;7(11):2495-2504. doi: 10.1016/j.ekir.2022.08.027.
13. McCort M, MacKenzie E, Pursell K, Pitrak D. Bacterial infections in lung transplantation. J Thorac Dis. 2021 Nov;13(11):6654-6672. doi: 10.21037/jtd-2021-12.
14. Singh N, Limaye AP. Infections in Solid-Organ Transplant Recipients. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 2015:3440–52. doi: 10.1016/B978-1-4557-4801-3.00313-1.
15. Cohen-Bucay A, Gordon CE, Francis JM. Non-immunological complications following kidney transplantation. F1000Res. 2019 Feb 18;8:F1000 Faculty Rev-194. doi: 10.12688/f1000research.16627.1.