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Infection-Related Mortality in Kidney Transplant Recipients: a retrospective study in a Portuguese tertiary hospital center

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Infection-Related Mortality in Kidney Transplant Recipients: a retrospective study in a Portuguese tertiary hospital center

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

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Declaração de Integridade Científica

Eu, Rita Maria Amaral e Silva, estudante com o número de inscrição 202004879 do Mestrado Integrado em Medicina do Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, declaro que a presente dissertação, intitulada *"Infection-Related Mortality in Kidney Transplant Recipients: a retrospective study in a Portuguese tertiary hospital center"*, é um trabalho original e genuíno. Durante o processo de investigação e elaboração deste trabalho, segui os princípios éticos e as normas académicas estabelecidas pela comunidade científica. Assumo a total responsabilidade pelo conteúdo e estou ciente das possíveis consequências da violação dos princípios de integridade científica.

Rita Maria Amaral e Silva

(Rita Maria Amaral e Silva)

Porto, junho de 2026

Porque os homens são anjos nascidos sem asas,

é o que há de mais bonito, nascer sem asas e fazê-las crescer.

José Saramago

In *Memorial do Convento*

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Resumo

Introdução: A taxa de sobrevivência dos recetores de transplante renal melhorou significativamente nas últimas duas décadas, sendo a maioria das mortes associada à doença cardiovascular, à infeção e à malignidade. As infeções bacterianas e virais adquiridas na comunidade destacam-se como as mais prevalentes, não se podendo desprezar as infeções oportunistas.

Objetivos: Este estudo pretende avaliar a mortalidade associada à infeção em doentes submetidos a transplante renal num hospital terciário português. O *outcome* primário consiste na avaliação da incidência de mortalidade por infeção. Como *outcome* secundário, pretende-se analisar a associação entre a mortalidade relacionada com infeção e fatores de risco conhecidos do recetor.

Metodologia: Trata-se de um estudo de coorte retrospetivo que inclui doentes submetidos a transplante renal entre 2014 e 2024, identificados através da base de dados hospitalar da Unidade de Transplante Renal de um hospital terciário português. Foram incluídos todos os adultos (idade igual ou superior a 18 anos) com doença renal crónica terminal submetidos a transplante renal entre 1 de janeiro de 2014 e 31 de dezembro de 2024, exceto os doentes submetidos a transplante renal em idade pediátrica e/ou a transplante multiorgânico. A análise estatística foi realizada com recurso ao IBM® SPSS®, versão 30.

Resultados: A incidência de mortalidade associada à infeção foi de 49,9 por 10000 doentes-ano. A maioria das mortes ocorreu entre 2019 e 2022 e 6 meses após o transplante, sendo a sépsis e a infeção pulmonar as categorias mais prevalentes. As infeções fatais foram predominantemente virais e bacterianas, destacando-se, respetivamente, o SARS-CoV-2 e as bactérias Gram-negativo como principais agentes etiológicos. A diabetes mellitus, como causa de doença renal terminal, foi o único preditor independente de mortalidade associada à infeção.

Conclusões: A incidência de mortalidade associada à infeção foi comparável à descrita em coortes internacionais, contudo, verificou-se uma alteração da predominância histórica das infeções bacterianas para infeções virais, determinada pela pandemia COVID-19. Ao fornecer dados contemporâneos provenientes de um centro terciário português, este estudo contribui para o conhecimento da mortalidade associada à infeção após transplante renal em Portugal.

Palavras-chave: Transplante renal; Transplante de órgão sólido; Mortalidade; Infeções bacterianas; Infeções virais; Infeções oportunistas.

Abstract

Introduction: The survival rate of kidney transplantation recipients has improved significantly over the last two decades due to advances in immunosuppressive agents, and most deaths are associated with cardiovascular disease, infectious complications, and malignancy. Community-acquired bacterial and viral infections are the most prevalent, although opportunistic infections should not be overlooked.

Objectives: This study aims to evaluate infection-related mortality in patients undergoing kidney transplantation at a Portuguese tertiary hospital. The primary outcome is to assess the incidence of infection-related mortality. As a secondary outcome, the aim is to analyze the association between infection-related mortality and known risk factors of the transplant recipient.

Methods: This is a retrospective cohort study that includes patients who underwent kidney transplantation between 2014 and 2024, identified using the Kidney Transplant Unit database of a Portuguese tertiary hospital center. All adults (aged 18 years or older) with end-stage chronic kidney disease who underwent kidney transplantation between January 1st, 2014, and December 31st, 2024, were included, except for those who underwent kidney transplantation during childhood and/or multi-organ transplantation. Statistical analysis was performed using IBM® SPSS®, version 30.

Results: The incidence of infection-related mortality was 49.9 per 10,000 patient-years. Most deaths occurred between 2019 and 2022 and beyond six months post-transplant, with sepsis and pulmonary infection being the most prevalent categories. Fatal infections were predominantly viral and bacterial, with SARS-CoV-2 and Gram-negative bacteria as the main etiological agents, respectively. Diabetes mellitus as the cause of end-stage kidney disease was the only independent predictor of infection-related mortality.

Conclusions: The incidence of infection-related mortality was comparable to that reported in international cohorts. However, there was a shift from the historical predominance of bacterial infections to viral infections shaped by the COVID-19 pandemic. By providing contemporary data from a Portuguese tertiary center, this study improves the understanding of infection-related mortality after kidney transplantation in Portugal.

Keywords: Kidney Transplantation; Solid Organ Transplantation; Mortality; Bacterial Infections; Viral Infections; Opportunistic Infections

List of Abbreviations

SOT	Solid-organ transplantation
CAIs	Community-acquired infections
MDR	Multidrug-resistant
UTI	Urinary tract infection
GI	Gastrointestinal
CMV	Cytomegalovirus
ATG	Antithymocyte globulin
OKT3	Muromonab-CD3
CNI	Calcineurin inhibitor
PDN	Prednisolone
ESKD	End-stage kidney disease
GN	Glomerulonephritis
CNS	Central nervous system
SOFA	Sequential Organ Failure Assessment
MRSA	Methicillin-resistant *Staphylococcus aureus*
HR	Hazard ratio

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Introduction

The first successful human kidney transplant was performed in 1954. Over the past two decades, the survival rates of solid organ transplant (SOT) recipients have improved, mainly due to advances in immunosuppressive regimens, antimicrobial prophylaxis, and improved graft longevity [(1)]. According to the United States Renal Data System, in 2017, the adjusted 1-year graft survival after living-donor kidney transplantation reached an unprecedented 98.1%, subsequently declining slightly to 97.4% for transplants performed in 2021. Among recipients of deceased-donor grafts, the one-year graft survival probability was 93.8% in 2017 and decreased to 92.2% in 2022 [(2)]. Among kidney transplant recipients, approximately half of all cases of graft failure are attributable to patient death with a functioning graft, primarily due to cardiovascular disease, infectious complications, and malignancy. Patients undergoing chronic renal replacement therapy have substantially higher mortality rates than the general population. Although cardiovascular disease remains the leading cause of death, non-cardiovascular causes, particularly infection and malignancy, account for a large proportion of fatal events [(3)].

Infections are the leading cause of complications after a kidney transplant [(4)]. The most prevalent etiologies include common community-acquired infections (CAIs), as well as opportunistic infections, which are particularly significant given the immunosuppressed state inherent in solid organ transplantation [(5)]. Over recent decades, the incidence of infection caused by multidrug-resistant (MDR) bacteria has been increasing worldwide, resulting in poorer outcomes and more limited therapeutic options. SOT recipients are particularly vulnerable to MDR bacterial infections and have a higher risk of recurrence compared to those infected with non-MDR organisms [(6)].

Traditionally, the post-transplant course can be divided into three time periods according to the predominant infection risk: (1) the first month post-transplant, (2) the period from one month to six months post-transplant, and (3) beyond the six months post-transplant [(5)]. In the early post-transplant period, most infections are bacterial and often associated with postoperative complications. Whereas opportunistic infections are more prevalent within the first six months and may result from newly acquired infections, donor-derived infections, or reactivation of latent pathogens. In the late post-transplant period, the overall risk of infection approaches that of the general population, with community-acquired pneumonia, upper respiratory tract infection, urinary tract infection (UTI), and gastrointestinal (GI) infection being the most common [(5)]. A recent Swiss cohort study of 2,761 SOT recipients evaluated the incidence of clinically relevant infections within the first 12 months after transplantation and found that infectious complications were highly

frequent and remained common beyond six months post-transplant, with 55% of recipients experiencing at least one infection during the first year after transplantation. Bacterial infections were the most prevalent, and opportunistic infections were uncommon throughout the 12-month follow-up period. The first month after transplantation carried the highest infectious burden, reinforcing the first post-transplant year as a particularly critical period for infection[7].

Across studies evaluating infection-related mortality in kidney transplant recipients, there is a consistent predominance of severe bacterial infections over viral and fungal infections. In a Spanish cohort comprising 1,218 kidney transplants performed between 1995 and 2004, 57% of infection-related deaths were attributed to bacterial infections, mainly sepsis, pneumonia, and intra-abdominal infections, whereas invasive viral and invasive fungal infections accounted for 24% and 18% of fatal events, respectively [8]. Likewise, in a nationwide Finnish cohort of 3,249 first kidney transplant recipients between 1990 and 2012, the leading causes of infection-related death were bacterial pneumonia and sepsis. Among bloodstream infections with an identified pathogen, *Staphylococcus aureus* and Gram-negative *bacilli* were the predominant microorganisms. In contrast, deaths directly related to opportunistic infections, such as Cytomegalovirus (CMV) or opportunistic fungal disease, were uncommon [9]. Data from an Australian and New Zealand registry, including more than 12,519 first kidney transplant recipients, show a similar pattern, with most infection-related deaths resulting from bacterial infections, particularly pneumonia and sepsis/urosepsis, with a comparatively smaller contribution from viral and fungal causes [10].

After kidney transplantation, the risk of infection is largely determined by the net state of immunosuppression and specific donor-recipient factors. High-intensity immunosuppression during the first six months, particularly antirejection immunosuppression with antilymphocyte antibodies (such as antithymocyte globulin [ATG] or muromonab-CD3 [OKT3]), is associated with opportunistic infections, including CMV. A CMV-seropositive donor paired with a seronegative recipient is a major risk factor for primary CMV infection and is associated with an increased risk of graft dysfunction, rejection, and subsequent opportunistic infections. Additional important risk factors include the maintenance immunosuppressive regimen, such as triple therapy with a calcineurin inhibitor (CNI), mycophenolate, and prednisolone (PDN), particularly when corticosteroids are used at high doses or for prolonged periods, as well as recipient-related factors such as advanced age, deceased-donor kidney transplantation, and prolonged pre-transplant dialysis, which also contribute to an increased risk of infection. [11; 12].

Methods

Study design

We conducted a cohort retrospective study of infection-related mortality in adult kidney transplant recipients who underwent transplantation at a Portuguese tertiary hospital center, between January 2014 and December 2024. All adults (aged 18 years or older) with end-stage chronic kidney disease (ESKD) who underwent kidney transplantation between January 1st, 2014, and December 31st, 2024, were included, except for patients who received a kidney transplant in childhood and/or multiorgan transplantation. The primary outcome is the calculation of the incidence of infection-related mortality from January 1st, 2014, to April 20th, 2026. The secondary outcome is to evaluate infection-associated mortality risk factors, particularly older age, female sex, pre-transplant dialysis, deceased-donor kidney transplantation, antirejection immunosuppression with T-cell-depleting therapy, and maintenance immunosuppression combining a CNI, mycophenolate, and PDN.

Data Collection

Patients were identified from the Renal Transplant Unit database of a Portuguese tertiary hospital center, and data were obtained by reviewing electronic medical records. It included recipient characteristics (age, sex, cause of ESKD, pre-transplant dialysis modality, CMV status and date of death), donor characteristics (living/deceased and CMV status), transplant characteristics (date, maintenance immunosuppression, and antirejection immunosuppression), cause of death (infection, cardiovascular, malignancy, and other causes) and fatal infection details (sepsis, site of infection, etiology, Gram stain for bacterial infections and etiological agents in each etiology category).

The cause of ESKD was categorized as chronic glomerulonephritis (GN), cystic kidney disease, diabetic kidney disease, interstitial nephritis, indeterminate, and other. The pre-transplant dialysis modality was classified as previous dialysis or pre-emptive transplantation. The risk of CMV infection was obtained through the combination of the donor and the recipient CMV status and classified regarding the risk of CMV infection as high risk (CMV-seropositive donor and CMV-seronegative recipient), intermediate risk (CMV-seropositive, CMV-seronegative, or indeterminate donor and CMV-seropositive recipient), or low risk (CMV-seronegative donor and CMV-seronegative recipient) [(11)]. The date of death was divided into three periods: 2014-2018, 2019-2022, and 2023-2026.

Maintenance immunosuppressive therapy was categorized into three regimens, including CNI (tacrolimus or cyclosporine) combined with mycophenolate and PDN, CNI (tacrolimus or cyclosporine) and PDN, or other. Additionally, the induction immunosuppressive regimen was divided into T-cell-depleting and non-T-cell-depleting therapies. The post-transplant period was defined as the first month, one to six months, and beyond six months.

Infection was subsequently classified by etiological agent type (bacterial, viral, fungal, parasitic, polymicrobial, or no etiological agent identified) and by site of infection (sepsis, pulmonary, urinary tract, central nervous system [CNS], GI, and others). Regarding Gram stain, bacterial infections were classified as Gram-positive or Gram-negative. Sepsis was defined according to the Surviving Sepsis Campaign guidelines (2021) as life-threatening organ dysfunction caused by a dysregulated host response to infection, with an increase of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score, and was classified according to its source as pulmonary, urinary tract, GI, abdominal, skin, bone, and not identified [13]. Polymicrobial infection was defined as the presence of more than one etiological agent directly related to the patient's death.

Statistical Analysis

Statistical analysis was performed using IBM® SPSS®, version 30. Descriptive analysis was carried out for all variables, and categorical variables were presented as absolute and relative frequencies, whereas continuous variables were presented as mean and standard deviation, after confirming that the data followed a normal distribution using the Kolmogorov–Smirnov and Shapiro–Wilk tests.

Incidence rates were calculated by dividing the number of events (deaths) by the total person-time (patient-years) at risk, defined as the time from transplantation to the date of death or censoring. The end of follow-up was defined as death or April 20th, 2026, whichever occurred first. Incidence rates were calculated for all-cause mortality and infection-related mortality.

The Cox proportional hazards model was used to assess factors associated with infection-related mortality. Univariable analysis was performed first, followed by multivariable analysis, with statistical significance set at $p<0.05$ and 95% confidence intervals.

Ethics considerations

Approval for the study was granted by the Hospital Ethics Committee (approval number 2025.294 [252-CAC-252-CE]). Compliance with relevant ethical and regulatory standards was maintained through the anonymization and confidentiality of patient data. Informed consent from individual participants was not required, given that the research involved only a retrospective review of existing medical records. Anonymity was further protected by assigning each case a unique random identification number.

Results

Study population

A total of 998 adults with ESKD who received a kidney transplant at a Portuguese tertiary hospital center from 2014 to 2024 were included (Table I).

The mean age was 58.3 ± 11.9 years (range 19-84), and most patients were male (n=637, 63.9%). Chronic GN was the leading cause of ESKD (n=316, 31.7%), followed by indeterminate causes (n=212, 21.2%), cystic kidney disease (n=135, 13.5%), diabetes mellitus (n=98, 9.8%), and interstitial nephritis (n=97, 9.7%). Other causes of ESKD accounted for 14% (n=140) of the patients. Most patients had undergone pre-transplant dialysis (n=907, 91.1%), with only 8.9% (n=89) receiving pre-emptive transplantation. Deceased-donor transplantation predominated (n=716, 71.7%) in comparison with living-donor transplantation (n=282, 28.3%). Most patients were at intermediate risk for CMV infection (n=858, 89.2%), with high-risk patients accounting for 8.6% (n=83) of cases and low-risk patients for 2.2% (n=21). Standard triple immunosuppressive therapy with a CNI, mycophenolate, and PDN was used in 92.6% (n=924) of patients, CNI and PDN were used in 0.2% (n=2) of patients, and 7.2% (n=72) received other regimen options. Regarding antirejection immunosuppression, 17.0% (n=170) received T-cell-depleting induction therapy, while the other patients received non-T-cell-depleting induction therapy (n=828, 83%).

Incidence of infection-related mortality

During the study period, 98 patients died (9.8%). Infection was the cause of death in 32 cases (32.7%), while 19 were associated with cardiovascular disease (19.4%) and 23 with malignancy (23.5%). The remaining deaths were attributed to other causes (n=4 4.1%) or unknown causes (n=20, 20.4%) (Table II).

The incidence of all-cause mortality was 152.7 per 10,000 patient-years, and the overall incidence of infection-related mortality was 49.9 per 10,000 patient-years.

Infection-related mortality by date of death and post-transplant period

From 2014 to 2018, two patients (6.3%) died from infection-related causes, while between 2019 and 2022, the cases of infection-related mortality increased to 22 (68.8%), and, in the most recent period, from 2023 to 2026, there was a decrease to eight (25.0%) cases (Figure 1, A). Most of the deaths occurred beyond six months post-transplant, with 25 cases (78.1%) in that period,

while the remaining seven cases (21.9%) occurred during the period from one to six months. There were no deaths within the first month post-transplant during the study period (Figure 1, B).

Infection-related mortality by site of infection

Regarding the site of infection, sepsis was the most frequent group, accounting for 15 cases (46.9%) of the 32 observed during the study period, followed by pulmonary infection with 14 cases (43.8%), while UTI, CNS infection, and GI infection accounted for one case each (3.1% each).

The infection pattern varied over the study period, with an early predominance of sepsis (2014-2018), which resurfaced as the most frequent category in the most recent years (2023-2026), and a peak in pulmonary infections between 2019 and 2022. In 2014-2018, there were two cases of sepsis (100.0%). From 2019 to 2022, there were 12 cases of pulmonary infection (54.5%), the most frequent site of infection during this period, followed by sepsis with nine cases (40.9%) and UTI with one case (4.5%). In the period from 2023 to 2026, sepsis again became the most frequent category, with four cases (50.0%), followed by two pulmonary infections (25.0%), one CNS infection, and one GI infection (12.5% each) (Figure 2, A).

Regarding the classical post-transplant timeline, during the one to six months period post-transplant, four cases were due to sepsis (57.1%) and three to pulmonary infections (42.9%). Beyond six months post-transplant, sepsis and pulmonary infections were tied for the most frequent categories, with 11 cases each (44.0% each), while there was one UTI, one CNS infection, and one GI infection (4.0% each) (Figure 2, B).

Within the sepsis category, which accounted for a total of 15 related deaths, the urinary tract was the most prevalent source of infection (n=6, 40.0%), followed by pulmonary-related sepsis (n=4, 26.7%), and one case each of GI, abdominal, skin, and bone as sepsis sources (6.7% each). In one case (6.7%), the source was not identified.

In the 2014-2018 period, two cases were recorded, with gastrointestinal and urinary tract as the primary sites of infection (50.0% each). Most sepsis-related deaths occurred between 2019 and 2022, with nine cases recorded (60.0%). The most frequent primary sites of infection were pulmonary infection (n=3, 33.3%) and UTI (n=2, 22.2%), followed by one case each of abdominal, skin, and bone infections as sepsis sources (11.1% each). The primary site of infection was not identified in one case (11.1%) during this period. In the 2023-2026 period, the most prevalent sepsis source was the urinary tract (n=3, 75.0%), followed by pulmonary-related sepsis (n=1, 25.0%) (Figure 3).

Infection-related mortality by infectious etiology

Overall, viral infections were the most frequent cause, accounting for 12 cases (37.5%), of which 11 occurred during the 2019-2022 period. There were 11 bacterial infections (34.4%), two fungal infections (6.3%), and one parasitic infection (3.1%). Two cases were linked to polymicrobial infections (6.3%), and in four cases, no etiological agent was identified (12.5%).

From 2014 to 2018, there was one parasitic infection and one polymicrobial infection (50.0% each). In 2019-2022, 11 infections were viral (50.0%), seven were bacterial (31.8%), one was polymicrobial (4.5%), and three (13.6%) had no etiological agent identified. In the later period, from 2023 to 2026, there were four bacterial infections (50.0%), two fungal infections (25.0%), and one case each of viral and unidentified etiological agent infections (12.5% each) (Figure 4, A).

Based on the classical post-transplant timeline, the period between one and six months post-transplant was characterized by three bacterial infections, three viral infections (42.9% each), and one parasitic infection (14.3%). Beyond six months post-transplant, viral infections were the most frequent etiology, accounting for nine cases (36.0%), followed by bacterial infections, with eight cases (32.0%). Fungal and polymicrobial infections each accounted for two cases (8.0% each). During this post-transplant period, there were four cases (16.0%) in which no etiological agent was identified (Figure 4, B).

Of the 11 bacterial infections recorded during the study period, eight were caused by Gram-negative bacteria (72.7%) and three by Gram-positive bacteria (27.3%). Regarding Gram-negative bacteria, the agents found were *Escherichia coli* (n=2, 18.2%), *Klebsiella pneumoniae* (n=4, 36.4%), and *Pseudomonas aeruginosa* (n=2, 18.2%). Among Gram-positive bacteria, *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus* (MRSA), and an unknown agent classified as Gram-positive *cocci* were isolated (n=1, 9.1% each). All 12 viral infections identified within the study period were caused by SARS-CoV-2 (100.0%). Concerning the two fungal infections and the one parasitic infection, *Cryptococcus neoformans* (100.0%) and *Strongyloides stercoralis* (100.0%) were isolated, respectively (Table 3).

Factors associated with infection-related mortality

Univariable analysis showed a statistically significant association between recipient age and infection-related mortality (p=0.014), with a higher hazard per additional year of age (hazard ratio [HR] 1.043). The cause of ESKD was also statistically significant (p<0.001). Compared to diabetes mellitus, cystic kidney disease (HR 0.065), chronic GN (HR 0.130), other causes (HR 0.128),

and indeterminate cause (HR 0.345) were associated with a lower hazard of infection-related mortality. Interstitial nephritis was not significantly associated with the outcome. Compared with deceased-donor transplantation, living-donor transplantation was associated with a statistically significant (p=0.010) lower risk of infection-related mortality (HR 0.153). In contrast, sex (p=0.869), pre-transplant dialysis modality (p=0.262), maintenance immunosuppression (p=0.991), and anti-rejection immunosuppressive therapy (p=0.469) were not significantly associated with infection-related mortality (Table IV).

In the multivariable analysis, recipient age (p=0.154) and donor type (p=0.061) were no longer independently associated with the outcome. The cause of ESKD remained significantly associated with the hazard of infection-related mortality (p=0.010), indicating that it independently contributed to risk after adjustment, with diabetes mellitus conferring a higher risk. Sex (p=0.661), pre-transplant dialysis modality (p=0.776), maintenance immunosuppression regimen (p=0.999), and antirejection therapy (p=0.338) remained not independently associated with the outcome (Table IV).

Discussion

In this single-center retrospective cohort of 998 kidney transplant recipients, infection accounted for almost one-third of all deaths (32.7%), with an incidence of infection-related mortality of 49.9 per 10,000 patient-years. Most infection-related deaths happened between 2019 and 2022 and beyond six months post-transplantation. Sepsis and pulmonary infection were the most frequent categories regarding site of infection, and urinary and pulmonary sources were the most common among sepsis-related deaths. Among bacterial infections, Gram-negative agents (*Escherichia coli*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*) predominated, and all viral infections were related to SARS-CoV-2. Although older age and deceased-donor transplantation were associated with infection-related mortality in univariable analyses, these associations disappeared after adjustment in the multivariable analysis. However, diabetes mellitus, as the cause of ESKD, remained independently associated, suggesting that it may be a major contributor to infectious risk in this cohort.

The incidence of infection-related mortality in this cohort was 49.9 per 10,000 patient-years from 2014 to 2026 (12-year period), which is close to the ANZDATA (Australia and New Zealand) registry [(10)], which reported an incidence of 45.8 per 10,000 patient-years between 1997 and 2015 (18-year period), and to a Finnish cohort [(9)], regarding the secular trends in infection-related mortality, with an incidence rate of approximately 46 per 10,000 patient-years during its most recent era, between 2000 and 2012 (12-year period). These findings suggest that an infection-related mortality rate of 49.9 per 10,000 patient-years is within the range reported in recent kidney transplant cohorts and appears to follow the progressive decline in infection-related mortality over time, as was shown by the decrease from approximately 91 to 46 per 10,000 patient-years from 1990-1999 to 2000-2012 in the Finnish cohort [(9; 10)]. Despite the comparable incidence of infection-related mortality with other studies, the absolute number of fatal infections in this cohort increased greatly during 2019-2022, mainly due to SARS-CoV-2 infection.

The temporal distribution of infection-related deaths in this cohort differed from the classical post-transplant timeline described by Fishman and Rubin. Classically, infection-related mortality is expected to peak during the first one to six months post-transplant, when nosocomial bacterial infections and opportunistic pathogens, such as *Pneumocystis jirovecii*, *Aspergillus* spp., *Toxoplasma gondii*, *Cryptococcus* spp., and CMV, are most frequent [(5)]. However, in this cohort, only 21.9% of fatal infections occurred within six months, while 78.1% occurred beyond this period. Likewise, the ANZDATA registry showed that infection-related mortality (mainly

by viral and bacterial infections) occurred after the first year post-transplant, so beyond the six-month post-transplant mark [10].

There were only two cases attributable to a classical opportunistic agent, *Cryptococcus neoformans*, and both occurred in the latest defined post-transplant period, suggesting effective prophylaxis against traditional opportunistic pathogens, particularly trimethoprim-sulfamethoxazole for *Pneumocystis jirovecci* and valganciclovir for CMV, based on pre-transplant risk assessment with donor and recipient screening [5]. Nevertheless, this study reported a fatal *Strongyloides stercoralis* infection, highlighting the importance of incorporating endemic helminthic infections into pre-transplant risk assessment and implementing ivermectin prophylaxis in patients with geographic or occupational exposure [14].

Previous studies with quantitative data on infection-related mortality in kidney transplant recipients have reported pulmonary infections and sepsis as the leading causes. These findings align with our cohort, however, the relative frequencies differed, with pulmonary infection predominating in prior studies, whereas sepsis was the most frequent category in this cohort [9; 10]. A Spanish cohort showed a similar predominance of sepsis among infection-related deaths [8]. In the Swiss cohort of SOT recipients, 63% of events were bacterial, with UTIs being the most frequent among kidney transplant recipients [7], consistent with previous reports identifying the urinary tract as the predominant site of infection in this population, even though it is not related to most infection-related deaths [15]. The urinary tract is also a frequent source of sepsis in kidney transplant recipients, and, in this study, it was the most frequent category in the 2023-2026 period (75.0%) and tied with the GI source in the earliest period, from 2014 to 2018 (50.0%). However, a different pattern was observed in 2019-2022, when the pulmonary source (33.3%) was more frequent than the urinary tract source (22.2%), reflecting the peak in pulmonary infections during this period, likely associated with the COVID-19 pandemic [16].

Large cohort studies of kidney transplantation have consistently identified bacterial infections as the main etiology of infection-related mortality [7-10]. The Finnish cohort (1990-2012) reported bacterial infections as the leading etiology, with viral and fungal infections each representing only 2-3% of infection-related deaths [9]. The Spanish series (1995-2004) found that bacterial infections accounted for 57% of infection-related deaths, followed by viral (25%) and fungal (18%) etiologies [8]. Similarly, the ANZDATA registry found bacterial causes in 54% of infection-related deaths, while fungal and viral causes were reported in 18% and 9% of the cases, respectively [10].

A distinct pattern emerged in our study, with viral infections representing the most frequent etiology (37.5%), followed by bacterial infections (34.4%). This trend was largely driven by SARS-CoV-2-related deaths, likely reflecting the disproportionate impact of the COVID-19 pandemic on kidney transplant recipients. This is consistent with national and international data showing substantial SARS-CoV-2-related mortality in kidney transplant recipients compared to the general population [17; 18]. In a Portuguese cohort of kidney transplant recipients with SARS-CoV-2 infection there was reported an age and sex standardized mortality rate almost four times higher than in the general population [19], while at a broader European level, the ERACODA registry described a 28 day mortality of 21.3% among kidney transplant recipients, significantly higher that what was reported in general population cohorts [17; 20-22]. In our cohort, SARS-CoV-2 was the leading etiology of infection-related mortality, accompanied by a shift from sepsis with a urinary tract source to sepsis with a pulmonary source during 2019-2022. These findings highlight how the COVID-19 pandemic temporarily altered the usual profile of infection-related mortality in kidney transplant recipients.

In this cohort, bacterial infections were predominantly caused by Gram-negative *bacilli*, particularly *E. coli*, *K. pneumoniae,* and *P. aeruginosa*, while Gram-positive bacterial infections were caused by *S. aureus* (including MRSA) and unidentified Gram-positive *cocci*. This pattern is consistent with the Swiss SOT cohort for non-fatal infections in the first year post-transplant, in which bacteria accounted for 63% of infections, and the most frequent etiological agents in kidney transplant recipients were *Enterobacteriaceae* (including *E. coli* and *K. pneumoniae*) [7].

The analysis of the risk factors showed that in this cohort, after the multivariable adjustment, the most important determinant of infection-related mortality was the cause of ESKD, with diabetes mellitus conferring the highest risk, as was shown in other studies, which concluded infection risk is far higher in diabetic than non-diabetic immunosuppressed individuals [23].

Recipient age and donor type were associated with infection-related mortality in the univariable analysis but lost statistical significance after multivariable adjustment, suggesting that these variables may reflect the influence of other recipient-related factors rather than acting as independent predictors. In contrast to the ANZDATA registry, which showed that infection-related mortality was independently associated with older age, female sex, deceased-donor transplantation and T-cell-depleting therapy, our analysis did not include detailed recipient comorbidity data, so it is plausible that older recipients and those receiving a deceased-donor graft may carry a higher burden of comorbidities that could partly explain the increased risk observed in the univariable analysis [10]. The absence of statistically significant associations between infection-

related mortality and sex, pre-transplant dialysis modality, antirejection immunosuppression, and maintenance immunosuppressive regimen may reflect limited statistical power.

Study limitations

The present study is a retrospective single-center design, limiting the extent to which these findings can be generalized and making them more representative of local clinical practice and epidemiological context. Additionally, the relatively low number of infection-related deaths (32 of 98 deaths among 998 patients) may have reduced the statistical power, particularly in the multivariable analyses.

The unavailability of certain variables of interest, such as recipients' comorbidities (cardiovascular disease, diabetes mellitus, body mass index and others), also represented a limitation, as these factors may have acted as confounders in the multivariable risk factor analysis. Moreover, these variables have been included in other studies, thereby limiting comparability between this cohort and international registries. In addition, although causes of death were coded, coding practices may differ between centers and countries, which may also limit comparability across studies.

Another important limitation is the effect of the COVID-19 pandemic on the interpretation and comparability of temporal trends. During the 2019-2022 period, the number of deaths recorded was strongly influenced by SARS-CoV-2, so comparisons with earlier cohorts should be made cautiously, since viral mortality in this study is not directly comparable to virus-related mortality reported in earlier studies, such as CMV-associated deaths.

A further limitation of this study is the lack of information on the antimicrobial susceptibilities of the isolated etiological agents, since MDR bacterial infections are increasingly recognized as markers of infection severity, treatment failure, and patient survival [(6)]. Without these data, it is impossible to determine whether infections caused by MDR bacteria were associated with a higher risk of infection-related mortality or whether outcomes varied according to antibiotic susceptibility, thereby reducing the level of detail of the risk assessment in this cohort.

Conclusions

In this single-center cohort of 998 kidney transplant recipients, infection accounted for almost one-third of all mortality, and the incidence of infection-related mortality was 49.9 per 10,000 patient-years. Most fatal infections occurred six months after transplantation, unlike traditional post-transplant paradigms, and SARS-CoV-2 and Gram-negative *bacilli* emerged as the leading etiological agents. Within the sepsis category, urinary and pulmonary sources were the most common. Diabetes mellitus as the cause of ESKD was the only independent predictor of infection-related mortality after multivariable analysis, whereas age, sex, donor type, pre-transplant dialysis modality, and immunosuppressive therapy regimens were not independently associated with the outcome.

SARS-CoV-2-related mortality was a major contributor to the infection-related burden, particularly between 2019 and 2022, reflecting national and international data showing substantially higher mortality in kidney transplant recipients compared to the general population.

To our knowledge, this is the first study to characterize the incidence, temporal trends, and risk factors for infection-related mortality in a Portuguese cohort of kidney transplant recipients. Given that current evidence in this field is predominantly derived from international cohorts, these findings provide important national data that may help inform and contextualize infection prevention and risk management strategies in Portuguese kidney transplant centers.

Tables and Figures

Table I – Characteristics of all kidney transplant patients included in the study

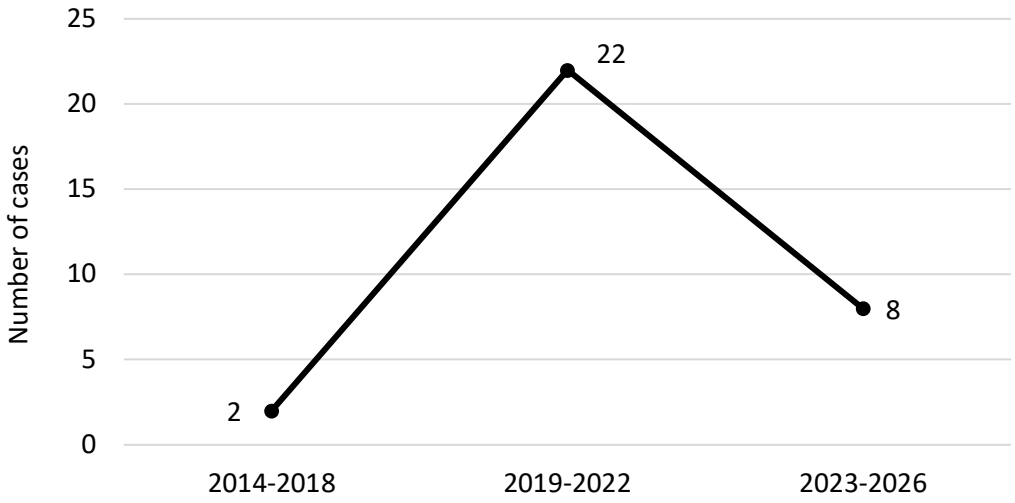
ESKD, end-stage kidney disease; GN, glomerulonephritis; CMV, cytomegalovirus; CNI, calcineurin inhibitor; PDN, prednisolone

	Total population (*n*=998)	
Characteristics	***n***	**%**
RECIPIENT		
Sex		
Female	360	36.1
Male	637	63.9
Cause of ESKD		
Diabetes mellitus	98	9.8
Cystic kidney disease	135	13.5
Chronic GN	316	31.7
Interstitial nephritis	97	9.7
Others	140	14.0
Indeterminate	212	21.2
Pre-transplant dialysis modality		
Dialysis	907	91.1
Pre-emptive transplantation	89	8.9
CMV risk		
High risk	83	8.6
Intermediate risk	858	89.2
Low risk	21	2.2
DONOR		
Deceased	716	71.7
Living	282	28.3
TRANSPLANT		
Maintenance immunosuppression		
CNI + mycophenolate + PDN	924	92.6
CNI + PDN	2	0.2
Other	72	7.2
Antirejection immunosuppression		
T-cell-depleting therapy	170	17.0
Non-T-cell-depleting therapy	828	83.0

Table II – Patients included in the study who died between 2014 and 2026

	Total deaths (*n*=98)	
	n	**%**
CAUSE-SPECIFIC DEATH		
Infection	32	32.7
Cardiovascular	19	19.4
Malignancy	23	23.5
Others	4	4.1
Unknown	20	20.4

A



B

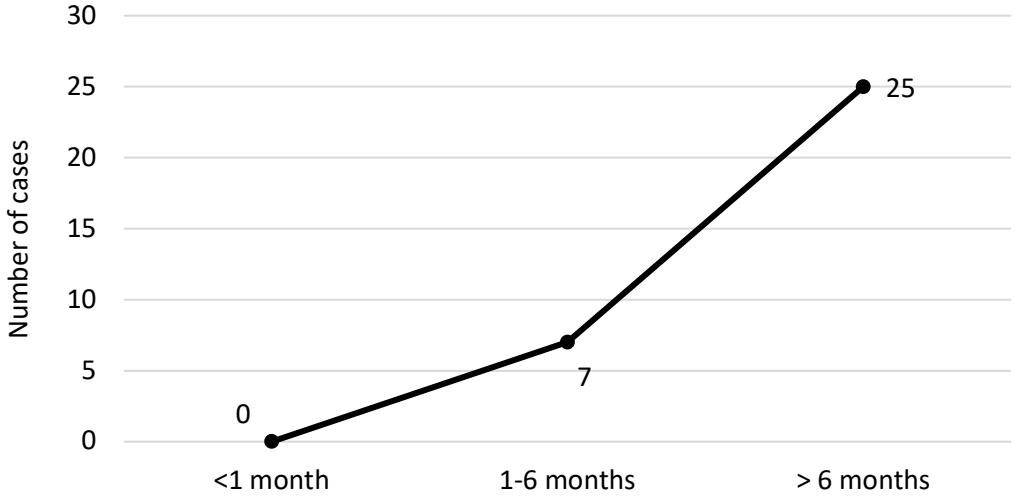
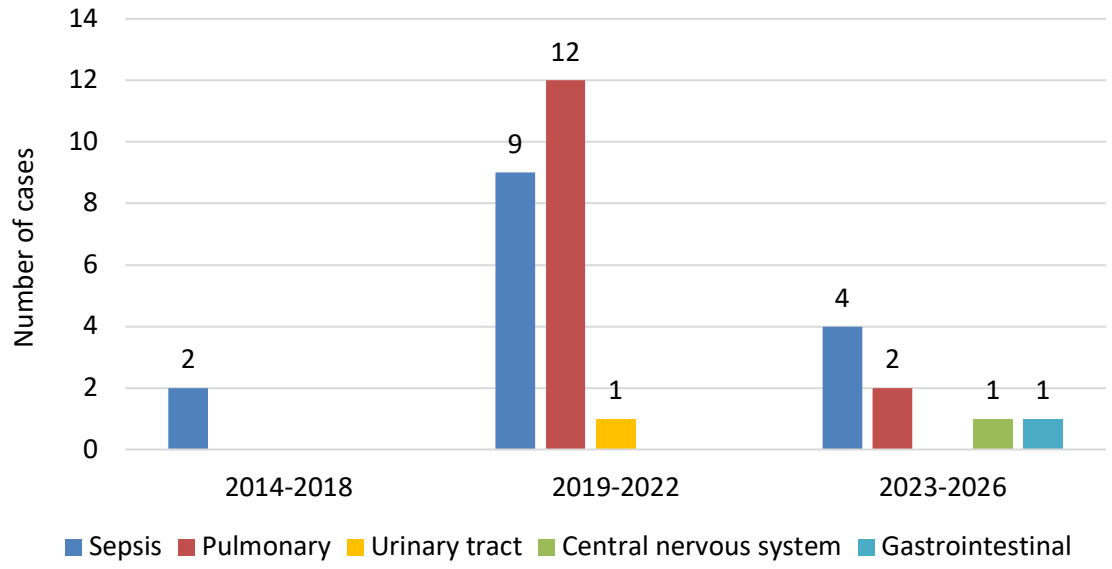


Figure 1 – Infection-related mortality according to the date of death (A) and post-transplant period (B)

A



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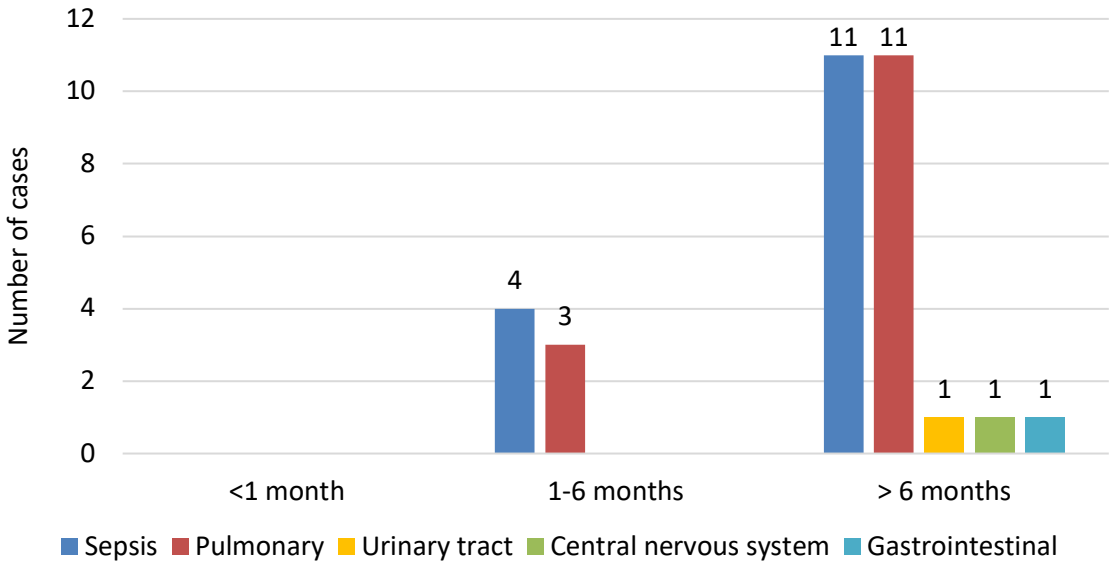


Figure 2 – Infection-related mortality by site of infection, according to the date of death (A) and post-transplant period (B)

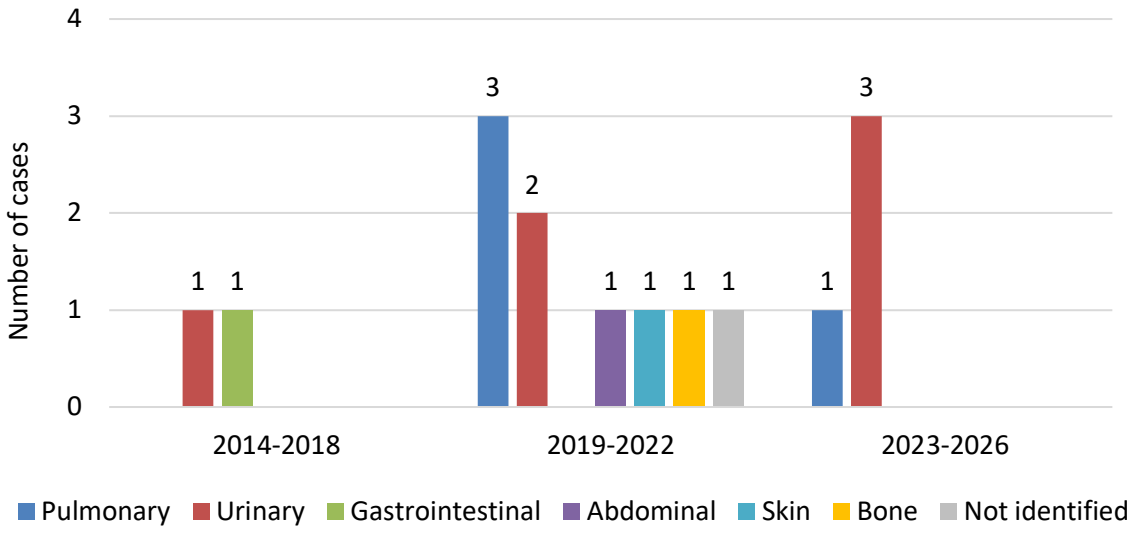
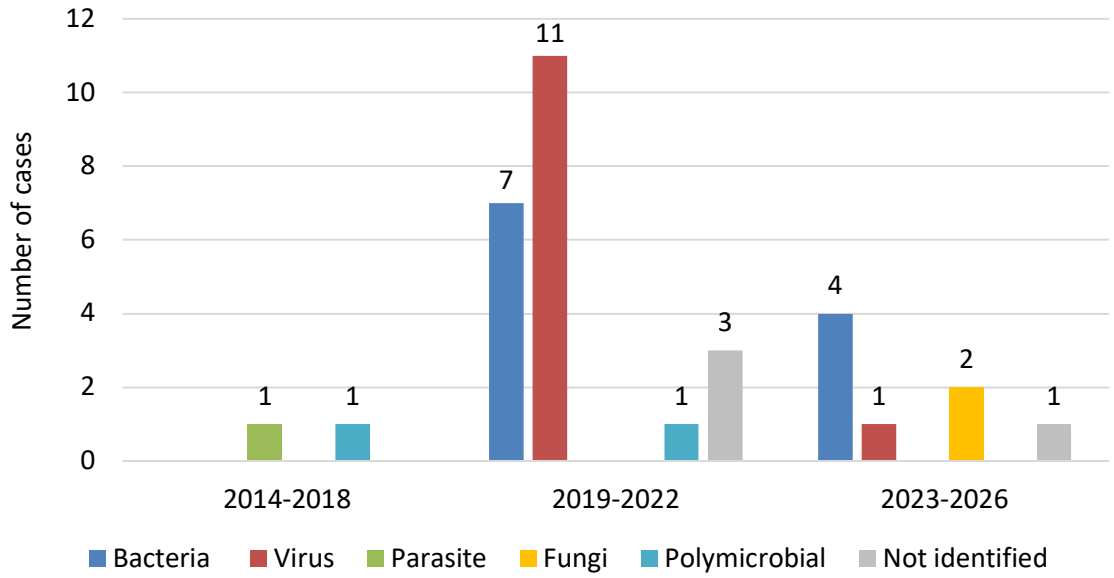


Figure 3 – Source of sepsis according to the date of death period

A



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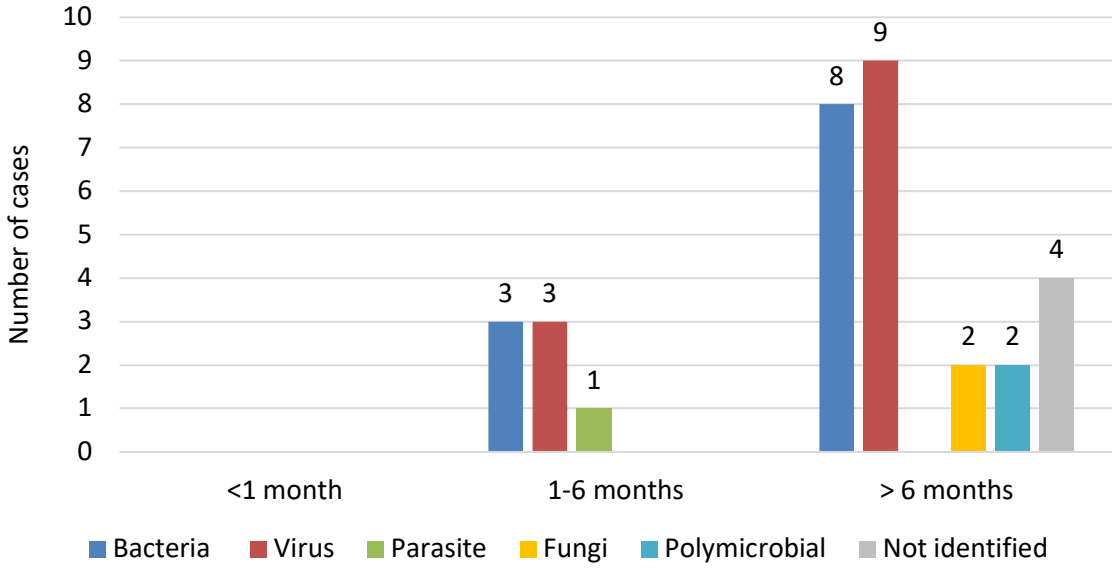

Figure 4 – Infection-related mortality by etiology, according to the date of death (A) and post-transplant period (B)

Table III – Infection etiological agents

MRSA, Methicillin-resistant *Staphylococcus aureus*

	Total infection-related deaths (*n*=32)	
Etiology	***n***	**%**
BACTERIAL	**11**	**34.4%**
Gram-negative	8	72.7%
E. coli	2	18.2%
K. pneumoniae	4	36.4%
P. aeruginosa	2	18.2%
Gram-positive	3	27.3%
S. aureus	1	9.1%
MRSA	1	9.1%
Unknown Gram-positive *cocci*	1	9.1%
VIRAL	**12**	**37.5%**
SARS-CoV-2	12	100%
FUNGAL	**2**	**6.3%**
C. neoformans	2	100%
PARASITIC	**1**	**3.1%**
S. stercoralis	1	100%
POLYMICROBIAL	**2**	**6.3%**
NOT IDENTIFIED	**4**	**12.5%**

Table IV – Factors associated with infection-related mortality among all patients included in the study

HR, hazard ratio; ESKD, end-stage kidney disease; GN, glomerulonephritis; CNI, calcineurin inhibitor; PDN, prednisolone

Characteristics	Univariable analysis			Multivariable analysis		
	n	**HR** (95% CI)	***P* value**	*n*	**HR** (95% CI)	***P* value**
RECIPIENT						
Age	998	1.043 (1.009 to 1.079)	**0.014**	998	1.028 (0.990 to 1.068)	**0.154**
Sex			**0,869**			**0.661**
Female	360	1		359	1	
Male	637	0.942 (0.460 to 1.927)		636	0.849 (0.409 to 1.762)	
Cause of ESKD			**<0.001**			**0.010**
Diabetes mellitus	98	1		98	1	
Cystic kidney disease	135	0.065 (0.008 to 0.507)		134	0.084 (0.011 to 0.655)	
Chronic GN	316	0.130 (0.045 to 0.375)		316	0.211 (0.071 to 0.625)	
Interstitial nephritis	97	0.426 (0.148 to 1.226)		96	0.782 (0.247 to 2.481)	
Others	140	0.128 (0.028 to 0.578)		140	0.178 (0.039 to 0.817)	
Indeterminate	212	0.345 (0.139 to 0.859)		211	0.455 (0.180 to 1.153)	
Pre-transplant dialysis modality			**0.262**			**0.776**
Dialysis	907	1		906	1	
Pre-emptive transplantation	89	0.320 (0.044 to 2.346)		89	1.410 (0.133 to 14.972)	
DONOR			**0.010**			**0.061**
Deceased	716	1		713	1	
Living	282	0.153 (0.037 to 0.641)		282	0.198 (0.036 to 1.080)	
TRANSPLANT						
Maintenance immunosuppression			**0.991**			**0.999**
CNI + mycophenolate + PDN	924	1		921	1	
CNI + PDN	2	0 (0 to 4,209E+291)		2	0 (0 to 1,606E+280)	
Other	72	1.082 (0.329 to 3.560)		72	1.025 (0.310 to 3.391)	
Antirejection immunosuppression			**0.469**			**0.338**
T-cell-depleting therapy	170	1		169	1	
Non-T-cell-depleting therapy	828	1.473 (0.516 to 4.203)		826	1.678 (0.582 to 4.840)	

References

(1) Dash, S. C., Nair, R., & Behera, V. (2023). Kidney transplantation: The journey across a century. *Medical Journal Armed Forces India*, *79*(6), 631-637. https://doi.org/https://doi.org/10.1016/j.mjafi.2023.08.013

(2) US Renal Data System. (2024). End-stage renal disease, Kidney transplant. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; disponível em: https://usrds-adr.niddk.nih.gov/2024/end-stage-renal-disease/7-kidney-transplant Consultado pela última vez a 10-11-2025.

(3) Vogelzang, J. L., van Stralen, K. J., Noordzij, M., et al. (2015). Mortality from infections and malignancies in patients treated with renal replacement therapy: data from the ERA-EDTA registry. *Nephrology Dialysis Transplantation*, *30*(6), 1028-1037. https://doi.org/10.1093/ndt/gfv007

(4) Alangaden, G. J., Thyagarajan, R., Gruber, S. A., et al. (2006). Infectious complications after kidney transplantation: current epidemiology and associated risk factors. *Clin Transplant*, *20*(4), 401-409. https://doi.org/10.1111/j.1399-0012.2006.00519.x

(5) Fishman, J. A. (2017). Infection in Organ Transplantation. *American Journal of Transplantation*, *17*(4), 856-879. https://doi.org/10.1111/ajt.14208

(6) Gong, L., Zhang, L., Liu, X., et al. (2021). Distribution and Antibiotic Susceptibility Pattern of Multidrug-Resistant Bacteria and Risk Factors Among Kidney Transplantation Recipients with Infections Over 13 Years: A Retrospective Study. *Infect Drug Resist*, *14*, 5661-5669. https://doi.org/10.2147/idr.S318941

(7) van Delden, C., Stampf, S., Hirsch, H. H., et al. (2020). Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study. *Clinical Infectious Diseases*, *71*(7), e159-e169. https://doi.org/10.1093/cid/ciz1113

(8) Linares, L., Cofán, F., Cervera, C., et al. (2007). Infection-related mortality in a large cohort of renal transplant recipients. *Transplant Proc*, *39*(7), 2225-2227. https://doi.org/10.1016/j.transproceed.2007.07.047

(9) Kinnunen, S., Karhapää, P., Juutilainen, A., Finne, P., & Helanterä, I. (2018). Secular Trends in Infection-Related Mortality after Kidney Transplantation. *Clin J Am Soc Nephrol*, *13*(5), 755-762. https://doi.org/10.2215/cjn.11511017

(10) Chan, S., Pascoe, E. M., Clayton, P. A., et al. (2019). Infection-Related Mortality in Recipients of a Kidney Transplant in Australia and New Zealand. *Clin J Am Soc Nephrol*, *14*(10), 1484-1492. https://doi.org/10.2215/cjn.03200319

(11) Tang, Y., Guo, J., Li, J., et al. (2022). Risk factors for cytomegalovirus infection and disease after kidney transplantation: A meta-analysis. *Transpl Immunol*, *74*, 101677. https://doi.org/10.1016/j.trim.2022.101677

(12) Ramirez, C., & McCauley, J. (2018). *Contemporary Kidney Transplantation*. https://doi.org/10.1007/978-3-319-19617-6

(13) Evans, L., Rhodes, A., Alhazzani, W., et al. (2021). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Critical Care Medicine*, *49*(11), e1063-e1143. https://doi.org/10.1097/ccm.0000000000005337

(14) Thomas, C. M., Butts, J., Czachura, J., et al. (2022). Evaluation of a Geographic Screening Protocol for Chronic Parasitic Infections Before Kidney Transplant: An Institutional Experience in Minnesota. *Am J Trop Med Hyg*, *107*(5), 1041-1046. https://doi.org/10.4269/ajtmh.22-0413

(15) Nascimento, E. H. G., Nascimento, E., Lasmar, M. F., & Fabreti-Oliveira, R. A. (2022). Effects of Bacterial Urinary Tract Infection on Clinical Outcome and Survival of Kidney Transplant Patients. *Transplantation Proceedings*, *54*(5), 1262-1269. https://doi.org/https://doi.org/10.1016/j.transproceed.2022.03.031

(16) Cia CT, Li MJ, Li CW, et al. (2016). Community-onset bacteremia in kidney transplant recipients: The recipients fare well in terms of mortality and kidney injury. *Journal of Microbiology, Immunology and Infection*, *49*(5), 685-691. https://doi.org/https://doi.org/10.1016/j.jmii.2014.08.027

(17) Hilbrands, L. B., Duivenvoorden, R., Vart, P., et al. (2020). COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant*, *35*(11), 1973-1983. https://doi.org/10.1093/ndt/gfaa261

(18) Vishnu, D. S., Tilve, P., Bodke, S. Y., et al. (2025). Infection Patterns and Survival Among Renal Transplant Recipients. *Indian J Nephrol*, *35*(4), 490-496. https://doi.org/10.25259/ijn_453_23

(19) Tavares, J., Oliveira, J. P., Reis, P., et al. (2022). COVID-19 in kidney transplant recipients: what have we learned one year later? A cohort study from a tertiary center. *J Bras Nefrol*, *44*(4), 533-542. https://doi.org/10.1590/2175-8239-JBN-2021-0257en

(20) Rosenberg, E. S., Dufort, E. M., Udo, T., et al. (2020). Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *Jama*, *323*(24), 2493-2502. https://doi.org/10.1001/jama.2020.8630

(21) Myers, L. C., Parodi, S. M., Escobar, G. J., & Liu, V. X. (2020). Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. *Jama*, *323*(21), 2195-2198. https://doi.org/10.1001/jama.2020.7202

(22) Goyal, P., Choi, J. J., Pinheiro, L. C., et al. (2020). Clinical Characteristics of Covid-19 in New York City. *N Engl J Med*, *382*(24), 2372-2374. https://doi.org/10.1056/NEJMc2010419

(23) Weinrauch, L. A., D'Elia, J. A., Weir, M. R., et al. (2018). Infection and Malignancy Outweigh Cardiovascular Mortality in Kidney Transplant Recipients: Post Hoc Analysis of the FAVORIT Trial. *Am J Med*, *131*(2), 165-172. https://doi.org/10.1016/j.amjmed.2017.08.038

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