Secular trends in Infection-related Mortality after Kidney Transplantation

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Abstract

Background and objectives Infections are the most common non-cardiovascular causes of death after kidney transplantation. We analyzed the current infection-related mortality among kidney transplant recipients in a nationwide cohort in Finland.

Design, setting, participants, and measurements Altogether 3249 adult recipients of a first kidney transplant during 1990-2012 were included. Infectious causes of death were analyzed and the mortality rates for infections were compared between two eras (1990-1999 and 2000-2012). Risk factors for infectious deaths were analyzed with Cox regression and competing risk analyses.

Results Altogether 953 patients (29%) died during the follow-up, with 204 infection-related deaths. Mortality rate (per 1000 patient-years) due to infections was lower in the more recent cohort (4.6, 95% CI 3.5–6.1) compared to the older cohort (9.1, 95% CI 7.6–10.7); the incidence rate ratio of infectious mortality was 0.51 (95% CI 0.30–0.68).

The main causes of infectious deaths were common bacterial infections: septicaemia in 38% and pulmonary infections in 45%. Viral or fungal infections caused only 2% and 3% of infectious deaths (such as individual cases of Cytomegalovirus pneumonia, Herpes simplex virus meningoencephalitis, Varicella zoster virus encephalitis and *Pneumocystis jirovecii* infection). Similarly, opportunistic bacterial infections rarely caused death; only one death was caused by *Listeria monocytogenes* and two by *Mycobacterium tuberculosis*. Only 23 (11%) of infection-related deaths occurred during the first posttransplant year. Older recipient age, higher plasma creatinine concentration at the end of the first posttransplant year diabetes as a cause of end-stage renal disease, longer pretransplant dialysis duration, acute rejection, low albumin-level, and earlier era of transplantation were associated with increased risk of infectious death in multivariable analysis.

Conclusions The risk of death due to infectious causes after kidney transplantation in Finland dropped by half since the 1990s. Common bacterial infections remained the most frequent cause of infection-related mortality, whereas opportunistic viral, fungal or unconventional bacterial infections rarely caused deaths after kidney transplantation.

Key words: kidney transplantation, mortality, infections

Introduction

Patient survival after kidney transplantation has improved markedly during the past decades (1, 2). The frequency of acute rejection has decreased, whereas infectious concerns have increased, and infections remain the most common non-cardiovascular causes of death after kidney transplantation accounting for approximately 15–20% of deaths (3-5).

Due to improved diagnostic tools and antiviral agents, common opportunistic viruses such as Cytomegalovirus (CMV) and BK polyomavirus rarely cause life-threatening infections or graft losses (6, 7). On the other hand, new infectious threats have emerged such as influenza, especially influenza A (H1N1) (8), and currently deaths from bacterial infections predominate the infectious causes of deaths after kidney transplantation (9).

Despite being highly increased after kidney transplantation, little is known about the current infection-related mortality after kidney transplantation, especially about the specific infectious causes of death.

The aim of this study is to present current nationwide data on infection-related mortality among kidney transplant recipients in a modern developed country. We furthermore looked into the risk factors for infection-related mortality and specific causes of deaths, and evaluated whether these have changed during the past decades.

Material and methods

Data collection

All adult recipients of a primary kidney transplantation between 1990 and 2012 (N=3249) in Finland were included in this observational inception cohort study. During 1990 and 2012, altogether 41 patients received a combined transplant (11 pancreas-kidney and 30 liver-kidney transplants) and were included in the analyses. Data were retrieved from the Finnish Registry for Kidney Diseases, which has been estimated to cover 97% to 99% of all patients accepted for renal replacement therapy (RRT, dialysis or kidney transplantation) in Finland since 1965. All patients have provided written informed consent and permission to use the data anonymously in registry reports and for research purposes. Following data were obtained from the registry for all patients at the start of RRT: age, gender, cause of ESRD as International Classification of Diseases -10 (ICD-10) codes, date of start of first renal replacement therapy (RRT), initial and last modality of RRT before transplantation (hemodialysis or peritoneal dialysis), date of first kidney transplantation, date of return to dialysis after transplantation, date of death (also after transplantation) and cause of death. Primary kidney disease was categorized as glomerulonephritis, polycystic kidney disease, diabetes mellitus type 1 or type 2, pyelonephritis, amyloidosis, nephrosclerosis, miscellaneous, or unknown. Data on body mass index (BMI) and laboratory data from the end of the year before transplantation and from the end of the first year after transplantation and data about immunosuppression were available since 1992. Patients with missing data were excluded from the analyses. For laboratory data and BMI, sensitivity analyses were performed including patients with the data available. Data about creatinine were missing from 288 patients, and data about plasma albumin were missing from 678 patients. Patients with missing data were excluded from the analyses. In addition, to address potential source of bias, data about acute rejections and induction therapy were retrieved from the Finnish Transplant Registry, and sensitivity analyses were performed including these data.

Causes of death are reported to the Finnish Registry for Kidney Diseases by the treating nephrologist. The statistics on mortality in Finland are based on death certificates, in which ICD

codes for the cause of death are assigned by the physician who treated the deceased during the final illness. In addition, all death certificates in Finland are submitted for verification to a forensic medicine specialist in the competent authority, and after approval sent to the official National Death Register at the Statistics Finland.

If the cause of death was not reported to the Finnish Registry for Kidney Diseases, it was acquired from Statistics Finland based on the individual social security code. Since 1996, causes of death statistics have been compiled according to the 10th revision of the ICD code (ICD-10). Before 1996, ICD-9 was used, and these were converted to ICD-10. There were no missing causes of death.

Causes of death were grouped into four categories: infection, cardiovascular, malignancy and other. Causes of infection-related deaths were classified into seven categories: bacterial or unspecified septicemia (ICD-10 codes A04.7–A49.9), pulmonary infection defined as bacterial or unspecified pneumonia (J13–J16, J18–J20, J40,J69) or empyema/pleural effusion, specified viral infection (B25.0, G05.1, J17.1), specified fungal infection (B37.7, B59, J17.2), gastroenterological infection (K65–K81), tuberculosis (A15.9) and other infection (I33.0, G00.8, I52.0*A39.5, L03.1, N39.0 M86.1, T87.4).

Statistical Analyses

Comparisons between the groups were performed using Mann-Whitney U test for continuous variables and the x^2–test for categorical variables. Nonparametric statistics were applied, as all distributions were not normal. Survival probabilities were estimated using the Kaplan-Meier method with death as the event and patients were censored at the end of the follow-up. Cause-specific mortality rates were reported per 1000 person-years (py) and calculated separately for deaths due to infections, cardiovascular causes, malignancies and due to other causes. Incidence rate ratios (IRR) were calculated to compare mortality in patients transplanted during the two different eras. Confidence intervals were calculated according to the Poisson Exact method.

Cox regression models were used to identify risk factors for infection-related mortality, such as age at transplantation, gender, cause of end stage renal disease, era of transplantation, initial modality of pretransplant dialysis, dialysis duration before transplantation and immunosuppressive therapy. Cause of end stage renal disease was categorized as glomerulonephritis, polycystic kidney disease, diabetes including both type 1 and type 2 diabetes, and other. Variables that were significant in univariable model (<0.05) were selected to multivariable models. Cumulative incidence of death due to infectious causes was calculated using a competing risk method that takes death due to other causes into account as competing risk events. As an alternative to Cox regression, relative risks of death due to infection were also estimated fitting a proportional subdistribution hazards regression model that takes death due to other causes into account as competing risk events (10, 11). First-degree interactions between all the exposure variables were analyzed, and all statistically significant interactions are reported. For statistical analyses we used IBM SPSS Statistics (version 22.0) and the R statistical software 2.14.2 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org). Two-sided *P*-values less than 0.05 were considered statistically significant.

Results

Study Population

A total of 3249 adult patients (aged => 18) received their first kidney transplantation in Finland between 1990 and 2012, 1283 during 1990–1999 and 1966 during 2000–2012. The patients were followed for a maximum of 22 years from the day of first transplantation until death (N=953) – also after graft loss – or the end of follow-up period on 31 December 2012, or loss to follow-up (N=12). The median follow-up time was 14.1 years for patients transplanted during 1990–1999 and 5.7 years for patients transplanted in 2000–2012.

Patients included in the study are described in Table 1. Compared to the patients transplanted during 1990–1999 the patients transplanted during 2000–2012 were significantly older, had more often type 2 diabetes as cause of ESRD, were less frequently on peritoneal dialysis and had longer

duration of dialysis before transplantation. There were significant differences in the immunosuppressive regimen between the two decades as tacrolimus and mycophenolate mofetil were not available during the earlier era. During the recent era all patients with data available on immunosuppression received either cyclosporine- or tacrolimus-based immunosuppression at baseline.

Mortality by cause of death

953 (29%) patients died during the follow-up. 204 patients (21% of all deceased patients) died due to infections, 442 (48%) due to cardiovascular causes, 129 (13%) due to malignancies, and 178 (19%) from other causes. During the most recent vs. the earlier cohort the cause of death was infectious in 18% vs. 23%, cardiovascular disease in 48% vs. 45% and malignancy in 16% vs. 12%. Altogether 710 (76% of all deceased patients) patients died with a functioning graft.

The overall patient survival in the whole study population was 97% at one year, 89% at 5 years and 73% at 10 years after transplantation.

Mortality due to infections, cardiovascular causes and malignancies was lower in the recent cohort (Table 2). The mortality rate (per 1000 patient-years) due to infections was 4.6 vs. 9.1 for patients transplanted in 2000–2012 vs. 1990–1999 with a mortality rate ratio of 0.51. The mortality rate ratio was 0.67 for CVD mortality and 0.80 for mortality due to malignancies.

Infection-related mortality and its causes

A total of 204 (21% of all deaths) infection-related deaths occurred during the follow-up of which 147 (72%) among patients with a functioning graft. Cumulative incidence of infection related-death was lower in 2000-2012 than in 1990-1999 (Figure 1). During both eras, the most frequent causes of infectious death were common bacterial infections: pulmonary infection in 45% (36% vs. 49% during 2000–2012 vs. 1990–1999) and septicemia in 38% (42% vs. 37%) of the cases (Table 3, supplementary table 1).

Bacteremia caused 78 deaths of which 31 (40%) were described as unspecified septicemia, while the causative pathogen was known in 43 (55%) of the cases. *Staphylococcus aureus* accounted for 11 and unspecified Gram-negative sepsis for 8 of the bacteremia deaths while there were only individual cases *of Meningococceal* and *Streptococcal* septicemia. Invasive viral or fungal infections comprised 2% and 3% of all infectious deaths. Only individual cases of fatal Cytomegalovirus (CMV) pneumonia, Herpes simplex virus (HSV) meningoencephalitis, Varicella zoster virus (VZV) encephalitis and *Pneumocystis jirovecii* infection occurred. Opportunistic bacterial infections rarely caused death; only one death was caused by *Listeria monocytogenes*. Two deaths were caused by *Mycobacterium tuberculosis*.

Mortality within the first year after kidney transplantation

Of all deaths 83 (9%) occurred within the first year after transplantation. The cause of death was cardiovascular in 59% vs. 49%, infection in 21% vs. 33%, and malignancy in 6% vs. 10% during the recent vs. the earlier cohort. During the first year after transplantation, mortality rate due to infections was significantly lower in 2000-2012 (3.7 per 1000 py, 95% CI 1.8–7.9) than in 1990-1999 (12.8 per 1000 py, 95% CI 7.8–21.0) with a mortality rate ratio of 0.29 (95% CI 0.12–0.71).

Of the 23 infection-related deaths that occurred during the first year after transplantation, the cause was septicemia in 44% and pulmonary infection in 30%. There were only one cytomegalovirus-related death and individual cases of HSV-meningoencephalitis and viral pneumonia as a cause of death during the first year after transplantation.

Infection-related mortality risk factors

Older age was the strongest predictor of infection-related mortality. When adjusting for age and gender, earlier era of transplantation (HR=1.78, 95% CI 1.25-2.53), diabetes as the cause of ESRD (HR=1.78, 95% CI 1.21-2.62), and dialysis duration for more than two years before transplantation (HR=1.59, 95% CI 1.12-2.25) were associated with infection-related death (Table 4).

Laboratory data from the end of the calendar year of the transplantation were available for 91% of the patients on plasma creatinine and for 79% on plasma albumin. When adjustment was made for age and gender, higher plasma creatinine (HR=1.001 per 1 µmol/l increment, 95% CI 1.000-1.002, p= 0.002) and plasma albumin level below 36 g/l (HR=1.58, 95% CI 1.13-2.23, p =0.008). were associated with risk of infection-related mortality.

During the recent era, the risk of death from infection was almost twofold in men, whereas this was not the case in the earlier era (Table 4). The association of diabetes as the cause of ESRD or pretransplant dialysis duration with infection-related mortality lost statistical significance during the recent era, but no interaction was observed between diabetes or dialysis duration and era with respect the risk of infectious death (p=0.18).

Sensitivity analyses

A separate analysis that included as events only infection-related deaths of patients with a functioning graft showed similar hazard ratios for the risk factors as in Table 4 (table S2).

As an alternative method of analysis, competing risk models were built on the whole study population using death due to infection as the primary outcome, and death resulting from cardiovascular causes, malignancies and other causes as competing risk events. These models showed no important differences compared to the Cox regression models presented in Table 4 (table S3).

Data about acute rejections or induction immunosuppression were available for 88% of the patients transplanted between 1990-2012. Frequency of acute rejection was 13 % among patients transplanted in 2000-2012 vs. 23% among patients transplanted in 1990-1999 (P<0.001). When included in the Cox regression model analyzing the risk of infectious mortality (adjusted for patient age, gender, era of transplantation, cause of ESRD, pretransplant dialysis duration), acute rejection was independently associated with an increased risk of infectious death (HR=1.66, 95% CI 1.20-2.30, P=0.002). There was a significant interaction between the era of transplantation and acute rejection with regard to the risk of infectious death (P=0.02). Acute rejection lost statistical

significance during the most recent era (P=0.36), whereas among patients transplanted in 1990-1999, acute rejection was associated with increased risk of infectious death (HR=1.92, 95% CI 1.35-2.74, P<0.001).

Induction with ATG was given to 1.6% of patients transplanted in 1990-1999 and to 2.6% of patients transplanted in 2000-2012, and induction with basiliximab was given to 7.3% of patients transplanted in 2000-2012 (basiliximab not available in the 1990s). Induction was not associated with increased infectious mortality risk after transplantation (HR=0.80, 95% CI 0.41-1.57, p=0.52, adjusted for age and gender).

Discussion

Our current study shows that patient survival after kidney transplantation in Finland has improved and the risk of death from all causes has decreased. Additionally, the risk of death due to infectious causes is lower in the recent in comparison to the historic cohort. This is in line with a recent ERA-EDTA Registry report showing that the risk of cardiovascular and infectious death has fallen by 29% and 8% between 1998–2002 and 2003–2007 (12). All-cause and infection-related mortality have decreased in spite of transplanting older recipients with increasing degree of comorbidity, longer pretranplant dialysis duration, more powerful immunosuppressive therapy, and also the increased use of marginal donors. The incidence of acute rejection has decreased between the two eras in our cohort, and acute rejection was an independent risk factor for infectious death only in patients transplanted in the 1990s, suggesting that lower frequency of acute rejection and especially the treatment of acute rejection is the most important factor explaining the reduced infectious mortality in our cohort. In addition, better and faster diagnostic tools for infections together with increased awareness of severe opportunistic infections may have contributed to the reduced infectious mortality.

The particular causes of death among kidney transplant recipients have changed over time. Infections were the most common cause of death in the early years of transplantation (42% in 1980 to 1989 and decreasing to 28% in 1990 to 1999) (3). According to the United States Renal Data System Annual Data Report 2012 33% of the known death causes among transplant patients were cardiovascular while infections accounted for 18% of deaths (4). Notably, the cause of death was missing or unknown for 68% of these transplant patients. The UK Renal registry has demonstrated a marked decrease in the proportion of cardiovascular deaths among all renal replacement therapy patients (from 34% in 2000 to 22% in 2011), but a similar trend was not observed for infection-related mortality, which has remained stable at approximately 18% of all mortality. Among transplant patients infection was responsible for 23% and cardiovascular disease for 18% of the deaths (5). Compared to the general population kidney transplant recipients have a 32-fold risk of dying of infection, and the risk is particularly emphasized in young women (13). In kidney transplant recipients the mortality secondary to septicemia is 20-fold and the mortality secondary to pulmonary infection is 2-fold compared to the general population (14, 15).

Although the incidence of fatal infections after kidney transplantation has decreased over time, studies assessing infectious mortality are scarce and current information on specific infectious causes of death following kidney transplantation has not been available. In our current analysis common bacterial infections remain the most frequent cause of infection-related mortality, whereas viral, fungal or unconventional bacterial infections rarely caused deaths after kidney transplantation. It is well known that the spectrum of infections after transplantation varies over time. Early infections during the first month after transplantation are likely to be nosocomial bacterial infections. Opportunistic pathogens occur during the following five months as a result of the high level of immunosuppression, and later infections are either opportunistic infections or conventional ones (16, 17). Accoding to USRDS 2003 annual report 70% of all kidney transplant recipient will experience an infection episode by three years after transplantation and hospitalization for bacterial infections after kidney transplantation is roughly twice as common as hospitalization for viral infections despite much greater attention to posttransplant viral infections in

the published literature (18), and infections may be a more common reason for hospitalization after transplantation than acute rejections (19). According to a recent registry analysis among the deceased kidney transplant recipients, in whom the causative infectious agent was known, 85% died of bacterial infections whereas only 9% died of viral infections and 6% of other types of infections (13).

Interestingly, most fatal infections occurred late after transplantation. Mortality rate of infection within one year from transplantation was not higher compared to later follow-up. Of the 3249 transplant patients in this study only 2.6% died within the first year after transplantation. Infections accounted for 28% of all deaths during the first year while cardiovascular disease was the most common cause of death. This is in contrast with previous studies reporting that within the first year after transplantation infections are the leading cause of death (20, 21). The risk of death from infections has declined which may have contributed to the improvement in the 1-year survival rate after kidney transplantation. As the survival of transplant patients improve, long-term complications of immunosuppression, such as malignancies, raise increased concern and cancer-related deaths may replace infections as causes of death. In our current study, however, both all-cause and cancer related mortality rate was smaller in the more recent cohort compared to the older cohort.

The low incidence of viral- and fungal-related deaths even in the first year after transplantation was somewhat surprising. Only one patient died because of CMV-infection. CMV is the most common viral infection after kidney transplantation affecting 10–19% of recipients receiving conventional immunosuppressive therapy, but serious disease caused by CMV is rare (6). Antiviral prophylaxis in the highest-risk (D+/R-) population has reduced the incidence of CMV disease by 60% which has contributed to the reduced all-cause mortality (22). Data about donor or recipient serostatus were unfortunately not available for the current study. Similarly, only one patient died due to *Pneumocystis jirovecii (PJP),* arguing either for successful use of prophylaxis in our cohort, or on the other hand that the incidence of PJP is very low, calling into question the wisdom of extensive prophylaxis with trimethoprim, which is also associated with toxicity and concerns about antimicrobial resistance.

Specific data for infection prophylaxis were not available for the purpose of this study. However, according to the policy in our country, only prophylaxis against *pneumocystis jirovecii* for the first six months after transplantation with either trimethoprim-sulfamethoxazole or pentamidine inhalations was given. Other infection prophylaxis was not routinely used, with the exception of six months valganciclovir prophylaxis for CMV seronegative recipients of a kidney from a seropositive donor initiated in 2004. Our study cohort may also otherwise differ from other kidney transplant cohorts, especially with regard to almost exclusively Caucasian population in Finland, the high frequency of cyclosporine use, and low frequency of induction therapy, and therefore our findings may not be directly applicable to other cohorts.

Our study has a few limitations. Death certificates may have limitations in their quality. The Finnish Registry for Kidney Diseases allows only one cause of death to be reported and some patients may have had several factors leading to death. On the other hand, kidney transplant recipients are under continuous medical follow-up and the causes of death were reported by the treating nephrologist and are the best available data. Earlier Finnish studies have verified the validity and good quality of Finnish death certificates, death certification practices, and the cause of death validation procedures producing the register data on mortality, justifying their use for endpoint assessment in epidemiological studies (23-25). In addition, no standardized definition of infectious death exists in the registry or in the death certificates, e.g. with regard to the microbiological or radiological diagnosis of the infection or timing of death in relation to the infectious diagnosis, but is only based on the evaluation of the treating physician, which limits the accuracy of our data. Another limitation is that this study focused only on infectious causes of death, and no data were available about non-fatal infections, which also cause substantial morbidity after kidney transplantation. In addition, although some speculations about the reduced risk of infectious deaths can be made with regard to lower incidence of acute rejections in the most recent cohort, our study is limited by the inability to determine with confidence the mechanisms behind the reduced infectious mortality seen between the eras.

In accordance with earlier studies among immunocompromised patients, pulmonary infections remain a major cause of death (26). Pulmonary infection was responsible for most (45%) deaths from infection and in 55% of these cases the cause of death was unspecified pneumonia (J18.9). Septicemia accounted for over a third of infectious deaths and information on the sites of infection or the defined pathogen associated with septicemia was not available in 40% of these cases. This is in accordance with the fact that a pathogen can be identified by blood culture in no more than 30- 40% of patients with sepsis (27). In addition to microbiological criteria, clinical criteria have provided the basis for epidemiological studies of sepsis since the 1990s (28, 29) and clinical sepsis codes have been included in ICD-10 since 2005**.** In addition, conversion from the older ICD 9 codes to ICD 10 codes may explain some inaccuracy in the diagnoses.

On the other hand the key strength of this study is the virtually complete coverage of kidney transplantations in Finland with complete follow-up data of a large representative national cohort allowing us to compare mortality in different eras of transplantation. Data about the cause of death were available for all patients included in this study – no deaths were coded as unknown or missing, which minimizes selection bias.

In conclusion, the survival after kidney transplantation in Finland continues to improve. The risk of death due to infections after kidney transplantation has dropped by half since the 1990s. Common bacterial infections remain the most frequent cause of infection-related mortality, whereas opportunistic viral, fungal or unconventional bacterial infections rarely cause deaths after kidney transplantation.

Disclosure

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Table 1. Baseline characteristics of first kidney transplant recipients enrolled in the Finnish Registry for Kidney Diseases (N=3249).

Variables	**All**	**1990-99, n=1283**	**2000-12, n=1966**
Men, %	2041 (63)	778 (61)	1263 (64)
Age (yr) at transplantation	49±13	45±12	51±13
Age group at transplantation,%			
18-44	1233 (38)	606 (47)	627 (32)
45-65	1690 (52)	606 (47)	1084 (55)
over 65	326 (10)	71 (6)	255 (13)
Treatment before transplantion			
Hemodialysis	1936 (60)	716 (56)	1220 (62)
Peritoneal dialysis	1300 (40)	562 (44)	738 (38)
Pre-emptive	13 (0.4)	5 (0.4)	8 (0.4)
Time (yr) on dialysis prior to transplantation	1.8±1.6	1.4±1.3	2.1±1.7
Cause of ESRD, %			
Glomerulonephritis	769 (24)	343 (27)	426 (22)
Polycystic disease	591 (18)	208 (16)	383 (20)
Diabetes type 1	786 (24)	327 (26)	459 (23)
Diabetes type 2	143 (5)	25 (2)	118 (6)
Chronic pyelonephritis	214 (7)	107 (8)	107 (5)
Amyloidosis	76 (2)	40 (3)	36 (2)
Nephrosclerosis	101 (3)	39 (3)	62 (3)
Other	366 (11)	147 (11)	219 (11)
Unknown	203 (6)	47 (4)	156 (8)
Immunosuppression, %			
Cyclosporine		906 (71)	1452 (74)
Tacrolimus		0	407 (21)
Mycophenolate mofetil		94 (7)	1524 (78)
Steroid		963 (75)	1697 (86)
Azathioprine		806 (63)	201 (10)
Missing		308 (24)	98 (5)

Mean ± standard deviation unless otherwise indicated.

Table 2.

Mortality rates (deaths/1000 patient years) and mortality rate ratios from all causes, cardiovascular causes, malignancy and infections in first kidney transplant recipients in Finland segregated by the era of transplantation, IRR=incidence rate ratio.

Cause of mortality	**1990-1999 (95%CI)**	**2000-2012 (95%CI)**	**IRR**	**95% CI**
All-cause	39.8 (37.0-43.1) (n=666)	24.9 (22.2-28.0) (n=287)	0.63	0.55-0.72
Infection	9.1 (7.6-10.7) (n=151)	4.6 (3.0-5.4) (n=53)	0.51	0.30-0.68
1-year Infectious mortality	12.8 (7.81-20.98) (n=16)	3.7 (1.78-7.86) (n=7)	0.29	0.12-0.71
Cardiovascular	18.2 (16.0-20.7) (n=303)	12.1 (10.2-14.4) (n=139)	0.67	0.56-0.76
Malignancy	5.0 (4.0-6.2) (n=83)	4.0 (3.0-5.4) (n=46)	0.80	0.63-0.95

Table 3.

Infectious causes of death after kidney transplantation among first kidney transplant recipients enrolled in the Finnish Registry for Kidney Diseases (N=3249).

Type of infection	**All** (n=204)	**1990-1999** (n=151)	**2000-2012** (n=53)
Pulmonary infection,%	92 (45)	73 (48)	19 (36)
Septicemia,%	78 (38)	56 (37)	22 (42)
Gastroenteric infection,%	12 (6)	9 (6)	3 (6)
Fungal infection,%	6 (3)	3 (2)	3 (6)
Viral infection,%	4 (2)	1 (1)	3 (6)
Tuberculosis,%	2 (1)	1 (1)	1 (1)
Other,%	10 (5)	8 (5)	2 (3)

Table 4.

Risk factors for infectious death among first kidney transplant recipients enrolled in the Finnish Registry for Kidney Diseases.

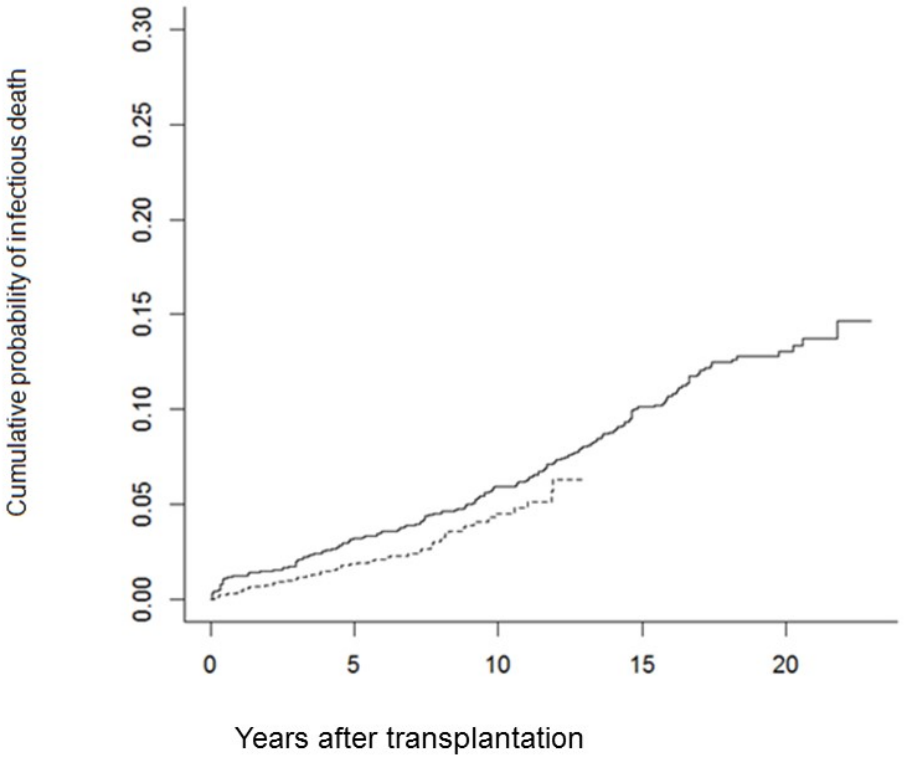
A)	**All patients (N=3249)**		
	Adjusted * HR (95%CI)	Adjusted ** HR(95% CI)	Number of infectious deaths
Age (per 1-year increment)	**1.06 (1.04-1.07), p<0.001**	**1.07 (1.05-1.08), p<0.001**	204
Sex			
Men	1.20 (0.90-1.59)	1.13 (0.85-1.52)	131
Women	1	1	73
Era of transplantation			
1990-1999	**1.78 (1.25-2.53), p=0.002**	**2.07 (1.44-2.98), p<0.001**	151
2000-2012	1	1	53
Cause of end stage renal disease			
Glomerulonephritis	1	1	52
Polycystic kidney disease	0.78 (0.51-1.20)	0.83 (0.54-1.28)	36
Diabetes	**1.78 (1.21-2.62), p=0.003**	**1.89 (1.28-2.79), p=0.001**	60
Other	0.90 (0.61-1.31)	0.90 (0.61-1.32)	56
Pretransplant dialysis duration			
0-12 mo	1	1	72
12-24 mo	**1.39 (1.00-1.94), p=0.05**	**1.41 (1.01-1.97), p=0.04**	70
>24 mo	**1.59 (1.12-2.25), p=0.009**	**1.75 (1.23-2.50), p=0.002**	62

B)	Patients transplanted 1990-1999 (N=1283)		
	Adjusted * RR (95%CI)	Adjusted *** RR(95% CI)	Number of infectious deaths
Age (per 1-year increment)	**1.05 (1.03-1.06), p<0.001**	**1.06 (1.04-1.08), p<0.001**	151
Sex			
Men	1.05 (0.76-1.45)	1.0 (0.72-1.39)	91
Women	1	1	60
Cause of end stage renal disease			
Glomerulonephritis	1	1	40
Polycystic kidney disease	0.81 (0.49-1.33)	0.85 (0.51-1.40)	26
Diabetes	**2.01 (1.29-3.14), p=0.002**	**2.03 (1.30-3.18) p=0.002**	46
Other	0.86 (0.55-1.35)	0.83 (0.53-1.30)	39
Pretransplant dialysis duration			
0-12 mo	1	1	60
12-24 mo	1.57 (1.08-2.27), **p=0.018**	**1.51 (1.04-2.19), p=0.029**	53
>24 mo	1.80 (1.08-2.99), **p=0.004**	**1.90 (1.26-2.87) p=0.002**	38
C)	**Patients transplanted 2000-2012 (N=1966)**		
	Adjusted * RR (95%CI)	Adjusted *** RR(95% CI)	
Age (per 1-year increment)	**1.10 (1.07-1.135), p<0.001**	**1.11 (1.07-1.14), p<0.001**	53
Sex			
Men	**1.92 (1.03-3.60), p=0.04**	1.81 (0.96-3.41) p=0.68	40
Women	1	1	13
Cause of end stage renal disease			
Glomerulonephritis	1	1	12
Polycystic kidney disease	0.86 (0.37-2.00)	0.85 (0.37-2.00)	10
Diabetes	1.64 [0.74-3.62), p=0.22	1.58 (0.71-3.51)	14
Other	1.04 (0.49-2.2)	1.02 (0.48-2.14)	17
Pretransplant dialysis duration			
0-12 mo	1	1	12
12-24 mo	1.09 (0.52-2.30)	1.03 (0.49-2.17)	17
>24 mo	1.38 (0.68-2.79)	1.28 (0.62-2.62)	24

* Adjusted for patient age and gender. ** Adjusted for patient age, gender, era of transplantation, cause of ESRD, and dialysis duration. *** Adjusted for patient age, gender, cause of ESRD, and dialysis duration

Figure Legends

Figure 1. Cumulative probability of infectious death in transplant recipients. Continuous line: years 1990 to 1999, dotted line: years 2000 to 2012.


Cumulative probability of infectious death
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0
5
10
15
20
Years after transplantation