Supplementary appendix

Standard treatment protocol

All RTR received a combination of prednisolone, calcineurin inhibitors and cell proliferation inhibitors. Up to 2007 all patients were treated with cyclosporine A. From 2007 patients under the age of 50 years with a normal oral glucose tolerance test and a body mass index < 28 kg/m² were treated with tacrolimus instead of cyclosporine A. From 2009 steroid doses were reduced. Prior to 2001 the patients were treated with azathioprine, after which it was substituted with mycophenolate. In addition, in the year 2000 and after 2007, induction therapy with basiliximab was given. Rejections were treated with intravenous methylprednisolone followed by an increased dose of oral prednisolone. Steroid-resistant rejections were treated with anti-thymocyte globulin or anti-CD3 monoclonal antibodies.

Extraction of lipids

Extraction of total lipids was performed by a modified Folch method (1). Five hundred uL plasma was extracted with 5 mL of chloroform-methanol (2:1) containing 50 ug/mL butylated hydroxytoluene (BHT) as antioxidant. After adding 0.75 mL of 0.9% sodium chloride, the tubes were mixed and centrifuged at 3220 g at 10º C for 10 minutes. The upper aqueous phase was discharged and the protein disk reextracted with 5 mL of chloroform-methanol (2:1) containing 50 ug/mL BHT and 1 mL 0.9% sodium chloride. The organic phases were combined and dried under nitrogen for 45 minutes at 40º C and dissolved in 1 mL of chloroform.

Separation and analysis of plasma phospholipid fatty acids

The phospholipid fraction was isolated essentially as described by Burdge (2). The lipids dissolved in 1 mL chloroform were transferred to a Bond Elut NH2 column (200mg, Agilent Technologies, US) preconditioned with 4 mL of hexane followed by washing with 4 mL of chloroform. The phospholipid fraction was eluted with 2 mL chloroform-methanol (3:2) followed by 2 mL of methanol, after which the phospholipid fraction was dried under nitrogen for 1 hour at 40º C.

Transmethylation of phospholipid fatty acids was performed after dissolving in 500 uL warm heptane (50º C), mixing briefly and then adding 25 uL of 2M potassium hydroxide in methanol and heating for 2 minutes at 50º C. After mixing the tubes were centrifuged at 3220 g for 10 minutes at 10º C and the upper phase transferred to gas chromatographic injection tubes.

The fatty acids were quantitated using a Varian 3900 gas chromatograph with a CP-8400 autosampler, a flame ionization detector and a CP-Sil 88 60 m x 0.25 mm capillary column (Varian, Middleburg, The Netherlands). We used a split injection mode, constant flow rate, temperature programing from 90 - 210º C and helium as the carrier gas. Fatty acids were identified from their relative retention time, and quantitated as the weight percent of total fatty acids (*wt%*).

Identification of confounders and effect-measure modifiers, fitting of Cox proportional hazard models and graphing

Stratified analysis was used to identify mortality risk factors that confounded the effects of marine n-3 PUFA. Recipient age was identified as a strong confounder and mortality rates by marine n-3 PUFA was studied in different age categories. Additional confounding was introduced by eGFR, albumin and n-6 PUFA levels (the sum of arachidonic, linoleic, gammalinoleic, eicosadienoic, dihomogammalinolenic and adrenic acid levels). Other traditional and transplant-specific mortality risk factors in RTR (3) were included as predefined variables in both Cox models. Recipient age was identified as an effect-measure modifier for marine n-3 PUFA and a product term was included in the Cox models. We identified no other two-way interactions that affected the result or any collinear variables among the covariates in the Cox models.

Since we do not have any dietary data to adjust for effects of various nutrients, we cannot know whether dietary intake of marine n-3 PUFA and n-6 PUFA are individual risk factors or separate or shared risk markers reflecting adherence to a specific diet profile. To rule out potential collider effects, we developed two Cox models, where model 1 excluded and model 2 included n-6 PUFA levels. The rationale for presenting results obtained by both models is that model 1 produced a more conservative estimate of marine n-3 PUFA effects and model 2 included all confounders identified in the stratified analyses and adjusted for the potential influence of n-6 PUFA levels on the relationship between marine n-3 PUFA levels and mortality.

EPA competes with the pro-inflammatory n-6 PUFA arachidonic acid as substrate in the cyclooxygenase pathway, which produces the prostaglandin hormones that initiate the inflammation process. High levels of EPA may reduce inflammation and subsequent risk of death from infectious disease, cancer or cardiovascular disease, but not independently of levels of arachidonic acid or total n-6 PUFA. The high n-6 PUFA to n-3 PUFA ratio, including both marine n-3 PUFA and alpha-linolenic acid levels, found in populations with a typical Western diet, have been associated with increased risk of cardiovascular morbidity and mortality. In this population, with more patients adherent to a Nordic diet, n-6 PUFA to n-3 PUFA ratios were lower. The higher variance in n-3 PUFA levels compared with n-6 PUFA levels implies that marine n-3 PUFA levels determine most of the variance in n-6 PUFA to n-3 PUFA ratio. This may partly explain why results for n-6 PUFA to n-3 PUFA ratio mirrors that of marine n-3 PUFA levels (Supplemental Table S4).

Individual marine fatty acids are found in roughly the same mutual proportion in different species of fish and most marine n-3 PUFA supplements (4). Therefore, to evaluate the effect of the highly correlated individual marine n-3 PUFA, they were analyzed separately by Cox regression analysis. The immunosuppressive treatment changed over time. We performed age-stratified analysis and Cox regression analysis in three strata according to transplant period (30th of September 1999 to 31st of December 2006, 1st of January 2007 to 31st of December 2008 and 1st of January 2009 to 13th of October 2011) to adjust for transplant era effects.

Adjusted survival probabilities and corresponding survival probability curves were created using R® version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria). First, we estimated the

survival probabilities for each individual from the Cox proportional hazard model 2 with potential confounders averaging over all included patients. The adjusted survival probabilities, time since transplantation and codes for quartiles of covariates were extracted from the fitted model to a new data file for graphing.

Baseline characteristics of patients not included in the study and assessment of bias

Baseline characteristics of adult patients (≥ 16 years) not included and study participants are described in Supplemental Table S1. Adult patients not included in the study were older than the study participants. When stratifying for age categories, study participants more often had a living donor, otherwise there were no significant differences between the two groups. The proportion of patients who died during follow-up was lower in adult patients not included in the study (11.2% vs 20.4%). However, the study participants were followed for a longer period of time and the overall mortality rate was slightly higher in adult patients not included in the study (mortality rate ratio 1.08). When grouped according to transplant era, the mortality rate for patients included and not included in the study was similar in the era of 2007 to 2008 where many eligible patients had missing blood samples (Supplemental Table S6). In addition, revision of medical records of 100 non-eligible patients who were transferred early to local hospital (Figure 1) revealed a myriad of reasons for transferal not necessarily associated with increased comorbidity or mortality risk. This could provide some explanation to why there were only minor differences in baseline characteristics between study participants and adult patients not included in the study.

Before 2007 and after 2009 the mortality rate was lower in the study participant group (Supplemental Table S6). However, they were also younger, which would probably influence mortality rates. More importantly, we do not know the composition of plasma fatty acids or have any dietary data for patients not included in the study. Therefore, we do not know if our findings apply to the whole population of adult Norwegian RTR. Nonetheless, when grouping the study participants according to marine n-3 PUFA levels, there were only minor differences in mortality rate ratios for each transplant era despite variance in inclusion rates (Supplemental Table S2), indicating a limited degree of selection bias in this study.

Competing risk, relative survival rates and diagnosis misclassification

We analyzed the effect of marine n-3 PUFA levels on cause-specific mortality in isolation, without adjustments for competing risk. The simple rate ratio interpretations obtained by Cox regression analysis is easy to interpret in contrast to models that adjust for competing risk and regarding death from cancer, we found no associations with marine n-3 PUFA levels. Since cancer and CVD share some common risk factors, patients with an increased risk of death from cancer were also at increased risk of death from CVD. In patients under the age of 45 years, where competing risk from CVD mortality is minimal, patients with high marine n-3 PUFA levels were less likely to die from cancer compared with patients with low levels (mortality rate ratio 0.90). In the higher age groups, patients with high compared with low levels of marine n-3 PUFA were more likely to die from

cancer (Table 2), possibly due to the effects of competing risk. However, even with analysis of excess hazard rate for cancer using maximum likelihood estimation of relative survival rate, there was no significant association between marine n-3 PUFA levels and cancer mortality.

We found no association between death from MI and marine n-3 PUFA levels. However, many cases of SCD could be related to MI and associations between marine n-3 PUFA levels and death from MI would depend on diagnosis classification. In addition, SCD, MI and stroke mortality rates could be influenced by competing risk, while estimates for overall cardiovascular mortality are probably more reliable.

References

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Table S1. **Baseline characteristics of adult patients not included in the study compared with the study participants**

Variables	**Study participants**	**Adult patients not included**	**p**
Number of patients	1990	769	
Median follow-up time, *years*	6.8	3.7	
Recipient age, *years*	51.6 (14.6)	55.1 (13.7)	<0.001
Gender (male), *%*	66.9	69.3	0.22
Coronary disease, *%*	15.3	13.2	0.16
Cerebrovascular disease, *%*	5.2	4.5	0.42
Peripheral vascular disease, *%*	8.0	7.2	0.49
Diabetes mellitus, *%*	18.2	17.2	0.52
Current smoker, *%*	16.0	17.6	0.30
Former smoker, *%*	36.2	36.5	0.82

Tacrolimus, *%*	23.1	36.4	<0.001
Cyclosporine A, *%*	74.2	63.5	<0.001
Time in dialysis, *months*	9 (0-19)	10 (0-24)	0.07
Donor age, *years*	47.2 (16.1)	50.5 (15.6)	<0.001
Living donor transplantation, *%*	37.8	28.8	<0.001

Baseline characteristics of study participants and adult patients (≥ 16 years) not included in the study. Results are presented as proportions for categorical data, median and interquartile range for time in dialysis and mean and standard deviations for other continuous data. Differences in baseline characteristics were evaluated using Chi-square for categorical data, Mann-Whitney U-test for time in dialysis and t-test for other continuous data. Pre-transplant diabetes mellitus, coronary, cerebrovascular and peripheral vascular disease were recorded before first renal transplantation. Recipient and donor age, deceased or living donor, time in dialysis and smoking status were recorded at the time of transplantation. Choice of calcineurin inhibitor were recorded at a clinical appointment 10 weeks post-transplant for study participants and within the first weeks after transplantation, for patients not included in the study.

Table S2. **The transplantation era effect on mortality rates by marine n-3 polyunsaturated fatty acid levels in different age categories**

	Transplantation era					
	1999-2006		**2007-2008**		**2009-2011**	
Marine n-3 PUFA	**High**	**Low**	**High**	**Low**	**High**	**Low**
Patients < 60 years at the time of transplantation						
Mortality rate, *cases / 1000 person-years*	13.0	18.5	9.4	12.8	8.8	12.4
Mortality rate ratio	0.70		0.73		0.71	
Patients ≥ 60 years at the time of transplantation						
Mortality rate, *cases / 1000 person-years*	67.5	79.5	52.6	73.7	28.7	39.3
Mortality rate ratio	0.84		0.71		0.73	

The mortality rate according to marine n-3 polyunsaturated fatty acid (*PUFA*) levels (the sum of eicosapentaenoic, docosapentaenoic and docosahexaenoic acid levels in weight percentage *(wt%)* of total plasma phospholipid fatty acids; ≥ 7.95 wt% (high) and < 7.95 wt% (low) in different transplantation eras. Shown are mortality rates in patients younger than 60 years and patients aged 60 years or more. Mortality rate ratios for each time period (30th of September 1999 to 31st of December 2006, 1st of January 2007 to 31st of December 2008 and 1st of January 2009 to 13th of October 2011)

was obtained by dividing the mortality rate of patients with high marine n-3 PUFA levels by the mortality rate of patients with low levels for each age group.

Table S3. **Baseline fatty acid composition of the study participants according to levels of marine n-3 polyunsaturated fatty acids.**

Marine n-3 PUFA levels	**All patients**	**Q1**	**Q2**	**Q3**	**Q4**	**p for trend**
wt%	1.35 – 23.87	≤ 6.20	6.21 – 7.94	7.95 – 10.02	≥ 10.03	
Nr. of patients	1990	499	499	495	497	
Saturated fatty acids, *wt%*	42.67 (0.85)	42.42 (0.99)	42.63 (0.80)	42.81 (0.78)	42.81 (0.78)	<0.001
MUFA, *wt%*	11.03 (1.65)	11.66 (1.93)	11.23 (1.65)	11.83 (1.44)	11.42 (1.26)	<0.001
Total n-6 PUFA, *wt%*	35.44 (3.32)	38.40 (2.38)	36.61 (2.10)	34.96 (1.87)	31.79 (2.63)	<0.001
Linoleic acid, *wt%*	24.76 (3.29)	26.85 (3.06)	25.78 (2.77)	24.36 (2.48)	22.03 (2.66)	<0.001
Arachidonic acid, *wt%*	7.89 (1.67)	8.16 (1.83)	7.96 (1.67)	7.90 (1.62)	7.55 (1.50)	<0.001
Trans fatty acids, *wt%*	0.40 (0.13)	0.39 (0.13)	0.41 (0.14)	0.40 (0.12)	0.42 (0.14)	0.01
α-Linolenic acid, *wt%*	0.24 (0.07)	0.25 (0.08)	0.25 (0.08)	0.24 (0.07)	0.22 (0.07)	<0.001

Baseline plasma phospholipid fatty acid composition. Patients divided into quartiles according to marine n-3 polyunsaturated fatty acids (PUFA) levels, defined as the sum of plasma phospholipid eicosapentaenoic, docosapentaenoic and docosahexaenoic acid levels in weight percentage *(wt%)* of total plasma phospholipid fatty acids. Results are presented as means and standard deviations. Trend was evaluated using linear regression. *MUFA:* Monounsaturated fatty acids. *Q*: quartiles.

Table S4. **Estimated mortality risk according to quartiles of n-6 to n-3 polyunsaturated fatty acid ratio using multivariable Cox proportional hazard regression**

Quartiles	**Q1**		**Q2**			**Q3**			**Q4**	
n-6 to n-3 PUFA ratio	≤ 3.31		3.31 – 4.36			4.37 – 5.77			≥ 5.78	
Nr. of patients	495		498			492			491	
Mortality	HR	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
All-cause	1.0	1.07	(0.80-1.43)	0.63	1.26	(0.89-1.77)	0.19	1.51	(0.93-2.45)	0.10
Cardiovascular	1.0	1.23	(0.77-1.95)	0.39	1.17	(0.64-2.13)	0.61	2.08	(0.89-4.90)	0.09

MI	1.0	0.79	(0.30-2.11)	0.64	0.67	(0.20-2.26)	0.52	1.34	(0.27-6.73)	0.73
SCD	1.0	1.49	(0.65-3.45)	0.35	2.50	(0.86-7.22)	0.09	3.71	(0.78-17.67)	0.10
Stroke	1.0	1.64	(0.60-4.50)	0.33	1.52	(0.41-5.74)	0.53	2.89	(0.42-19.81)	0.28
Infectious disease	1.0	0.95	(0.52-1.72)	0.86	1.93	(1.05-3.56)	0.04	2.34	(0.96-5.69)	0.06
Cancer	1.0	0.93	(0.53-1.66)	0.81	0.97	(0.50-1.91)	0.94	0.66	(0.24-1.83)	0.43

The estimated risk of total and cause-specific mortality according to n-6 polyunsaturated fatty acids (PUFA) to n-3 PUFA ratio using multivariable adjusted Cox proportional hazard regression analysis. Results are presented as multivariable adjusted hazard ratio (*HR*) for developing mortality endpoints relative to the lower quartile of n-6 to n-3 PUFA ratio (n-6: the sum of linoleic acid, gammalinolenic acid, eicosadienoic acid, dihomogammalinolenic acid, arachidonic acid and adrenic acid levels in weight percentage (*wt%*) of total plasma phospholipid fatty acids, n-3: the sum of alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid levels in weight percentage (*wt%*) of total plasma phospholipid fatty acids). In addition to n-6:n-3 ratio, the following variables were included in the model: Recipient age, a product term of recipient age and n-6 to n-3 PUFA ratio, gender, estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula, time in dialysis prior to transplantation, preemptive transplantation, body mass index, number of antihypertensive drugs, diabetes mellitus, coronary artery, cerebrovascular and peripheral vascular disease, albumin and total plasma cholesterol concentrations. *Q*: quartile. *CI:* confidence interval. *MI*: myocardial infarction. *SCD:* sudden cardiac death.

Table S5. **Estimated mortality risk according to quartiles of individual marine n-3 polyunsaturated fatty acid levels using multivariable Cox proportional hazard regression**

				Eicosapentaenoic acid						
				Model 1						
Quartiles	**Q1**		**Q2**			**Q3**			**Q4**	
wt%	≤ 1.12		1.13 – 1.76			1.77 – 2.89			≥ 2.90	
Nr. of patients	495		498			492			491	
Mortality	HR	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
All-cause	1.0	0.78	(0.58-1.07)	0.12	0.56	(0.39-0.79)	0.001	0.46	(0.29-0.73)	0.001
Cardiovascular	1.0	0.76	(0.47-1.22)	0.25	0.59	(0.34-1.00)	0.05	0.34	(0.16-0.71)	0.004
MI	1.0	1.49	(0.41-5.40)	0.54	0.82	(0.19-3.46)	0.78	0.64	(0.10-4.23)	0.65
SCD	1.0	0.72	(0.36-1.45)	0.36	0.46	(0.21-1.04)	0.06	0.34	(0.11-1.07)	0.07

Stroke	1.0	0.50	(0.16-1.55)	0.23	0.73	(0.21-2.49)	0.61	0.19	(0.03-1.21)	0.08
Infectious disease	1.0	0.41	(0.23-0.76)	0.004	0.29	(0.14-0.59)	0.001	0.24	(0.09-0.62)	0.003
Cancer	1.0	1.60	(0.78-3.29)	0.20	1.11	(0.50-2.47)	0.80	1.37	(0.51-3.68)	0.53

Model 2

Quartiles	**Q1**		**Q2**			**Q3**			**Q4**	
wt%	≤ 1.12		1.13 – 1.76			1.77 – 2.89			≥ 2.90	
Nr. of patients	495		498			492			491	
Mortality	HR	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
All-cause	1.0	0.76	(0.55-1.03)	0.07	0.50	(0.34-0.72)	<0.001	0.39	(0.24-0.64)	<0.001
Cardiovascular	1.0	0.75	(0.46-1.21)	0.24	0.54	(0.31-0.96)	0.04	0.29	(0.13-0.63)	0.002
MI	1.0	1.67	(0.44-6.28)	0.45	1.00	(0.21-4.77)	1.0	0.59	(0.08-4.49)	0.61
SCD	1.0	0.69	(0.34-1.40)	0.30	0.46	(0.20-1.07)	0.07	0.33	(0.10-1.06)	0.06
Stroke	1.0	0.52	(0.16-1.63)	0.26	0.67	(0.18-2.48)	0.55	0.15	(0.02-1.01)	0.05
Infectious disease	1.0	0.38	(0.21-0.70)	0.002	0.24	(0.12-0.51)	<0.001	0.20	(0.08-0.54)	0.001
Cancer	1.0	1.57	(0.76-3.26)	0.23	1.00	(0.43-2.31)	1.00	1.20	(0.43-3.34)	0.73

Docosahexaenoic acid

Model 1

Quartiles	**Q1**		**Q2**			**Q3**			**Q4**	
wt%	≤ 4.00		4.01 – 5.07			5.08 – 6.16			≥ 6.17	
Nr. of patients	495		498			492			491	
Mortality	HR	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
All-cause	1.0	0.75	(0.55-1.03)	0.08	0.62	(0.44-0.88)	0.01	0.52	(0.32-0.83)	0.01
Cardiovascular	1.0	0.66	(0.40-1.08)	0.10	0.45	(0.26-0.77)	0.004	0.32	(0.15-0.67)	0.003
MI	1.0	0.40	(0.09-1.89)	0.25	1.15	(0.30-4.46)	0.84	0.67	(0.11-4.10)	0.66
SCD	1.0	0.74	(0.37-1.47)	0.39	0.27	(0.11-0.65)	0.004	0.26	(0.09-0.83)	0.02
Stroke	1.0	0.80	(0.27-2.34)	0.68	0.33	(0.09-1.20)	0.09	0.24	(0.04-1.40)	0.11
Infectious disease	1.0	0.63	(0.33-1.19)	0.15	0.50	(0.25-1.02)	0.06	0.41	(0.16-1.08)	0.07
Cancer	1.0	0.95	(0.47-1.92)	0.89	0.91	(0.43-1.94)	0.80	1.19	(0.46-3.09)	0.73

				Model 2						
Quartiles	**Q1**		**Q2**			**Q3**			**Q4**	
wt%	≤ 4.00		4.01 – 5.07			5.08 – 6.16			≥ 6.17	
Nr. of patients	495		498			492			491	
Mortality	HR	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
All-cause	1.0	0.76	(0.55-1.04)	0.09	0.58	(0.40-0.84)	0.004	0.47	(0.29-0.76)	0.002
Cardiovascular	1.0	0.67	(0.41-1.09)	0.11	0.42	(0.24-0.75)	0.003	0.29	(0.14-0.62)	0.001
MI	1.0	0.49	(0.10-2.38)	0.38	1.55	(0.36-6.71)	0.56	0.86	(0.12-5.89)	0.76
SCD	1.0	0.73	(0.37-1.46)	0.37	0.27	(0.11-0.67)	0.01	0.28	(0.09-0.90)	0.03
Stroke	1.0	0.90	(0.30-2.67)	0.84	0.35	(0.09-1.32)	0.12	0.22	(0.04-1.28)	0.09
Infectious disease	1.0	0.62	(0.33-1.19)	0.15	0.46	(0.22-0.95)	0.04	0.38	(0.14-1.00)	0.05
Cancer	1.0	0.96	(0.47-1.94)	0.90	0.84	(0.38-1.86)	0.66	1.02	(0.38-2.77)	0.96

The estimated risk of total and cause-specific mortality using multivariable adjusted Cox proportional hazard regression models 1 and 2. Results presented as multivariable adjusted hazard ratio (*HR*) for developing mortality endpoints relative to the lower quartile of the individual marine n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid in weight percentage (*wt%*) of total plasma phospholipid fatty acids. In addition to either eicosapentaenoic acid or docosahexaenoic acid levels, model 1 included the following variables: Recipient age, a product term of recipient age and either eicosapentaenoic acid or docosahexaenoic acid as appropriate, gender, estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula, time in dialysis prior to transplantation, preemptive transplantation, body mass index, number of antihypertensive drugs, diabetes mellitus, coronary artery, cerebrovascular and peripheral vascular disease, albumin and total plasma cholesterol concentrations. Model 2 include in addition n-6 polyunsaturated fatty acids levels as a covariate. *Q*: quartiles. *CI:* confidence interval.

Table S6. **The transplantation era effect on mortality rates by study participation**

	Transplantation era					
	1999-2006		**2007-2008**		**2009-2011**	
Study participation	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Mortality rate, *cases / 1000 person-years*	41.3	29.3	26.6	26.3	39.3	19.3
Mortality rate ratio	1.41		1.01		2.04	

Recipient age, *years*	52.0	51.1	48.2	51.3	56.7	53.0
Patients participating in the study, *%*	97.2		37.8		79.5	

The mortality rate for adult patients (≥ 16 years) who were not included in the study and study participants grouped according to transplantation era (30th of September 1999 to 31st of December 2006, 1st of January 2007 to 31st of December 2008 and 1st of January 2009 to 13th of October 2011). Mortality rate ratios for each time period was obtained by dividing the mortality rate of adult patients not included in the study by the mortality rate of patients included in the study. Shown are also mean recipient age at the time of transplantation and the proportion of patients participating in the study for each time period. The proportion of participating patients was obtained by dividing the number of patients who received a renal transplant and were included in the study by the sum of all patients who received a renal transplant for each time period.