ORIGINAL ARTICLE

Seasonality of mortality and graft failure among kidney transplant recipients in the US – a retrospective study

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SUMMARY

Mortality in the general population and in patients on chronic hemodialysis is significantly higher in winter than summer. It is unknown whether such a seasonal difference exists for mortality or graft failure among kidney transplant recipients. We analyzed United Network for Organ Sharing (UNOS) data to assess whether the annual distribution of deaths and graft failures differed significantly from expected. There was significant annual variation in both deaths (n = 52 523) and graft failures (n = 50 301; both $P < 0.001$). The number of observed deaths exceeded the number expected by 8.9% in winter ($P < 0.001$), whereas the number of deaths was 4.8% lower than expected in summer ($P < 0.01$). The pattern was strongest for deaths attributable to cardiovascular disease (n = 11 509; 21.9%). Similarly, there was an excess of graft failures in winter (3.6%; $P < 0.01$) and a deficit in other seasons (all $P \leq 0.02$). This pattern was observed for graft failures due to chronic rejection ($P < 0.001$) and other causes ($P < 0.001$), but not for acute rejection ($P = 0.28$) or recurrent disease ($P = 0.27$). Potential explanations for this variation include changes in physiologic parameters, changes in medication adherence and other behaviors, or changes in insurance coverage or clinical care. Further studies are necessary to identify specific mechanisms.

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Key words
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Kidney transplantation offers a significant survival advantage over chronic dialysis [1,2]. Long-term graft and patient survival following kidney transplantation, however, remain suboptimal. More than half of kidney transplant recipients in the US die with a functioning graft. Roughly, two-thirds of these deaths are attributable to cardiovascular disease (CVD), infection, or malignancy [3,4]. The most common cause of late graft failure is chronic rejection, with a significant minority of graft failures due to acute rejection and recurrent disease. Management of transplant recipients requires a constant balance of adequate immunosuppression to prevent rejection versus over-immunosuppression and the concomitant higher risk of opportunistic infections, malignancy, and toxicity. Identification of factors placing patients at higher risk of these specific outcomes is needed to tailor this balance and individualize immunosuppressive therapy.

The incidence of cardiovascular disease and mortality in the general population is significantly higher in

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Table 1. Number of deaths and % mean annual peak-trough difference among kidney transplant recipients in the US, 2000–2014

	Number of deaths	%	% Annual mean peak-trough difference (95% CI)	*P* for periodicity	*P* for difference
Overall	52 523	–	13.9 (10.4, 17.5)	<0.001	–
Age					
<60 years	32 613	62.1	13.3 (9.9, 16.7)	<0.001	0.49
≥60 years	19 910	37.9	15.1 (11.2, 19.0)	<0.001	
Sex					
Female	19 619	37.35	15.7 (11.6, 19.8)	<0.001	0.23
Male	32 904	62.65	12.5 (9.2, 15.7)	<0.001	
Race					
White	33 789	64.3	14.0 (10.7, 17.4)	<0.001	Reference
Black	11 455	21.8	15.1 (9.9, 20.2)	<0.001	0.72
Other	7279	13.9	10.5 (4.3, 16.7)	0.004	0.33
Region					
North	11 306	21.5	15.2 (9.5, 21.0)	<0.001	Reference
Central	30 670	58.4	13.0 (8.5, 17.5)	<0.001	0.55
South	10 547	20.1	16.2 (9.7, 22.7)	<0.001	0.82
Donor type					
Deceased	37 918	72.2	14.1 (10.9, 17.1)	<0.001	0.70
Living	14 605	27.8	13.1 (8.2, 18.1)	<0.001	
Cause of death					
Cardiovascular disease	11 509	21.9	20.6 (14.7, 26.5)	<0.001	Reference
Infection	6446	12.3	12.7 (5.3, 20.1)	0.003	0.10
Malignancy	5399	10.3	8.0 (−0.8, 16.1)	0.14	0.02
Other	16 453	31.3	10.1 (5.8, 14.5)	<0.001	0.005
Unknown	12 716	24.2	15.8 (8.7, 22.9)	0.001	0.31

winter than in summer [5,6]. A similar pattern of higher incidence of deaths during winter also has been reported in patients on chronic hemodialysis [7–9]. It is unknown whether such a seasonal difference exists for mortality or graft failure among kidney transplant recipients in the US. We analyzed 15 years of national data to assess the distribution of deaths and graft failures by month.

Methods

Data from the United Network for Organ Sharing (UNOS) Standard Transplant and Research (STAR) Files were analyzed. Analyses were limited to single-organ kidney transplants that occurred from 1 October 1987 through 31 December 2014. Multiple organ transplants were excluded. Deaths and graft failures occurring from 1 January 2000 through 31 December 2014 were analyzed. Deaths and graft failures occurring within 90 days of transplantation were excluded.

Deaths attributed to graft failure ($n = 474$) were excluded from analyses of death. The primary cause of death was classified as cardiovascular (including cerebrovascular), malignancy, infection, other cause, or unknown. Only the first occurrence of graft failure for each recipient during the study period was included. Death with a functioning graft was not included as graft failure. The primary cause of graft failure was classified as chronic rejection, acute rejection, recurrent disease, or other cause.

Analyses

We first calculated the total number of deaths occurring during each of the 180 months from 1/1/2000 to 12/31/2014. Based on the results of a plot of the number of deaths by month, we regressed the month, modeled using a restricted cubic spline with four knots, on the number of deaths per month using Poisson regression. A cosinor analysis was then performed on the residuals of this model to test for annual variation in the number of deaths per month after accounting for the longer-term trends [10]. The cosinor analysis models cyclical variations over time (e.g., 1 year) as a function of a sine wave [sin(t)] and a cosine wave [cos(t)]. The resulting coefficients were used to calculate the amplitude and phase shift of the sinusoidal curve. The variance of the amplitude, a function of the coefficients of sin(t) and

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cos(t), was calculated using the Delta method. The mean annual peak-trough difference, calculated as twice the amplitude of the modeled sinusoidal wave, and its 95% confidence interval is reported as the percentage of the total number of monthly deaths. Likelihood ratio tests were used to test improvement in fit between nested models.

We then stacked the number of deaths per calendar month over all 15 years to more concisely show the annual patterns [11]. The expected number of deaths per month was based on the Poisson regression model, accounting for the number of days in each calendar month, including leap days. The difference between the observed and expected number of deaths was then calculated as a percentage of the expected number. We then performed similar analyses by season (winter: December–February; spring: March–May; summer: June–August; fall: September–November).

Similar analyses were performed for cause-specific deaths and after stratification by age (<or ≥60 years at time of transplant for death and < or ≥45 years for graft failure), sex, race (white, black or other), type of donor (living or deceased), and geographic location based on the permanent state of residence of the recipient at the time of transplantation. States in the northern region were AK, ID, ME, MA, MI, MN, MT, NH, NY, ND, OR, RI, SD, VT, WA, WI, and WY. States in the southern region were AL, AZ, AR, FL, GA, HI, LA, OK, NM, SC, and TX. All others were considered in the central region. Interaction terms were added to the cosinor model to assess effect modification.

Similar analyses were performed for all-cause and cause-specific graft failure. Analyses were performed using Stata/MP 13.1 (StataCorp, www.stata.com).

Results

Death

A total of 52 523 deaths occurred during the study period (Table 1). A total of 11 509 (21.9%) deaths were attributed to cardiovascular disease, 6446 (12.6%) to infection, 5399 (10.3% to malignancy, and 16 453 (31.3%) to other causes. Cause of death was unknown in 24.2% of deaths. There was a significant increase in the number of deaths per month from 2000 to 2012 and a slight decrease thereafter, due to the growing number of recipients at risk and the changing age distribution of living recipients over time (Figure 1).

There was substantial evidence of annual variation in the number of deaths after accounting for the longer-term trends, as the cosinor model substantially improved the fit to observed data ($P < 0.001$). The mean annual peak-trough difference was 13.9% (10.4, 17.5). Significant periodicity was detected for all subgroups stratified by age, sex, race, region, and donor type, with no significant differences observed in the estimated mean peak-trough differences. The annual peak-trough difference was greatest for deaths due to cardiovascular disease (20.6%; $P < 0.001$). There was also evidence of annual variation for deaths due to infection and other and unknown cause, but with lower amplitude than for deaths due to cardiovascular disease. The cosinor model

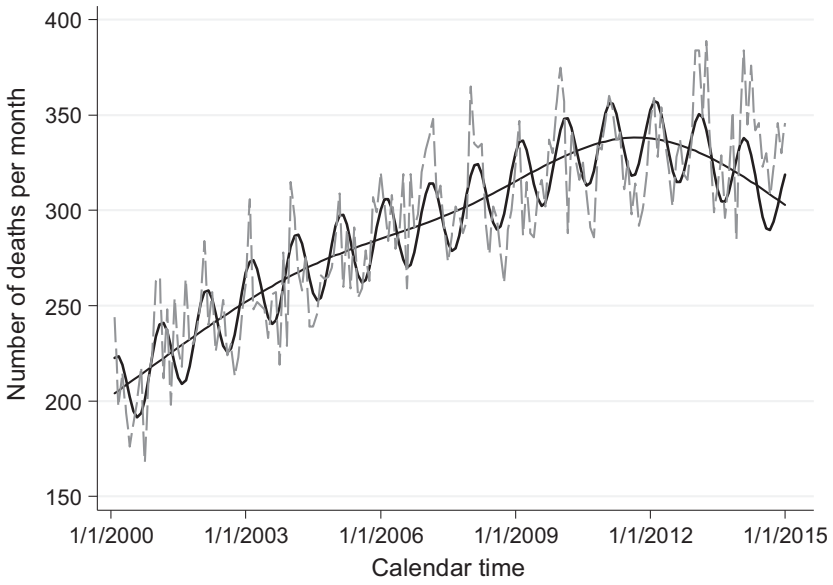

Figure 1 Number of deaths per month among kidney transplant recipients in the US, 2000–2014. Gray dashed line: observed number of deaths per month. Solid smooth line: predicted number of deaths per month from restricted cubic spline model with four knots. Sinusoidal curve: predicted number of deaths per month from cosinor model.

did not significantly improve the fit for deaths due to malignancy ($P = 0.14$) and the mean peak-trough difference was significantly less than for deaths due to cardiovascular disease (P-difference = 0.02).

Combining all years, the number of deaths exceeded the number expected by 9.1% in December ($P < 0.001$), 11.2% in January ($P < 0.001$), 7.7% in February ($P = 0.002$) and 3.4% in March ($P = 0.02$; Figure 2). In contrast, the number of deaths was 3.0 to 7.1% lower than expected in May–September (all $P < 0.05$). By season, there were 8.9% more deaths than expected during winter ($P < 0.001$), 4.8% fewer than expected in summer ($P < 0.001$), and 2.9% fewer than expected during fall ($P = 0.008$; Figure 3a). A similar but even stronger pattern was observed for deaths due to cardiovascular disease (Figure 3b). There were 12.9% more deaths due to cardiovascular disease than expected in winter, 7.5% fewer than expected in summer, and 5.8% fewer than expected in fall. A similar pattern was observed for deaths due to infections (Figure 3c) and deaths due to unknown causes (Figure 3e).

Graft failure

A total of 50 301 graft failures occurred, including 24 442 (48.6%) due to chronic rejection, 6430 (12.8%) due to acute rejection, 3324 (6.6%) due to recurrent disease, and 16 105 (32.0%) due to other causes (Table 2). As with deaths, there was a significant increase in the number of graft failures per month from 2000 to 2012 and a decrease thereafter (Figure 4). There also was substantial evidence of annual variation in the number of graft failures after accounting for the longer-term trends ($P < 0.001$). The mean peak-trough difference was 8.0 (4.8, 11.3). Significant periodicity was detected for all subgroups stratified by age, sex, race, region, and donor type, with no significant differences observed in the estimated mean peak-trough differences. Graft failures due to chronic rejection showed a strong annual pattern, with a mean peak-trough difference of 10.7%. No significant annual periodicity was observed for graft failures due to acute rejection ($P = 0.67$) or recurrent disease ($P = 0.92$).

Combining all years, the number of deaths exceeded the number expected by 7.8% in January ($P = 0.004$), 4.7% in February ($P < 0.001$), and 5.5% in March ($P < 0.01$; Figure 5). In contrast, the number of deaths was 1.3 to 4.7% lower in July–December ($P < 0.05$ for July and September).

There were 3.6% more graft failures than expected during winter ($P = 0.006$) and 2.8% more than

Table 2. Number of graft failures and % mean annual peak-trough difference among kidney transplant recipients in the US, 2000–2014.

	Number of graft failures	%	% annual mean peak-trough difference (95% CI)	*P* for periodicity	*P* for difference
Overall	50 301	–	8.0 (4.8, 11.3)	<0.001	–
Age					
<45 years	26 118	51.9	6.7 (2.4, 10.9)	0.008	0.30
≥45 years	24 183	48.1	9.8 (5.6, 13.9)	<0.001	
Sex					
Female	20 525	40.8	8.9 (4.5, 13.4)	<0.001	0.62
Male	29 776	59.2	7.4 (3.5, 11.4)	0.001	
Race					
White	25 382	50.5	8.2 (4.0, 12.5)	<0.001	Reference
Black	16 731	33.3	8.2 (3.8, 12.6)	0.001	0.99
Other	8188	16.3	9.3 (2.5, 16.0)	0.02	0.80
Region					
North	9697	19.3	10.0 (3.7, 16.2)	0.008	Reference
Central	30 821	61.3	5.2 (1.0, 9.3)	0.05	0.21
South	9783	19.5	16.2 (9.5, 23.0)	<0.001	0.18
Donor type					
Deceased	34 549	68.7	6.5 (3.0, 10.1)	0.001	0.18
Living	15 752	31.3	11.3 (6.1, 16.6)	<0.001	
Cause of graft failure					
Chronic Rejection	24 442	48.6	10.7 (6.5, 14.9)	<0.001	Reference
Acute rejection	6430	12.8	3.3 (−4.0, 10.7)	0.67	0.09
Recurrent disease	3324	6.6	1.9 (−7.9, 11.8)	0.92	0.11
Other	16 105	32.0	8.6 (3.6, 13.6)	0.001	0.54

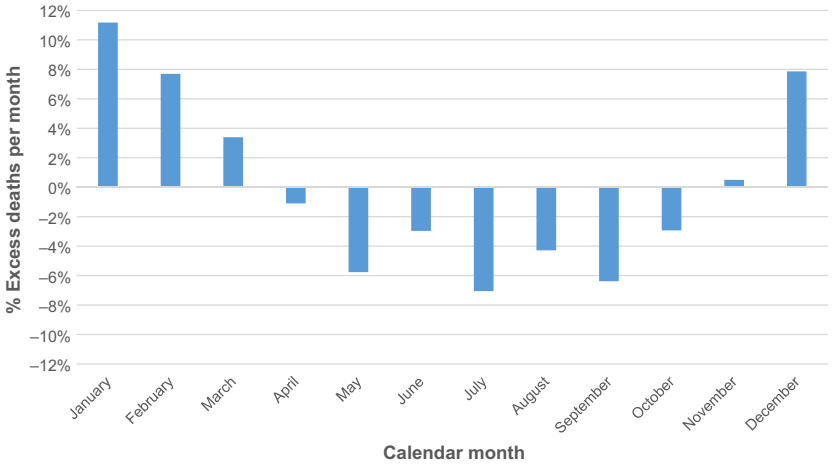

Figure 2 Excess deaths as a percentage of the expected number of deaths by month, stacking all data from 2000 to 2014.

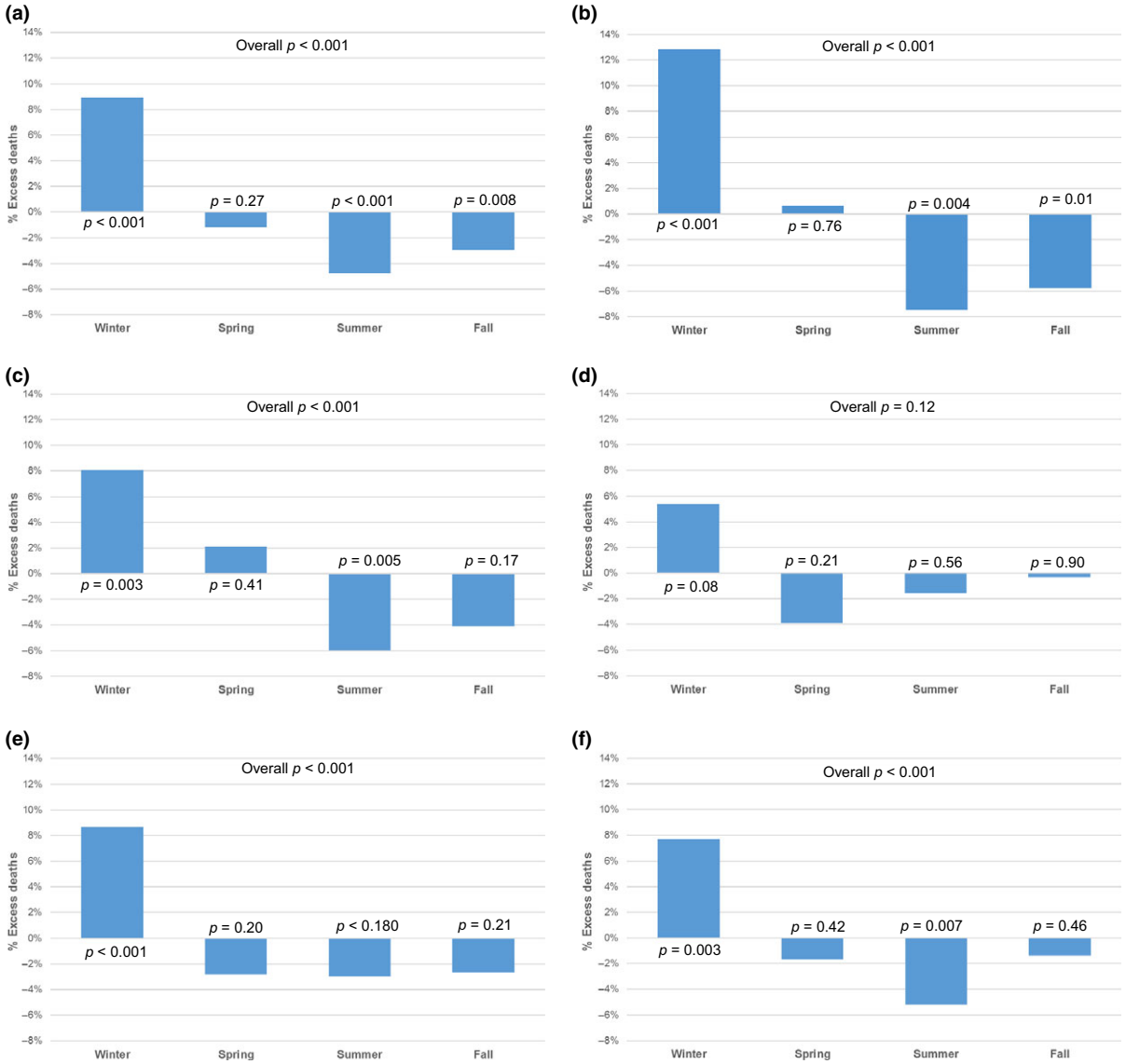

Figure 3 Excess deaths as a percentage of the expected number of deaths by season, stacking all data from 2000 to 2014, for (a) all deaths, (b) deaths due to cardiovascular disease, (c) deaths due to infection, (d) deaths due to malignancy, (e) deaths due to other causes, and (f) deaths due to unknown causes.

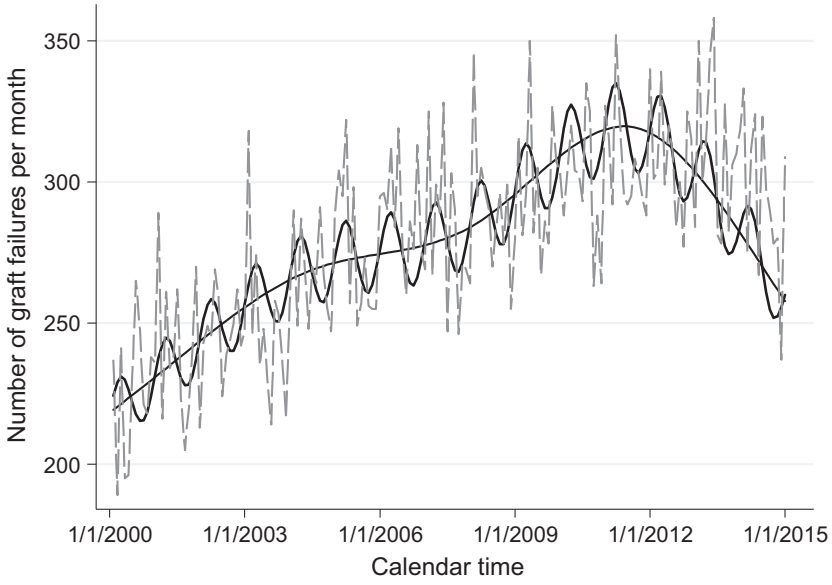

Figure 4 Number of graft failures per month among kidney transplant recipients in the US, 2000–2014. Gray dashed line: observed number of graft failures per month. Solid smooth line: predicted number of graft failures per month from restricted cubic spline model with four knots. Sinusoidal curve: predicted number of graft failures per month from cosinor model.

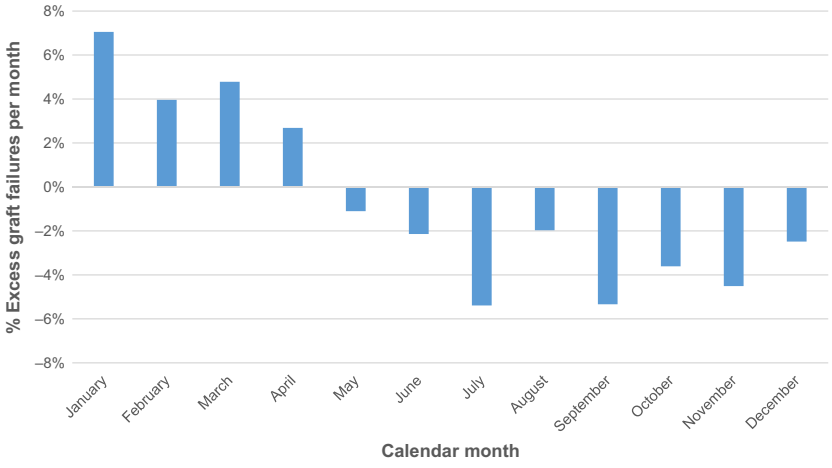

Figure 5 Excess graft failures as a percentage of the expected number of graft failures by month, stacking all data from 2000 to 2014.

expected in spring ($P = 0.02$; Figure 6a), whereas there were 2.5% fewer than expected in summer ($P = 0.02$) and 3.8% fewer than expected during fall ($P < 0.001$). A similar but stronger pattern was observed for graft failures due to chronic rejection and other causes (both $P < 0.001$), but no such variation was observed for graft failures due to acute rejection ($P = 0.28$) or recurrent disease ($P = 0.27$).

Discussion

Using 15 years of national data, we observed significant annual variation in both the number of deaths and the number of graft failures among kidney transplant recipients in the US. The number of deaths was highest in winter and lowest in summer, primarily due to deaths attributed to cardiovascular disease. A similar but somewhat weaker pattern was observed for deaths attributed to infection. The number of graft failures also was highest in winter but was lowest in fall. This pattern was most pronounced for graft failures attributed to chronic rejection, which represented nearly half of all graft failures. No significant periodicity was observed for graft failures attributed to acute rejection or recurrent disease. We did not find evidence that these patterns differed significantly by recipient demographics, geographic location, or donor type.

Previous studies in the general population have reported similar patterns for all-cause and cardiovascular mortality [5,6,9,12,13]. Colder temperatures were related to a higher incidence of mortality attributed to ischemic heart disease, cerebrovascular disease, and respiratory disease in several climactic regions in Europe [5,13]. Similarly, all-cause and cardiovascular mortality

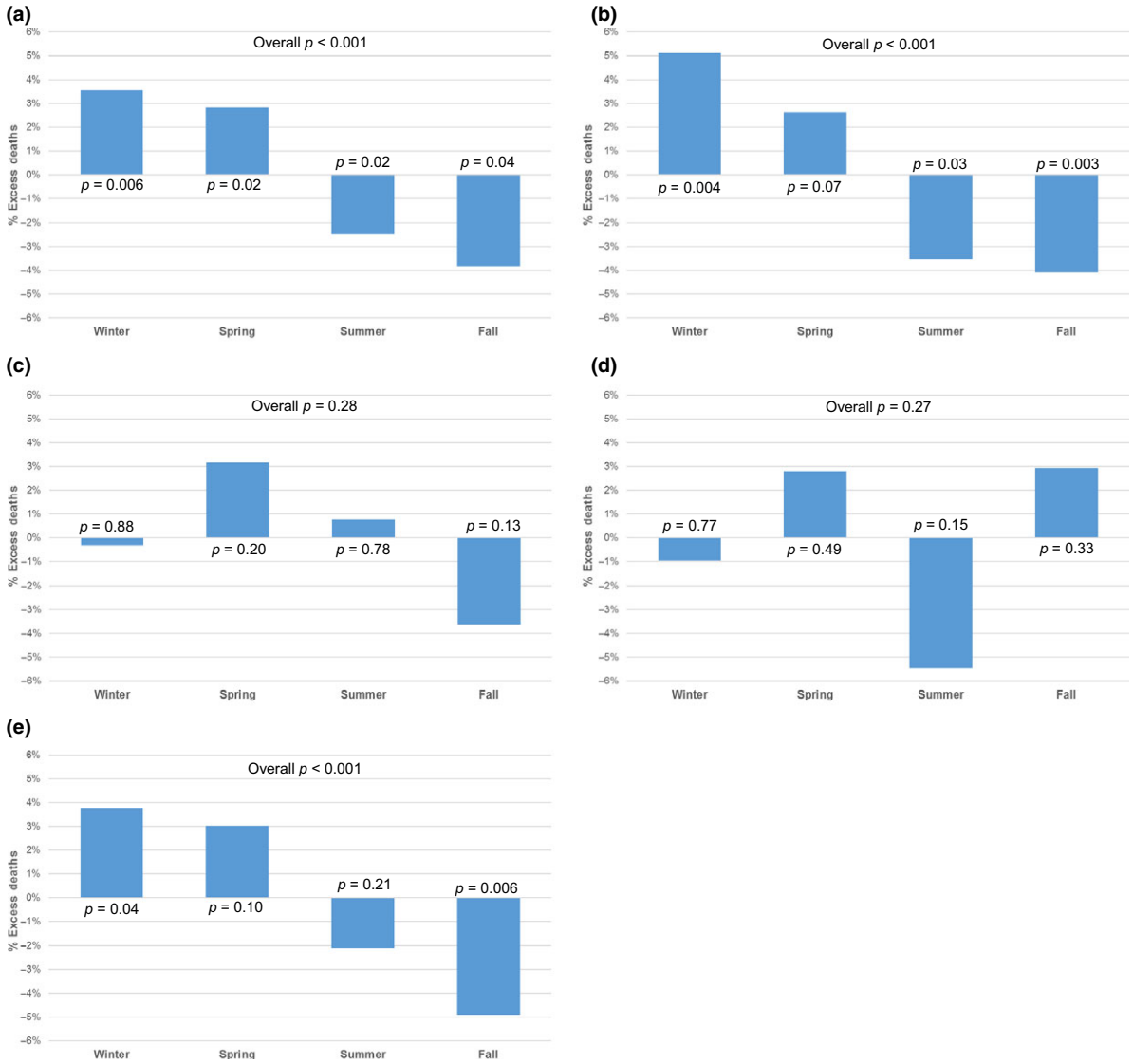

Figure 6 Excess graft failures as a percentage of the expected number of graft failures by season, stacking all data from 2000 to 2014, for (a) all graft failures, (b) graft failures due to chronic rejection, (c) graft failures due to acute rejection, (d) graft failures due to recurrent disease, and (e) graft failures due to other causes.

is higher in winter and lower in summer for patients receiving chronic hemodialysis [9,14]. Hospital admissions for a variety of conditions also are higher in winter than summer among patients on chronic hemodialysis, including pneumonia and influenza, chronic obstructive pulmonary disease, acute coronary syndrome, and heart failure [15]. This is the first report to our knowledge that extends these findings to kidney transplant recipients.

The reasons for these annual variations in cardiovascular mortality remain speculative. Increased propensity for thrombosis due to lower plasma volume and greater hemoconcentration may play a significant role in the increase in cardiovascular deaths in colder months [12,16,17]. In a 5-year study of over 15 000 dialysis patients, Usvyat *et al.* [9] found higher values of neutrophil/lymphocyte ratio, serum potassium, and platelet count in winter than in summer. The significant seasonal variation in mortality in that cohort was mostly explained by variation in these biochemical and clinical parameters. Data from the much larger International Monitoring Dialysis Outcomes (MONDO) consortium also found C-reactive protein levels to be higher in winter than summer. In that larger cohort, seasonal mortality remained significant after adjustment for other laboratory and clinical variables [8]. Season-related hypercoagulability may be an even more important element in kidney transplant recipients than in the general

population [18]. Long-term kidney transplant recipients have a chronic prothrombotic and persistent inflammatory state, with significantly elevated levels of fibrinogen, d-dimer, prothrombin activation fragments F1 + 2, and IL−6 [19]. Changes in sympathetic activity in colder months may also induce cardiac arrhythmias, which may also be of increased severity [20]. Increased incidence of infections during winter may also trigger cardiovascular events [21]. Seasonal variation in other biochemical parameters may also be related to increased cardiovascular events. A strong seasonal pattern was observed in serum 25-hydroxyvitamin D [25(OH)D] in a large community-based cohort of older adults [22]. Inverse seasonal variations also were found for intact parathyroid hormone and bone-specific alkaline phosphatase.

Infections themselves are a significant cause of morbidity and mortality in kidney transplant recipients [23]. Many viral infections in this population are due to reactivation of latent infection due to intense immunosuppression [24]. The seasonal pattern of deaths attributed to infection observed among kidney transplant recipients agrees with findings in the general population, despite their very different incidence rates of some specific infections [25].

This is the first report to our knowledge demonstrating seasonality in kidney allograft failure. The pattern was not observed for graft failures due to acute rejection or recurrent disease, but these represented only 12.8 and 6.6% of all failures, respectively. The number of graft failures was highest in winter and was progressively lower later in the year, with the lowest numbers in fall. The potential explanations for this finding also are speculative. Season-related infections may promote an immunologic response and/or a reduction in immunosuppression eventually resulting in graft rejection [26]. Sunlight exposure and other factors may affect biochemical parameters relevant to immune response, including 25(OH)D levels [27]. Interestingly, a recent study found that sunlight directly increases motility of T lymphocytes, which may be highly relevant for transplant recipients [28]. Other potential explanations include changes in medication adherence or changes in insurance coverage with the end of the calendar year.

There is an apparent shift toward later months for graft failure due to chronic rejection or other causes compared to mortality due to infection or cardiovascular disease. This is potentially explained by survivors of infectious or cardiovascular events remaining at high risk of graft failure following the nonfatal even due to the event itself or a reduction in immunosuppression in response to an infection. Additional studies in data sources including more detailed clinical data will be required to elucidate the role of these nonfatal events and interventions on subsequent graft failure.

Relevant strengths of this study include the large number of deaths and graft failures accrued over 15 years, the ability to exclude deaths due to graft failure and deaths with a functioning graft from the respective analyses, and the national representativeness of the data. A significant limitation of the study is the fact that causes of death and causes of graft failure cannot be verified. Nonetheless, we found significantly larger seasonal variations for cardiovascular deaths than for deaths attributed to other causes. We also observed much stronger effects for graft failures due to chronic rejection than those due to acute rejection or recurrent disease.

These findings have implications for both research and clinical care. These findings highlight the need for further studies to more fully understand the pathological mechanisms resulting in the observed seasonal variations, including the postulated link between nonfatal cardiovascular and infectious events and subsequent graft failure. As the number of deaths differed by approximately 14% on average over the course of a year, this may have a substantial impact on some research studies comparing interventions at different times. As such, the time of year may need to be considered in some settings to account for these seasonal differences. Clinical implications include the potential need for closer monitoring of recipients during times of higher risk, including obtaining monthly laboratories and timely clinic visits where appropriate, and potentially a lower threshold for performing biopsies or other diagnostic procedures or interventions.

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Conflict of interest

The authors have declare no conflict of interest.

REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.
2. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000; **342**: 605.
3. El-Zoghby ZM, Stegall MD, Lager DJ, *et al.* Identifying specific causes of kidney allograft loss. *Am J Transplant* 2009; **9**: 527.
4. Matas AJ, Smith JM, Skeans MA, *et al.* OPTN/SRTR 2013 annual data report: kidney. *Am J Transplant* 2015; **15**(Suppl 2): 1.
5. Keatinge W, Donaldson G, Bucher K, Jendritsky G. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. The Eurowinter Group. *Lancet* 1997; **349**: 1341.
6. Kalkstein AJ. Regional similarities in seasonal mortality across the United States: an examination of 28 metropolitan statistical areas. *PLoS One* 2013; **8**: e63971.
7. Broers NJH, Usvyat LA, Marcelli D, *et al.* Season affects body composition and estimation of fluid overload in haemodialysis patients: variations in body composition; a survey from the European MONDO database. *Nephrol Dial Transplant* 2015; **30**: 676.
8. Guinsburg AM, Usvyat LA, Etter M, Xu X, Thijssen S, Marcelli D, *et al.* Seasonal variations in mortality and clinical indicators in international hemodialysis populations from the MONDO registry. *BMC Nephrol* 2015; **16**: 139.
9. Usvyat LA, Carter M, Thijssen S, *et al.* Seasonal variations in mortality, clinical, and laboratory parameters in hemodialysis patients: a 5-year cohort study. *Clin J Am Soc Nephrol* 2012; **7**: 108.
10. Moen AN, Boomer GS. A tandem cosine algorithm for modeling rhythmic change. *Ecol Model* 2000; **134**: 275.
11. Hillman D, Fernández JR, Cornélissen G, Berry DA, Halberg J, Halberg F. Bounded limits and statistical inference in chronobiometry. *Prog Clin Biol Res* 1990; **341B**: 417.
12. Crawford VLS, McCann M, Stout RW. Changes in seasonal deaths from myocardial infarction. *QJM* 2003; **96**: 45.
13. Shephard RJ, Aoyagi Y. Seasonal variations in physical activity and implications for human health. *Eur J Appl Physiol* 2009; **107**: 251.
14. Wetmore JB, Gilbertson DT, Liu J, Collins AJ. Improving outcomes in patients receiving dialysis: The peer kidney care initiative. *Clin J Am Soc Nephrol* 2016; **11**: 1297.
15. Weinhandl E, Constantini E, Everson S, *et al.* Peer kidney care initiative 2014 report: dialysis care and outcomes in the United States. *Am J Kidney Dis* 2015; **65**: Svi, S1.
16. Keatinge WR. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling. *BMJ* 1985; **290**: 75.
17. Neild PJ, Syndercombe-Court D, Keatinge WR, Donaldson GC, Mattock M, Caunce M. Cold-induced increases in erythrocyte count, plasma cholesterol and plasma fibrinogen of elderly people without a comparable rise in protein C or factor X. *Clin Sci* 1994; **86**: 43.
18. Parajuli S, Lockridge JB, Langewisch ED, Norman DJ, Kujovich JL. Hypercoagulability in kidney transplant recipients. *Transplantation* 2016; **100**: 719.
19. Irish AB, Green FR. Environmental and genetic determinants of the hypercoagulable state and cardiovascular disease in renal transplant recipients. *Nephrol Dial Transplant* 1997; **12**: 167.
20. Stephenson EA, Collins KK, Dubin AM, *et al.* Circadian and seasonal variation of malignant arrhythmias in a pediatric and congenital heart disease population. *J Cardiovasc Electrophysiol* 2002; **13**: 1009.
21. Reddan DN, Klassen PS, Szczech LA, *et al.* White blood cells as a novel mortality predictor in haemodialysis patients. *Nephrol Dial Transplant* 2003; **18**: 1167.
22. Shoben AB, Kestenbaum B, Levin G, *et al.* Seasonal variation in 25-Hydroxyvitamin D concentrations in the cardiovascular health study. *Am J Epidemiol* 2011; **174**: 1363.
23. Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 2012; **7**: 2058.
24. Cukuranovic J, Ugrenovic S, Jovanovic I, Visnjic M, Stefanovic V. Viral infection in renal transplant recipients. *Scientific World J* 2012; **2012**: 1.
25. Reichert TA. Influenza and the winter increase in mortality in the United States, 1959–1999. *Am J Epidemiol* 2004; **160**: 492.
26. Cippa PE, Schiesser M, Ekberg H, *et al.* Risk stratification for rejection and infection after kidney transplantation. *Clin J Am Soc Nephrol* 2015; **10**: 2213.
27. Lee JR, Dadhania D, August P, Lee JB, Suthanthiran M, Muthukumar T. Circulating levels of 25-hydroxyvitamin D and acute cellular rejection in kidney allograft recipients. *Transplantation* 2014; **98**: 292.
28. Phan TX, Jaruga B, Pingle SC, Bandyopadhyat BC, Ahern GP. Intrinsic photosensitivity enhances motility of T lymphocytes. *Sci Rep* 2016; **6**: 39479.