INVITED COMMENTARY

The "cold" hard facts—seasonal variation in outcomes after kidney transplantation

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Seasonal variation in the incidence and cardiovascular disease complications in the general population has been well documented [1]. According to the analysis of data from the United States Renal Data System (USRDS) of all prevalent end-stage kidney disease (ESKD) patients between 2000 and 2013, the transition to ESKD (i.e., initiation of renal replacement therapy) and the incidence of all-cause and cause-specific mortality in patients with ESKD were highest during winter months (particularly January) compared to summer months, suggesting the possibility of season-specific precipitants during winter months contributing to adverse outcomes in both the general population and in patients with ESKD [2]. Similar associations have also been observed in a large cohort of 15 056 in-center hemodialysis patients in the USA, with all-cause mortality highest during winter months [14, 95% confidence intervals (CI) 13–15 deaths per 100 patient-years], with lowest mortality during summer months (12, 95% CI 11–13 deaths per 100 patient-years), which may be related to seasonal variations of clinical parameters that are known to influence mortality such as hypertension, intradialytic weight gain, and hyperkalemia [3].

A large-scale observational study, published in this issue of the journal by *Astor et al.*, used data from the United Network for Organ Sharing (UNOS) Standard Transplant and Research (STAR) Files (1978 and 2014) and time series cosinor analysis and Poisson regression model to calculate the expected number of deaths and allograft loss, taking into consideration the longer term annual variability in the number of deaths per month and potential effect modification by other covariates.

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The analyses were repeated after stratification by prespecified covariates that may potentially modify the study findings such as recipient age, gender, race, donor type, and geographic locations.

There is an excess number of expected deaths and allograft failure during the winter months between December and February, with lower than expected number of deaths and allograft failure in the other seasons [4]. The number of all-cause deaths and allograft failures exceeded the number expected by 9% ($P < 0.001$) and 4% ($P = 0.006$), respectively, during the winter months, with lower than expected number observed during the summer months [5% ($P < 0.001$) and 3% ($P = 0.02$), respectively]. The pattern of cause-specific deaths suggests an excess of cardiovascular disease (13%, $P < 0.01$) and infections (8%, $P = 0.003$) during the winter months suggesting the likelihood that environmental factors are likely to contribute to these excess risks.

The statistical analyses were robust and appropriate, but a number of residual methodological issues remain. As with any observational cohorts, the presence of selection, confounding, and indication biases must be carefully weighed against the accurate interpretation of the study findings. Unmeasured (e.g., intercurrent illnesses) and residual confounders (e.g., presence and severity of comorbid conditions such as diabetes, donor characteristics, waiting time prior to transplantation), and socioeconomic determinants may mediate or moderate the relationship between seasonality and allograft and patient outcomes.

Given the potential limitations of the study, could one be confident about the association between seasonality and mortality after kidney transplantation observed in the study by *Astor et al.* plausible or is this purely a coincidental occurrence? There are multiple potential conceivable factors that could contribute to this association as discussed in this study. Cold weather can trigger an excess cardiac sympathetic activity, hypercoagulopathy, and excess inflammatory response that may have contributed to the excess of CVD mortality during winter months. In addition, viral infections tend to be more frequent during winter seasons, which may explain the surplus of infection mortality observed in this study. However, it is likely that the association between seasonality and outcomes is much more complex than perceived.

The challenges in the interpretation of big registry data are the expected trade-off with a lack of granularity in the collected data to accurately translate the findings arising from observational cohorts. Data linkage of registry data to other databases to collect information such as the type and nature of cause-specific mortality (e.g., is CVD death attributed to cardiac failure or myocardial ischemia or the organism/affected sites contributing to infectious deaths), varying clinical practice patterns between sites, socioeconomic status, and patient-level characteristics such as the presence and severity of comorbidities, all of which may have modified the association between seasonality and outcomes. Nevertheless, appropriate analysis of large data remains informative. For example, in this study, examining for cluster-level random effects and to determine whether there are season-specific risk factors or intercurrent illnesses that may have mediated or moderated the association between seasonality and allograft and patient outcomes will add to the understanding of these study findings and could potentially identify modifiable factors that may be targeted to influence outcomes. In addition, validating this association in other population registry cohorts outside of the United States may provide greater confidence in the robustness of the estimates between seasonality and outcomes.

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Conflicts of interest

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