Practice of Epidemiology

From Cancer to Transplantation: An Evaluation of Period Analysis for Calculating Up-to-date Long-term Survival Estimates

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The timeliness of survival monitoring is particularly important in a field such as transplantation medicine, where progress occurs rapidly. Period analysis, a method successfully applied for improving the timeliness of survival monitoring in population-based cancer survival analysis, could potentially be useful in the field of transplantation as well. Using data from the Collaborative Transplant Study, the authors compared the ability of traditional, cohort-based analysis methods and the period analysis method to provide timely 5-year graft and patient survival estimates for kidney, heart, and liver transplants in 6 age groups (0–17, 18–29, 30–39, 40–49, 50–59, ≥60 years) on 378 occasions between 1990–1992 and 2000–2002. Overall, period estimates provided superior predictions for the survival of most recent transplants on 344 of 378 occasions (91%); in the organ-specific analysis, this proportion ranged between 83% for heart and 100% for kidney graft survival. This evaluation provides evidence that the period analysis method can improve the timeliness of survival monitoring in solid organ transplantation. The method appears useful for providing more up-to-date long-term survival estimates than traditional methods, and its use in pertinent studies is encouraged.

epidemiologic methods; organ transplantation; survival analysis

Timely quantification of survival trends is particularly important in a field such as transplantation medicine, where changes in survival-influencing factors, such as immunosuppression practices (1), organ allocation policies (2), or surgical techniques (3), may take place rapidly. The most recent long-term (5- and 10-year) graft and patient survival estimates currently available, derived by traditional survival analysis approaches such as the Kaplan-Meier method or actuarial cohort analysis technique, are based on cohorts of transplants performed in the mid-1990s or at the turn of the century (4–9). Potential change in prognosis over time makes these estimates likely outdated because they are based on the survival experience of patients who received transplants many years ago.

The period analysis approach (10, 11), with which cumulative survival estimates are derived on the basis of graft and patient survival experience during a most recent period only, can be expected to enable the calculation of more up-to-date long-term survival estimates than those derived by traditional approaches. This method has been successfully evaluated and is now used in cancer survival analysis for deriving more up-to-date long-term survival estimates. In this paper, using data on graft and patient survival from the database of the Collaborative Transplant Study, we compare the performance of the period analysis method with traditional analysis methods for deriving up-to-date long-term survival estimates in organ transplantation. Because of better timeliness obtainable with the use of period analysis, in instances when survival changes over time (which have been characteristic of the field of transplantation medicine in recent decades), substantially better performance of period analysis over traditional methods of survival analysis can be expected.

MATERIALS AND METHODS

Data sources

We used the database of the Collaborative Transplant Study, a voluntary collaborative effort of more than 400 transplant centers from 43 countries all over the world. At the time of analysis, the study’s data set contained
transplant and follow-up information on over 400,000 solid organ transplantations performed between 1985 and 2007. To analyze graft survival, we selected kidney transplants, orthotopic heart transplants, and liver transplants from deceased donors (available from 1988 onward). For kidney transplants, patient survival estimates were also considered. All analyses were restricted to first transplants only. Patient death with a functioning graft was considered a graft failure; to calculate patient survival estimates, patients were followed up until the last available information on vital status.

Traditional versus period survival analysis approach

Cumulative survival estimates are obtained in actuarial analysis as the product of interval-specific mortality proportions, and, when data sets with continuously updated baseline and follow-up data are analyzed, there exist different approaches to utilizing the available survival proportions to calculate cumulative survival estimates. For survival monitoring in transplantation, cohort-based approaches have been applied traditionally, with 2 variants: survival estimates were based on the survival experience of past cohorts with a full follow-up only (classic cohort analysis) (12) or, in addition to the former, on the survival experience of more recent cohorts with less than full follow-up as well (complete analysis) (13). In contrast, period estimates are based on survival experience from a most recent calendar period only, which are obtained through left truncation of the follow-up of contributing past cohorts in addition to the usual right censoring at the end (10, 11). The approach is, in principle, alike to the one used in demography to calculate the life expectancy of a newborn on the basis of age-specific conditional survival probabilities observed in current generations in some very recent calendar year.

In the field of population-based cancer survival analysis, period analysis was proposed for improving the timeliness of survival monitoring in 1996 (10), and its ability to provide more up-to-date long-term survival estimates—that is, in times when survival changes, better survival predictions for most recently treated patients than survival estimates derivable by traditional analysis approaches at the same time—has been repeatedly demonstrated by extensive empirical evaluations (11, 14–19). The method is currently applied by, among others, large international cancer survival studies (20, 21) as well as the Surveillance, Epidemiology, and End Results (SEER) Program (22).

Statistical analysis

Survival estimates should provide the most relevant information by reflecting the prognosis of the most recent transplants possible (13). Defining the latter as transplants carried out in the 3 most recent years included in the data set of each evaluation round, we evaluate the timeliness of the 3 estimates (cohort, complete, period) derivable on the basis of that data set by comparing them with the (later-observed) survival of the cohort receiving transplants in those 3 most recent years. The years 1990–1992 represent the first interval for which data in the Collaborative Transplant Study first made it possible to derive 5-year survival estimates by traditional approaches as well as the period analysis approach (for liver transplants, the first interval was 1993–1995 because data were available from 1988 onward only).

Figure 1 shows the data utilization approaches for the first evaluation round: when transplant and follow-up data to the end of 1992 were considered, a most recent derivable cohort estimate pertains to patients and organs transplanted in 1985–1987 (within solid straight lines), a most recent derivable complete estimate is based on patients and organs transplanted in 1985–1992 (entire shaded area), while a period estimate utilizes the survival experience of patients and organs transplanted between 1985 and 1992 but with the survival function based on survival experience during 1990–1992 only (area within the dotted lines). The estimates derived by the 3 approaches were then compared with the later-observed survival of patients and organs transplanted in 1990–1992 and followed up until 1997 (within dashed lines). Thereafter, the analysis framework shown in Figure 1 was moved ahead 1 year, and the same 3
estimates, as well as the later-observed survival (now for the cohort of 1991–1993), were derived again. This procedure was repeated until the cohort of 2000–2002 was reached, which was the last cohort for which the later-observed 5-year survival could be derived, altogether providing 11 rounds for evaluation. Using the age-specific estimates calculated by the 3 methods in each evaluation round, we also calculated overall estimates of 5-year survival, adjusted to the organ-specific age distribution in 2000–2002.

RESULTS

Table 1 presents overall and age-specific numbers of first kidney, heart, and liver transplants included in the evaluation from the Collaborative Transplant Study database between 1985 and 2002, as well as the period-specific age distribution of registered transplants from the first and last evaluation period included in this analysis. Recipients in the age group 40–49 years made up the largest proportion of recipients of kidney transplants from deceased donors as well as of recipients of heart and liver transplants in both the 1990–1992 and 2000–2002 periods. Recipients of kidney transplants from living donors were mostly between 18 and 49 years of age. For all types of transplants, the proportion of recipients older than 60 years of age rose notably between 1985 and 2002, as well as the period-specific age distribution of registered transplants from the first and last evaluation period included in this analysis. Recipients in the age group 40–49 years made up the largest proportion of recipients of kidney transplants from deceased donors as well as of recipients of heart and liver transplants in both the 1990–1992 and 2000–2002 periods. Recipients of kidney transplants from living donors were mostly between 18 and 49 years of age. For all types of transplants, the proportion of recipients older than 60 years of age rose notably from 1990–1992 to 2000–2002.

Table 2 presents detailed results of the first and last rounds of the evaluation for kidney graft survival as an example. Detailed results of all evaluation rounds for the evaluated organ types and survival measures are available as online supplementary tables (Web Table 1 and Web Table 2 for kidney graft and kidney patient survival, and Web Table 3 and Web Table 4 for heart and liver graft survival, respectively. These 4 Web tables are posted on the Journal’s Web site (http://aje.oupjournals.org/)).

Results for the evaluation period 1990–1992 show that 5-year survival for kidney grafts transplanted to recipients aged 0–17 years rose from 55.0% to 62.6% between cohorts receiving transplants in 1985–1987 and cohorts receiving transplants in 1990–1992 (as shown by the difference between the cohort estimate and the later-observed survival derived in this evaluation round). When follow-up data until the end of 1992 were used, the most up-to-date estimates of 5-year survival were 55.0% by cohort, 56.0% by complete, and 60.0% by period analysis. In other words, the period estimate for 1990–1992 was much closer to the later-observed survival of transplants carried
out in those calendar years than estimates derived by the other 2 approaches.

Analogously, between 1985–1987 and 1990–1992, marked rises were seen in survival for kidney grafts independently of donor type in all age groups, except for grafts from living donors in the age group 18–29 years. Overall, estimates derived by period analysis provided a best estimate of the later-observed survival in 10 of 12 occasions in the first evaluation period, while a best estimate was derived 2 and 0 times by cohort and complete analysis, respectively.

With regard to the evaluation period 2000–2002 (in which the cohort estimates pertain to transplants from 1995 to 1997), substantial rises were seen in kidney graft survival in all age groups independently of donor type (deceased or living) between 1995–1997 and 2000–2002. Compared with estimates by other analysis approaches, period analysis came much closer to the later-observed survival on all occasions.

Figure 2 provides plots of age-adjusted 5-year survival estimates calculated by the 3 evaluated methods and the later-observed survival in each evaluation round for the 6 transplant survival measures included. All 6 panels of the figure document an ongoing rise in actual 5-year survival throughout the examined calendar periods. Apart from the 1995–1997 evaluation round of kidney patient survival analysis (deceased donor) and of the 1990–1992 evaluation round of kidney patient survival analysis (living donor), in which all 3 estimates essentially

### Table 2. Survival Estimates by Cohort, Complete, and Period Analysis and the Differences Between These Estimates and the Later-Observed Actual 5-Year Survival for Kidney Grafts, Collaborative Transplant Study Database

<table>
<thead>
<tr>
<th>Evaluation Period, Donor Type, and Age Group, years</th>
<th>5-Year Survival Estimate</th>
<th>Difference From Actual</th>
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<td>Period</td>
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Abbreviations: PE, point estimate; SE, standard error.

* The best performing methods.
performed equally well, period estimates of 5-year survival provided a consistently better prediction of later-observed survival than estimates derived by cohort or complete analysis.

Table 3 presents the age-specific and total numbers of best predictions provided by the 3 evaluated methods in all 11 evaluation rounds for kidney and heart transplants and all 8 evaluation rounds for liver grafts. Overall, among the 378 age-specific, later-observed survival estimates included in this evaluation, period analysis provided a best prediction 344 times (91%) compared with 23 and 24 times by cohort and complete analysis, respectively. In the individual organ-specific analyses, the overall proportion of best estimates provided by period analysis ranged from 83% (heart graft survival) to 100% (kidney graft survival, deceased donors).

Figure 2. Age-adjusted, later-observed, actual 5-year survival (solid line) and estimates derivable by cohort (dashed line), complete (dashed-dotted-dashed line), and period (dotted line) analysis in corresponding evaluation rounds. Shown are results for kidney graft survival, deceased (A) and living (B) donor; kidney patient survival, deceased (C) and living (D) donor; and liver (E) and heart (F) graft survival. For liver grafts, analysis started in 1993-1995 because data were available from 1988 onward only, Collaborative Transplant Study Database.
DISCUSSION

The results of this empirical evaluation demonstrate that estimates derived by period analysis provide, across age groups and transplant survival measures, and in the overwhelming majority of historical periods analyzed herein, a better prediction of the later-observed survival of transplanted grafts and patients than estimates derivable at the same time by traditional analysis approaches. This result is not surprising: the database for deriving a classic cohort estimate has nothing in common with the underlying data set that provides the base for deriving the later-observed survival, that is, a truly most recent cohort (Figure 1). On the other hand, although both complete and period analyses include data from most recent cohorts, the large amount of additional older data included in complete analysis makes the latter estimates inevitably less up-to-date. With period analysis, underlying survival experience is closest in time to that applicable to the later-observed survival. Consequently, numeric differences between the estimates derived by the 3 examined approaches are explained generally by an ongoing underlying (in this case, upward) trend in survival in the examined years—in the absence of any change in survival, all 3 approaches would have provided numerically similar results.

The interpretation of cohort, complete, and period estimates is different. Taking the example of the last evaluation round, the cohort estimate (based on transplants performed between 1995 and 2002) quantifies the actually observed overall survival experience of all cohorts between these years up to 2002, includes more up-to-date survival experience than the cohort estimate, and may be interpreted as the expected survival of the cohort of 1995–2002, under the assumption that the interval-specific survival proportions seen for this cohort until the end of the follow-up (2007) will be on average the same as the average interval-specific survival proportions already observed during the partial follow-up. A period estimate for 2000–2002 can be interpreted as the expected survival of the cohort of 2000–2002, under the assumption that the conditional survival probabilities for various years after transplantation observed during this period will remain unchanged. If those conditional survival probabilities yet unknown at the time of analysis further increase over time, which may often be expected because of progress in medical care, period as well as complete estimates may likely turn out to be conservative, that is, be lower than the later-observed survival.

Concern may arise that period estimates might unduly overestimate the later-observed survival, which is theoretically possible if only a postponement rather than a reduction in graft failures/patient deaths within 5 years of transplantation occurs (i.e., in the calendar years for which a period estimate is derived, interval-specific survival proportions in the already observed part of follow-up are improved compared with those seen in preceding calendar years but are worsened for the yet-unobserved part of follow-up). However, as Figure 2 indicates, period estimates remained consistently below the later-observed survival of grafts and patients.
patients in this evaluation, providing empirical evidence that the above scenario is probably rare in practice. Both this empirical finding and the assumption used to interpret the period estimates suggest that period estimates can be considered usually conservative for the later-observed survival.

The results of the empirical evaluation provided here are remarkably consistent with results of evaluations of the period analysis method in cancer survival studies (15, 16, 18, 19). After the demonstration of its advantages in the cancer field, period analysis has been widely adopted in recent years as the method of choice for deriving up-to-date long-term survival estimates (21, 24–26). Our analysis suggests that application of this approach might be equally useful in up-to-date monitoring of long-term graft and patient survival in solid organ transplantation.

In general, the survival analysis approaches applied in this evaluation may be considered special cases of a more general and flexible modeling approach. In the cancer survival analysis field, various modeling approaches have been explored (27–31) and shown to be useful. The evaluation of modeling approaches in transplant survival analysis and the use of period analysis in other fields should be explored in further analyses.

Several easy-to-use applications exist that may facilitate calculation of period estimates: the open source application used in this analysis is available in SAS software (23, 32) and the R environment (33). Period estimates may also be calculated with the Surveillance, Epidemiology, and End Results Programs Statistical Package for data analysis (34), as well as with the “survlt” macro written at the Mayo Clinic (Rochester, Minnesota) to analyze left-truncated data (35).

Several limitations of this work require careful consideration. The period estimates derived in this evaluation are simple descriptive survival measures, which consequently provide no information about the reasons for changes in survival. We considered 5-year survival estimates, but we were unable to consider 10-year survival estimates because the currently available time series of data did not enable systematic evaluation of a series of 10-year survival estimates. However, given the even larger time lag and the even older cohorts utilized for deriving a cohort or complete estimate of 10-year survival, the advantages of period analysis can be expected to be at least similar to or even larger than for the 5-year estimate (14), as well as for the analysis of even longer-term survival (36–38).

In conclusion, this empirical evaluation provides evidence that period analysis can improve the timeliness of survival monitoring in solid organ transplantation. When progress in the field occurs rapidly, timely disclosure of progress in survival is particularly important for clinicians, patients, and policy makers alike. Period analysis may therefore provide a useful additional tool for supplying more up-to-date long-term survival estimates in solid organ transplantation, and its use may be encouraged in studies for such a purpose.

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