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REVIEW

Competing Risks Analysis of Kidney Transplant Waitlist Outcomes: Two Important Statistical Perspectives

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Modern competing risks analysis has 2 primary goals in clinical epidemiology as follows: (i) to maximize the clinician's knowledge of etiologic associations existing between potential predictor variables and various cause-specific outcomes via cause-specific hazard models, and (ii) to maximize the clinician's knowledge of noteworthy differences existing in cause-specific patient risk via cause-specific subdistribution hazard models (cumulative incidence functions [CIFs]). A perfect application exists in analyzing the following 4 distinct outcomes after listing for a deceased donor kidney transplant (DDKT): (i) receiving a DDKT, (ii) receiving a living donor kidney transplant (LDKT), (iii) waitlist removal due to patient mortality or a deteriorating medical condition, and (iv) waitlist removal due to other reasons. It is important to realize that obtaining a complete understanding of subdistribution hazard ratios (HRs) is simply not possible without first having knowledge of the multivariable relationships existing between the potential predictor variables and the cause-specific hazards (perspective #1), because the cause-specific hazards form the "building blocks" of CIFs. In addition, though we believe that a worthy and practical alternative to estimating the median waiting-time-to DDKT is to ask, "what is the conditional probability of the patient receiving a DDKT, given that he or she would not previously experience one of the competing events (known as the cause-specific conditional failure probability)," only an appropriate estimator of this conditional type of cumulative incidence should be used (perspective #2). One suggested estimator, the well-known "one minus Kaplan-Meier" approach (censoring competing events), simply does not represent any probability in the presence of competing risks and will almost always produce biased estimates (thus, it should never be used).

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Modern competing risks analysis is a powerful statistical tool which now has a long history in the biostatistics literature.[1-9] Its application to clinical epidemiology has 2 primary goals as follows: (i) to maximize the clinician's knowledge of etiologic associations existing between potential predictor variables and various cause-specific outcomes via cause-specific hazard models, and (ii) to maximize the clinician's knowledge of noteworthy differences existing in cause-specific patient risk via cause-specific subdistribution hazard models, that is, CIFs.[10-13] However, a clear picture of the results obtained by such an analysis should be provided, including the use of proper estimators; otherwise, misleading interpretations can be drawn.

A perfect application of modern competing risks methodology exists in analyzing kidney transplant waitlist outcomes following listing for a DDKT. Specifically, once a patient has been waitlisted, the following 4 distinct cause-specific outcomes exist: (i) receiving a DDKT, (ii) receiving an LDKT, (iii) waitlist removal due to patient mortality or a deteriorating medical condition, and (iv) waitlist removal due to other reasons.[14] In some analyses, patient mortality is considered as a distinct outcome, whereas waitlist removal due to a deteriorating medical condition and other reasons are combined as one outcome.[15,16] In other analyses, patients who receive an LDKT are treated as censored observations.[17]

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Although the recent mini-review by Sapir-Pichhadze *et al.*[12] offers insight into understanding how competing risks methodology can be applied to the analysis of kidney transplant waitlist outcomes, their report does not provide full clarity. For example, Sapir-Pichhadze *et al.*[12] conclude that, "study questions focused on etiologic associations are better addressed using cause-specific hazard models, whereas studies concerned with the prediction of an individual patient's risk and those informing resource allocation are better analyzed using subdistribution hazard models." What is omitted from this statement is the fact that obtaining a full interpretation of subdistribution HRs is simply not possible without first having knowledge of the multivariable relationships existing between the potential predictor variables and the cause-specific hazards.[4] From our perspective, tests of etiologic associations via cause-specific hazard models can be performed without the consideration of subdistribution hazard models; however, if subdistribution hazard models are utilized for investigating cause-specific patient risk, then a full interpretation of the subdistribution HRs would still require knowledge of the cause-specific HRs.

In the recent report by Stewart *et al.*,[16] the estimated probabilities of experiencing one of the competing causes (LDKT, waitlist mortality, and other waitlist removal) were not negligible; therefore, the estimated probability of ever receiving a DDKT did not come close to reaching 50%. Stewart *et al.*[16] investigated an alternative way to estimate the median waiting-time-to DDKT by making a worthy (and very practical) argument that the patient would want to know, "what is his/her probability of receiving a DDKT, given that he/she would not previously experience one of the competing events." This alternative approach to estimating cumulative incidence is known in the biostatistics literature as the cause-specific conditional failure probability (i.e., conditional cumulative incidence).[8,9] From our perspective, however, Stewart *et al.*[16] chose to use an inappropriate estimator.

In this review, we offer 2 important statistical perspectives regarding the analysis of "kidney transplant waitlist outcomes" data. First (perspective #1), we plan to demonstrate that no matter what the primary study goal is, the most important results to obtain first are the HRs obtained from cause-specific hazard rate modeling. These HRs essentially form the building blocks for determining the subdistribution HRs, because cumulative incidence (and conditional cumulative incidence) are functionals of the cause-specific hazards.[2-5,7,18-21] Obtaining a complete understanding of the subdistribution HRs is simply not possible without first having knowledge of the cause-specific HRs. Second (perspective #2), though we agree fully with Stewart *et al.*[16] that it is a worthy goal to consider nonparametric estimation of conditional cumulative incidence (i.e., cumulative incidence for a particular cause conditional on not previously failing from any of the competing causes), proper formulation exists and should be used. The "one minus Kaplan-Meier" approach taken by Stewart *et al.*,[16] which treats competing risks as censored observations, simply does not represent any type of probability in the presence of competing risks (empirically or theoretically) and will almost always provide biased estimates.

Statistical Methods: Modern Competing Risks Formulas and Heuristic Descriptions

Consider 2 random variables T and K, where T denotes the time to failure (from any cause), and K denotes the cause of failure (from one of c distinct competing causes). The cause-specific hazard rate (for cause k) at time t can be written as the instantaneous rate of failure from cause k, i.e.,

$$\lambda_k(t) = \text{limit}_{\Delta t \to 0} \{\Pr[t \le T < t + \Delta t, K = k \mid T \ge t] / \Delta t\}, \quad (1)$$

k = 1, …, c. The probability portion of the cause-specific hazard can be thought of as approximating the conditional probability of failing from cause k within the infinitesimal interval (t, t+Δt], given that the individual is failure-free at time t. In analyzing the cause-specific hazard, patients who fail from the cause of interest are treated as events, and patients who fail from competing causes are treated as censored observations. The cause-specific hazard rate is completely estimable from the data at hand, and no assumption about independence among competing causes of failure is made when estimating the cause-specific hazards.[2,4,7,18–21]

The cumulative hazard for cause k at time t is simply the integral of the cause-specific hazard (for cause k) over the time interval (0, t], that is,

$$\wedge_k(t) = \int \lambda_k(u)\, du \Big\}, \quad (2)$$

where the integral is from 0 to t, k = 1, …, c. The exponential function of the negative of the cumulative hazard for cause k at time t, denoted here as $S_k(t)$, is another relevant statistical term, which has a 1-to-1 mathematical relationship with the cause-specific cumulative hazard,

$$S_k(t) = \exp\{-\wedge_k(t)\}, \quad (3)$$

k = 1, …, c, and whose product over the c causes of failure equals the overall probability of survival (from all causes) beyond time t, that is,

$$S(t) = \Pr(T > t) = \exp\left\{ - \sum\nolimits_k \wedge_k (t) \right\}. \quad (4)$$

Of note, in the presence of competing risks, $S_k(t)$ has no probabilistic meaning.

Now, for an individual to fail from cause k at time t, that individual must first survive from all causes (failure-free) up to time t. Therefore, the probability of failing from cause k within an infinitesimally small interval around time t is essentially equal to the probability of surviving from all causes up until time t multiplied by the cause-specific hazard rate for cause k at time t. The sum of these discrete probabilities (or integral in the continuous case) from time 0 up to a certain time t is equal to the CIF for cause k at time t, that is,

$$CIF_k(t) = \int \lambda_k(u) \cdot S(u)\, du, = \int \lambda_k(u) \cdot \exp\left\{ - \left(\sum\nolimits_j \wedge_j(u) \right\} du, \quad (5)$$

where j = 1, …, c, and the integral is from 0 to t. The CIF for cause k at time t is also known as the subdistribution function for cause k at time t, and its hazard rate is known as the subdistribution hazard rate for cause k at time t (formula not shown).[6] The CIF for cause k at time t, $CIF_k(t)$, represents the cumulative probability that an individual will fail from a particular cause k during the time interval (0, t] (in the presence of the other competing causes of failure), k = 1, …, c. As can be seen from equation (5), $CIF_k(t)$ is a mathematical function of all the cause-specific hazards, not solely a function of the cause-specific hazard rate for cause k. Thus, identification of the functional form of the CIF for a particular cause requires knowing the functional form of each of the cause-specific hazards, that is, the cause-specific hazards form the "building blocks" of the CIF.[2-4,7,18-21]

If, for example, the CIF for cause k at time t was higher for one patient subgroup versus another, one would not necessarily understand why it is so. It could be directly due to that patient subgroup having a higher hazard rate for cause k, or it could be indirectly due to that subgroup having a lower cause-specific hazard for one or more of the competing causes, that is, the probability of surviving to time t (and thus, being at risk at time t) would be higher for that subgroup, indirectly causing more events from cause k to occur (even if the hazard rate for cause k was the same for the 2 patient subgroups). Without knowledge of the relationships existing between patient subgroups and the cause-specific hazards (i.e., without knowing the cause-specific HRs), clear interpretations of the CIFs are simply not possible.[2-4,7,18-21]

The conditional CIF for cause k at time t, denoted here as conditional $CIF_k(t)$ (also known as the conditional probability function for cause k at time t), is defined as the CIF for cause k at time t divided by 1 − the sum of the CIFs for each of the competing causes (all causes other than k) at time t, that is,

$$\text{Conditional}\, CIF_k(t) = CIF_k(t) \Big/ \left(1 - \sum\nolimits_{oth \neq k} CIF_{oth}[t] \right), \quad (6)$$

for k = 1, …, c. The conditional $CIF_k(t)$ therefore represents the probability of failing from cause k by time t, conditional on not having previously failed from one of the competing causes, k = 1, …, c. Of note, it can easily be shown[22] that the following important mathematical relationship exists:

$$CIF_k(t) \leq 1 - S_k(t) \leq \text{Conditional}\, CIF_k(t), \text{for k} = 1, \ldots, c. \quad (7)$$

Finally, without providing details, even when considering the (older) latent failure times approach to the analysis of competing risks, from our perspective, "in the absence of prior failures from other causes" should require a conditional probability statement, yielding the same conditional $CIF_k(t)$ formulation as shown in equation (6), not $1 - S_k(t)$. From our perspective, the marginal distribution for cause k (treating cause k as a single cause without consideration of the other causes), which yields $1 - S_k(t)$, does not represent "in the absence of prior failures from other causes;" only a conditional probability statement such as that shown in equation (6) would be able to do so.[18]

Statistical Methods: Nonparametric Estimates

Formulas for nonparametric estimation of the cause-specific cumulative hazard (Nelson-Aalen estimator) and CIF are well known and will not be shown here.[2-4,7-9,20,21,23] It should be noted that the KM estimator for cause k, whereby events are determined by individuals who fail from the cause of interest, and competing causes of failure are treated as censored observations, is the nonparametric estimator of the exponent of the negative of the cause-specific cumulative hazard ($S_k(t)$, as described above in equation (3)). As evidenced by equations (2) and (3) above, a 1-to-1 mathematical relationship essentially exists between the KM (or 1 − KM) estimator for cause k and the nonparametric Nelson-Aalen cumulative hazard estimator for cause k[2-4,7-9,18,19,21]; thus, graphical display of group differences in the cause-specific hazard rate for cause k can be properly displayed via Nelson-Aalen, KM, or 1 − KM estimates for cause k.

Table 1. Three examples comparing multivariable Cox model results of testing a specific prognostic factor's effect on various cause-specific versus subdistribution hazards following waitlisting for a deceased donor kidney transplant

First example: adjusted hazard ratios [95% confidence Intervals] for the effects of PRA 80% to 100% (vs. PRA 0% as the Reference) – Sapir-Pichhadze *et al.*[12]

Cause-specific hazard rate of mortality while waitlisted	Cause-specific hazard rate of being transplanted while waitlisted	Subdistribution hazard rate of mortality while waitlisted
1.20 [1.14–1.28]	0.59 [0.57–0.62]	1.52 [1.44–1.62]

Second example: adjusted hazard ratios [95% confidence intervals] for the effects of minority race (vs. White race as the reference) - Sapir-Pichhadze *et al.*[12]

Candidate race	Cause-specific hazard rate of mortality while waitlisted	Subdistribution hazard rate of mortality while waitlisted
Black	0.67 [0.65–0.69]	0.96 [0.94–0.99]
Hispanic	0.56 [0.54–0.58]	0.84 [0.81–0.86]
Asian	0.51 [0.48–0.54]	0.81 [0.77–0.85]
Other	0.59 [0.54–0.64]	0.83 [0.77–0.90]

Third example: adjusted hazard ratios [95% confidence intervals] for the effects of longer dialysis duration at listing (vs. 0 duration as the reference) - Hart *et al.*[14]

Cause-specific hazard rate of receiving a DDKT while waitlisted	Cause-specific hazard rate of receiving a LDKT while waitlisted	Cause-specific hazard rate of death or deteriorating condition while waitlisted	Cause-specific hazard rate of waitlist removal for another reason
Nonsignificant	Nonsignificant	1.18 [1.17–1.19]	Nonsignificant

DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant; PRA, panel reactive body.

However, it must be emphasized that in the presence of competing risks, the KM and 1 − KM estimators for cause k have no probabilistic meaning.

The nonparametric estimator of the conditional CIF at time t is simply obtained by dividing the nonparametric estimator of the CIF for cause k at time t by 1 − the sum of the nonparametric cumulative incidence estimators for each of the competing causes (all causes other than k) at time t. As we will demonstrate below, given the inequalities shown in equation (7) for $1\text{-}S_k(t)$ in relation to both $CIF_k(t)$ and conditional $CIF_k(t)$, from our perspective, the 1 − KM estimator for cause k should never be used for nonparametric estimation of any probability in the presence of competing risks.

Statistical Methods: Multivariable Cox Models

Determining multivariable predictors for each of the cause-specific hazards can easily be performed via Cox's (semiparametric) model, whereby in analyzing the hazard rate for cause k, individuals who fail of competing causes are treated as censored observations.[1–3,7,23] Use of Cox's model for determining multivariable predictors of the CIF (via its subdistribution hazard) has also been developed.[6] Here, when analyzing multivariable predictors of the subdistribution hazard for cause k (i.e., hazard rate of $CIF_k[t]$), the risk set at a given time t includes the usual risk set of failure-free individuals immediately before time t along with all individuals who have previously failed of causes other than k.[7]

Perspective #1: Always Include an Analysis of the Cause-Specific Hazards

The results by Sapir-Pichhadze *et al.*[12] highlight the importance of always analyzing the cause-specific hazards, even if the primary goal is to estimate the cumulative incidence of cause-specific events for various patient subgroups. In that report,[12] 161,308 adults who were listed in the United States (via the United Network for Organ Sharing) for a first DDKT between January 1, 2000 and October 1, 2009 (last follow-up date: November 30, 2010) were analyzed. The study purpose was to assess the relationship between time-fixed panel reactive antibody (PRA) category (measured at waitlist activation) and the following 4 primary outcomes via Cox proportional hazards models: (i) the hazard rate of all-cause mortality while on the waitlist, (ii) the hazard rate of being transplanted while on the waitlist, (iii) the subdistribution hazard rate of all-cause mortality (with transplantation as a competing risk) while on the waitlist, and (iv) the hazard rate of a composite end point defined as removal from the waiting list due to mortality or transplantation.

Adjusted HRs (aHRs) along with 95% confidence intervals (CIs) comparing PRA 80% to 100% versus PRA 0% (as shown in Table 1 of Sapir-Pichhadze *et al.*[12]) for the 4 primary outcomes were as follows: 1.20 [1.14–1.28], 0.59 [0.57–0.62], 1.52 [1.44–1.62], and 0.74 [0.71–0.77], respectively (Table 1, first example). Although the significant aHR of 1.52 for the subdistribution hazard of mortality while on the waitlist indicates that a high PRA was associated with a significantly higher probability of dying while on the waitlist (and a relatively higher aHR in comparison with its effect on the hazard rate of waitlist mortality), this subdistribution hazard or cumulative incidence finding does not identify the exact reason(s) for this higher probability; only results of the cause-specific hazard rate analysis would be able to do so. Specifically, the significant aHRs obtained from the cause-specific hazard rate analysis, 1.20 for waitlist

Table 2. Three "eyeballed" data sets from 2 reports

First data set: "eyeballed" cumulative incidence estimates for the whole cohort in Stewart *et al.*[16]

Year since listing	Received a DDKT while waitlisted	Received an LDKT while waitlisted	Death while waitlisted	Waitlist removal for other reasons
1	0.15	0.06	0.03	0.12
2	0.21	0.12	0.09	0.16
3	0.28	0.17	0.12	0.17
4	0.31	0.20	0.14	0.17
5	0.33	0.22	0.17	0.17
6	0.34	0.23	0.18	0.18

Second data set: "eyeballed" cause-specific Kaplan-Meier estimates for the whole cohort in Hart *et al.*[14]

Year since listing	Received a DDKT while waitlisted	Received an LDKT while waitlisted	Death or waitlist removal for being too sick	Waitlist removal for other reasons
1	0.91	0.88	0.96	0.98
2	0.81	0.83	0.89	0.96
3	0.68	0.81	0.82	0.92
4	0.59	0.79	0.74	0.88
5	0.50	0.78	0.66	0.84
6	0.45	0.78	0.57	0.79
7	0.41	0.78	0.50	0.74
8	0.38	0.78	0.44	0.68
9	0.37	0.78	0.38	0.64
10	0.36	0.77	0.33	0.57
11	0.35	0.77	0.28	0.51
12	0.34	0.77	0.25	0.46

Third data set: "eyeballed" cumulative incidence estimates for the whole cohort in Hart *et al.*[14]

Year since listing	Received a DDKT while waitlisted	Received an LDKT while waitlisted	Death or waitlist removal for being too sick	Waitlist removal for other reasons
1	0.09	0.11	0.04	0.02
2	0.17	0.13	0.08	0.03
3	0.27	0.13	0.13	0.06
4	0.30	0.16	0.18	0.06
5	0.34	0.16	0.19	0.07
6	0.37	0.16	0.22	0.08
7	0.38	0.17	0.24	0.08
8	0.40	0.17	0.24	0.09
9	0.41	0.17	0.24	0.10
10	0.42	0.17	0.25	0.10
11	0.43	0.17	0.25	0.11
12	0.44	0.17	0.26	0.12

DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant.

mortality and 0.59 for being transplanted on the waiting list, establish 2 compounding reasons for high PRA implying a significantly higher probability of waitlist mortality (vs. PRA 0%). First, patients with a high PRA had a significantly higher hazard rate of mortality while waitlisted, which directly leads to a higher probability of mortality. Second, the hazard rate of receiving a transplant while waitlisted was significantly lower for high PRA, implying that patients with a high PRA would remain at risk of death for longer periods of time while waitlisted, also leading indirectly to a greater proportion of such patients dying while waitlisted (thus, a compounded effect of high PRA on the incidence of waitlist mortality). These more detailed interpretations would not be known if a cause-specific hazard rate analysis had not been performed.

As a second example showing the importance of always analyzing the cause-specific hazards, consider the impact of race as reported by Sapir-Pichhadze *et al.*[12] As shown in Table 2 of their report, the aHRs and 95% CIs for Black, Hispanic, Asian, and Other races versus White race for the cause-specific hazard rate of mortality while waitlisted were 0.67 [0.65–0.69], 0.56 [0.54–0.58], 0.51 [0.48–0.54], and 0.59 [0.54–0.64], respectively (Table 1, second example). For the subdisribution hazard rate of mortality while waitlisted, the effects of race were clearly attenuated, with aHRs and 95% CIs for Black, Hispanic, Asian, and Other races versus White race being 0.96 [0.94–0.99], 0.84 [0.81–0.86], 0.81 [0.77–0.85], and 0.83 [0.77–0.90], respectively. If the only outcome analyzed had been the subdistribution hazard rate of waitlist mortality, then one might simply conclude that minority races have a modestly more favorable probability of death while waitlisted (compared to Whites). However, a complete understanding is not possible without also knowing the exact relationships of race with the cause-specific hazards. Clearly, as Sapir-Pichhadze *et al.*[12] show, the hazard rates of mortality while waitlisted are much more favorable for the minority races in comparison with Whites. Therefore, what is the explanation for this attenuation of the race effect on the incidence of mortality while waitlisted? Whereas Sapir-Pichhadze *et al.*[12] do not report it, other studies have previously shown that the minority races are also associated with significantly lower hazard rates of transplantation while waitlisted (in comparison with Whites),[24–27] indicating that the minority races remain at risk of dying for longer time periods while waitlisted, leading indirectly to relatively more minority patients dying while waitlisted, counteracting to a large degree their actually significantly more favorable hazard rates of mortality while waitlisted.

In the report by Hart *et al.*,[14] 163,636 adults who were listed in the United States for a first DDKT and were on the waitlist between January 1, 2007 and December 31, 2011 (last follow-up date) were analyzed. Patients who were removed from the waitlist for any reason, including transplant before January 1, 2007, were excluded to allow for a more contemporary sample. The following 4 distinct outcomes were analyzed: (i) receiving a DDKT, (ii) receiving a LDKT, (iii) waitlist removal due to patient mortality or a deteriorating medical condition, and (iv) waitlist removal due to other reasons. As a third example highlighting the importance of always analyzing the cause-specific hazards, longer dialysis duration at listing was

reported by Hart *et al.*[14] to be associated with a significantly higher hazard rate of death or being too sick, with aHR and 95% confidence interval reported in their Table 3 as 1.18 [1.17–1.19], but not with any of the other 3 cause-specific hazard rates (Table 1, third example). Thus, the cumulative incidences of receiving a DDKT, LDKT, and being removed due to other reasons would be lower for longer dialysis duration, not directly due to higher hazard rates for those causes but indirectly due to having a higher hazard of death or being too sick (i.e., fewer patients with longer dialysis duration still being at risk at a given time). Conversely, if one only knew that longer dialysis duration was associated with lower cumulative incidences of receiving DDKT, LDKT, and waitlist removal for other reasons, one would still not know why—was it directly due to patients with longer dialysis durations having lower cause-specific hazards for those 3 causes or indirectly due to those patients having a higher hazard rate of death/being too sick?

Perspective #2: Always Use Proper Nonparametric Estimation of Conditional Cumulative Incidence

As a simple example showing the inequalities in equation (7), consider 10 patients, 2 competing causes of failure, and cause 1 being of primary interest. Assume no censoring: 5 patients fail of cause 1, and 5 patients fail of cause 2. Consider case 1: all failure times for cause 1 occur after the failure times for cause 2, and case 2: all failure times for cause 1 occur before the occurrence of any cause 2 failure times. In both cases, proper nonparametric estimation of cumulative incidence and conditional cumulative incidence for cause 1 at last follow-up yields 50% and 100%, respectively. In case 1, 1 − KM for cause 1 equals 100% (double the cumulative incidence estimate, but equal to the conditional cumulative incidence estimate). In case 2, 1 − KM for cause 1 equals 50% (equal to the cumulative incidence estimate, but only one-half of the conditional cumulative incidence estimate). Thus, when failures from cause 1 all occur after failures from cause 2 have occurred (case 1), the bias in using 1 − KM for cause 1 to estimate $CIF_1(t)$ is maximized, whereas no bias exists in estimating the conditional $CIF_1(t)$. Conversely, when failures from cause 1 trend earlier so that all of them occur before any cause 2 failures (case 2), the bias in using 1 − KM for cause 1 shifts to becoming zero for estimating $CIF_1(t)$ and maximized for estimating the conditional $CIF_1(t)$.

To provide an example using clinical data, Stewart *et al.*[16] analyzed 147,769 incident DDKT candidates who were waitlisted in the United States during 2015 to 2018. In Figure 1a (and Table 2, first data set), we show the nonparametric cause-specific cumulative incidence curves for the whole cohort (based on using "eyeballed" annual values from their Supplementary Figure S2). "Eyeballed" cumulative incidence estimates at 6 years postlisting were 34% for DDKT, 23% for LDKT, 18% for waitlist mortality, and 18% for other waitlist removal. Again, Stewart *et al.*[16] made a worthy argument that alternative cumulative incidence estimates should be considered, because none of their reported cumulative incidence estimates came close to reaching 50% (i.e., median times-to-those cause-specific events could not be reported). Stewart *et al.*[16] essentially proposed estimating the probability of receiving a DDKT by t years on the waitlist, conditional on not previously being removed from the waitlist for any of the 3 competing reasons (receiving an LDKT, death while waitlisted, and waitlist removal for some other reason). Although their proposal to estimate the time-to-DDKT distribution in the absence of any previously occurring competing causes (i.e., conditional cumulative incidence for DDKT) would be a practical tool for patients to use, the problem existed in their choice of using 1 − KM. Specifically, in Figure 1b, we show proper nonparametric estimates of conditional cumulative incidence for each of the 4 causes (i.e., conditional on not previously experiencing any of the competing causes). Whereas the median waiting time-to-DDKT using 1 − KM was reported as 5.28 years in Table 1 of Stewart *et al.*,[16] in Figure 1b, we estimate the median waiting time-to-DDKT as slightly less than 3 years (i.e., 1 − KM for DDKT is distinctly lower than the conditional CIF for DDKT, reflecting the inequality as shown in equation (7)). In fact, in Figure 1b, we show that the estimated conditional cumulative incidence of receiving a DDKT was 82.9% (i.e., 34.0% / [1 − (23.0% + 18.0% + 18.0%)]) at 6 years postlisting (again, conditional on not previously experiencing one of the competing events).

As a second clinical example, consider the whole cohort as analyzed by Hart *et al.*[14] In Figure 2a (and Table 2, second data set), we show cause-specific KM curves (based on "eyeballed" annual values from their Figure 1a), and in Figure 2b (and Table 2, third data set), we show cause-specific cumulative incidence curves (based on "eyeballed" annual values from their Figure 1b). "Eyeballed" cumulative incidence estimates at 12 years postlisting were 44.0%, 17.0%, 26.0%, and 12.0% for DDKT, LDKT, waitlist mortality or removal for being too sick, and other waitlist removal, respectively. Again, with an estimated probability of receiving a DDKT by 12 years postlisting (in the presence of the 3 other competing risks) being only 44.0%, one might reasonably ask, "What is the probability of receiving a DDKT by t years postlisting, conditional on not

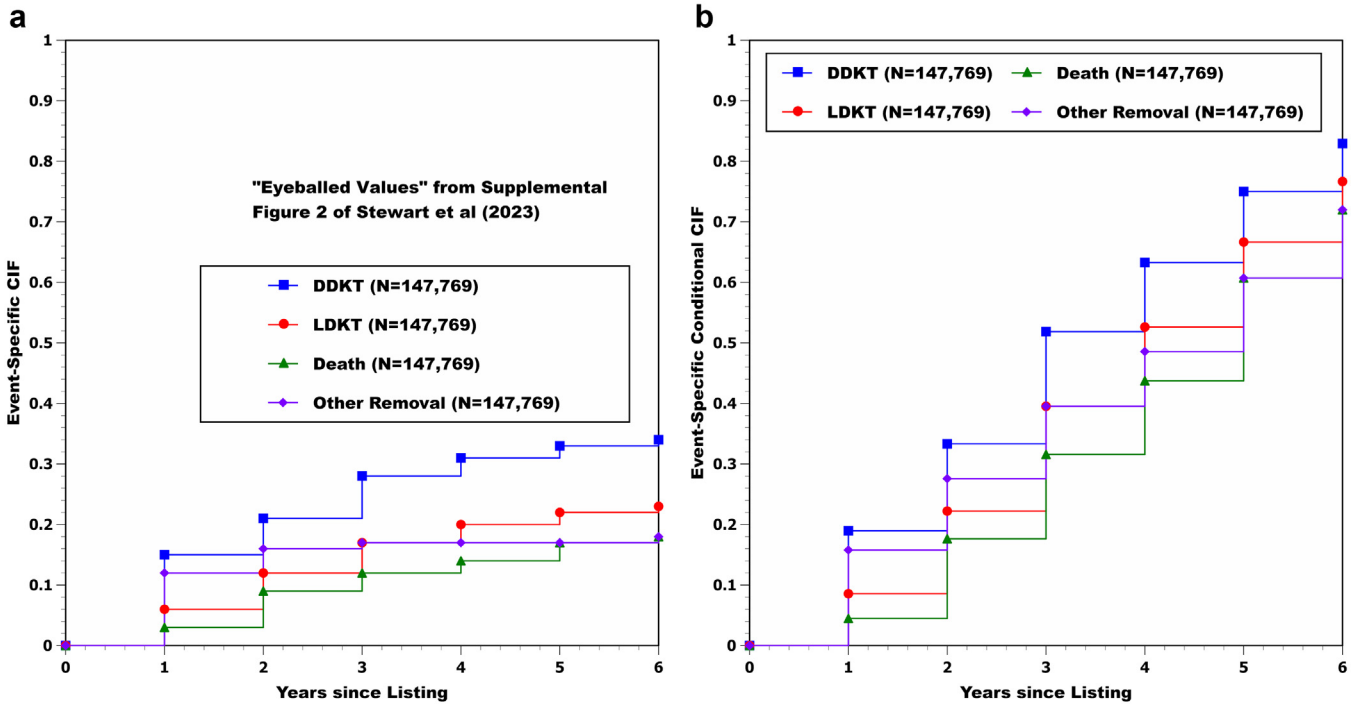

Figure 1. (a) Nonparametric cause-specific cumulative incidence curves for the whole cohort in Stewart *et al.*[16] (based on "eyeballed" annual values from their Supplementary Figure S2). (b) Proper nonparametric cause-specific conditional cumulative incidence curves for the whole cohort in Stewart *et al.*[16] CIF, cumulative incidence function; DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant.

previously experiencing any of the other 3 competing risks?" In Figure 2c, we show the 1 − KM curves for each event type, and in Figure 2d, we show the nonparametric conditional cumulative incidence curves for each event type (i.e., cumulative incidence for each event type divided by 1 − the sum of the cumulative incidences for the 3 competing event types). The estimated median waiting time-to-DDKT was approximately 5 years by 1 − KM versus slightly less than 4 years when using the proper estimator in Figure 2d. In fact, in comparing later percentiles for each of the 4 competing events, in Figures 2c and d, we show even more dramatic differences between these 2 estimators, demonstrating extensive bias in using 1 − KM (again, reflecting the inequality in equation (7)). For example, the conditional cumulative incidence estimates at 12 years postlisting are correctly shown in Figure 2d to be 97.8% (i.e., 44.0% / [1 − (17.0% + 26.0% + 12.0%)]), 94.4%, 96.3%, and 92.3% for DDKT, LDKT, waitlist mortality or removal for being too sick, and other waitlist removal, respectively, versus 66.1%, 23.0%, 75.0%, and 54.0% when using 1 − KM (Figure 2c). Overall, the cause-specific 1 − KM estimates in Figure 2c are much higher than their respective cumulative incidence estimates in Figure 2b and much lower than their respective conditional cumulative incidence estimates in Figure 2d, reflecting inequality (7) that was specified in the Methods section.

Brief Discussion

This review has presented 2 important statistical perspectives regarding competing risks analysis of kidney transplant waitlist outcomes. Our main goal was to emphasize examples over technical details; however, we also attempted to help the interested reader gain greater insight by including in the Methods section some of the most relevant statistical formulations. Included were the statistical definitions of cause-specific hazards, cause-specific cumulative hazards, exponential function of the negative cause-specific cumulative hazard (i.e., the statistical term precisely estimated by the cause-specific KM formula), the CIF (also known as the subdistribution function), and conditional cumulative incidence.

In terms of statistical perspective #1, it should be noted that if a prognosticator of interest influences only one cause-specific hazard and none of the competing hazards, then the aHRs obtained for this particular prognosticator by performing separate analyses of the cause-specific hazards and subdistribution hazards will be nearly identical. Nonetheless, even in this case, a full interpretation of the observed subdistribution aHRs will only be possible if the aHRs obtained from the cause-specific hazards analysis are included.

Additional applications of the conditional CIF outside of estimating waiting time-to-DDKT distributions clearly exist. For example, in adult kidney transplantation, we

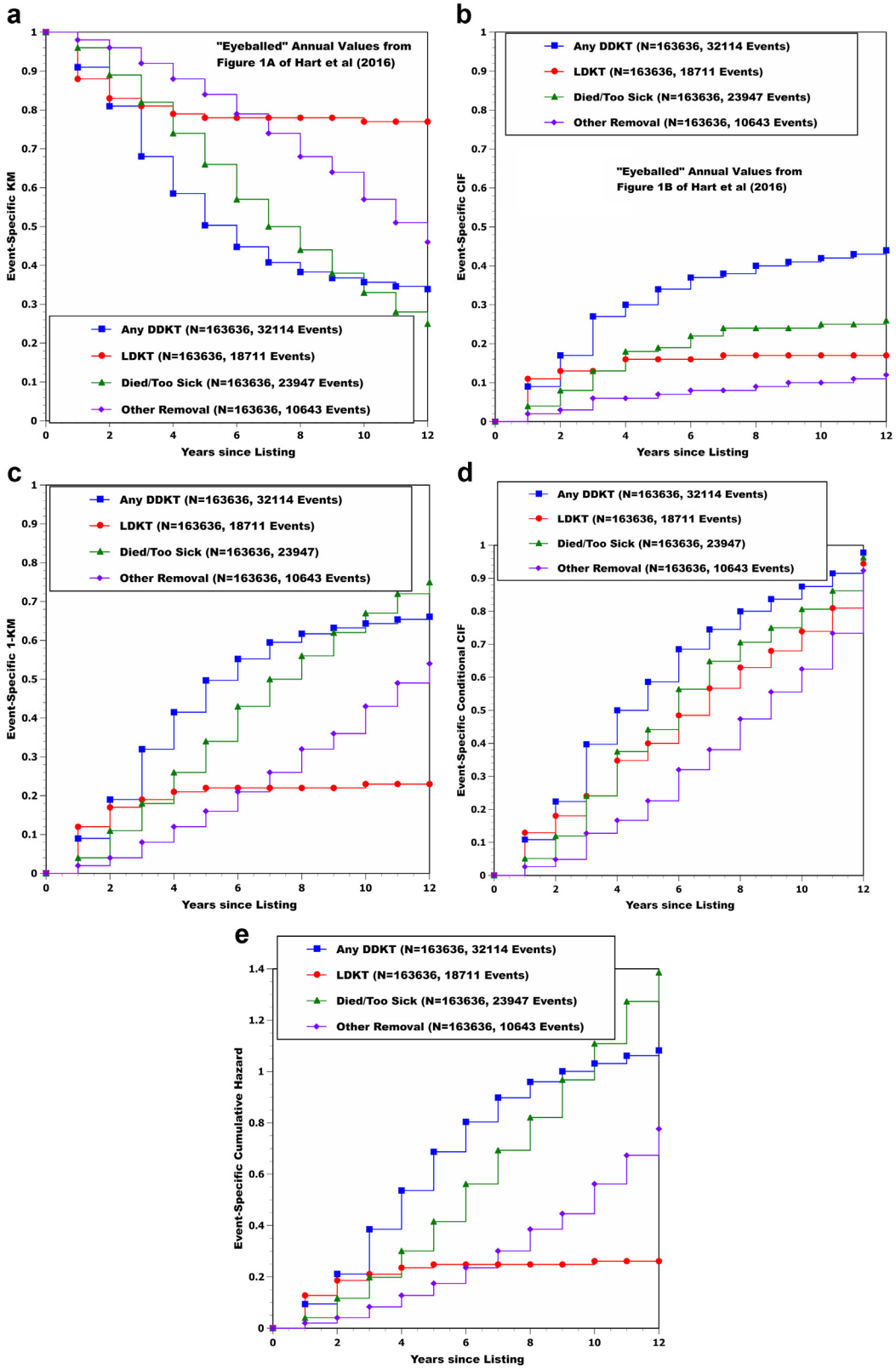

Figure 2. (a) Nonparametric cause-specific Kaplan-Meier curves for the whole cohort in Hart *et al.*[14] (based on "eyeballed" annual values from their Figure 1a). (b) Nonparametric cause-specific cumulative incidence curves for the whole cohort in Hart *et al.*[14] (based on "eyeballed" annual values from their Figure 1b). (c) Nonparametric cause-specific 1 − Kaplan-Meier curves for the whole cohort in Hart *et al.*[14] (d) Nonparametric cause-specific conditional cumulative incidence curves for the whole cohort in Hart *et al.*[14] (e) Nonparametric cause-specific cumulative hazard curves for the whole cohort in Hart *et al.*[14] CIF, cumulative incidence function; DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant.

recently reported that the estimated cumulative incidences of graft loss due to overt nonadherence and graft loss without overt nonadherence were 0.288 and 0.443 at 18 years posttransplant, respectively, among 82 patients who were aged <50 years at transplant.[28] Overall graft survival at 18 years posttransplant was estimated for this subgroup to be 0.269 (1.00 − [0.288 + 0.443]). A clinician might therefore want to suggest to a newly transplanted recipient aged <50 years that conditional on his or her not previously experiencing graft loss due to overt nonadherence (i.e., avoiding overt nonadherence), graft survival at 18 years posttransplant would be estimated to improve to 0.378, that is, 0.269 / (1.0 − 0.288).

Although formulas for estimating the standard error of the conditional CIF are known,[8,9] one limitation in using this function is that no widely accepted strategy for performing a multivariable analysis of conditional cumulative incidence currently exists in the statistical literature, although one such proposal has been reported.[29]

Lastly, as stated in the Methods section, whereas the KM and 1 − KM estimators for a particular cause k have no probabilistic meaning in the presence of competing risks, graphical display of group differences in the cause-specific hazard rate for cause k can be properly displayed via Nelson-Aalen cumulative hazard, KM, or 1 − KM estimates for cause k (due to the 1-to-1 mathematical relationships existing among these 3 formulas). Cumulative hazard plots are particularly useful for visualizing the cause-specific hazards, because the focus is simply on the slopes of the curves.[4,23,30] For example, a cause-specific cumulative hazard plot for the whole Hart *et al.*[14] cohort (computed by taking the negative of the natural logarithm of the KM values in Figure 2a) is shown in Figure 2e. The slopes show that the hazard rate of receiving a DDKT is initially increasing with time postlisting, achieves a maximum value at about 3 years postlisting, and then decreases thereafter. The hazard rate of receiving a LDKT is noticeably higher than the DDKT hazard during the first year postlisting, but then decreases quite sharply thereafter. Conversely, the hazard rate of death or being too sick appears to be at its minimum during the first post-listing year and slowly increases thereafter, surpassing the DDKT hazard rate sometime after 5 years postlisting. Very similar descriptions can also be made by visualizing the cause-specific KM (and 1 − KM) curves in Figure 2a and c; thus, KM curves may still serve a useful purpose even in the presence of competing risks.

Conclusion

Modern competing risks analysis has many important applications, including the attempt to provide a detailed understanding of cause-specific waiting time-to-event distributions and their predictors following listing for a DDKT. Often, the primary study goal will be to determine for various patient subgroups, the estimated probabilities of experiencing the following cause-specific events: (i) DDKT, (ii) LDKT, (iii) waitlist removal due to death or being too sick, and (iv) waitlist removal for other reasons. Obtaining a complete picture of the significant multivariable predictors of these outcomes requires knowing the multivariable relationships of these predictors with the cause-specific hazards (perspective #1). Furthermore, though the use of nonparametric estimates of conditional cumulative incidence may enhance the physician's ability to provide practical information to waitlisted patients, proper formulation should always be used, not 1 − KM (perspective #2).

DISCLOSURE

All the authors declared no competing interests. In addition, there were no funding sources to declare for the performance of this study.

DATA AVAILABILITY STATEMENT

Deidentified data will be made available upon request.

AUTHOR CONTRIBUTIONS

JJG designed the research/study, performed the research/study, collected data, analyzed data, and wrote the paper. GG, RV, MMT, and ELG performed the research/study. GC designed the research/study, performed the research/study, analyzed data, and wrote the paper.

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