Modeling Survival of Arteriovenous Accesses for Hemodialysis: Semiparametric versus Parametric Methods

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Background and objectives: Comparing outcomes of arteriovenous grafts and fistulas is challenging because the pathophysiology of access dysfunction and failure rate profiles differ by access type. Studying how risks vary over time may be important.

Results: The hazard for failure of fistulas and grafts declined over time, becoming proportional only after 3 months from surgery, with a graft versus fistula hazard ratio of 3.2 (95% confidence interval 1.9 to 5.3; Cox and Weibull estimation) and time ratio of 0.11 (i.e., the estimated access survival time was approximately one tenth shorter in grafts; 95% confidence interval 0.04 to 0.28; Weibull estimation only). Considering the entire observation period, grafts had slower hazard decline (P < 0.001) with shorter median survival times than fistulas (8.4 versus 38.3 months; Weibull regression only).

Conclusions: Parametric models of arteriovenous access survival may provide relevant information about temporal risk profiles and predicted survival times.


Cox regression and its extensions have become standard methods for survival analysis (1). These are semiparametric models because they estimate the covariate coefficients (i.e., risk ratios, or effects on the risk scale) without specification of the instantaneous risk (hazard) distribution. In contrast, parametric models specify also how the hazard varies over time (hazard shape or profile, or underlying hazard), which may provide insights into certain disease processes and guidance on how best to compare outcomes (2). For example, comparing outcomes of arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs) is challenging because the temporal profile of their hazard for failure differs, probably reflecting differences in the underlying pathophysiology (3–7). This hazard is highest immediately after placement of either access and then declines over time, decreasing more quickly in AVFs than in AVGs (8), with nonconstant (nonproportional) hazard ratios (HRs) (9). Cox regression can still be used in such circumstances to estimate time-dependent risk ratios, but information about the hazard profile is not directly accessible.

Parametric methods may offer other complementary information to standard survival analyses (10). Most parametric models have a time metric formulation, whereby the coefficients estimate the extent to which survival time accelerates or decelerates as the covariate varies (“time ratio”). Although the HR is a more familiar measure of association, this interpretation has an intuitive appeal for describing disease processes and intervention effects. Finally, when events repeat in the same subject (e.g., access thromboses), parametric models can help investigators study the individual tendency to fail and how this individual frailty affects the frailty of the studied population (frailty effect).

We report data from incident hemodialysis patients who were followed in centers where local policies favor AVF creation, early transition from catheters to arteriovenous accesses, and limited use of AVGs (11). We studied access survival using both Cox and parametric models. We highlight the merits of both methods, focusing on objectives that are directly addressed by parametric models (i.e., underlying hazard modeling, frailty effect, time ratio interpretation, and survival times prediction).

Materials and Methods

Study Protocol

Data for this analysis were generated from a multicenter longitudinal cohort study that examined arteriovenous access outcomes of consecutive patients who started long-term hemodialysis during a 6-year period. Consenting individuals who were older than 18 years were eligible for inclusion. Demographics and clinical and follow-up information were collected prospectively in a computerized database. The vascular access programs
at all centers share the same policies, diagnostic and intervention strategies, staff training, and education protocols (8,11).

Variables Specification and Outcomes
Access type (AVG versus AVF) was the exposure of interest. Although those who received grafts are likely biased in favor of adverse outcomes, this comparison was chosen to illustrate the options for studying survival times whose distribution may vary by level of the exposure. Possible confounders considered were age, gender, predialysis care, body mass index, hypertension, diabetes, and cardiovascular diseases (11). Dialysis status was treated as a time-varying covariate (not yet on dialysis, on dialysis using catheters or the arteriovenous access) to control for differences in access surveillance and possible impact of access use. Survival times were measured from the access surgery date. The terminating date of unassisted (intervention-free) survival times was defined by the date of a new temporary or permanent access placement for access abandonment was the terminating date of assisted survival times, independent of the number of salvage procedures to maintain patency of the same access (11).

Statistical Analysis
Risk Set Definition. Survival times were modeled as a function of the access type using semiparametric Cox proportional hazard regression and fully parametric methods. Patients were censored when switched to peritoneal dialysis, were transferred to other centers, received a kidney graft, died, or had a functioning access on the final observation date (December 31, 2002). Repeat access data were organized according to the conditional risk set from previous event stratified by access surgery number (12). This “gap time risk set” assumes that the recurrent events are of the same type, that each patient is not at risk for an additional event unless a previous event has occurred, and that the “risk clock” is reset to 0 after each failure. Correlation in the failure data was accounted for using either robust variance methods or frailty models (13).

Modeling. The choice of the parametric model that best fit the data was made by splitting time into quantiles within which failure rates were reasonably constant and modeling the effect of time (2). Crude rates and piece-wise exponential regression indicated that the hazard declined monotonically over time and the Weibull model fit the data well. As opposed to Cox regression (free from distributional assumptions), Weibull regression has one shape parameter specifying the underlying hazard (decreasing in this case), in addition to the usual scale parameters that determine the change in risk at any point in time (covariate coefficients or effects; the word “effect” is a statistical term that does not imply causation but rather refers to “association” in observational studies). The same model can be formulated in either the proportional hazard (as Cox regression) or time metric, whereby the scale effects are respectively interpreted as hazard or time ratios (TRs). TRs indicate the degree of time stretching or shrinking as a result of the decelerating or accelerating effects of the covariates on survival time. For example, another way to say that dogs age 7 times faster than humans is that the TR of dogs versus humans is 1/7. The impact of the access type was estimated using the Weibull model by studying its time varying scale effect while holding the shape parameter constant across accesses (i.e., assuming two hazard curves with the same shape) and allowing the hazard form to vary by access type (i.e., assuming two hazard curves with different shapes). Final models were adjusted only if history of heart failure and late nephrology referral (11) and their interaction, hypertension, and vascular diseases, because none of the remaining covariates changed the exposure regression coefficient by >0.1 or had an independent effect at the two-sided $P < 0.1$.

Frailty Effect. The individual tendency to fail was studied parametrically by modeling the between-subject heterogeneity unexplained by available information (“unshared frailty”) and the within-subject correlation (dependency) of repeated observations (“shared frailty”). Influence of access type was sought contrasting the population frailty (which always declines over time as more frail individuals succumb to disease) with the individual frailty, which may have a different pattern (2).

Model Checking. Parametric model validity was assessed comparing estimated and observed rates and parametric HRs with those from the corresponding Cox model. There was no significant interaction between any covariate and the stratifying variable. Results did not change when observations censored for death were treated as events. Hazard and time proportionality assumption, model specification, and overall fit were checked by graphical and formal tests based on residuals. Analyses were performed using Stata 11SE (StataCorp, College Station, TX) and R (14).

Results
Study Patients and Arteriovenous Accesses
Of the 535 patients enrolled, 513 received an AVF (96%) as their first permanent access and the remaining 22 an AVG (4%). Patients’ mean ± SD age was 66.5 ± 14.2 years. They tended to be male (57.7%), have diabetes (27%), and have cardiovascular disease (51.2%). During the 6-year study period, they received 633 AVFs and 67 AVGs (700 total arteriovenous accesses), and no patient was lost to follow-up or received a transplant. The access survival data from these individuals recorded up to four recurrent accesses per patient: 404 individuals received one access, 101 received two accesses, 26 received three accessed, and four received four accesses. Table 1 summarizes the baseline characteristics by access type. As compared with patients who received only AVFs ($n = 473$), those who received at least one AVG ($n = 62$) were of larger body size and more likely to have diabetes and vascular disease.

Unadjusted Access Survival
The initial access was successfully used for the duration of the study in 313 patients without any salvage procedures and in an additional 49 patients with at least one salvage procedure. Considering repeated accesses, 310 (unassisted) access failures occurred during the study period (245 nonsalvageable): 222 failures of the first access (176 nonsalvageable), 72 of the second access (55 nonsalvageable), 13 of the third access (11 nonsalvageable), and three of the fourth access (three nonsalvageable). The risk for access failure tended to decline over time; however, the way in which rates varied over time differed initially between the two access types, making the hazards nonproportional (Figure 1).

Weibull and Cox Models with Time-Dependent Effects on the Hazard Scale
The estimated risks for failure were 20 to 30% lower in AVGs during the first 1 to 2 months after surgery but with 95% confidence intervals (CIs) crossing the null effect. When time was broken into two pieces (at 3 months), parameter estimates of the Weibull model were very close to those of Cox regression, supporting the adequacy of the chosen parameterization (Table 2). Efficiency or precision (width of the 95% CI) was also unexpectedly similar, likely as a result of the small sample size relative to the four additional parameters of the Weibull model (intercept, shape parameter, time, and stratifying variable [surgery number]).
In this model, AVGs changed the scale of the hazard from the third month (greater hazard) but did not affect the hazard shape. Formulating the same model in the time metric, AVGs showed significantly shorter survival times than AVFs only after 3 months. In other words, the predicted median survival time of AVFs (53.4 months; 95% CI 4.6 to 83) was approximately 10 times longer than AVGs (4.5 months; 95% CI 0.5 to 9.1), provided that the accesses survived beyond 3 months.

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AVF (n = 473)a</th>
<th>AVG (n = 62)b</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean ± SD)</td>
<td>66.3 ± 14.6</td>
<td>68.3 ± 10.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Male gender (n [%])</td>
<td>277 (58.5)</td>
<td>32 (51.6)</td>
<td>0.29</td>
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<td>BMI (kg/m²; mean ± SD)</td>
<td>24.1 ± 4.2</td>
<td>26.0 ± 4.7</td>
<td>&lt;0.01</td>
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<tr>
<td>Hypertension (n [%])</td>
<td>396 (83.7)</td>
<td>51 (82.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Chronic lung diseases (n [%])</td>
<td>57 (12.0)</td>
<td>12 (19.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes (n [%])</td>
<td>120 (25.3)</td>
<td>24 (38.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart failure (n [%])</td>
<td>79 (16.7)</td>
<td>5 (8.05)</td>
<td>0.08</td>
</tr>
<tr>
<td>Arrhythmia (n [%])</td>
<td>71 (15.0)</td>
<td>15 (24.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Vascular diseases (n [%])</td>
<td>182 (38.4)</td>
<td>34 (54.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Neoplasm (n [%])</td>
<td>85 (17.9)</td>
<td>12 (19.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>Systemic diseases (n [%])c</td>
<td>63 (13.3)</td>
<td>8 (12.9)</td>
<td>0.93</td>
</tr>
<tr>
<td>Predialysis care &lt;3 months (n [%])</td>
<td>129 (27.2)</td>
<td>20 (32.2)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

BMI, body mass index.
aPatients who received only AVFs.
bPatients who received at least one AVG.
cSystemic lupus erythematosus, scleroderma, amyloidosis, myeloma, light-chain deposition disease, hemolytic uremic syndrome, Goodpasture syndrome, and vasculitis syndromes.

Figure 1. Unassisted (intervention-free) survival probability plots (top) and log–log survival plots (bottom) over time at risk. The hazard for failure is greater in grafts only after 3 months from surgery. Left panels include all observations (nonproportional risks); right panels include only observations longer than 3 months (proportional risks). Log survival curves are parallel when risks are proportional (constant products on the exponential scale correspond to constant difference on the log scale). AVF, continuous lines; AVG, dashed lines.
AVGs to the frailty effect, or change in the studied population hazard as a consequence of the individual hazards. The hazard for failure declines at both the individual and population levels as time goes by; however, the individual hazard decline was slower for AVGs.

Weibull Model with Effect on the Hazard Shape

Figure 3 shows the estimated hazards and survival probabilities by access type from a Weibull model with the same scale covariates (except access type and time). In this model, the study period is not broken into segments and the shape parameter is allowed to vary by access type, whereas the scale effect of the access type is constrained to be null. It can be seen that the hazards vary nonproportionally and the survival probabilities are initially higher for AVGs and then become lower than those of AVFs; however, predicted median survival times over the whole observation period were longer for AVFs (38.3 months; 95% CI 1.2 to 67.7) than for AVGs (8.4 months; 95% CI 1.7 to 16.5). Similar results were obtained for assisted survival analysis.

Discussion

In this study, we compared two approaches to the analysis of arteriovenous access data: semiparametric Cox regression and parametric modeling. Our findings highlight merits and limitations of each method (Table 3). Although one or the other approach may more easily address certain analytical goals, the use of both methods may help to achieve a more comprehensive analysis and provide meaningful insights into mechanisms of disease.

Ease of interpretation is the major advantage of semiparametric
modeling. Moreover, with Cox regression, hazards can be compared ignoring how they change over time, provided that they are proportional by level of the covariates. When they are not, time can be split into smaller and smaller pieces, within which risks are proportional, and one effect is estimated per time piece (time-dependent risk ratios); however, in Cox regression, estimates are made at times when events occur, and at least 10 events are necessary for each parameter estimate (2). Using Cox regression in our analysis, we found that the risk for failure did not vary significantly by access type in the first 3 months, probably because AVFs are characterized by greater initial hazard but faster hazard decline, resulting in proportionally smaller risks only after 3 months; however, with Cox regression, effects can be assessed only in terms of proportional hazard change, and average survival times cannot be estimated directly.

Parametric models make more efficient use of the data because estimation is based on both time and event information. There are several parametric models with specific hazard shapes (2). The simplest is the exponential model, which assumes that the hazard is constant over time. Breaking time into pieces and using this model, we found that the form of the hazard for access failure is consistent with the Weibull distribution, which assumes that the hazard declines (or increases) monotonically over time. The main advantage of Weibull regression is that the effects can also be formulated in terms of time ratios. Although semiparametric estimates of hazard functions and summary statistics of survival distributions are available, comparisons beyond times when all survival information is known are not possible. Parametric models overcome this limitation by extrapolating beyond the range of the data using the assumed distribution (2).

The decision to use a semiparametric or a parametric approach can be guided by the goal of the analysis. For example, although differences in quantiles of survival distributions can be estimated semiparametrically, the task is achieved more directly with parametric models. Furthermore, semiparametric analysis may be more reliable in the absence of a priori knowledge about the shape of the hazard; however, if the interest is to predict survival times, then some parametric assumption about the hazard is necessary (2). With Weibull regression, it is possible to predict median times to failure by levels of a covariate when the covariate alters either or both the “scale” and the “shape” of the hazard. We found that when access type was used as the scale covariate, median predicted survival times were similar in the first 3 months but changed thereafter, being approximately 10 times longer in AVFs. When access type is used as a shape covariate only, the comparison cannot be made formally (the scale is not affected), but median times can still be predicted. In our study, for example, over the whole observation period, the expected median survival times of AVGs were 8.4 months and those of AVFs were almost 40 months. Even in the absence of hazard proportionality, time estimation is possible using parametric models that consider the entire observation period without splitting time into pieces. The major limitation with all parametric models is that the risk profile cannot be ignored and must belong to the family distribution of the chosen model. This limitation in fitting general survival distributions can be overcome by using the piece-wise exponential model.

Another advantage of parametric models is related to the analysis of repeated events. Risk data are heterogeneous both because patients differ for reasons that are unexplained by available information (unshared frailty) and because within-patient observations are correlated (shared frailty). In fact, observations from the same individual are more likely to be similar than observations from different individual. One way to account for this lack of independence is to incorporate the (shared) frailty into the model. This can be done with both semiparametric and parametric methods; however, with parametric models, it is uniquely possible also to model the extravariability in the data as unshared frailty and contrast shared and unshared frailties. This helps distinguish individual frailty and population frailty, a phenomenon known as frailty effect. In any risk study, the population frailty declines over time as more frail individuals succumb to disease (2); however, the individual frailty may have a different pattern. We found that the hazard declines at both the population and the individual levels but remains higher for AVGs at the individual level. Changes in the individual frailty may be studied for interventions that favor AVF maturation or reducing the risk for AVG stenosis (4) in addition to (or even instead of) the standard effects on the risk scale.

Our analysis has limitations. First the cohort is small and patients who received an AVG as first or subsequent form of access were few. Despite the small number of AVGs, the study had a power of 90% to show as significant (two-sided \( P < 0.01 \)) a relative hazard for failure of 3 under both semiparametric and parametric assumptions. Results are also consistent with the available literature in terms of estimated HR, although effect estimation was not the aim of this study. Second, the parameterization choice was partly dictated by the intention to compare the results with those from Cox regression, a proportional hazard model. The exponential and Weibull models were chosen because they are relatively easy to understand and have both the hazard and time metrics,
allowing comparison of the two interpretations. It is possible that for some survival problems or different populations, nonproportional solutions or different parametric models may perform better (15). Last, the hazards for different specific complications (of the same or different access types) may have different shapes. For example, the distributions of the risk for stenosis and the risk for infection may differ.

Conclusions

Although Cox models have traditionally been used and are easy to interpret, parametric models may provide complementary data to clinicians and researchers about how risks vary over time. This information may help in the understanding of the physiopathology of hemodialysis access dysfunction and designing intervention studies of access outcomes.

Acknowledgments

The analyses in this study were part of the PhD thesis work of P.R. P.R. designed the study and performed the analyses; F.M., G.B., and S.M. were responsible for data management and contributed to the design; P.P., B.H., and B.B. contributed to data interpretation and reporting as supervisory committee members; J.M., M.J., R.Q., B.M., and M.T. contributed to data interpretation and reporting, and all authors approved the final manuscript.

Disclosures

None.

References

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Table 3. Characteristics of semiparametric and parametric models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Semiparametric</th>
<th>Parametric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard distributiona</td>
<td>No assumption</td>
<td>Different choices</td>
</tr>
<tr>
<td>Shape parameter</td>
<td>None</td>
<td>At least oneb</td>
</tr>
<tr>
<td>Scale parameter</td>
<td>Log-hazard ratios</td>
<td>Log-time ratiosc</td>
</tr>
<tr>
<td>Time estimation</td>
<td>Unavailable</td>
<td>Available</td>
</tr>
<tr>
<td>Random effectsd</td>
<td>Yes (no frailty effect)</td>
<td>Yes (plus frailty effect)</td>
</tr>
</tbody>
</table>

a The hazard distribution is the form (or shape) of the hazard over time (how the hazard varies over observation time).

bE.g., the Weibull model has one shape parameter “k”: When k > 1, the hazard increases over time; when k = 1, the hazard is constant (the model reducing to the exponential model); when k < 1, the hazard decreases over time.

Some models (exponential and Weibull) have both the hazard and time metrics; other models (gamma, log-normal, and log-logistic) have only the time metric; some others (Gompertz) have only the hazard metric.

d For recurrent event processes, data correlation can be accounted for by incorporating the individual frailty into the (frailty) models.

d Estimate of the frailty effect (how the hazard varies over time at the population as opposed to the individual level) is possible only in the presence of distributional assumptions (parametric models). Besides the ease of coefficient interpretation (HRs), freedom from distributional assumption is the greatest advantage of Cox regression. When parametric models can be used, the effects of the covariates can be interpreted as TRs, time estimates can be made, and the frailty effect can be studied.