Measuring Patient Survival on Hemodialysis

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Considering the progression of ESRD—left untreated and in the context of maintenance hemodialysis—there can be little doubt that the delivered dose of hemodialysis impacts patient survival. What remains at issue is how best to operationally define hemodialysis dose, a necessary precondition to defining the dose that represents “enough” dialysis. Presently, hemodialysis dose is most often measured in terms of $Kt/V_{urea}^{1}$, a mathematical ratio that seeks to balance urea removal (rate of removal, $K$, times treatment time, $t$) with metabolic needs (represented loosely by the volume of distribution, $V$).$^{2}$ Curiously, data on the association between $Kt/V_{urea}$ and mortality are mixed, with some studies showing a potent and statistically significant relationship,$^{3,4}$ and others finding none.$^{5,6}$

In this issue of JASN, Argyropoulos et al.$^{7}$ examine data from a nationally representative cohort of incident hemodialysis patients to further examine the association between $Kt/V_{urea}$ and mortality and to explore incongruity between biologic mechanism and statistical modeling assumptions as one potential explanation for inconsistent findings among prior studies.

The authors analyzed data from 491 participants in the Choices for Health Outcomes in Caring for ESRD (CHOICE) study for whom complete covariate data were available, finding that each (unitless) increment in $Kt/V_{urea}$ is associated with a 42% (95% CI: 2–98%) increase in median survival time using adjusted accelerated failure time (AFT) analysis. The clinical significance of this finding should be judged by the magnitude of association. Smaller, more clinically relevant $Kt/V_{urea}$ increments, such as 0.2 and 0.4, correspond to more modest 7.5 and 15% increases in median survival time. Furthermore, given the observational nature of the study, results may have been influenced by residual confounding, particularly on the basis of dialysis access type, which was not considered as a covariate term despite known associations with both $Kt/V_{urea}$ and mortality.$^{8,9}$

Recently, nephrologists have challenged the validity of $Kt/V_{urea}$ as a metric of hemodialysis dose on both theoretical and empirical grounds. Some argue that given the known association between greater $V$ and improved survival, normalizing urea removal to $V$ (i.e., placing $V$ in the denominator of $Kt/V$) seems illogical and may lead to suboptimal dialysis delivery to patients with small body habitus.$^{10}$ Others argue, in an era where high-efficiency dialyzers enable rapid removal of low molecular weight compounds, use of any urea-based metric of hemodialysis dose may result in treatment durations that are too short to enable adequate removal of middle molecules and excess volume.$^{4,11}$ Assuming that residual confounding did not overly influence results, the authors’ demonstration that $Kt/V_{urea}$ is significantly associated with mortality offers a small modicum of support for the currently pervasive $Kt/V_{urea}$-centric paradigm of hemodialysis dose titration. However, without data on other urea- or non-urea-based measures of adequacy, these data cannot address whether other metrics may be superior to $Kt/V_{urea}$.

More than its clinical message, the methodological implications of the study of Argyropoulos et al. deserve notice. That $Kt/V_{urea}$ was significantly associated with mortality on AFT but not proportional hazards analysis may bear analytical relevance to future studies. Proportional hazards analysis is by far the most common analytical technique applied to time-to-event analyses in the medical literature. It makes the implicit assumption that the risk associated with exposure (e.g., $Kt/V_{urea}$) remains constant over time: for example, the hazard ratio in year 1 equals that in years 3, 5, etc.$^{12}$ This assumption is inconsistent both with the underlying biology of uremia—continued accumulation of uremic solutes in response to lower $Kt/V_{urea}$ causes risk to increase over time—and with the empirical data.$^{7}$ When data do not conform to the proportional hazards assumption, these models will generate biased and imprecise effect estimates.$^{13}$ Conversely, because AFT models do not require the data to conform to the proportional hazards assumption,$^{14}$ they render more accurate and precise effect estimates in instances where relative hazard varies over time. The authors show greater accuracy and precision of AFT (versus proportional hazards) models empirically in the form of greater agreement between predicted and observed (Kaplan-Meier) survival curves and narrower confidence intervals, respectively. Consideration of the proportional hazards assumption applies equally to observational and randomized studies; thus, both future epidemiologic studies and randomized trials of hemodialysis dose should consider using AFT models.

Successful application of AFT models requires appropriate specification of the baseline hazard (unlike proportional hazards models, which do not require specification of baseline hazard).$^{15}$ Correct specification leads to increased precision.
and thereby greater statistical power to detect true differences; incorrect specification leads to bias and may render findings meaningless.\textsuperscript{15} Therefore, application of AFT models is advisedly done in consultation with an experienced statistician.

Argyropoulos \textit{et al.} did not compare results from AFT to those from time-updated proportional hazards models, which are less subject to violations of the proportional hazards assumption than standard, baseline proportional hazards models. Time-updated proportional hazards models may be particularly relevant to observational studies such as \textit{CHOICE}—in which exposure ($Kt/V_{urea}$) is not fixed according to randomization but instead varies as the result of therapeutic titrations—given that time-updating reduces the potential for exposure misclassification bias. Further work is needed to clarify the relative merits of AFT versus time-updated proportional hazards approaches.

In summary, the study by Argyropoulos \textit{et al.} suggests the use of AFT models instead of proportional hazards models in studies where risk may vary over time because of cumulative exposure. This represents an important analytical consideration in future studies measuring the association of dialysis dose and clinical outcomes.

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\textbf{REFERENCES}


\textbf{Does a Statistical Method Suggest a New Pathobiology for Hemodialysis Patients?}

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You will find elsewhere in these pages of \textit{JASN} a paper by Argyropoulos \textit{et al.} entitled “Considerations in the Statistical Analysis of Hemodialysis Patient Survival.” The claim of this work—a comparative statistical analysis—is that the authors have proven their \textit{a priori} hypothesis that the natural history of

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