Oh! What a Tangled Web We Weave

Neihia Arora and Glenn M. Chertow

When Sir Walter Scott wrote “Marmion” in 1808, he told a story of love, lust, honor, and deception in the setting of war between the kingdoms of England and Scotland. After reading the work by Flythe et al. (1) entitled “Disentangling the ultrafiltration rate–mortality association: The respective roles of session length and weight gain,” one cannot help but recall the poem’s most memorable verse: “Oh! What a tangled web we weave.” Although few would consider ultrafiltration with hemodialysis as complex as the affairs of the heart, the factors that contribute to optimal ultrafiltration are more intricate than the plot lines of most gothic romantic novels or modern soap operas.

In their article, Flythe et al. (1) entertain the reader, as did Scott, with a carefully crafted story. Flythe and colleagues note that attempting to disentangle related factors (i.e., dialysis session length and interdialytic weight gain) can be difficult or arguably, nearly impossible, when these factors are highly correlated. Therefore, they analyzed data on 14,643 randomly selected prevalent adult patients on three-times-per-week hemodialysis and examined associations between dialysis session length, interdialytic weight gain, and mortality in parallel. In other words, for analyses examining the association between dialysis session length and mortality, patients were matched on a narrow range of interdialytic weight gain (±0.25 kg) along with other key covariates. For analyses examining the association between interdialytic weight gain and mortality, patients were similarly matched on the same covariates (age, sex, vascular access, and post-dialysis weight) along with dialysis session length rounded to the nearest 5-minute increment. Matched pairs were very well balanced on the matched factors (as expected); on other factors, including race, diabetes mellitus, and heart failure, there were important imbalances.

In their primary analyses, Flythe et al. (1) reported a 32% increase in the relative mortality hazard (95% confidence interval, 3% to 69%) associated with dialysis session lengths less than 240 minutes relative to sessions 240 minutes or more and a 29% increase in the relative mortality hazard (95% confidence interval, 1% to 65%) associated with interdialytic weight gains of more than 3 kg relative to 3 kg or less. Unlike previous reports that either examined one of two parameters or examined both simultaneously in multivariable regression models, the matching approach used by Flythe et al. (1) allows us to more confidently conclude that dialysis session length and interdialytic weight gain are independently associated with mortality. We agree with the contention of Flythe and colleagues that an association between shorter dialysis session length and mortality is “highly plausible” (1). As session lengths shorten, removal of plasma water will, at some point, exceed the rate at which water can be recruited from the interstitial and/or intracellular spaces. Hypotension may develop, or BP may be sustained by heightened sympathetic and other neurohumoral stress (2). Myocardial ischemia (stunning) has been put forth by some as a mechanism for the shorter dialysis session length–mortality association and by some as a rationale for extending session length or performing more frequent hemodialysis (3). The association between higher interdialytic weight gain and mortality is more complex, and the explanation is more nuanced. Higher interdialytic weight gains could indicate excessive thirst driven by heart or liver failure, diabetes-associated hyperglycemia, retained organic solutes, or personal inattention; alternatively, higher interdialytic weight gains could indicate a robust appetite or intake related to social or other generally healthy activities.

Most of the study’s limitations were acknowledged by Flythe et al. (1). Matching was desirable, although a relatively low fraction of the source cohort was successfully matched in both parallel analyses, and the matched population was not representative of the overall population with respect to body size. Residual confounding was noted, but dose targeting bias was not (4). Patients able to achieve their prescribed (longer) dialysis session lengths may have been more resilient in ways not measured or accounted for in the work by Flythe et al. (1). In their article, Flythe and colleagues mentioned the lack of data on residual kidney function, but they may have underestimated its importance (5). Although Flythe et al. (1) appropriately tout their matching approach as a means of limiting overlap between the two key exposures, it is highly likely that residual kidney function overlaps with both; residual kidney function in a prevalent sample could easily explain away the association between interdialytic weight gain and mortality. An analysis restricted to patients of longer vintage (4 or more years) would have been informative. Finally, we should note that both analyses, although statistically significant, were marginally significant. Accounting for the fact that two related analyses were conducted (using...
Bonferroni or related corrections), neither would have reached conventional levels of statistical significance.

After digesting the results reported by Flythe et al. (1), one cannot help but reach the same conclusions—“Further prospective studies are needed to confirm and generalize findings” (1). To reconsider Sir Walter Scott, we should recall the latter half of the most notable verse of “Marmion”: “Oh! What a tangled web we weave, when first we practice to deceive.” Flythe et al. (1) did not intend to deceive; indeed, they deftly clarified the respective roles of dialysis session length and interdialytic weight gain in epidemiologic analysis. However, we the readers and practitioners cannot depend on observational data to guide clinical practice. Observational data have deceived us on too many occasions. Too much is at stake for too many patients.

As such, we were delighted to learn that the Dialysis Research Network, a consortium of academic institutions and two large for-profit dialysis providers, has proposed a large, cluster-randomized pragmatic trial—the Time to Reduce Mortality in ESRD trial—to examine the effects of longer dialysis session length on mortality, hospitalization, and health-related quality of life (https://www.nihcollaboratory.org/demonstration-projects/Pages/TIME.aspx). Perhaps the tangled web of hemodialysis might become less tangled after all.

Disclosures

N.A. serves as an advisor to Satellite Healthcare. G.M.C. serves on the Board of Directors for Satellite Healthcare and is on the Scientific Advisory Board for DaVita Clinical Research.

References


Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Disentangling the Ultrafiltration Rate–Mortality Association: The Respective Roles of Session Length and Weight Gain,” on pages 1151–1161.