High Ultrafiltration Rates and Mortality in Hemodialysis Patients: Current Evidence and Future Steps

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Background

The advent of hydrostatic ultrafiltration and other technological advances allowed for more efficient hemodialysis (HD) and volume removal over shorter treatment times (1). Although shorter session length may be preferred by many patients, there is concern that higher ultrafiltration rates (UFR) could lead to end-organ damage *via* hypoperfusion-induced ischemic injury (2). Further, several observational studies have demonstrated that higher, compared with lower, UFR is associated with increased mortality in the maintenance HD patient population (3–6). On the basis of these findings, the Center for Medicare and Medicaid Services includes the recording of UFR in its Quality Incentive Program (7,8). Further, the Kidney Care Quality Alliance performance guidelines include the avoidance of UFR ≥13 ml/h per kg (9). Working within these parameters, when patients are unable to meet dietary sodium and fluid recommendations and/or optimized diuretic regimens are not sufficient, physicians are left with the option of extending treatment times or bringing patients in for isolated ultrafiltration sessions. Busy HD unit schedules, patient availability and willingness, and transportation issues may limit the utility of these mechanisms to manage hypervolemia. Further, unplanned longer or extra HD sessions may have serious ramifications for the morale and quality of life of the maintenance HD patient.

Evidence backing the discouragement of high UFR has, to date, been observational. There therefore remains concern that residual confounding associated with hypervolemia, and the need for higher UFR, could partially explain the associated worse outcomes (10). The lack of randomized controlled trials to support avoidance of high UFR and concerns for complications associated with hypervolemia if ultrafiltration goals are not met have led to disagreement around policies advising limitations on UFR (11).

Current Paper

In this issue of *Kidney360*, Navarrete *et al*. (12) report the results of an observational study demonstrating that patients with a higher proportion of HD sessions with UFR >13 ml/h per kg in their first 3 months of HD are at a higher risk of mortality, even when the average UFR over that period was <13 ml/h per kg. Patients in the highest quartile (26% of HD sessions with UFR >13 ml/h per kg; average UFR 9.8 ml/h per kg; median survival 5.6 years) had a higher risk of death compared with those in the lowest quartile (0% of HD sessions with UFR >13 ml/h per kg; average UFR 4.7 ml/h per kg; median survival 8.8 years; adjusted hazard ratio 1.54; confidence interval, 1.13 to 2.1).

The study is novel in that the proportion of sessions with higher UFR, rather than single session UFR or average UFR, has rarely been assessed as the predictor of mortality. On the basis of their findings, the authors suggest the potential importance of frequency-based definitions of high UFR, rather than assessing UFR 1 day a month, for quality metrics.

The analyses are also novel for examining the association of high UFR with mortality in the incident HD patient population. The authors suggest that shorter treatment times should perhaps be avoided in incident HD patients, even if there is perceived high residual kidney function in the first 3 months of HD, because shorter treatment times may lead to higher required UFR to achieve an estimated dry weight. The Center for Medicare and Medicaid Services and the Kidney Care Quality Alliance quality improvement measures already discourage the use of high UFR, but incident HD patients are excluded from this recommendation (7–9). The findings of this study may lead some to suggest that this quality metric could potentially be expanded to include incident HD patients, but many of the existing debates would likely apply here also.

The data are from a large (N=1050) and contemporary (from 2010 to 2020) dataset. The authors were also able to follow their patients longitudinally for a long period (median 2.4 years; interquartile range 1.1–4.7 years). Further, 91% of subjects were Black. The study thus has the strength of having assessed the association of UFR with mortality in a more vulnerable patient subgroup. Although the study is valuable, because insufficient studies have focused on this subgroup in the past, this may compromise the

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generalizability of the results to the larger population of maintenance HD patients.

The authors adjust for several important covariates (age, vascular access, Kt/V, history of diabetes, history of heart failure, serum albumin, and mean arterial pressure post HD). However, there remain potential confounders, known and unknown, for which the authors did not account. For example, they report that men, shorter HD session length, and lower weight were associated with a higher proportion of sessions with high UFR. However, these parameters were not included in their models. Another important confounder for which this study does not adjust is residual kidney function. It is possible that those with less residual kidney function are the same patients who require higher UFR. Lower residual kidney function is independently associated with increased mortality (13), and further studies in the incident HD patient population should account for this potential confounder. This study also did not control for general adherence to medical recommendations, which could affect both fluid overload, creating an indication for higher UFR, and other aspects of patient care that could affect their outcomes. Patients who have difficulty following recommendations regarding salt and water restrictions may be the same patients who have difficulty adhering to other aspects of their care, including medication adherence and the maintenance of healthy diet and exercise. Especially in the incident HD patient population, a setting in which many new recommendations are given to patients, accounting for their ability to follow medical recommendations may be important.

Future Directions

There is a wealth of observational research that demonstrates the association of higher UFR with mortality. The manuscript by Navarrete *et al*. (12) expands our awareness of this association to the incident HD patient population. However, there remains a deficiency in prospective evidence to guide optimal management of hypervolemia. Fortunately, there are evolving mechanisms by which we may improve the management of volume for our patients in the future.

Point-of-care ultrasound is becoming widely used as an objective tool to assess volume status. For example, pulmonary B lines as a proxy for the need for ultrafiltration have been used to guide nephrologists' prescriptions of ultrafiltration without increasing symptoms of hypovolemia, defined as hypotension, cramping, nausea, or vomiting (14). Further, studies have demonstrated the potential feasibility of inferior vena cava imaging in HD patients as another dynamic metric of volume status (15). Point-of-care ultrasound is becoming increasingly available, is being incorporated as part of many training programs, and may provide important information to guide UFR prescriptions in the future.

The use of algorithms to analyze data and predict intradialytic hypotension in real time is another mechanism by which we may improve outcomes. For example, it is known that high relative blood volume decreases are associated with more intradialytic hypotension and increased mortality (16,17). Feasibility of intradialytic monitoring to predict higher decrease in relative blood volume in the subsequent 15 minutes of HD *via* the use of optical sensing devices (which give information about hematocrit, oxygen saturation, and intravascular blood volume in real time) and patient data has previously been demonstrated (18). Biofeedback mechanisms using such techniques could be used to guide UFR prescriptions dynamically throughout the course of an HD session. Overall, use of artificial intelligence and deep learning approaches could help clinicians respond rapidly to large quantities of patient data to optimize UFR prescriptions to minimize intradialytic hypotension and the potentially associated compromise to end-organ perfusion.

There are many opportunities for individualizing and improving volume management for our patients. Given the advances in artificial intelligence and in point-of-care ultrasound as just two examples, we have many opportunities to advance HD and improve outcomes related to hemodynamic stability and volume and the patient experience. Randomized controlled trials will ultimately be required to assess whether implementation of such technological advances improves outcomes. Ultimately, algorithms for the management of hypervolemia have the potential to lead to vast improvement of patient experience and outcomes if we optimally use technological advances for our patients in the future.

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K.S. Ravi has nothing to disclose.

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Author Contributions

K.S. Ravi was responsible for conceptualization, wrote the original draft of the manuscript, and reviewed and edited the manuscript.

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