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evolve and is an example of a well-developed tool that has the potential to improve care. The proposed mechanism is that by augmenting clinical decision-making with accurate risk predictions, patients at high risk of deterioration can be identified and their future trajectory altered by some clinical intervention. Key future steps, beyond external validation and confirmation of generalizability, will be to determine the spectrum of the hypothesized gains in clinical outcomes. Clinical utility methods exist for this but require estimating the impact of the tool on clinical decision-making and the average treatment response according to risk strata. Although it would be possible (and worthwhile) to determine any incremental improvement in risk prediction when using this model in comparison to intuitive clinical judgment, the impact of treatment will remain unknown until children are routinely included in clinical trials. The exclusion of children from trials is not only inequitable but also a lost opportunity to intervene for people with IgA before irreversible kidney damage occurs.

One final aspect to consider regarding the development of clinical risk prediction tools more broadly is how to effectively convey uncertainty about individual predictions. The app provided with the pediatric postbiopsy tool gives risk as a percentage to 2 decimal points. The presentation of a point estimate without quantification of uncertainty is standard practice for such tools, but makes it difficult for clinicians to know how much weight to place on model output when incorporating that information into clinical care.⁸ The topic of estimating and conveying uncertainty in individual risk distributions is an area of active research, and becomes more important as we attempt to incorporate increasingly sophisticated models into clinical care.^{9,10}

DISCLOSURE

All the authors declared no competing interests.

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Dialysis modality and quality of life: more answers yet more questions



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Persons with end-stage kidney disease treated with dialysis experience distressing reductions in quality of life and increased mortality. Few large, randomized trials in nephrology have reported on health-related quality of life. Rose *et al.* report beneficial effects of high-volume hemodiafiltration versus high-flux hemodialysis on secondary end points of health-related quality of life in the CONVINCe trial (Comparison of High Dose Hemodiafiltration with High Flux Hemodialysis Trial). These results raise questions regarding hemodiafiltration as a potential modality to preserve health-related quality of life in end-stage kidney disease.

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[see clinical trial on page 961](#)

Persons with end-stage kidney disease (ESKD) treated with renal replacement therapy experience distressing reductions in quality of life and elevated risk of mortality. Despite

the quality of life of patients with ESKD on dialysis being lower than that of patients with malignancy,¹ few large randomized trials in nephrology have reported on health-related quality of life (HRQoL) or patient-centered outcomes. Improvement of dialysis adequacy has been suggested as one among many potential measures to improve HRQoL.²

Clinical trials of hemodialysis frequency and modality specifically

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investigating effects on HRQoL in patients treated with dialysis have yielded variable results. The Frequent Hemodialysis Network trial showed a statistically significant improvement in RAND-36 physical-health composite score among persons in the frequent hemodialysis group compared with conventional hemodialysis, but no change in objective physical performance measured using the short physical performance battery.³ Despite smaller studies suggesting some benefit in HRQoL for hemodiafiltration (HDF) over hemodialysis, in the largest randomized controlled trial before the one reported by Rose *et al.*, the Convective Transport Study (CONTRAST), Mazairac *et al.* found no difference in longitudinal HRQoL assessments between both groups using the Kidney Disease Quality of Life—Short Form.⁴

HDF is a dialysis modality that has demonstrated beneficial effects on multiple risk markers associated with poor health outcomes. HDF improves middle molecule removal by combining convective and diffusive clearance, resulting in a wide array of positive effects, such as better intradialytic hemodynamic stability, with fewer ischemic insults to end organs, reduced endothelial dysfunction, oxidative stress, and inflammation in patients with ESKD.⁵ Despite these positive effects, studies have been conflicting on whether HDF results in improved patient-reported HRQoL.^{4,6}

In this edition of *Kidney International*, Rose *et al.* report on the HRQoL secondary outcomes of a large prospective randomized trial in patients receiving conventional high-flux hemodialysis versus high-volume HDF,⁷ after previously reporting that high-volume HDF resulted in a lower risk of death from any cause and similar rates of hospitalization compared with conventional high-flux hemodialysis.⁸ The authors used the validated Patient-Reported Outcomes Measurement Information System (PROMIS)-29 v2.0 profile, an instrument that includes 4-item short forms for 7 health domains as well as a single item measuring pain intensity. PROMIS-29 v2.0 domains

were aggregated into physical health summary scores, largely determined by physical function and pain scores, and mental health summary scores mainly representing affective health (depression, anxiety), fatigue, sleep disturbance, as well as social participation. Patient-reported outcomes were assessed at baseline, and then every 3 months. The study population was on average healthier than the general dialysis population, with lower prevalence of diabetes, well-controlled hypertension, and relatively low reported mortality. Notably, physical function scores at baseline were only half an SD below the general population mean, with a small to modest persistent decline in both groups across all domains of HRQoL, more pronounced in the hemodialysis group. The greatest declines were observed in the domains of physical function, cognitive function, and social participation. In fact, after 3 years of follow-up, the physical function score of the hemodialysis group decreased to the 14th percentile of the general US population. This trend highlights the importance of the nephrology community placing more focus on interventions that improve physical, cognitive, and social performance for dialysis patients. Particularly, with the increasing realization that patients value these outcomes as much if not more than survival on dialysis. Indeed, the Standardized Outcomes in Nephrology—Hemodialysis (SONG-HD) initiative investigators have highlighted patients treated with dialysis report fatigue to be the most important outcome.

Although the current study demonstrates a statistically significant positive effect of high-volume HDF on physical, cognitive, and social function of patients with ESKD on dialysis, it also raises several considerations helping inform future investigations. First, HRQoL was assessed as a secondary outcome, and the selected tool only broadly measured multiple domains of HRQoL. It can be argued that the selected questionnaire measuring HRQoL lacked specificity for assessing distinct domains of HRQoL. Future investigations should incorporate more specific tools to better assess each

domain impacted by HDF. This is particularly important when it comes to physical function, which includes mobility and strength, factors perhaps better captured by simple, objective physical performance testing. Second, the relatively modest treatment effect attributable to HDF leaves one to question how this translates to relevant improvements in how patients living with ESKD feel or function in their environment. The authors argue that a 3-point difference should be used as a meaningful cutoff; however, to achieve this level of separation in scores between HDF and hemodialysis requires substantial follow-up well beyond the duration of the current study. This underscores the need for patient and caregiver input to be incorporated into the determination of a clinically meaningful benefit. Additional evidence for a meaningful benefit can be obtained through assessments of objective improvements in physical performance and habitual physical activity using digital actigraphy. Physical performance is an important objective measure of functional limitation closely linked to quality of life and survival across populations. Corroborative evidence of improvements in physical performance with HDF would support clinically relevant treatment effects on physical health, particularly given the absence of blinding of patients, dialysis staff, and site investigators to treatment group allocation. Additionally, an important question that remains to be answered is which specific subgroup of patients stand to benefit most from high-volume HDF? The population in the study was somewhat healthier than the average hemodialysis population in the United States and Europe, raising considerations of generalizability of the findings to a dialysis population with a wider range of function and baseline HRQoL scores. More research is needed to define the target population most benefiting from HDF, allowing for a more personalized, patient-centered treatment approach. Finally, in the United States, there are barriers to the widespread use of HDF, including the potential cost of conversion of hemodialysis centers to the use of HDF, which encompass the cost of the

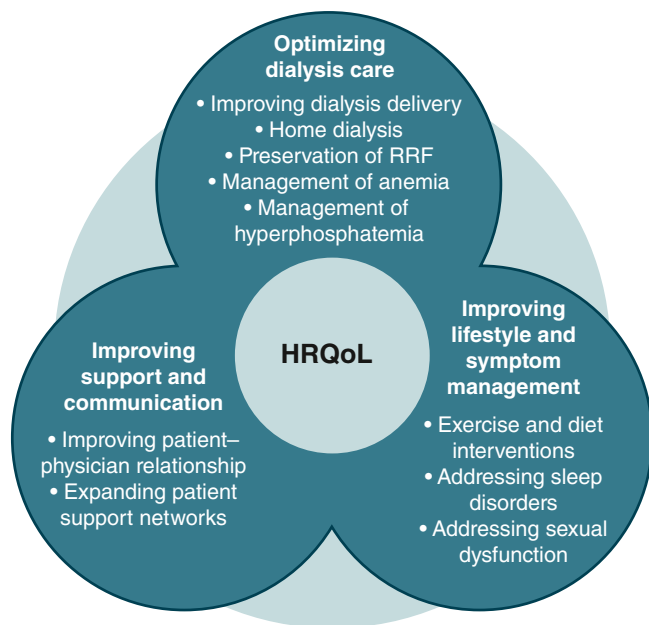


Figure 1 | Improving health-related quality of life (HRQoL) in patients with end-stage kidney disease on dialysis is likely best achieved with a multifaceted approach that focuses on optimizing dialysis care, promoting a healthy and active lifestyle, managing symptoms, and finally strengthening the patients' support and communication with their social circles and their providers. RRF, residual renal function.

equipment and staff training. Despite these barriers, progress has been made facilitating the availability of HDF in the United States via the Kidney Health Initiative, a public-private partnership spearheaded by the American Society of Nephrology, the US Food and Drug Administration, and member organizations promoting new therapies to treat kidney-related problems in the United States.⁹

This important study highlights the physical, cognitive, and social challenges faced by dialysis patients with ESKD and suggests that the HDF dialysis modality may be a component of an integrative approach to enhancing or maintaining HRQoL for a specific group of patients. It is important that more of such studies be conducted in a heterogeneous, generalizable dialysis population to improve understanding of the trajectory

of HRQoL outcomes and identify the specific subgroup of patients most likely to benefit and thus help guide personalized interventions. It is long overdue for nephrology studies to prioritize patient-centered outcomes. It falls on providers to help patients maintain their physical and cognitive health, allowing them to socially engage and live their lives to the fullest despite the challenge of living with advanced kidney disease. An integrative approach empowering patients to adopt effective lifestyle modification with equitable access to effective medical treatment forms the basis for preservation of physical function and slowing kidney disease progression. Similarly, a multifaceted approach is essential to address the complex issues of HRQoL in patients with advanced kidney disease requiring dialysis (Figure 1), and should include

lifestyle modifications (healthy diet and exercise), improved patient-physician communication to strengthen the therapeutic partnership, and optimized treatments to better preserve residual renal function, manage anemia and hyperphosphatemia, in addition to improving dialysis clearance.

DISCLOSURE

All the authors declared no competing interests.

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