Conservative Kidney Management Versus Dialysis Initiation: Can New Statistical Tools Help Understand the Bias in This Choice?

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Patients approaching kidney failure are faced with uncertainty regarding next steps, including not only when to start dialysis but whether they should start dialysis. For some individuals, there is concern that dialysis may provide minimal if any survival benefit because factors such as frailty[1,2] and older age[3] are associated with reduced survival with dialysis. Some may opt for conservative kidney management, an alternative to dialysis that seeks to actively preserve kidney function and palliate symptoms.[4] Choosing a plan of care should be informed not only by patient goals and values but also prognostic information.[5]

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At least 3 systematic reviews shed light on survival among those pursuing conservative kidney management. O'Connor and Kumar[6] reviewed 7 studies, which showed conservative kidney management achieving median survival ranging from 6.3 to 23.4 months. Foote et al[7] calculated pooled survival estimates from 89 studies that reported survival for patients with advanced chronic kidney disease (CKD) pursuing dialysis and/or supportive care. They found approximately similar 1-year survival of 73% for dialysis and 71% for supportive care but deferred statistical comparison and noted concern for lead-time and publication bias. Wongrakpanich et al[8] performed a meta-analysis of 3 cohort studies comparing mortality of dialysis versus conservative care among adults 65 years or older. They found a mortality hazard ratio (HR) of 0.53 (95% CI, 0.30-0.91; $P = 0.02$) favoring dialysis. Those choosing dialysis tended to be younger and had higher Karnofsky performance scale scores, suggesting greater functional status. In summary, the limited statistical comparison of these care pathways has favored better survival with dialysis but such comparisons are potentially limited by inherent bias. The underlying circumstances and characteristics of those opting for conservative kidney management may also portend higher mortality. This leaves us with key questions: does dialysis offer longer survival than conservative kidney management and if so, does a survival difference reflect residual confounding between the groups pursuing these distinct paths for which adjustment models have not accounted?

In the current issue of *Kidney Medicine*, Fu et al[9] provide an updated comparison of mortality with dialysis versus conservative kidney management and use new statistical methods to characterize the strength of association and potential residual confounding. They performed a meta-analysis of 12 cohort studies published from 2009 to 2019 comparing mortality of patients with advanced CKD who received dialysis or conservative kidney management using meta-analysis with random effects. They found a mortality HR of 0.47 (95% CI, 0.34-0.64) favoring dialysis. Outcomes of subgroup analyses in participants at least 65 years old were similar, suggesting that results were robust when restricted to older individuals. In more limited analyses, they found no difference in annual hospital days and identified 2 studies showing no difference in physical or mental health.

Notably, the authors quantified the strength of the association and degree of unmeasured confounding that would nullify these findings using a new statistical strategy from Mathur and VanderWeele.[10,11] First they selected a clinically significant threshold HR of 0.8 (ie, dialysis mortality is 20% lower than conservative kidney management) and estimated the proportion of effect sizes below this threshold. Of note, they aimed not to count the number of studies with an observed effect size below this threshold but rather made weighted inferences of the population size and precision of each study to estimate the true effect sizes below this threshold.[10] They found that 92% (95% CI, 50%-100%) of effect sizes had HRs < 0.8. Next, they calculated a bias factor, or in other words, the potential residual confounding that would reduce the proportion of effect sizes with an HR < 0.8 from 92% to $<10\%$, thereby nullifying the protective mortality findings of dialysis over conservative management. They found that the minimal strength of such a bias factor would be 2.31 (95% CI, 1.51-2.36), or when converted to the risk ratio scale, residual confounding associated with both a care strategy and mortality would have a risk ratio of at least 4.05 (95% CI, 2.39-4.15). A similar analysis was performed to determine that the proportion of effect sizes greater than the null value of 1 was 8% (95% CI, 0%-25%). The bias factor associated with increasing the proportion of effect sizes to 50% was at least 1.71 (95% CI, 1.41-1.76), corresponding to a residual confounding risk ratio of 2.81 (95% CI, 2.17-2.92). One could postulate that there are few residual factors, alone or in combination, outside those analyzed that would be associated with a 2-fold or greater risk for mortality for patients choosing a particular care strategy.

Overall, this study confirms that among patients who opt for dialysis over conservative management, dialysis works: those selecting dialysis on average live longer. This

outcome is expected because the study populations, though often targeting older patients, were not necessarily enriched for the sickest patients who may be most likely to pursue conservative kidney management and for whom the benefits of dialysis are most in doubt. However, the differences between those choosing conservative kidney management and dialysis are likely a source of selection bias that augments the observed mortality difference. Model adjustment for age, comorbid conditions, and functional impairment within cohorts ideally accounts for at least some of this, but this is limited by heterogenous covariate models in distinct cohorts. Despite this, the authors demonstrate a large and convincing bias factor that cannot easily be accounted for with unidentified residual confounding, likely reflecting a true mortality difference.

This study also introduces new statistical tools to the field of nephrology. The proportion of effects metric provides quantitative thresholds for clinical significance beyond statistical significance, and bias factor in meta-analysis can provide a benchmark to gauge the statistical rigor of findings. This provides another measure in meta-analyses to go alongside tests of heterogeneity, funnel plots, and risk-of-bias tools. This method may prove most beneficial to inform the use of randomized controlled trial or in answering questions that preclude randomization.

Clinically, this study solidifies that among patients with advanced CKD, those choosing dialysis tend to live longer. These results still do not tell us who lives longer with dialysis or what quality of life to expect. As reviewed by Couchoud et al,[5] there are existing tools to predict survival in the general population and specifically after dialysis initiation. To identify to whom dialysis offers minimal or no survival benefit, we should now enrich comparative mortality analyses for the sickest patients, continue identifying additional risk factors for survival, and adapt existing prognostic tools for the advanced CKD population. We must also shift focus to measuring how these strategies affect quality of life because our patients do not necessarily forgo dialysis to live longer, but to live better.

ARTICLE INFORMATION

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REFERENCES

1. Garcia-Canton C, Rodenas A, Lopez-Aperador C, et al. Frailty in hemodialysis and prediction of poor short-term outcome: mortality, hospitalization and visits to hospital emergency services. *Ren Fail*. 2019;41(1):567-575.
2. Alfaadhel TA, Soroka SD, Kiberd BA, Landry D, Moorhouse P, Tennankore KK. Frailty and mortality in dialysis: evaluation of a clinical frailty scale. *Clin J Am Soc Nephrol*. 2015;10(5):832-840.
3. Villar E, Remontet L, Labeeuw M, Ecochard R. Effect of age, gender, and diabetes on excess death in end-stage renal failure. *J Am Soc Nephrol*. 2007;18(7):2125-2134.
4. Davison SN, Tupala B, Wasylynuk BA, Siu V, Sinnarajah A, Triscott J. Recommendations for the care of patients receiving conservative kidney management focus on management of CKD and symptoms. *Clin J Am Soc Nephrol*. 2019;14(4):626-634.
5. Couchoud C, Hemmelgarn B, Kotanko P, Germain MJ, Moranne O, Davison SN. Supportive care: time to change our prognostic tools and their use in CKD. *Clin J Am Soc Nephrol*. 2016;11(10):1892-1901.
6. O'Connor NR, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. *J Palliat Med*. 2012;15(2):228-235.
7. Foote C, Kotwal S, Gallagher M, Cass A, Brown M, Jardine M. Survival outcomes of supportive care versus dialysis therapies for elderly patients with end-stage kidney disease: a systematic review and meta-analysis. *Nephrology*. 2016;21(3):241-253.
8. Wongrakpanich S, Susantitaphong P, Isaranuwatchai S, Chenbhanich J, Eiam-Ong S, Jaber BL. Dialysis therapy and conservative management of advanced chronic kidney disease in the elderly: a systematic review. *Nephron*. 2017;137(3):178-189.
9. Fu R, Sekercioglu N, Mathur MB, Couban R, Coyte PC. Dialysis initiation and all-cause mortality among incident adult patients with advanced chronic kidney disease: a meta-analysis with bias analysis. *Kidney Med*. 2020;3(1):64-75.
10. Mathur MB, VanderWeele TJ. New metrics for meta-analyses of heterogeneous effects. *Stat Med*. 2019;38(8):1336-1342.
11. Mathur MB, Vanderweele TJ. Sensitivity analysis for unmeasured confounding in meta-analyses. *J Am Stat Assoc*. 2020;115(529):163-172.