

Survival by Dialysis Modality—Who Cares?

Martin B. Lee* and Joanne M. Bargman†

Abstract

In light of the recent emphasis on patient-centered outcomes and quality of life for patients with kidney disease, we contend that the nephrology community should no longer fund, perform, or publish studies that compare survival by dialysis modality. These studies have become redundant; they are methodologically limited, unhelpful in practice, and therefore a waste of resources. More than two decades of these publications show similar survival between patients undergoing peritoneal dialysis and those receiving thrice-weekly conventional hemodialysis, with differences only for specific subgroups. In clinical practice, modality choice should be individualized with the aim of maximizing quality of life, patient-reported outcomes, and achieving patient-centered goals. Expected survival is often irrelevant to modality choice. Even for the younger and fitter home hemodialysis population, quality of life, not just duration of survival, is a major priority. On the other hand, increasing evidence suggests that patients with ESRD continue to experience poor quality of life because of high symptom burden, unsolved clinical problems, and unmet needs. Patients care more about how they will live instead of how long. It is our responsibility to align our research with their needs. Only by doing so can we meet the challenges of ESRD patient care in the coming decades.

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*Division of Nephrology, University Medicine Cluster, National University Health System, Singapore; and †Division of Nephrology, University Health Network, Toronto, Ontario, Canada

Introduction

After being asked to review a submission of yet another study analyzing the length of survival by dialysis modality with the newest statistical adjustments du jour, we contend that further studies of survival by dialysis modality have been, as it were, “done to death.” Given the shift in emphasis toward patient-centered care (1–4), this is an urgent call for investigators to focus on issues affecting quality of life instead of duration of survival. Patient input (5) and our own experience lead us to assert that patients care more about how they will live instead of how long.

The “Golden Era” of Dialysis as a Life-Prolonging Procedure

On March 9, 1960, Clyde Shields became the first patient to receive long-term hemodialysis (HD) in the United States; he survived for 11 years (6). A year earlier, the first patient in the United States started peritoneal dialysis (PD) in San Francisco, California. With progress in the understanding, technique, and availability of dialysis in the next four decades (6), survival on dialysis increased dramatically, with the assumption that quality of life would improve. It made sense in that nascent era to compare survival between modalities, with the intention of illuminating modality choice for patients, physicians, and policymakers.

The Survival Battle Begins: PD versus HD

In 1995, Bloembergen *et al.* published their retrospective observations on US Renal Data System (USRDS) data that patients receiving PD experienced higher mortality than those on HD (7). Their findings were followed by a host of survival studies from

around the world, with conflicting results and, at best, trends for better survival for one modality or the other depending on age, comorbid illness, and dialysis vintage (8).

As clinicians wrestled with the uncertainty about which modality conferred longer survival and investigators dug deeper into their databases, early reports of higher mortality with PD likely influenced modality choice, with PD use in the United States declining in the years that followed. Fears of increased mortality with PD prompted some to advocate transferring patients to HD after the initial “honeymoon” period on PD (9,10).

In 2005, Jaar *et al.* compared 274 incident PD patients with 767 conventional HD patients over 2.4 years in the prospective observational Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study in the United States, using Cox proportional hazards analysis of registry data (11). Although the unadjusted death rate for PD was actually lower than that for HD, the adjusted risk of death for PD became greater than HD only after adjustment for laboratory values was layered onto the initial adjustments for demographic and treatment factors, and only in the second year of dialysis. This analysis was published in a general medical journal (11), and the adjusted results were carried in the popular press (“Peritoneal dialysis death risk higher than hemodialysis” (12)) with no mention of the quality-of-life component of the study.

Of note, Longenecker *et al.* had performed an earlier validation study on comorbidity reporting with Form 2728, used to collect national dialysis data (Medical Evidence Report for End Stage Renal Disease). They showed that bias toward greater PD mortality could arise in survival analyses of registry comorbidity data because of higher comorbidity-reporting sensitivity in

Correspondence:

Dr. Joanne M. Bargman, University Health Network, 200 Elizabeth Street 8N-840, Toronto, Ontario M5G 2C4, Canada. Email: joanne.bargman@uhn.ca

PD compared with HD patients (13). We commented at the time that when statistics do not make sense they should be questioned rather than being blindly accepted (14). Not surprisingly, Schulman commented in an editorial that the CHOICE study did not definitively resolve the controversy over which modality was “superior,” defined as length of survival (15). Subsequent studies were equally hamstrung by nonrandomized study populations, selection bias (16), modality transfer, modality exposure (as-treated versus intent-to-treat), and retrospective datasets, requiring investigators to use complex analytical methods, such as propensity matching and marginal structural modeling, in an attempt to compensate for the heterogeneous data. The limitations of retrospective database studies led Motheral *et al.* to caution that large database sample sizes can give rise to statistically significant differences that may not be clinically meaningful and, conversely, in small samples, meaningful differences may not reach statistical significance (17).

The elderly are the latest target in this focus on duration of survival. Last year, Han *et al.* (18) published their database study of 13,065 incident PD and HD Korean patients aged ≥ 65 years, showing a hazard ratio of 1.20 (95% confidence interval, 1.13 to 1.28) for poorer survival on PD. Their meta-analysis of 631,421 elderly patients in 15 nonrandomized studies showed a hazard ratio for PD over HD of 1.10 (95% confidence interval, 1.01 to 1.20). These studies were heterogeneous (hazard ratio, 0.27–2.01; I^2 statistic as high as 94.3%), and all were database studies. Iyasere and Brown highlighted in their editorial (19) that these studies did not adjust for frailty, a strong predictor of mortality and a common indication for PD. They noted that in France, where frail patients aged ≥ 75 years are preferentially offered assisted PD, median survival was 2 years, similar to that in the corresponding cohort in the United Kingdom, which is largely on HD, suggesting no large survival difference between PD and HD across the English Channel (20). Should we invest more time and dollars on dissecting ever more finely the intricacies of survival advantage by age, subgroup, dialysis vintage, and a host of other variables? Does it make sense to analyze survival by modality in the elderly when modality choice is highly patient specific, thus introducing significant selection bias, and when we already know from registry data that life expectancy is much reduced for either modality (20–22)?

The only attempt at a randomized controlled trial failed because most enrolled patients insisted on choosing their modality, suggesting that these patients valued personal choice and the benefits of their chosen modality more highly than supporting the study of their own survival (23). In their recent review of survival studies, Merchant *et al.* noted that large observational studies have shown no consistent long-term survival differences between PD and thrice-weekly conventional HD patients (24). Observed survival differences were subgroup specific and dependent on dialysis vintage and the statistical method applied. Because randomized controlled trials are impracticable, these authors recommended that modality choice be individualized with a view to optimizing the patient’s quality of life rather than duration.

Home HD versus PD and In-Center Conventional HD

With the advent of home HD, survival comparisons with PD and conventional HD are inevitable, but patient

selection criteria for home HD often preclude randomization and confound such comparisons. Home HD patients in Australia and New Zealand are younger, with fewer comorbidities, especially diabetes and cardiovascular disease, than patients undergoing PD and in-center HD. Not surprisingly, they lived longer (25,26), an outcome that published studies and registry data on the effect of age and comorbidities on mortality could have predicted (20,21).

Attempts to compare smaller home HD cohorts with PD and in-center HD using registry databases can be instructive from a methodological standpoint. Suri *et al.* used USRDS data to show that patients receiving daily home HD were hospitalized less than those undergoing PD and in-center HD, but exclusion criteria and propensity matching removed 98.6% (192,681 of 195,465) of PD patients and 99.8% (1,516,436 of 1,519,609) of in-center HD patients from comparison with those receiving daily home HD, of whom only 55.4% (1385 of 2501) were removed from comparison (27). Most PD patients were removed not for clinical reasons but because they did not start dialysis between 2004 and 2009 at the same time as the matched daily home HD patients or because they were not on Medicare and therefore had incomplete data. The authors stated that “well-conducted prospective studies are needed to confirm (their) findings.”

Quality of Life Is Priceless, but Survival Studies Are Expensive

The cost of a registry study has been estimated to range from \$800,000 to \$5 million, with an average of \$2–\$4 million, while observational studies cost on average \$100,000–\$3 million depending on study size and duration (28). In a meta-analysis, Ross *et al.* identified 55 registry and 82 nonregistry studies of survival by dialysis modality between 1980 and 1997 (8), while Merchant *et al.* reviewed 19 registry studies (24), one of which was also used by Ross *et al.* (8). Assuming that registry studies cost on average \$3 million and observational studies \$1 million each, we estimate the total cost of these studies alone to be \$300 million.

Modality Choice in Practice

In reality, modality choice and transfer between modalities is driven by a host of factors, such as patient characteristics,

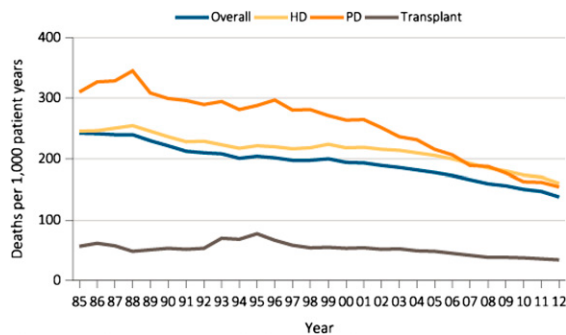


Figure 1. | All-cause patient mortality rates, overall and by modality, US Renal Data System ESRD Database, 2011. Adjusted for age, sex, race, and primary diagnosis. HD, hemodialysis; PD, peritoneal dialysis. Adapted from reference 21.

lifestyle constraints, clinical exigency, economics, modality availability, policy, and physician preference. In our experience, survival for a given modality does not figure prominently and is often irrelevant to the decision process. There is sufficient cumulative evidence that PD and conventional HD survival are similar enough (Figure 1; 8,21,29) that what our patients will need to guide them in choosing a modality are studies of the quality of life on different modalities and how that quality of life can be improved. The CHOICE, Netherlands Cooperative Study on the Adequacy of Dialysis, Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements, Frequent Hemodialysis Network, and other studies reported on quality of life in relation to dialysis modality but did not address the question of how to maximize quality of life within the constraints of the expected survival on a given modality (30–37). Patients, policymakers, and even physicians believe and hope that longer survival will mean better quality of life, but this is often not the case.

To this point, Gorodetskaya *et al.* reported that patients with stage 4 and 5 CKD had a dismal quality of life, similar to that of patients with metastatic colon cancer and stroke (38). Davison reported that 61% of prevalent dialysis patients wished they had not started dialysis (39) and that a third of them experienced high supportive and care needs (40). Dialysis patients experience a high symptom

burden for years, similar to that of patients with terminal cancer receiving palliative care (41,42), and symptoms correlate robustly with poorer quality of life after adjustment for depression (42). More than 58% of dialysis patients experienced chronic pain, and, of these, half rated the pain as moderate to severe (43). It would be instructive and sobering to know how many years patients like these survive with pain. Dialysis patients, especially the elderly, have significantly reduced quality of life, functional status, and ability to work (44,45), and this impairment begins during stage 4 and 5 CKD (38).

We contend that quality of life has been marginalized in the era of technology and the search for cures. There is currently no cure for ESRD. The lack of a cure should spur efforts to optimize quality of life in the time available to a patient. In cancer and palliative management this is intuitive, but it doesn't seem to be so for nephrologists (or journal editors).

Survival of the Fittest

Since duration of survival alone is no longer a sufficient criterion for the choice of dialysis modality, or dialysis versus conservative care, it leads to the question, "What do patients want us to address in research?"

Manns *et al.* reported 30 concerns important to patients (5). Only one related to the effect of dialysis modality on



Figure 2. | The patient-focused quality hierarchy or pyramid. The individual boxes are examples within the key layers that form the pyramid and are not meant to encompass all possible items within a layer. "What Matters Most" refers to outcomes that improve patients' health-related quality of life; "Measures of Effectiveness" refers to primary outcomes driven by lower complex programs and fundamental clinical areas of focus; "Complex Programs" refers to comprehensive and multifaceted clinical programs driven by fundamental clinical areas of focus and closely linked to highest-order outcomes; "The Fundamentals" refers to basic clinical information focusing largely on biochemical and surrogate data. AVF, arteriovenous fistula; CVD, cardiovascular disease; CVC, central venous catheter; EOL, end of life; HRQOL, health-related quality of life; MBD, mineral and bone disorder; Med, medical; mgmt, management; Pt., patient; PTH, parathyroid hormone; tx, treatment; URR, urea reduction ratio. Adapted with permission from reference 48.

survival duration, and even that was in the context of quality of life (5). Instead, patients want us to address problems of low energy, intractable itch, chronic pain, depression, difficulty sleeping, cramps, restless legs, and sexual dysfunction (5,42). They want better quality of life, education about their disease and treatment, communication, good dialysis access, infection control, and portable dialysis options. They want to exercise and travel. They want us to remove the barriers that impair their function and prevent them from realizing their potential. They want us to address caregiver and patient burnout. And they want the best possible care at the end of life. The overwhelming importance of quality of life to patients and caregivers was clear from the observations of Morton *et al.*, who found that patients were willing to trade off 15–23 months of life expectancy in return for greater freedom to travel and 7 months in exchange for fewer hospital visits (46,47).

Since 2009, the US Institute of Medicine and the Patient Centered Outcomes Research Institute have emphasized patient-centered care and research into the comparative effectiveness of dialysis modalities, with special attention to age, race, and ethnicity (1–4), factors that are highly relevant to the diverse aging ESRD population worldwide. To conceptualize this shift, Nissenson *et al.* proposed a Maslow-like “quality hierarchy or pyramid,” with quality of life at the apex, subserved by mortality, hospitalization, and patient experience (Figure 2; 48). These higher-order quality goals rest on a foundation of clinical fundamentals that has been the focus of dialysis quality assurance thus far, a fitting tribute to the work of the nephrology community to date. Only by shifting our collective mindset toward quality of life can we reorientate our research in a patient-centered manner (1,49). We have exhausted adjusted survival-by-modality studies, and it is time to look at what is more important to our patients and therefore should be more important to us.

What changes are necessary to shift our research focus? First, nephrologists need to be comfortable with qualitative research and metrics in addition to more familiar quantitative parameters such as Kt/V and left ventricular mass index. We must embrace the qualitative methods used in the social sciences (50), a field largely unfamiliar to nephrologists. Second, we need to explore the use of patient-reported outcomes as opposed to traditional quality-of-life measures, and determine whether existing quality-of-life instruments adequately assess patient issues in a racially and ethnically relevant manner. Third, there is a large unmet need for studies to elucidate racial and ethnic differences in quality-of-life issues. Fourth, research and policy changes should be driven by experienced practitioners with current patient contact to ensure that they are relevant to patient needs. Fifth, we need to support research to improve quality of life and discourage cookie-cutter survival studies. Research funding agencies and journal reviewers and editors are the gatekeepers who enable the continued performance and publication of studies of survival duration. We need the conviction and will to wean ourselves off such studies. Finally, quality-of-life metrics need to be incentivized in clinical practice to drive related research efforts. It is encouraging that from 2018, pain and depression will be included in the Clinical Measures for the ESRD Quality Improvement Program of the

US Centers for Medicare & Medicaid Services. Change may be painful, but the hope is that the pain will be worthwhile for the long-term benefit of patients.

Going beyond Survival

In summary, the initial rapid gains in survival on dialysis have slowed, leaving many unsolved problems that impair our patients’ quality of life. Although newer modalities have emerged, PD and conventional HD will continue to dominate dialysis practice globally for years to come. The survival studies that were relevant during the initial development of dialysis must now give way to greater focus on unmet patient needs that increase the burden of life on dialysis. It is our responsibility to use resources wisely for research that will truly make a difference in the lives of our patients.

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