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ASSOCIATION OF PRE-TRANSPLANT DIALYSIS MODALITY AND POST-TRANSPLANT OUTCOMES: A META-ANALYSIS

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♦ ***Background:*** **It remains unclear whether post-transplant outcomes differ according to the pre-transplant dialysis modality (peritoneal dialysis [PD] versus hemodialysis [HD]). We performed a meta-analysis of studies that assessed either post-transplant mortality, graft survival, or delayed graft function (DGF) in both PD and HD patients.**

♦ ***Methods:*** **Two independent authors searched English-language literature from January 1, 1980, through August 31, 2014, national conference proceedings, and reference lists. We used combinations of terms related to dialysis (hemodialysis, peritoneal dialysis, or renal replacement therapy), kidney transplant, and outcomes. Studies were included if they measured any of the 3 post-transplant study outcomes in both pre-transplant HD and PD.**

♦ ***Results:*** **A total of 16 studies were included in the final analysis. Of these, 6 studies reported adjusted hazard ratio for mortality, pooled adjusted risk ratio: 0.89 (95% confidence interval [CI] 0.82 – 0.97) in favor of PD ($p = 0.006$). The same 6 studies reported adjusted hazard ratio for graft survival, pooled adjusted risk ratio: 0.97 (95% CI 0.92 – 1.01, $p = 0.16$). A total of 13 studies reported unadjusted DGF. Pooled odds ratio: 0.5 (95% CI 0.41 – 0.63) in favor of PD ($p < 0.005$). Significant heterogeneity observed for all outcomes: I2 = 72.7%, I2 = 59.9%, and I2 = 66.8%, respectively.**

♦ ***Conclusions:*** **Based on these results, pre-transplant PD is associated with better post-transplant survival than HD. Pre-transplant PD was also associated with decreased risk for DGF compared with HD, although these results were unadjusted. There was no significant difference in graft survival between pre-transplant HD and PD. These results suggest that PD may be the preferred dialysis modality for patients expected to receive a transplant.**

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KEY WORDS: Dialysis; peritoneal; hemodialysis; transplant.

The burden of end-stage renal disease (ESRD) has been increasing, with over 600,000 prevalent ESRD patients in the US as of 2013 (1). The increasingly long transplant list and relatively small numbers of living donors means that a majority of patients will need dialysis prior to kidney transplant. While transplantation is the modality of choice for renal replacement therapy, there is not yet consensus on whether there is a preferred pre-transplant dialysis modality, i.e. hemodialysis (HD) versus peritoneal dialysis (PD) (2–4).

Increasing utilization of PD over recent years has prompted a renewed interest in this topic. While studies have indicated that there are certain advantages of PD over HD in the general ESRD population, such as patient satisfaction, preservation of residual renal function, and early survival advantage after initiating dialysis, the advantages in patients who go on to receive a transplant have been more difficult to ascertain (5). Early studies demonstrated that transplant outcomes in PD patients were at least equivalent to HD patients, leading to wider recognition of PD as an acceptable mode of pre-transplant dialysis (6). The consideration that pre-transplant PD may lead to superior post-transplant outcomes led to further investigation, but early studies produced conflicting results. Due to the variable results produced by these smaller studies, investigators analyzed large transplant databases in the 1990s, but even the 3 largest cohort studies done by Snyder *et al.*, Goldfarb-Rumyantzev *et al.*, and Molnar *et al.* again gave contradictory results (7–9).

The question of preferred pre-transplant dialysis modality therefore remains unanswered. As post-transplant patient mortality and graft loss continue to be of central interest to both transplant recipients and their providers, any benefit conferred by pre-transplant dialysis modality is important in making decisions regarding pre-transplant care for patients. In order to better elucidate if there is a true impact of pre-transplant dialysis modality on post-transplant outcomes, we performed a meta-analysis of all studies in the past 30 years which compared the post-transplant outcomes of delayed graft function (DGF), patient or graft survival in pre-transplant PD and HD patients.

METHODS

LITERATURE SEARCH

Two independent authors (EJ, AG) conducted a computerized PubMed (MEDLINE) search of English-language literature from January 1, 1980, through August 31, 2014. We used combinations of terms related to dialysis (hemodialysis, peritoneal dialysis, or renal replacement therapy), kidney transplant, and outcomes (Appendix A). The reference lists of

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all articles identified were hand searched for additional titles. Additionally, the Cochrane Database was searched for articles. We reviewed abstracts of the American Society of Nephrology and National Kidney Foundation annual scientific meetings from 2008 – 2013. We did not include any unpublished studies. The study protocol was designed to conform to MOOSE and PRISMA guidelines; this was independently verified by 2 authors (EJ, SW) (10,11).

INCLUSION CRITERIA

Observational, case control, and randomized controlled trials were included if they reported any 1 of the 3 study outcomes of interest (DGF, graft survival, or mortality) in both pre-transplant HD and PD patients. It was decided, *a priori*, to exclude non-English articles, pediatric studies, review articles, and commentaries. From the 6,548 citations initially identified, 111 were appropriate for further review. These articles were reviewed in depth by 2 independent authors (EJ, AG) to determine if they met inclusion criteria. If there was disagreement, this was resolved by consensus or arbitration by a third author (MRC).

STUDY SELECTION AND DATA ABSTRACTION

Of the 111 studies reviewed, 73 were excluded due to incorrect topic, and an additional 9 were non-English, review articles, pediatric studies, or commentaries. Five articles did not include the pertinent data or the pertinent outcomes were not measured. Finally, an additional 8 articles were eliminated for not including DGF or survival analyses (Figure 1). A total of 16 articles were included for final analysis.

Data from each article were abstracted by 2 authors (EJ, AG) using a standardized template, and data collected included dates of study, type of study, location of study centers, number of patients, and outcomes of interest including time-points for outcomes.

STATISTICAL ANALYSIS

Kappa scores were used to assess inter-observer agreement between the 2 reviewers. Analyses were performed for all studies and after stratification by study design (case control or observational) and dialysis modality (PD or HD).

The outcomes were pooled using random effects models to take into account the heterogeneity of studies (12). Publication bias was assessed using funnel plots. Heterogeneity across studies was assessed using the I^2 index. Stata/MP13 (Stata Corporation, College Station, Texas, USA) was used for all analyses. A p value of < 0.05 was considered statistically significant.

ASSESSMENT OF STUDY QUALITY

We assessed study quality by using a modification of the US Preventive Services Task Force criteria, described by Fletcher *et al.* (13,14). By these standards, properly designed randomized controlled trials constitute the highest tier evidence; well-designed non-randomized trials, case-control, or cohort analytic studies provide second-tier evidence. All studies that were identified provided second-tier evidence. The quality of individual studies was additionally assessed by 2 independent reviewers (EJ, SW) using the Newcastle-Ottawa Scale (15).

We defined studies as truly observational only in instances in which the study and data collection were explicitly planned at the time of collation of the study cohort (16). Only in such circumstances would study follow-up procedures be expected to be conducted for the purposes of the study question. Thus, post-hoc analysis of a prospective study cohort was considered observational.

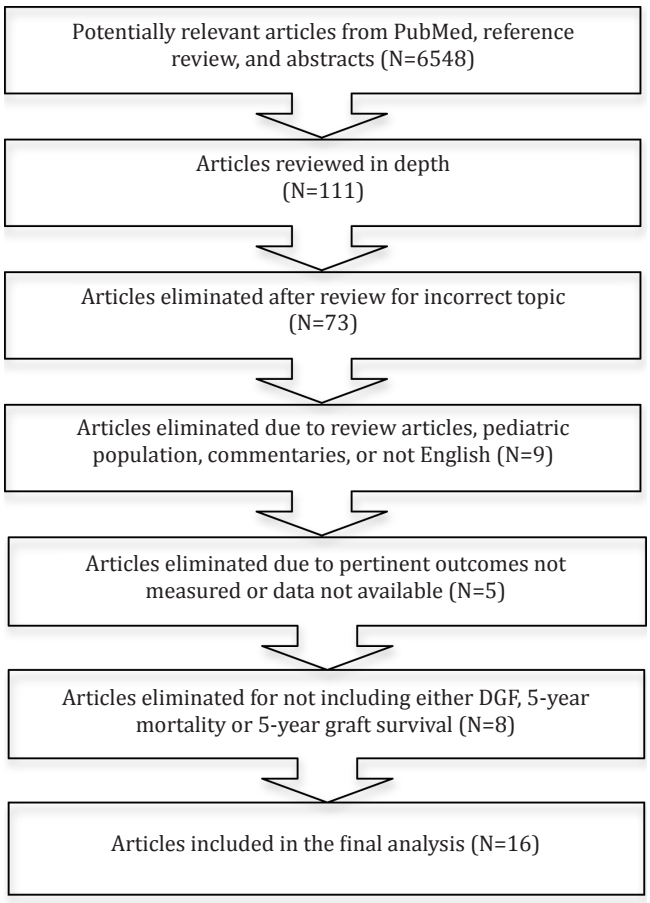

Figure 1 — Literature search strategy. DGF = delayed graft function.

RESULTS

The results of the literature search strategy are shown in Figure 1. The agreement in selection of studies between the reviewers was excellent ($\kappa = 0.87$; 95% confidence interval [CI] 0.78 – 0.97). There were a total of 16 studies that included at least 1 outcome of interest, and they are summarized in Table 1 (6–9,17–28). Individual studies reported different time points for graft survival and post-transplant mortality. As 5-year outcomes were the most frequent, we included only those studies

TABLE 1
Summary of Included Studies

Authors	Publication year (years of study)	Location	Type of study	Number of patients	Outcomes reported	Included living donors?
López-Oliva *et al.* (17)	2014 (1990–2002)	Spain	Case control	HD 118 PD 118	5-yr mortality 5-yr death-censored graft survival DGF	Yes
Molnar *et al.* (9)	2012 (2001–2006)	United States (SRTR data)	Retrospective, observational	HD 12,416 PD 2,092	5-yr mortality 5-yr death-censored graft survival DGF	Yes
Sharma *et al.* (18)	2012 (2000–2006)	United States (Virginia)	Retrospective, observational	HD 339 PD 62	DGF	Yes
Kramer *et al.* (19)	2012 (1999–2008)	Europe (16 registries)	Retrospective, observational	HD 18,953 PD 10,135	5-yr mortality 5-yr graft survival	Yes
Freitas *et al.* (20)	2011 (2004–2009)	Portugal	Retrospective, observational	HD 268 PD 38	DGF	Yes
Sezer *et al.* (21)	2011 (2000–2005)	Turkey	Retrospective, observational	HD 180 PD 70	DGF	Yes
Schwenger *et al.* (22)	2011 (1998–2007)	Europe, North America, New Zealand, Australia	Retrospective, observational	HD 45,651 PD 11,664	5-yr mortality 5-yr death-censored graft survival	No
Yang *et al.* (23)	2009 (not specified)	China	Retrospective, observational	HD 303 PD 99	DGF	No
Caliskan *et al.* (24)	2009 (1983–2006)	Turkey	Case control	HD 44 PD 44	DGF	Yes
Goldfarb-Rumyantzev *et al.* (8)	2005 (1990–1999)	United States (USRDS)	Retrospective, observational	92,844 (PD vs HD not specified)	5-yr mortality 5-yr death-censored graft survival	Yes
Snyder *et al.* (7)	2002 (1995–1998)	United States (Center for Medicare/ Medicaid Services)	Retrospective, observational	HD 17,115 PD 5,621	5-yr mortality 5-yr death-censored graft survival DGF	Yes
Joseph *et al.* (25)	2002 (1991–1996)	Glasgow, UK	Retrospective, observational	HD 117 PD 183	DGF	No
VanBiesen *et al.* (26)	2000 (1990–1995)	Belgium	Retrospective, observational	HD 79 PD 40	DGF	No
Vanholder *et al.* (27)	1999 (1985–1995)	Germany, Belgium (Eurotransplant)	Case control	HD 117 PD 117	DGF	No
Binaut *et al.* (28)	1997 (1986–1995)	France	Case control	HD 71 PD 71	DGF	No
Shapira *et al.* (6)	1985 (1980–1983)	Israel	Retrospective, observational	HD 105 PD 32	DGF	No

HD = hemodialysis; PD = peritoneal dialysis; DGF = delayed graft function.

with adjusted values for these outcomes for analysis of graft survival and mortality.

POST-TRANSPLANT MORTALITY

There were 6 studies that reported adjusted hazard ratios for 5-year mortality, which included 216,727 patients from United States, New Zealand, Australia, and Europe (Figure 2). Pre-transplant PD was associated with a lower 5-year mortality after transplant compared to HD (pooled adjusted hazard ratio 0.89; 95% CI 0.82 – 0.97, $p = 0.006$).

POST-TRANSPLANT GRAFT SURVIVAL

The same 6 studies also reported adjusted hazard ratio for 5-year graft survival (Figure 3). There was no significant difference in graft survival between patients on pre-transplant PD versus HD (pooled adjusted hazard ratio 0.97; 95% CI 0.92 – 1.01, $p = 0.16$).

DELAYED GRAFT FUNCTION

There were 13 studies that reported unadjusted DGF, which included 39,859 patients from the United States, Europe, Portugal, China, Turkey, and Israel (Figure 4). Pre-transplant PD was associated with lower risk of DGF compared with HD (pooled odds ratio 0.5; 95% CI 0.41 – 0.63, $p < 0.005$).

Significant heterogeneity was observed for all outcomes: $I^2 = 72.7\%$, $I^2 = 59.9\%$, and $I^2 = 66.8\%$, respectively.

PUBLICATION BIAS

Funnel plots to assess for publication bias for 5-year mortality, 5-year graft survival, and DGF are shown in Figures 5, 6, and 7, respectively. There appeared to be publication bias for 2 outcomes, DGF, and 5-year mortality.

Sensitivity analysis for 5-year mortality was performed after excluding 2 small studies that had large effect size and large standard errors (López-Oliva *et al.* and Molnar *et al.*) (17,9). In the sensitivity analysis, PD continued to show a 5-year mortality advantage over HD, with an adjusted hazard ratio of 0.92 (95% CI 0.86 – 0.97, $p = 0.006$), without publication bias.

STUDY QUALITY

The quality of all 16 studies included in this analysis was assessed using the Newcastle-Ottawa scale, the results of which are shown in Supplemental Table 1. Out of a total of 9 possible stars, the studies received between 5 and 7 stars for quality. Of the 6 studies that reported 5-year mortality and 5-year graft loss, 2 were given a score of 7, and 4 were given a score of 6.

DISCUSSION

Our meta-analysis found that pre-transplant PD is associated with lower 5-year mortality after transplant than HD, with a hazard ratio of 0.89 (95% CI 0.82 – 0.97). While there were only 6 studies reporting 5-year adjusted mortality for patients, this comprised a total 216,727 patients from multiple countries. These same 6 studies also reported adjusted 5-year graft survival in the pooled analysis, with no significant difference in graft survival between patients on pre-transplant PD versus

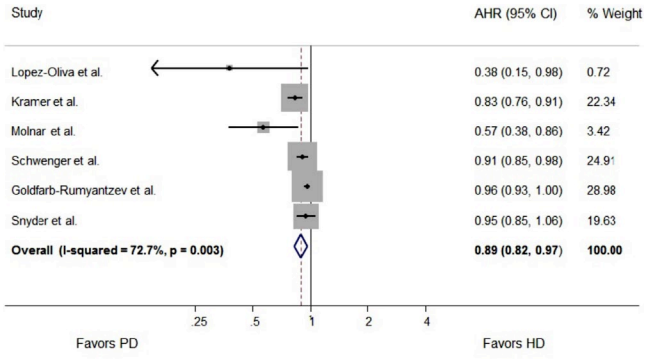

Figure 2 — Five-year post-transplant mortality. AHR = adjusted hazard ratio; CI = confidence interval; PD = peritoneal dialysis; HD = hemodialysis.

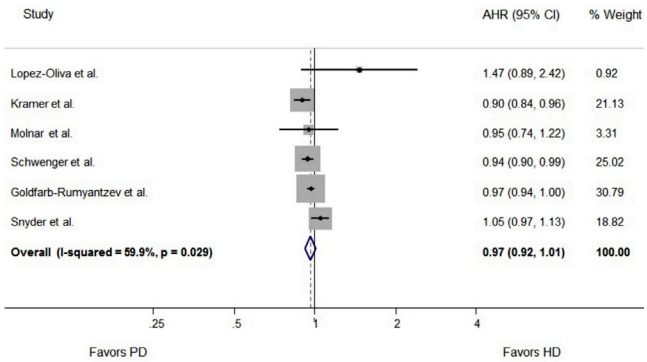

Figure 3 — Five-year post-transplant graft survival. AHR = adjusted hazard ratio; CI = confidence interval; PD = peritoneal dialysis; HD = hemodialysis.

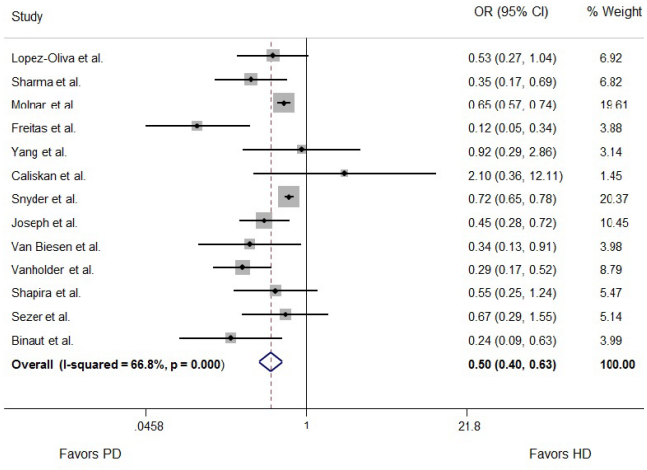

Figure 4 — Delayed graft function. OR = odds ratio; CI = confidence interval; PD = peritoneal dialysis; HD = hemodialysis.

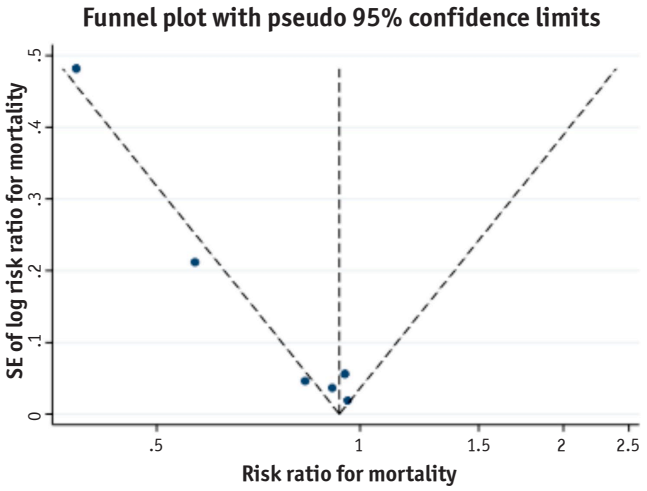

Figure 5 — Funnel plot for 5-year post-transplant mortality. SE = standard error.

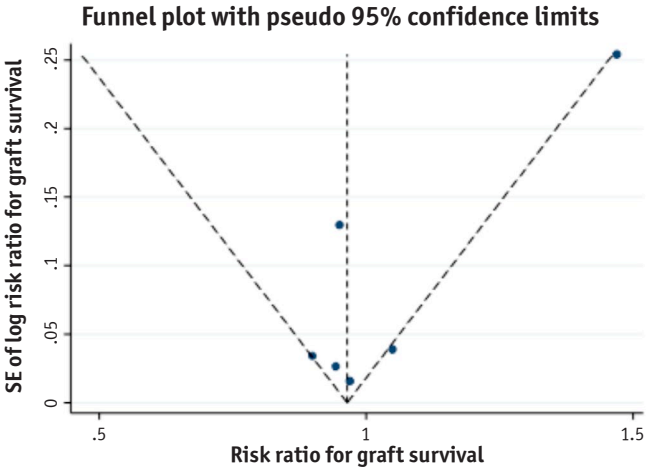

Figure 6 — Funnel plot for 5-year post-transplant graft survival. SE = standard error.

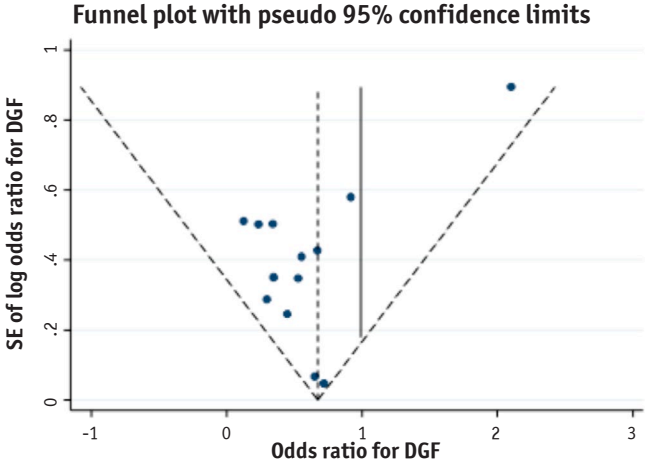

Figure 7 — Funnel plot for delayed graft function. SE = standard error; DGF = delayed graft function.

HD. Pre-transplant PD was associated with a lower risk of DGF compared with HD, with a pooled odds ratio of 0.5 (95% CI 0.41 – 0.63). There were a total of 39,857 patients included in this analysis; unfortunately, these results were all unadjusted.

Among the studies analyzed, the 2 largest studies published in the early 2000s comprised US data from overlapping time periods, yet yielded different results. While Snyder *et al.* showed there was no significant difference in mortality or graft survival according to dialysis modality, there was a 15% increased risk of death-censored graft failure with PD which occurred in the first 3 months after transplant (7). This was attributed to the increased rate of vascular thrombosis in patients who had been on PD. In contrast, Goldfarb-Rumyantzer *et al.* found that PD either immediately preceding transplant or as the predominant dialysis modality predicted better graft and patient survival (HR 0.97 and 0.94, respectively) (8).

The 3 largest more contemporary studies included in this analysis also had variable results for patient and graft survival. In their standard analysis of patients from 16 European registries, Kramer *et al.* showed that PD was associated with both better patient and graft survival (19). However, they also performed an instrumental variable analysis, which failed to show this advantage of PD. Schwenger *et al.* found that PD had a 10% lower all-cause mortality, but similar death-censored graft survival compared with HD (22). Molnar *et al.* reported lower all-cause and cardiovascular mortality among patients on PD, but no difference in graft survival (9). Each of these studies included over 10,000 patients, although the relative number of PD patients was small.

While the exact etiology of the differences observed in patients on HD versus PD are unknown, one theory regarding the apparent improved patient survival among those on pre-transplant PD is that these patients have a lower degree of inflammation compared with patients on HD (25). Hemodialysis has been shown to cause recurrent activation of inflammatory pathways, with dialysis membranes causing increase in circulating complement, phagocytic leukocyte activation, and free radical production, leading to a chronic micro-inflammatory state (27,29–32). Additionally, there is evidence that oxidative stress may be lower among patients on PD (30). However, it would be expected that increased oxidative stress among former HD patients would also lead to a decrease in graft longevity, which has not been consistently observed, and is not supported by the results of this meta-analysis.

Delayed graft function consistently appears to be lower among patients who were on pre-transplant PD. These results have been emphasized in many studies as a surrogate for improved post-transplant outcomes, as multiple separate studies have demonstrated that DGF is associated with increased patient mortality, graft failure (including death-censored graft failure), and higher creatinine post-transplant (7,27,33–41). However, this correlation was not seen in many of the individual studies of this meta-analysis and is not reflected in the pooled analysis. Theories as to the decreased rate of DGF reported among former PD patients include more stable volume

status, decreased oxidative stress, and greater residual renal function among patients on PD (27,30,42–45). However, given that the results were unadjusted, it is likely there are many confounding factors in the apparent lower DGF rate among PD patients. These factors include differences in baseline characteristics of PD patients, residual renal function among PD patients, and perhaps a propensity to dialyze HD patients with DGF earlier, provided they have existing vascular access. Additionally, our analysis did reveal publication bias among the studies reporting DGF, thus further limiting our ability to interpret these results.

The conflicting results for post-transplant outcomes even among large studies that adjust for many covariates highlights the difficulty in determining if there is a true effect of pre-transplant dialysis modality on patient or graft survival. One of the significant challenges in comparing outcomes according to dialysis modality is the inherent differences in patient populations: patients on PD are generally younger, healthier, have been on dialysis for a shorter time, and additionally receive transplants at a higher rate than those on HD (7). There may be additional selection bias in that patients who are perceived to be better transplant candidates are preferentially started on PD (8). Furthermore, PD patients tend to be more independent, engaged in their own health, and maintain employment at a higher rate than those on HD, making the transition to the rigorous regimen needed to maintain a transplant more streamlined (46). Even after adjusting for patient and transplant factors, it remains possible that these inherent differences between patients on PD and HD account for the improved survival seen with PD in our analysis. Additionally, there appeared to be publication bias among the studies for the mortality outcome, although after performing sensitivity analysis, the mortality benefit of PD persisted.

While it remains unclear to what degree PD may benefit patients who go on to receive a kidney transplant, there are other demonstrated benefits of PD compared to HD, including increased quality of life, improved psychosocial adaptation, physical function, mental health, and decreased pain (5,47–49). These factors, along with the mortality advantage demonstrated in this meta-analysis, support PD as a preferred modality for patients who will likely go on to be transplanted in the near future.

Limitations of this meta-analysis include the small number of studies with the same time points for mortality and graft survival. Of the 16 original studies included in this study, only 6 had data available for adjusted 5-year mortality or graft function, and this was the most frequent time point studied. Unfortunately, this removes some data from our meta-analysis, and also the few and variable other time points studied did not allow us to form conclusions about relative benefits of dialysis modalities early versus later in the post-transplant period.

The studies included in this meta-analysis additionally had a high rate of heterogeneity, implying a significant variation of effect across studies. We recognize this as an inherent deficiency given the different modalities of dialysis, duration of dialysis, and practice patterns, and we employed random effects models that consider intrinsic between-study variance of effect, in addition to variance due to sampling error or within-study variance (50,51). Additionally, the data reported for DGF were unadjusted, which leaves open the possibility that confounding affected the observed associations.

Finally, the data reported here were all from either retrospective observational or case-control studies. Although a randomized trial of PD versus HD would be helpful in eliminating selection bias, it is nearly impossible to randomize patients to a particular dialysis modality pre-transplant. However, more consistent data collection from transplant programs, including standardized reporting of outcomes at certain time points, could lead to a more thorough understanding of any possible benefits conferred by pre-transplant dialysis modality, help elucidate the reasons for these benefits, and ultimately help improve post-transplant outcomes.

CONCLUSION

This meta-analysis suggests that PD may be the preferred dialysis modality for those patients who go on to receive a renal transplant, as patients on PD had improved post-transplant survival and potentially lower risk of DGF. There was no difference in graft survival compared with patients on pre-transplant HD.

DISCLOSURES

Portions of the manuscript were presented in abstract form at the American Society of Nephrology Annual Scientific Meeting 2015, San Diego, CA, USA. The authors have no financial conflicts of interest to declare.

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