

Continuation of Peritoneal Dialysis in Adult Kidney Transplant Recipients With Delayed Graft Function



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Introduction: Peritoneal dialysis (PD) has been used increasingly in past decade. Many of these patients undergo transplantation and may require dialysis for delayed graft function (DGF). The outcomes of DGF based on the post-transplantation dialysis modality are not well known.

Methods: We retrospectively reviewed all adult kidney transplant recipients (KTRs) from the University of Wisconsin School of Medicine and Public Health who developed DGF between November 2015 and April 2019. Patients were divided into those who received hemodialysis (HD) or PD during the DGF period. Immediate graft explant, DGF among living donor KTRs, or those requiring just a single dialysis treatment were excluded.

Results: Of 224 KTRs with DGF during the study period, 167 fulfilled our selection criteria. There were 16 patients in the PD and 151 in the HD group. Baseline characteristics were similar between the two groups, except diabetes was more prevalent in the HD group. Five of 16 PD patients had to be transitioned to HD. There was no difference in DGF duration, hospital length of stay, infectious or surgical complications, rejection at various time periods, graft function at last follow-up, or graft failure. In multivariate analysis, only rejection within the first year of transplantation (hazard ratio [HR]: 4.26; 95% confidence interval [CI]: 1.20–15.08; $P = 0.02$) and post-surgical complications (HR: 3.79; 95% CI: 1.03–13.91; $P = 0.04$) were associated with death-censored graft failure (DCGF). The use of PD for treatment of DGF was not associated with DCGF.

Conclusions: In carefully selected patients, PD can be continued safely for DGF without any effect on short-term or long-term transplant outcomes.

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KEYWORDS: delayed graft function; hemodialysis; kidney transplantation; peritoneal dialysis; peritoneal fluid leak; peritonitis

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DGF is defined as the need for dialysis within the first 7 days of kidney transplantation.¹ The incidence of DGF is variable among different centers due to differences in definitions and thresholds to dialyze the patients.² In recent years, the overall incidence in the United States has increased from 24.4% to 29.2%.³ This has partly been attributed to the use of more organs with higher kidney donor profile index (KDPI).⁴ DGF is associated with poor outcomes including acute rejection and lower graft and patient survival rates.^{5–7} Additionally, it can lead to higher health care costs

because of the need for dialysis and prolonged hospitalization.⁸

The prevalence of PD has been increasing steadily.⁹ This is partly due to changes in reimbursement models for home dialysis therapies¹⁰ but also due to recognition of clinical benefits such as better preservation of residual renal functions, avoidance of central venous catheters (CVC), and higher patient satisfaction.^{11–14} In addition, PD patients are more likely to require kidney transplantation¹⁵ and have a lower risk of DGF.^{16,17} As a result, more patients on PD are undergoing kidney transplantation, and some of them develop DGF. This poses an important question as to whether PD can be performed safely in the postoperative period during DGF. Previous studies have raised concerns about the higher risk of peritonitis, wound infection, and other complications in the post-transplantation period, with

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some advocating removal of all PD catheters at the time of transplantation.¹⁸⁻²¹ On the other hand, some studies have shown a low rate of these complications.²²⁻²⁴ Consequently, there is no consensus on how long the PD catheter should be retained after transplantation and whether PD should be performed in DGF.²⁵

In 2015, our program implemented guidelines to continue PD in patients who developed DGF. This study aims to evaluate the outcomes of these patients and compare them with those who underwent HD during DGF.

METHODS

Study Population

We conducted a retrospective review of all KTRs from November 2015 to April 2019. We chose November 2015 as our starting point because our institution did not routinely use PD for the treatment of patients with DGF before then. Inclusion criteria were all adult patients who were on any form of dialysis, received kidney transplantation, and developed DGF. Exclusion criteria were patients who had immediate graft explant because of thrombosis or other technique-related failure, DGF among living-donor KTRs, and those who only required one dialysis session post-transplantation. We excluded DGF among living donors as DGF in the living-donor recipient is very rare and none of the patients with DGF in living-donor transplant received PD. All included recipients had at least two dialysis sessions. All patients who received PD post-transplantation had been receiving PD before transplantation. The project was approved by the University of Wisconsin Institutional Review Board. The activities in this paper conform to the Principles of the Declaration of Istanbul.

Guidelines for Using PD in DGF

Any patient who was receiving PD before the transplantation was considered for the continuation of PD during DGF. Before initiation, the treating team was required to confirm with the surgeons that the peritoneum was intact, no peritoneal window was created, and there was no ileus or an emergent indication for dialysis, particularly life-threatening hyperkalemia or volume overload. An approval from the transplantation surgeon was obtained before initiation. Continuous ambulatory PD (CAPD) was avoided to prevent an increase in intra-abdominal pressure and the risk of a leak. Before initiating PD, a test dwell with 500 ml of 1.5% dextrose PD solution was performed to ensure that there was no leak from the surgical incision or any abdominal discomfort. Subsequently, low-volume dwells, not exceeding 1 l, were performed in supine position to prevent higher intra-abdominal pressure.

Total volume was maintained at or below two-thirds of the patient's usual prescription. Heparin was not instilled in the PD solution. Modality was switched to HD if any complication was encountered. If patients required dialysis upon discharge, they were instructed to continue PD at home and were followed up in a dedicated DGF clinic every week until they had enough graft function to stop dialysis.

Immunosuppression

All patients received dexamethasone or methylprednisolone at the time of transplantation. Induction was performed using antithymocyte globulin, alemtuzumab, or basiliximab based on the patient's immunological risk, cause of end-stage renal disease (ESRD), or plan for an early steroid withdrawal as explained in Parajuli *et al.*²⁶ Maintenance immunosuppression included calcineurin inhibitors (tacrolimus), mycophenolate derivatives (mycophenolate mofetil or mycophenolic acid), and prednisone. Most of the patients got triple immunosuppression whereas some received early steroid withdrawal regimens. Calcineurin inhibitors were usually started within 24 hours of transplantation regardless of DGF.

Variables and Definitions

DGF was defined as the need for renal replacement therapy within the first week of kidney transplantation. Modalities included HD, PD, and continuous venovenous hemofiltration. Indications for dialysis included hyperkalemia, acidosis, anuria, uremia, or fluid overload refractory to diuretic therapy. Duration of DGF was defined as the time interval between the first and the last dialysis. Peritonitis was defined as peritoneal fluid total white cell count of at least 100/ μ l and >50% polymorphonuclear cells after 2-hour dwell of peritoneal fluid.²⁷ Central line-associated blood stream infection was defined as laboratory-confirmed blood stream infection that was not secondary to infection at any other body site.²⁸ Graft failure was defined as the return to dialysis, re-transplantation, or death. Clinical characteristics analyzed were age, sex, race, type of deceased donor transplant, type of induction therapy, previous transplants, cold ischemia time, human leukocyte antigen mismatch, causes of kidney failure, and mean KDPI.

Outcomes

Outcomes specific to DGF included duration of DGF and duration of hospital stay during DGF. Outcomes related to rejection included rejection episodes during the period of DGF, 3, 6, and 12 months post-transplantation. Complications such as BK or cytomegalovirus (CMV) viremia, peritonitis in PD patients,

Table 1. Reasons for Immediate Conversion From PD to HD During DGF^a

Reason for conversion	N
Surgeons' preference	12
Intraoperative removal of the PD catheter	11
Life-threatening hyperkalemia	5
Intraoperative breach in peritoneal membrane	3
Presence of a permanent hemodialysis access	3

^aDGF, delayed graft function; HD, hemodialysis; PD, peritoneal dialysis.

catheter-associated bacteremia in patients on HD via CVC, and those related to the surgical procedure were recorded. Outcomes at last follow-up included serum creatinine level and estimated glomerular filtration rate in a functioning graft, and incidence of graft failure and DCGF.

Statistical Analysis

Continuous data were compared using Student *t* test or the Wilcoxon rank sum test, when appropriate, and categorical data were analyzed using the Fisher exact test or the chi square test, when appropriate. Uncensored and DCGF was analyzed using Kaplan-Meier analyses. *P* values < 0.05 were considered statistically significant. Also, risk factors associated with DCGF were studied using univariate and multivariate stepwise Cox regression analyses. Most of the variables in Table 1 were included in the univariate analysis. Variables associated with outcomes at a *P* value of ≤ 0.10 in univariate analysis were kept in the multivariate analysis.

RESULTS

A total of 224 patients had DGF during the study period (Figure 1). One hundred sixty-seven patients fulfilled our selection criteria, of which 16 patients were in the PD and 151 were in the HD group. Fifty

patients were receiving PD, whereas 117 were receiving HD pretransplantation. Of the 50 DGF patients who were receiving PD, 34 were switched to HD immediately during DGF. The most common reasons for the conversion include surgeons' preference to avoid PD (*n* = 12), and intraoperative removal of PD catheter (*n* = 11) (Table 1).

Baseline Characteristics

Table 2 shows the baseline characteristics of both groups. Most of the baseline characteristics were similar between the groups, except glomerulonephritis as a cause of ESRD was more prevalent in the PD group and diabetes was more common in the HD group.

Outcomes specific to DGF

There was no difference in the mean length of hospital stay post-transplantation between the two groups (6.7 ± 2.7 days in PD vs. 6.6 ± 2.1 days in HD, *P* = 0.95). Similarly, there was no difference in the mean duration of DGF between the two groups (8.6 ± 12.5 days in PD vs. 9.9 ± 9.6 days in HD, *P* = 0.62) (Table 3). In the PD group, 5 of 16 (31.3%) were switched to HD during the DGF period. Three were switched due to poor clearance, whereas one was switched due to pain which was related to peri-graft hematoma and another due to peritonitis. Only one patient (6.25%) had peritonitis, and none had a fluid leak or wound infection. Among the patients who underwent HD, 58 had a CVC placed. Two patients (3.4%) developed central line-associated bacteremia.

Rejection, Graft Survival, and Other Complications

The mean follow-up period was 27.8 ± 15.4 months for the PD group and 24.4 ± 12.3 months for the HD group. There was no statistically significant difference

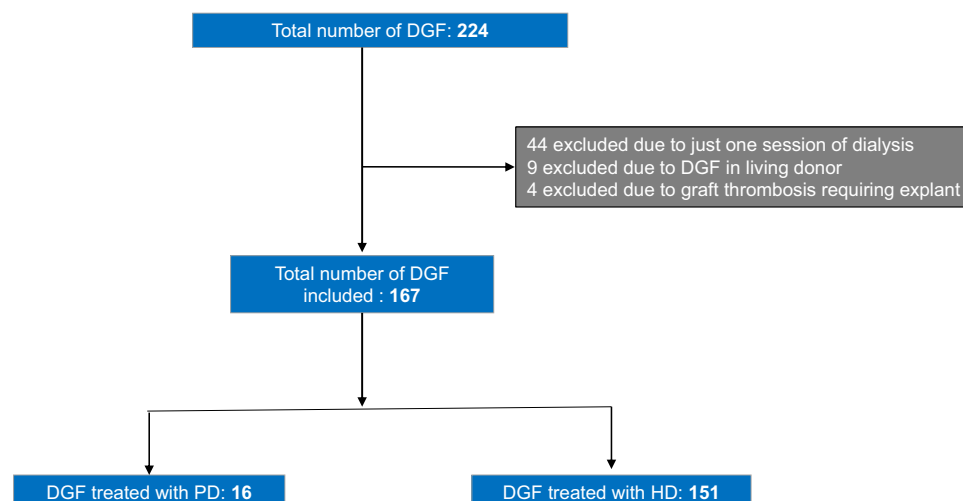


Figure 1. Study design. DGF, delayed graft function.

Table 2. Baseline Characteristics^{a,b}

Variables	PD (n = 16)	HD (n = 151)	P
Male	10 (63)	98 (65)	0.85
Mean age at time of transplantation, years	55.0 ± 11.7	55.5 ± 11.3	0.86
Caucasian	10 (63)	100 (66)	0.76
Types of transplantation			0.27
DBD	5 (31)	69 (46)	
DCD	11 (69)	82 (54)	
Induction immunosuppression			0.58
Basiliximab	5 (31)	41 (27)	
Antithymocyte globulin	7 (44)	85 (56)	
Alemtuzumab	4 (25)	25 (17)	
Previous transplants	1 (6)	30 (20)	0.18
Mean cold ischemia time, hours	15.6 ± 6.1	15.8 ± 6.8	0.94
Mean HLA mismatch (of 6)	4.1 ± 1.4	4.3 ± 1.6	0.69
Cause of kidney failure			0.001 ^c
Diabetes	3 (19)	52 (34)	
Glomerulonephritis	6 (38)	32 (21)	
Hypertension	1 (6)	31 (21)	
PKD	1 (6)	13 (9)	
Other	5 (31)	23 (15)	
Mean KDPI, %	65.4 ± 23.6	61.4 ± 24.3	0.55

^aDBD, donation after brain death; DCD, donation after cardiac death; HLA, human leukocyte antigen; HD, hemodialysis; KDPI, kidney donor profile index; PD, peritoneal dialysis; PKD, polycystic kidney disease.

^bValues are n (%) unless otherwise noted.

^cStatistically significant.

in serum creatinine and estimated glomerular filtration rate between the two groups at last follow-up (Table 3). In addition, there was no difference in the total number of graft failures (Figure 2a) or in DCGFs (Figure 2b) between the two groups. The rejection rates between the two groups were similar during the DGF period as well as in 3-, 6-, and 12-month periods. Similarly, rates of CMV and BK infections and surgical complications did not differ significantly between the groups (Table 3).

Factors Associated With DCGF

Table 4 describes the univariate and multivariate analyses of the factors associated with DCGF. Longer duration of DGF was associated with a higher risk of DCGF on univariate analysis (HR: 1.04; 95% CI: 1.01–1.08; $P = 0.02$), but not on multivariate analysis (HR: 1.01; 95% CI: 0.97–1.05; $P = 0.64$). Rejection within the first year and presence of post-surgery complications were associated with higher risk of DCGF in both univariate (rejection within first year: HR: 5.32; 95% CI: 1.61–17.56; $P = 0.006$; post-surgery complications: HR: 4.82; 95% CI: 1.46–15.92; $P = 0.009$) and multivariate analyses (rejection within first year: HR: 4.32; 95% CI: 1.21–15.43; $P = 0.02$; post-surgery complications: HR: 3.78; 95% CI: 1.02–13.96; $P = 0.04$). Receiving PD during the DGF period did not increase the risk of DCGF during the follow-up period.

Outcomes in All Pretransplantation PD Patients

As opposed to HD patients, PD patients may have certain pretransplantation characteristics that affect the duration of DGF, particularly better residual renal function. Therefore, we separately analyzed the cohort of all pretransplantation PD patients who had DGF to see if switching the modality to HD had any effect on DGF duration. Of the 50 pretransplantation PD patients, 16 continued PD, whereas 34 were switched to HD. There was no difference in the duration of DGF between these two groups (8.6 ± 12.5 days for those who continued PD vs. 8.4 ± 8.9 days for those who switched to HD; $P = 0.95$). Similarly, there was no difference in the uncensored or DCGF in this subgroup of recipients with DGF (Figure 3a and b)

DISCUSSION

In this series of 16 deceased donor kidney recipients, who were receiving PD pretransplantation and continued it during DGF post-transplantation, we found similar outcomes to those who underwent HD during the DGF period. This includes immediate DGF-related outcomes such as hospital length of stay and duration of DGF but also long-term outcomes such as rate of DCGF. Furthermore, complications such as rejections and infections were similar as well.

Multiple studies have looked at the incidence of PD-related side effects in the post-transplantation period.^{18–24} Some have reported high incidence of complications such as peritonitis, wound infection, and

Table 3. Comparison of Outcomes of DGF-PD and DGF-HD Groups^{a,b}

Variables	PD (n = 16)	HD (n = 151)	P
DGF specific			
Mean hospital stay, days	6.7 ± 2.7	6.6 ± 2.1	0.95
Mean duration of DGF, days	8.6 ± 12.5	9.9 ± 9.6	0.62
Kidney function at last follow-up			
eGFR, ml/min/1.73 m ²	49.5 ± 16.4	50.4 ± 17.8	0.85
SCr, mg/dl	1.5 ± 0.6	1.5 ± 0.7	0.98
Rejection			
During the DGF period	0 (0)	3 (2)	0.57
3 months post-transplantation	0 (0)	11 (7)	0.26
6 months post-transplantation	2 (13)	14 (9)	0.88
12 months post-transplantation	4 (26)	22 (15)	0.28
Infections/complications			
BK viremia	3 (19)	37 (25)	0.61
CMV	4 (26)	25 (17)	0.40
Other	3 (19)	37 (25)	0.61
Outcomes at last follow-up			
Total number of graft failure	1 (6)	23 (15)	0.33
Death-censored graft failure	1 (6)	10 (7)	0.95
Follow-up			
Mean follow-up post-transplantation, months	27.8 ± 15.4	24.4 ± 12.3	0.30

^aCMV, cytomegalovirus; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; SCr, serum creatinine.

^bValues shown are n (%) unless otherwise stated.

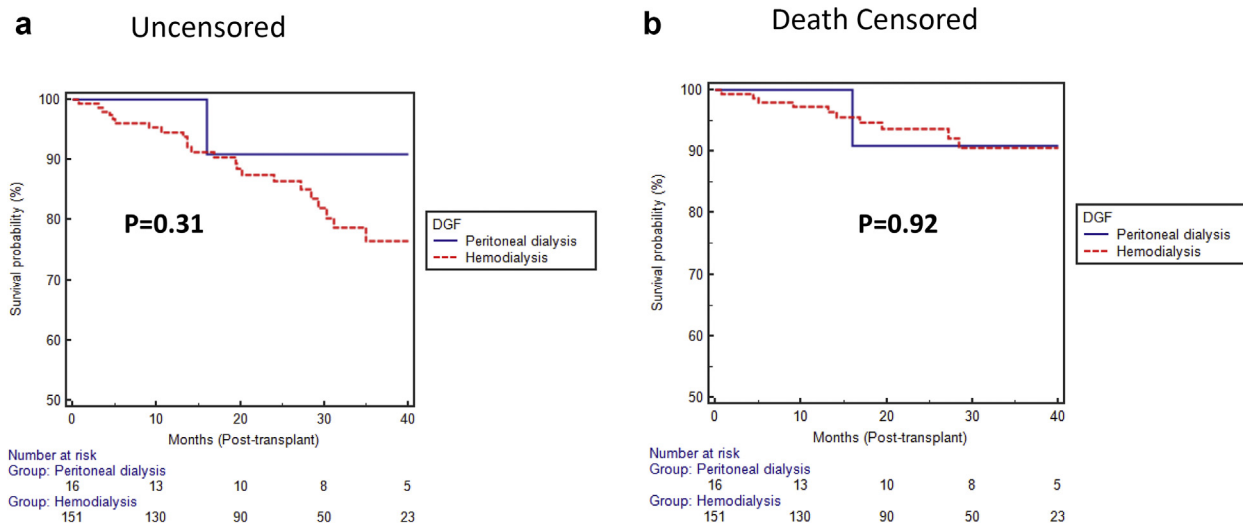


Figure 2. Comparison of graft failure in patients who did peritoneal dialysis during delayed graft function (DGF) to those who did hemodialysis. (a) Uncensored graft failure. (b) Death-censored graft failure.

fluid leak.^{19,21} However, very few studies have compared the short- and long-term outcomes of patients undergoing PD versus HD during DGF. Thomson *et al.*²⁹ compared the outcomes of 14 patients undergoing PD in DGF with those of 63 patients who underwent HD at two Canadian transplantation centers. DGF-PD had higher rates of wound infections and leakage but shorter hospital length of stay and duration of DGF. There was no difference in rates of acute rejections and glomerular filtration rate at 6 and 12 months between the two groups. Yan *et al.*³⁰ compared 42 PD patients with 96 HD patients undergoing dialysis for DGF at a single center in China. The PD failure rate was 23.8% and the peritonitis rate was 7.1% in this study. Contrary to the previous study, PD patients had longer duration of DGF and a higher risk of dialysis dependence for more than 30 days post-transplantation. However, 1-year patient and graft survival rates were not different.

Our peritonitis rate of 6.25% during DGF was much lower compared to some of the earlier studies reporting these outcomes.¹⁹⁻²¹ These were comparable to the study by Yan *et al.*³⁰ Contrary to the above-mentioned studies, our study did not find any case of wound infection or leakage in patients who underwent PD for DGF. One reason for the observed lower rate of complications could be a strict patient selection, as any patient with a potential breach in the peritoneal membrane was excluded. In addition, we followed guidelines of low-volume supine exchanges on a cyclor which would have helped to reduce the risk of leakage and wound infection. In addition, we avoided CAPD due to higher risk of these complications with this modality. A meta-analysis of three randomized controlled trials comparing CAPD with ambulatory PD

showed higher risk of peritonitis with CAPD.³¹ Frequent connection and disconnection between PD catheter and dialysate bag during CAPD could be the reason for higher infection rates.³² CAPD may also increase the risk of a fluid leak if patients ambulate with the fluid inside the peritoneal cavity resulting in higher intra-abdominal pressure.³³ For the same reason, daytime fill with icodextrin was also avoided. Five of 16 patients in our study had to be switched to HD. Our failure rate of 31.3% was slightly higher than what was observed by Yan *et al.*³⁰ However, three of five patients were switched due to poor clearance. In retrospect, this could have been managed by increasing the number of

Table 4. Factors Associated With Death-Censored Graft Failure^a

Variables	Univariate Analyses			Multivariate Analyses		
	HR	P	95% CI of HR	HR	P	95% CI of HR
Male	1.43	0.60	0.38–5.39			
Age	1.0	0.87	0.95–1.06			
White	4.83	0.13	0.62–37.75			
DCD kidney	0.88	0.83	0.27–2.88			
Depleting induction	1.21	0.78	0.32–4.57			
Previous transplant	1.51	0.54	0.40–5.71			
Cold ischemia time	0.94	0.25	0.86–1.04			
HLA mismatch	0.86	0.41	0.61–1.22			
ESRD due to diabetes	0.80	0.74	0.21–3.02			
KDPI	1.02	0.15	0.99–1.06			
Post-transplantation PD	0.91	0.93	0.12–7.10	0.82	0.85	0.10–6.62
DGF duration (per day)	1.04 ^b	0.02 ^b	1.01–1.08 ^b	1.01	0.64	0.97–1.05
Rejection within first year	5.32 ^b	0.006 ^b	1.61–17.56 ^b	4.32	0.02 ^b	1.21–15.43
BK viremia	0.69	0.63	0.15–3.18			
CMV infection	1.05	0.95	0.23–4.89			
Post-surgery complications	4.82 ^b	0.009 ^b	1.46–15.92 ^b	3.78	0.04 ^b	1.02–13.96

^aCMV, cytomegalovirus; DCD, donation after cardiac death; DGF, delayed graft function; ESRD, end-stage renal disease; HLA, human leukocyte antigen; KDPI, kidney donor profile index; PD, peritoneal dialysis.

^bStatistically significant.

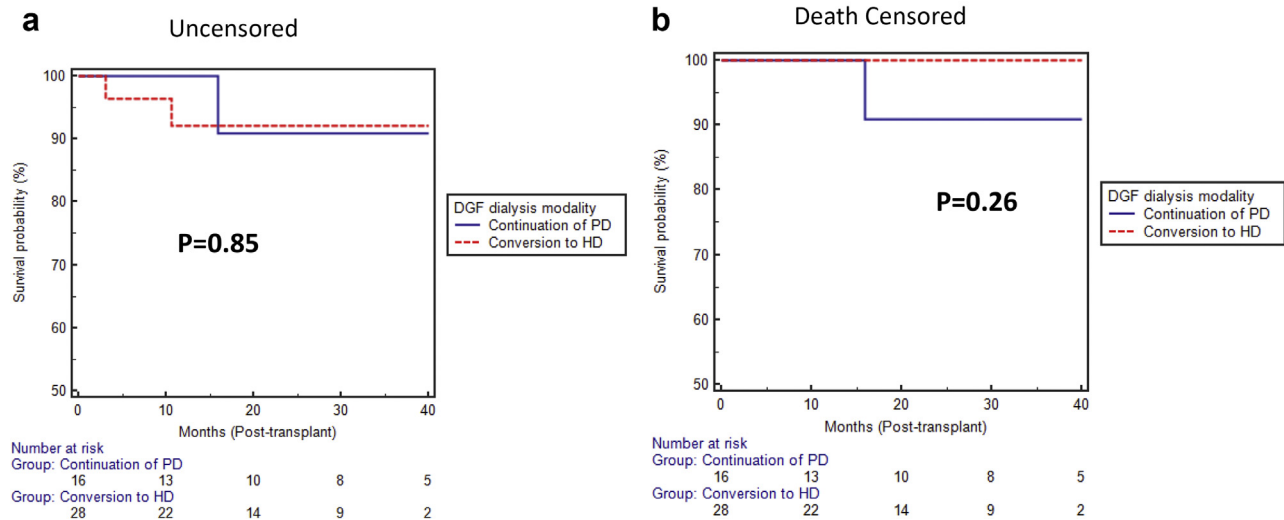


Figure 3. Comparison of graft failure between pretransplantation peritoneal dialysis (PD) patients who continued PD during delayed graft function (DGF) and those who were converted to hemodialysis (HD). (a) Uncensored graft failure. (b) Death-censored graft failure.

exchanges as none except one of these patients had inadequate clearance before transplantation.

Although we did not notice any difference in the duration of DGF between the two groups, Thomson *et al.*²⁹ observed a shorter duration of DGF in patients on PD. PD patients have better preservation of residual renal functions compared to those receiving HD.^{11,34} They have less fluctuation in volume status as opposed to the patients receiving HD.^{35,36} In addition, HD may expose the patients to more inflammation owing to less biocompatible dialyzer membranes compared with the peritoneal membrane.^{37,38} All of these factors may contribute to a speedy recovery of graft function in PD patients. Similar to the two studies mentioned above from Thomson *et al.*²⁹ and Yan *et al.*,³⁰ we did not notice any significant difference in long-term graft survival or graft function at the time of last follow-up, indicating that the choice of modality at the time of DGF may not impact long-term outcomes. Rejection within first year and the presence of post-surgery complications were the only factors associated with a higher risk of DCGF.

The pretransplantation PD population may be inherently different from the HD population.³⁹ They have usually spent less time on dialysis and have a higher residual renal function and better overall health.^{11,40-42} Thus, the comparison between the two is always subject to selection bias. We decided to analyze all the patients who were on PD pretransplantation separately and compared the ones who continued PD in DGF to those who were switched to HD immediately. We did not find any difference in the duration of DGF between these two groups, showing that the choice of modality did not affect DGF recovery, regardless of patients' pretransplantation dialysis status.

We excluded the patients who developed DGF after living-donor kidney transplantation. DGF is rare in this population. In fact, we did not have any PD patient during the study period who developed DGF after living-donor transplantation. Also, these kidneys are different as they may not have the traditional risk factors of DGF, such as longer cold ischemia time, and they have a better quality. The DGF in this group may be related to complications related to the procedure.

A concern which is repeatedly raised in previous studies is the higher risk of infections such as peritonitis and wound infections in patients who receive PD during DGF.^{18-21,43} Indeed, use of high-dose immunosuppression in the immediate post-transplantation period does increase the risk of infection, but with proper PD technique and precautions, the risks can be mitigated. In addition, we have to consider the risks associated with CVC placement. Catheter-related blood stream infection is one of the leading causes of morbidity and mortality among patients with kidney failure.⁴⁴ This risk may increase further post-transplantation due to immunosuppression.⁴⁵ In addition, placement of a CVC for conversion from PD to HD in the post-transplantation period may also increase the risk of central venous stenosis, which would not only cause symptoms but also reduce the options available for future dialysis access should the transplant fail.⁴⁶

Study Limitations

Our study has all the inherent weaknesses of a retrospective review. Our sample size was small which could have affected the results. However, it is not much different from the earlier studies on this topic and represents a general underuse of PD in DGF. There

was a large number of immediate post-transplantation conversions from PD to HD for DGF. This might have introduced a selection bias as the reason for their conversion could have been a suboptimal peritoneal membrane. However, most of the immediate conversions were due to either removal of PD catheter during transplantation or surgeons' preference to avoid PD. These two reasons represent a continuation of the long-established practice which could be due to a general perception among the transplantation surgeons that PD may increase the risk of complications in post-transplantation period. We did observe a reduction in the percentage of patients converted due to surgeon's preference with each year of the study period (42% during first year, 25% during the second year, and 6% during the third year) indicating that there was a gradual change in the perception and practice as PD was continued more often. We hope that our findings will help to improve this trend further. In addition to the above-mentioned limitations, we also did not have a record of patients' baseline residual renal function, which could have impacted the immediate outcomes of DGF. Furthermore, patients were discharged from the hospital relatively early because of the presence of a well-established outpatient DGF clinic.⁴⁷ Therefore, the monitoring was not as intense as it would have been for inpatient cases. A randomized controlled trial to compare PD and HD patients has always been challenging because of the patient's preference for the dialysis modality.⁴⁸ A prospective observational study including a large number of propensity-matched PD and HD patients with monitoring of all factors influencing DGF might provide the much-needed insight into this topic. However, to our knowledge, our study is the first to compare outcomes of the two dialysis modalities during DGF at a U.S. transplantation center. Another potential advantage of our single-center data is that it provides more detailed information about patients, and reflects a more homogeneous clinical approach to patient selection and DGF management, unlike registry data.

Home dialysis therapies and transplantation have been recognized as the best modalities for treatment of ESRD. The executive order on advancing American kidney health from the office of the President of the United States is further proof of this recognition.⁴⁹ The emphasis is on increasing the number of patients undergoing home dialysis as well as increasing the use of available organs for transplantation.⁵⁰ It is possible that we may see more DGF in PD patients after the implementation of these goals. It would be essential to have strong evidence-based plan to manage these patients to ensure the best outcomes with minimum complications.

DISCLOSURES

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