Would increasing centre volume improve patient outcomes in peritoneal dialysis?

Exploring robustness to unmeasured confounding and predicting intervention effects using data from the *Registre de Dialyse Péritonéale de Langue Française* and Monte Carlo simulations

David Evans*[1,2,3,4], Thierry Lobbedez[3,5], Christian Verger[3], Antoine Flahault[2,6]

1 Ecole des Hautes Etudes en Santé Publique 2 Inserm UMR-S 707
3 Registre de Dialyse Péritonéale de Langue Française 4 UPMC-Sorbonne Universités
5 Nephrology Department, CHU Clemenceau, Caën 6 Université Paris Descartes-Sorbonne Paris Cité
* Corresponding author: davidwevans1@gmail.com

Introduction:

A major clinical goal in peritoneal dialysis (PD) is delaying technique failure, which occurs when patients require permanent transfer to haemodialysis.

Studies have reported a lower risk of technique failure in centres treating more PD patients, leading to recommendations for minimum patient volumes.

However, these studies have not explored robustness to residual confounding or the impact of interventions to increase patient exposure to high-volume centres, making policy prescriptions premature.

We explored the robustness to residual confounding and estimated plausible effects of policies to change centre volumes using data from a French PD registry.

Methods:

Data source:

- Registre de Dialyse Péritonéale de Langue Française (80% coverage).

Population analyzed:

- Adult patients initiating PD between 1/1/2000 and 31/12/2009, followed-up until 1/1/2010 in metropolitan France (public and association centres only).

Variables:

- **Centre volume** as median number of patients on PD per day over the 12 months prior to initiating PD.
- **Outcomes** of time to death, technique failure, renal transplantation.
- **Potential confounders** of age, sex, Charlson comorbidity index (minus age score), diabetes, previous haemodialysis or transplantation, type of assistance, and type of centre.

Statistical analysis:

- Multiple imputation by chained equations of missing variables.
- Calculation of adjusted cause-specific hazard ratios (cs-HRs) and sub-distribution hazard ratios (sd-HRs) with robust-variance Cox and Fine & Gray regression models, respectively.
- Probabilistic analysis of sensitivity to residual confounding by
  - extracting centre random effect from mixed-effects Cox model;
  - imputing confounder B by $Pr(B=1)=expit(\beta_V . V_{SND} + \beta_R . R_{SND})$, with V_{SND} and R_{SND} as volume and random effect after normalization and standardization;
  - re-estimating the adjusted Cox regression model including B; and
  - calculating cs-HR and 95%CI from the median regression coefficient and median standard deviation over 1,000 runs under scenarios of low ($\beta_V=\beta_R=0.5$), mid ($\beta_V=\beta_R=1.0$), and high ($\beta_V=\beta_R=2.0$) confounding.
- Estimation of impact of interventions to change centre volumes by:
  - postulating probability distributions for changes in patients' exposure to centre volume for different interventions (table 1);
  - predicting outcome cumulative incidences at 5 years after PD initiation from the Fine & Gray models (pre-intervention);
  - drawing a new volume from the distributions and predicting cumulative incidences using this new value (post-intervention); and
  - calculating the difference in pre- and post-intervention cumulative incidences over 1,000 simulation runs and reporting the median difference with 95% central prediction intervals.

Table 1 Hypothetical interventions to change patients' exposure to centre volume

Intervention #1: Close centres and divert patients to existing larger centres	
Intervention closes small centres (<50 patients), allocating patients to larger centres.	If volume ≤50 patients, patient attributed to new centre with 51 to 60 or >60 patients with equal probability.*
Intervention #2: Close centres and divert patients to existing larger centres	
Intervention closes small centres (<30 patients), allocating patients to larger centres.	If volume ≤30 patients, patient attributed to new centre with 31 to 40, 41 to 50, 51 to 60, or >60 patients.*
Intervention #3: Close centres and divert patients to new larger centres	
Intervention closes small centres (<30 patients), allocating patients to larger centres mostly of type "association" (non-profit groupings of non-public-sector physicians).	If volume ≤30 patients, patient attributed to new centre with 31 to 40, 41 to 50, 51 to 60, or >60 patients* and treated in centre of type association (75%) or other centre type (25%) per empirical frequency in the data.
Intervention #4: Increase patients initiating PD in smaller centres without closing centres	
Intervention preferentially starts new dialysis patients on PD rather than haemodialysis, with largest proportional change in smallest-volume centres.	If volume ≤30 patients, patient attributed to new centre with volume equal to 2, 3, 4, 5, or 6** times the original volume.* If centre with >30 patients, patient attributed to new centre with volume equal to 1, 2, or 3 times the original volume.*

* Monte Carlo draw from uniform distribution over target volume categories
** Based on the relative proportions of patients initiating peritoneal dialysis and haemodialysis in France [REIN].

Results:

9 602 patients in 112 centres.

Diminishing cs-HR of technique failure with increasing volume, without association trend for transplantation or death (figure 1).

Diminishing sd-HR of technique failure with increasing volume, with increasing sd-HR for transplantation and death (figure 1).

In the probabilistic sensitivity analysis, a reduced but persistent protective association of cs-HRs for technique failure with no change in cs-HRs for transplantation or death (figure 2).

Despite strongly protective cs-HRs for technique failure, only modest predicted improvements in cumulative incidence of technique failure under different interventions, with small predicted increases in cumulative incidence of transplantation and death whilst on PD (table 2).

Figure 1 Cause-specific and sub-distribution hazard ratios

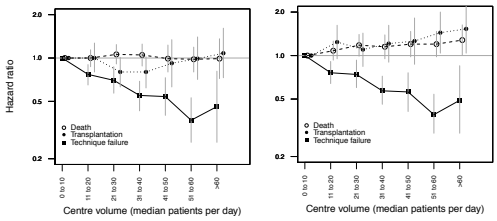

Figure 2 Cause-specific hazard ratios with unmeasured confounding

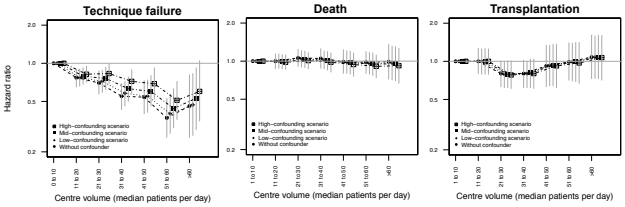

Table 2 Predicted change in cumulative incidences under hypothetical interventions

		Change in cumulative incidence	
		Difference	**95% central interval**
Intervention #1	Death	0.031	0.007 to 0.057
	Technique failure	-0.091	-0.115 to -0.068
	Transplantation	0.030	0.008 to 0.052
Intervention #2	Death	0.022	0.007 to 0.036
	Technique failure	-0.064	-0.078 to -0.050
	Transplantation	0.019	0.007 to 0.030
Intervention #3	Death	0.021	0.006 to 0.037
	Technique failure	-0.064	-0.077 to -0.050
	Transplantation	0.019	0.007 to 0.030
Intervention #4	Death	0.023	-0.010 to 0.056
	Technique failure	-0.059	-0.110 to -0.010
	Transplantation	0.024	-0.006 to 0.054

Conclusion:

Patients initiating PD in high-volume centres had a reduced risk (cs-HR) and cumulative incidence (sd-HR) of technique failure. This reduced risk (cs-HR) was robust to scenarios of strong residual confounding, suggesting that it may be a causal effect.

Patients in high-volume centres had no change in risk (cs-HR) for transplantation and death but had an increased cumulative incidence (sd-HR) of these outcomes in higher-volume centres. This was simply the result of the longer time spent on PD in these centres, where the risk (cs-HR) of technique failure was lower.

Hypothetically intervening to shift patients to high-volume centres only modestly reduced the cumulative incidence of technique failure. The largest benefit was from intervention #1, which induced a large change in volume exposures and so would probably be unrealistic in a real-world setting.

These findings raise questions about the relevance of the highly protective cs-HRs found in this and previous studies for health-services policy. It may be more fruitful to pursue other interventions to reduce technique failure.