Comparison of All-cause Mortality and Technique Failure Between Early-late and Very Late Start Peritoneal Dialysis: A Retrospective Cohort Study

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Abstract

Background: Glomerular filtration rate (GFR) is the gold standard for the detection and monitoring of chronic kidney disease (CKD). Controversy is remaining in the timing of peritoneal dialysis (PD).

Objective: This study compared all-cause mortality and technique failure between early-late and very late start PD in stage-5 CKD patients.

Method: A cohort of 828 stage-5 CKD patients from a tertiary hospital was reviewed and analyzed. Patients were categorized into groups of early-late or very late start PD according to their estimated-GFRs. The outcomes were all-cause mortality and technique failure. Survival analysis was performed.

Results: Median time to all-cause mortality was 35 months in early-late group, 40 months in very late group, while technique failure was found identical in both groups (25 months). There were no statistically significant association in cox regression models.

Conclusion: No clinical benefits were found by starting dialysis based on eGFR at the timing of PD (early or very late start PD plan). Asymptomatic patients with stage-5 CKD may be safely managed by very late start PD plan and patients may benefit from the delayed PD initiation.

Keywords: *End-stage renal disease, end-stage kidney disease, delayed PD, formula, equation.*

Introduction

Chronic kidney disease (CKD) patients often remain asymptomatic until the late stages of disease when the loss of renal function has already reached 90%[1]. Glomerular filtration rate (GFR) is considered the best clinical parameter to determine renal function but is not useful in clinical practices because it cannot be measured directly in an individual[2-4]. As a result, clinicians often use serum creatinine to diagnose and monitor renal disease. However, serum creatinine varies with age and muscle mass making it imperfect for determining renal function[5-9]. Current clinical practice guidelines recommend using eGFR to detect early kidney damage[3], diagnose chronic kidney disease

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(CKD), monitor renal function[4] and guide decision making about initiation of dialysis [3]. The decision to initiate dialysis requires consideration of multiple factors, including clinical symptoms, eGFR, rate of decline of eGFR, and patient preferences. The IDEAL study conducted in 2009 found early vs. delayed dialysis initiation made no difference in mortality [10]. Several guidelines recommend considering renal replacement therapy (RRT) when patients reach CKD stage-5 or eGFR <15 ml/min/1.73m^2[11, 12], and vary from country to country. Patients in Taiwan (5 ml/min/1.73m^2) and New Zealand (6.4 ml/min/1.73m^2) have a mean pre-dialysis eGFR level in the lower end of the spectrum, when compared with Australia (7.3 ml/min/1.73m^2), the United Kingdom (8.5 ml/min/1.73m^2)and the United States (11 ml/min/1.73m^2)[13]. A systematic review reported the average GFR when starting dialysis in several East Asian countries including Hong Kong (9.1 ml/min/1.73m^2), Korea (7.8 – 8.2 ml/min/1.73m^2) and Japan (5.0 ml/min/1.73m^2) [14]. While eGFR is very helpful in monitoring rate of decline in renal function and can provide parameters for decision making, clinical symptoms play a significant role in the initiation of RRT. Initiation of dialysis also occurs urgently when patients develop life threatening congestive heart failure which cannot be corrected with other therapeutic interventions. Monitoring the eGFR plays a key role in guiding nephrologists so they can plan and avoid emergent dialysis, or worse yet, a fatal event.

Despite yielding different results from eGFR calculation along with several formulae, treatment decisions based on CKD stage and eGFR such as the initiation of dialysis and other treatments are impacted. In the absence of clinical situations requiring dialysis, asymptomatic patients may experience a decrease in quality of life, and risk of complications due to the premature initiation of dialysis. It can also result in unnecessary health care expenditures. Therefore, this study intended to compare all-cause mortality and technique failure between early-late and very late start PD in stage-5 CKD patients.

Materials and Method

Study Design: This was a retrospective cohort study utilizing data from the hospital information system of a tertiary hospital in the Northeast Thailand. There were 996 CKD patients who underwent PD at the hospital from 2011 to 2018. All patients at least 15 years old with stage-5 CKD, were included regardless of gender. Patients with incomplete data required for analysis were excluded, resulting in a total of 828 study participants (Figure 1).

Dependent Variables: Theprimary outcome variable was all-cause mortality, including patients who died after switching from peritoneal to hemodialysis. The secondary dependent variable was the composite outcome of technique failure which comprised of discontinuation of dialysis, change from PD to hemodialysis, kidney transplantation and death. Patient survival rates were calculated from the date of initiation of continuous PD until the date of death or up to 31 December 2018. Time from initiation of PD until technique failure was calculated from the date of commencing PD until the first date change to hemodialysis, kidney transplantation or death, or up to 31 December 2018.

Independent Variables: The following information was collected for each patient at the time PD was initiated: age, gender, body mass index, blood pressure, diagnosis of diabetes or cardiovascular disease (CVD). Laboratory results including albumin (g/dL); hemoglobin (g/dL); bicarbonate (mmol/L) and hypokalemia (yes/no), were also collected.

Definition of Comparing Groups: The early-late group and the very late group were defined by a well-known randomized, controlled trial of early versus late initiation of dialysis [10], the range of eGFR for PD initiation plan was explained as eGFR = 10.0 to 14.0 ml/min/1.73m^2(early start), eGFR = 5.0 to 7.0 ml/ min/1.73m^2(late start). Therefore, we set the eGFR 5.0 ml/min/1.73m^2 as a cut-of-point to divide group, patients who had eGFR 3-month before starting PD > 5 ml/ min/1.73m^2 were included in the early-late group, while those who had eGFR < 5 ml/min/1.73m^2 were assigned in the very late group. All eGFR were calculated by CKD-EPI formula in the hospital.

Statistical Analysis: Categorical variables were reported as number and percentage. Mean and standard deviation, median and range (Minimum: Maximum) were used to describe continuous variables.

To answer the research question, all-cause mortality and technique failure were considered individually. Time to events were reported as incidence density rate of events in 100 per patient-month. Survival probability was presented using Kaplan Meier method comparing both groups. Test of equality was employed using log-rank test.

A Cox proportional hazard model was performed to estimate the effect of the start PD on each outcome variable adjusting for gender, age, DM, hypertension, CVD, BMI, blood pressure, albumin, bicarbonate and hypokalemia. Hazard ratios (HR) with their 95% confidence interval (CI) were reported. Data analysis was performed using StataCorp Stata MP 16. All statistical tests considered a probability of 0.05 as statistically significant level.

Results

Baseline Characteristics of the stage-5 CKD patients: The demographic information, health and disease conditions of the stage-5 CKD patients were presented in Table 1.

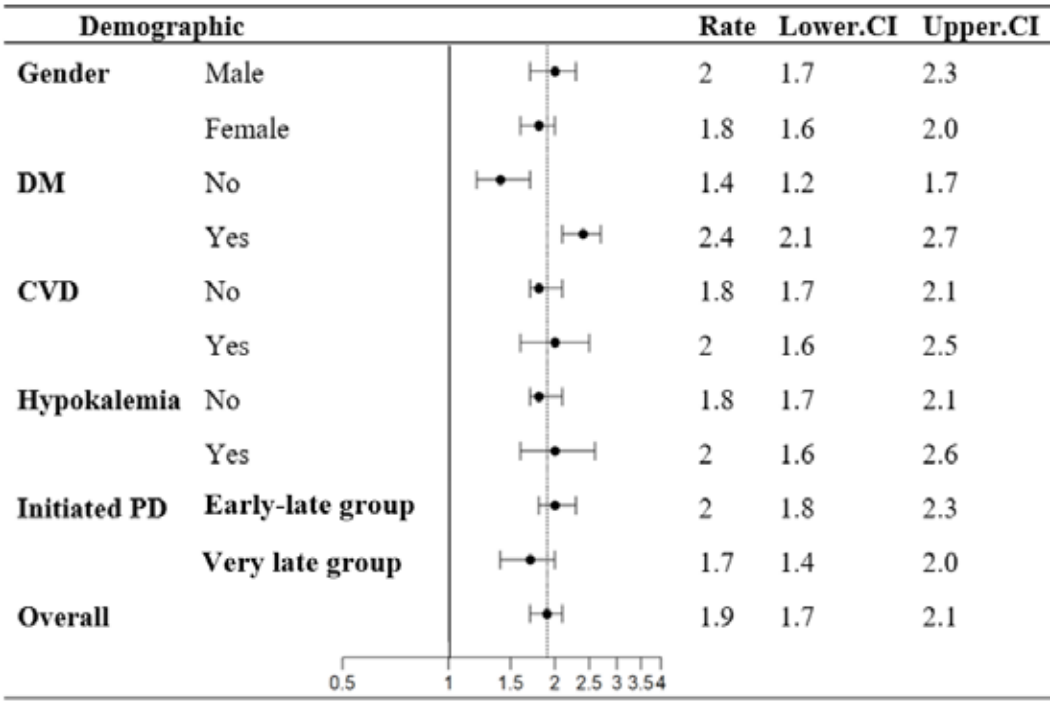
Table 1: Baseline information of participants number and percentage (n (%))

Characteristics	Initiated PD Group	
	Early-late (n = 484)	Very late (n = 344)
Gender (n, %)		
Male	253 (52.3)	146 (42.4)
Female	231 (47.7)	198 (57.6)
Age (years)		
Mean (SD)	56.1 (13.4)	55.9 (11.9)
Median (min: max)	57.5 (18.0:87.0)	57.0 (19.0:86.0)
Diabetes Mellitus (n, %)		
No	219 (45.3)	178 (51.7)
Yes	265 (54.7)	166 (48.3)
Cardiovascular Disease (n, %)		
No	385 (79.5)	299 (86.9)
Yes	99 (20.5)	45 (13.1)
Body mass index (kg/m^2)		
Mean (SD)	22.7 (3.6)	23.3 (3.8)
Median (min: max)	22.2 (14.2:33.7)	23.0 (14.2:35.6)
Systolic Blood Pressure (mmHg)		
Mean (SD)	142.6 (22.5)	143.9 (22.7)
Median (min: max)	141.0 (85.0:199.0)	145.0 (84.0:198.0)
Diastolic Blood Pressure (mmHg)		
Mean (SD)	77.3 (12.8)	78.1 (11.9)
Median (min: max)	77.0 (50.0:100.0)	78.0 (50.0:100.0)
Albumin (g/dL)		
Mean (SD)	3.3 (0.6)	3.4 (0.6)
Median (min: max)	3.4 (1.4:5.0)	3.4 (1.6:4.9)
Hemoglobin (g/dL)		
Mean (SD)	8.2 (1.4)	7.9 (1.4)
Median (min: max)	8.2 (3.9:13.1)	7.9 (3.9:14.5)
Bicarbonate (mmol/L)		
Mean (SD)	25.1 (4.6)	23.8 (5.3)
Median (min: max)	25.0 (10.0:40.5)	24.0 (4.0:42.5)

Characteristics	Initiated PD Group	
	Early-late (n = 484)	Very late (n = 344)
Hypokalemia (n, %)		
No	408 (84.3)	305 (88.7)
Yes	76 (15.7)	39 (11.3)
Pre-dialysis		
Mean (SD)	7.5 (2.5)	3.2 (0.8)
Median (min: max)	7.0 (5.0:14.0)	3.0 (1.0:4.0)

Incidence rates of all-cause mortality and technique failure

All-cause mortality rate: Of the 828 patients revealed the overall mortality rate as 1.9/100 patients per month (95% CI: 1.7-2.1) (Figure 1). Patients with DM had highest mortality rate. Patients at early-late start PD was slightly higher mortality rate (2/100 patient-month (95%CI: 1.8-2.3)) than those beginning PD at very late (1.7/100 patient-month (95%CI: 1.4-2)).

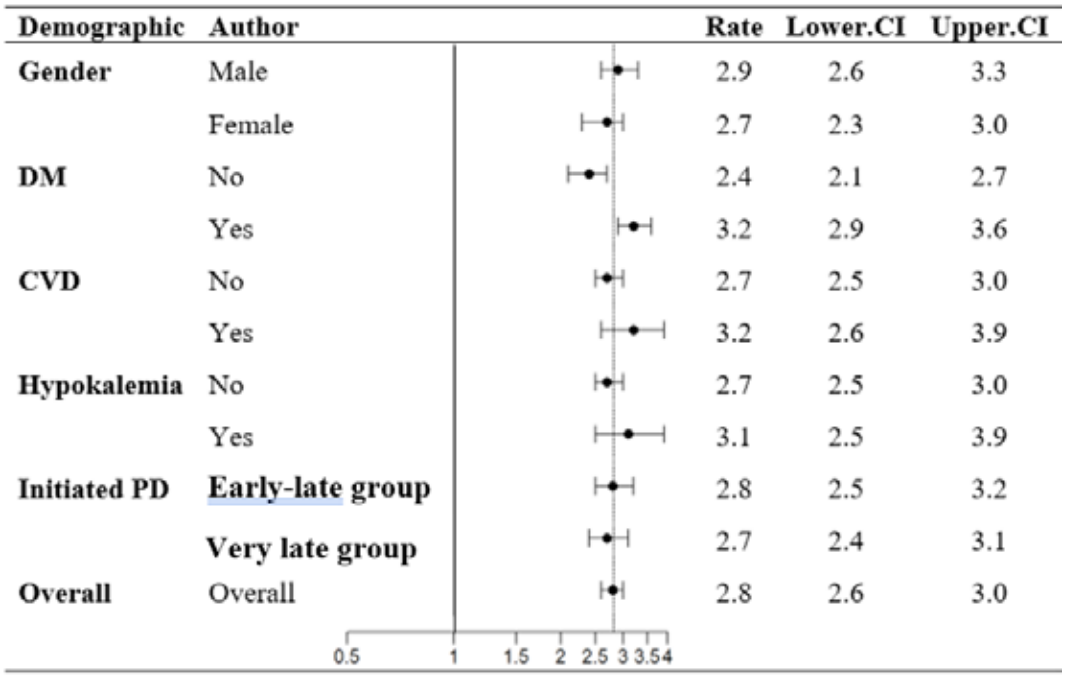


Rate per 100 person-month,

CI confidence interval; DM diabetes mellitus; CVD cardiovascular disease; PD peritoneal dialysis.

Figure 1 All causes of death rate

Technique survival rate: Patients in early-late group had similar rate of technique failure 2.8/100 patient-month (95%CI: 2.5-3.2) compared to those in very late group, 2.7/100 patient-month (95%CI: 2.4-3.1) (Figure 2). Technique failure rates were higher in diabetic patients and in patients with CVD. While the overall technique failure rate demonstrated somewhat difference from other attributes (2.8/100 patients per month; 95%CI: 2.6-3.0).



Rate per 100 patient-month

Figure 2 Technique survival rate

Survival probability of all-cause mortality and technique failure: Kaplan-Meier survival curves of all-cause mortality demonstrated a slightly lower median survival time (35 months) in early-late group than that in very late group (40 months) (Figure 3). The median time to technique failure in both groups were similar (25 months). The log rank test of the two curves were not statistically significant different.

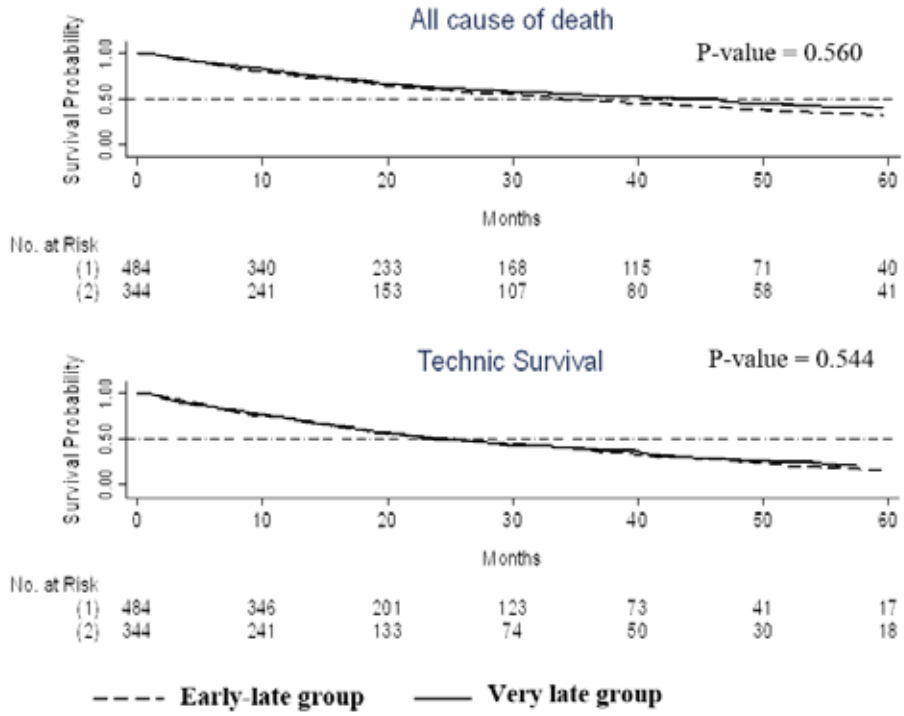


Figure 3: Survival probability of all-cause mortality and technique failure by groups

Association between two equations on all-cause mortality and technique failure: There were no statistically significant association between two groups for outcome variables (Table 2). Adjusted HRs of both all-cause mortality and technique failure were 0.92 (95%CI: 0.74-1.14, P-value = 0.45) and 1.01 (95%CI:0.84-1.23, P-value = 0.88), respectively. The analysis also demonstrated that low albumin level, diabetes were risk factors for death and technique failure.

Table 2 Association between two equations on all-cause mortality and technique failure

	All-cause mortality			Technique failure		
Characteristics	**Crude HR**	**Adj.HR** (95%CI)**	**P**	**Crude HR**	**Adj.HR** (95%CI)**	**P**
Group						
Early-late	1	1		1	1	
Very late	0.86	0.92(0.74-1.14)	0.45	0.96	1.01(0.84-1.23)	0.88
Gender						
Male	1	1		1	1	
Female	0.90	0.87(0.70-1.07)	0.17	0.90	0.83(0.69-1.00)	0.05
Age (years)	1.0	1.02(1.01-1.03)	<0.01	1.01	1.00(0.99-1.01)	0.87
DM						
No	1	1		1	1	
Yes	1.64	1.41(1.12-1.76)	<0.01	1.37	1.22(0.99-1.49)	0.06
CVD						
No	1	1		1	1	
Yes	1.10	0.85(0.65-1.10)	0.22	1.17	1.04(0.82-1.31)	0.76
BMI (kg/m^2)	1.00	0.98(0.95-1.10)	0.18	1.01	1.00(0.97-1.02)	0.84
SBP (mmHg)	1.00	1.00(0.99-1.01)	0.48	1.00	1.00(0.99-1.01)	0.71
DBP (mmHg)	0.99	0.99(0.98-1.00)	0.12	0.99	0.99(0.98-1.00)	0.11
Albumin (g/dL)	0.42	0.43(0.36-0.51)	<0.01	0.45	0.45(0.38-0.52)	<0.01
Hemoglobin (g/dL)	1.11	1.17(1.09-1.26)	<0.01	1.00	1.05(0.98-1.12)	0.16
Bicarbonate	0.97	0.96(0.94-0.98)	<0.01	0.98	0.98(0.96-1.00)	0.02
Hypokalemia						
No	1	1		1	1	
Yes	1.13	1.05(0.80-1.38)	0.71	1.15	1.16(0.90-1.49)	0.25

**Adjusted for gender, age, DM = diabetes mellitus, CVD = cardiovascular disease, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, albumin, hemoglobin, bicarbonate in mmol/L, hypokalemia. Early-late = eGFR of >5 ml/min/1.73m^2, Very late = eGFR < 5 ml/min/1.73m^2, *P* = P-value. 95%CI = 95% confidence interval.

Discussion

This is the first observational study utilizing real world nephrology data from a tertiary referral hospital in Thailand. It compares all-cause mortality and technique failure based on the time of peritoneal dialysis initiation in a large cohort of stage-5 CKD patients. Our results found no statistically significant difference in median time from initiation of PD to mortality or technique failure comparing between patients who early-late started PD (eGRF>5 ml/min/1.73m^2) and those whose eGFR less than 5 ml/min/1.73m^2. The mean pre-dialysis eGFR in the early-late group was 7.5 (range: 5.0 to 14.0) ml/min/1.73m^2 and was 3.2 (range: 1.0: 4.0) ml/min/1.73m^2 in the very late group.

Mean pre-dialysis eGFR in patients who start PD at >5 ml/min/1.73m^2 is higher than some countries

including Taiwan (5.0), New Zealand (6.4), Australia (7.3), and lower than the United Kingdom (8.5), the United States (11.0), Hong Kong (9.1) and Korean (7.8 – 8.2)[13]. While mean pre-dialysis eGFR before starting PD of less than 5 ml/min/1.73m^2 seems very low, however, it is closely in comparison with some Asian countries that it covers the ranges of 3.29 to 8.9 ml/min/1.73m^2[14]. These differences may be due to various estimated-GFR formula used and racial differences across country.

Several studies suggested that when the GFR falls less than 6 ml/min/1.73m^2 recommend initiation of dialysis with no consideration of uremia or malnutrition, or should be initiated before the GFR has fallen to 6 mL/min/1.73 m^2, even if optimal pre-dialysis care has been provided and patient is asymptomatic[15].

While the guidelines recommend that PD consideration be taken as soon as 6 mL/min/1.73 m^2 or less, the absence of difference in the effect on mortality or technique failure comparing from very late PD start to early-late PD start planning was observed. Since the higher eGFR, nephrologists and patients may feel more comfortable deferring the start of RRT knowing there with no significant difference in rates of all-cause mortality and rates of technique failure. Both peritoneal and hemodialysis have a significant impact on the quality of life of patients and their caregivers. Both forms of RT also have potential complications such as infection, blood pressure instability, and metabolic abnormalities. Previous studies have shown that starting dialysis with high eGFR could be a cause of death [14],however, considering patients' clinical conditions should be taken into this critical decision[10, 11, 13-18]. Although the current study found no benefit on clinical outcomes compared between initiating PD at very late or at early-late, clinical symptoms were not included in the analysis. Another potential benefit is reduction in resource utilization, which could reduce the finanicial burden to the health system. This is an especially important consideration in Thailand where the government health system covers the cost of renal replacement therapy for many patients, and the prevalance of chronic kidney disease patients is growing.

Our study has several strengths. We have a large sample size, with data was obtained from the largest database of stage-5 CKD patients in Thailand, which also contained information about important confounders such as diabetes and cardiovascular diseases that included in the analysis. There were no patients lost to follow-up. Our mortality rates and cause of death are reliable as they were confirmed with data from the Ministry of Interior, Thailand.

A limitation of our findings is that they are based on an observational study using eGFR values. However, it provides a compelling evidence for further studies of using the GFR-estimating formula between the popular use in healthcare setting in Thailand to compare with the Thai eGFR formula to inform decisions regarding the initiation of dialysis.

Conclusion

We found that there are no differences in the time from initiation of dialysis to death or technique. The high eGFR calculated by CKD-EPI formula is more likely to provide the same treatment results comparing to the very low eGFR. Therefore, nephrologists should plan to start PD for patients based on eGFR and patients' symptoms or without symptom. Asymptomatic patients with stage-5 CKD may be safely managed with eGFR <5 ml/min/1.73m^2, by doing this, patients may benefit from the delayed PD initiation.

Ethical Considerations: The Ethical Committee of KhonKaen University approved the exemption for obtaining informed consent in this study with the reference number of HE622214. The administrative board of a participant hospital allowed the research to use the data (EC number: 22/62).

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Conflict of Interest: No conflicts of interest to declare.

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