

Death and cardiovascular outcomes in end-stage renal failure patients on different modalities of dialysis

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ABSTRACT

Introduction: Cardiovascular morbidity and mortality in end-stage renal failure (ESRF) patients are high. We examined the incidence and predictors of death and acute myocardial infarction (AMI) in ESRF patients on different modalities of dialysis.

Methods: Data were obtained from a population-based database (National Registry Disease Offices) in Singapore. The study cohort comprised all adult patients initiated on dialysis between 2007 and 2012 who were closely followed for the development of death and AMI until September 2014. Cox regression methods were used to identify predictors of death and AMI.

Results: Of 5,309 patients, 4,449 were on haemodialysis and 860 on peritoneal dialysis (PD). Mean age of the cohort was 61 (± 13) years (44% women), of Chinese (67%), Malay (25%) and Indian (7%) ethnicities. By September 2014, the incidence of all-cause death was 34%; close to a third of the patients died from a cardiovascular cause. Age >60 years and the presence of ischaemic heart disease, diabetes, stroke, peripheral vascular disease and PD were identified as independent predictors of all-cause death. PD patients had lower odds of survival compared to patients on haemodialysis (hazard ratio 1.51, 95% confidence interval 1.35–1.70, $P < 0.0001$). Predictors of AMI in this cohort were older age (>60 years) and the presence of ischaemic heart disease, diabetes, stroke, peripheral vascular disease and current/ex-smokers. There were no significant differences in the incidence of AMI between patients on PD and haemodialysis.

Conclusion: The short-term incidence of death and AMI remains high in Singapore. Future studies should investigate the benefits of a tighter control of cardiovascular risk factors among ESRF patients on dialysis.

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Keywords: Acute myocardial infarction, end-stage renal failure, mortality, nephrology

INTRODUCTION

End-stage renal failure (ESRF) is a major cause of morbidity and mortality worldwide, including Asia.¹ In Singapore, incidence of chronic kidney disease (CKD) stage 5 has increased from 383.9 per million population (PMP) in 2010 to 414.8 PMP in 2015. Incidence of patients requiring dialysis has increased in tandem. The age-standardised rate of patients requiring definitive dialysis has increased from 144.7 PMP in 2010 to 185.3 PMP in 2016.² Cardiac disease is one of the most

important causes of death in these patients. There is a high incidence of acute coronary syndrome (ACS) in patients on chronic dialysis. In a study of 3,374 patients in the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Study Wave II, incidence of ACS was 29/1,000 person-years.³ Furthermore, patients tend to do worse after an episode of acute myocardial infarction (AMI). Overall mortality after AMI among patients on long-term dialysis in the US was 59% at 1 year and 89.9% at 5 years.³

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CLINICAL IMPACT

What is New

- The short-term incidence of death and acute myocardial infarction (AMI) among patients with end-stage renal failure (ESRF) on dialysis remains high in Singapore.
- Patients on peritoneal dialysis patients harbour a poorer survival outcome compared to those on haemodialysis.

Clinical Implications

- Findings from this population-based study provide quantitative estimates of all-cause death and AMI among ESRF patients in Singapore
- ESRF patients on dialysis may benefit from a tighter control of cardiovascular risk factors.

The predictors of death and AMI on patients newly initiated on dialysis, as well as the impact of different modalities of dialysis on death and AMI outcomes remain an area of uncertainty. Studies have shown conflicting results on the effect of peritoneal dialysis (PD) versus haemodialysis (HD) on clinical outcomes. Population-based studies performed in the US suggest that dialysis modality was not a predictor of adverse cardiovascular outcomes.⁴ This is in contrast to most Asian studies where PD has been found to be an independent predictor of adverse clinical outcomes in ESRF patients.⁵⁻⁷ In Southeast Asia, such data remain limited. The primary aim of this study is to describe the incidence and predictive factors of death and AMI in ESRF patients on different modalities of dialysis in a multiracial Asian society. In addition, difference in outcomes (mortality, AMI) between patients on HD and PD were studied.

METHODS

This study was approved by the SingHealth Centralised Institutional Review Board, with the need for consent waived as anonymised data were used.

Data were obtained from the National Registry Diseases Offices (NRDO) in Singapore. Use of data collected by NRDO has been previously described.^{8,9} The NRDO was established in 2001 and contains data on reportable non-communicable diseases in Singapore such as AMI, cancer, stroke and CKD. These data are validated on a regular basis to ensure accuracy. Since

1999, the renal NRDO registry has collected data on patients with CKD stage 5 (defined as patients with serum creatinine $\geq 10\text{mg/dL}$ or $880\mu\text{mol/L}$ or initiation on renal replacement therapy). In 2007 and 2009, 2 of the largest hospitals in Singapore contributed listings of patients with estimated glomerular filtration rate (eGFR) $< 15\text{mL/min}$ (corrected for body surface area [BSA] 1.73m^2). These hospitals account for more than 50% of the new CKD stage 5 cases. By 2010 a subsidiary legislation was put into place, which made it mandatory for the remaining restructured hospitals in Singapore to provide the Registry Office with particulars of patients with advanced CKD using previously determined criteria. There was a broader inclusion of all patients with serum creatinine $\geq 500\mu\text{mol/L}$ or $\text{eGFR} < 15\text{mL/min}$ (corrected for BSA 1.73m^2) or those who were started on renal replacement therapy (PD, HD or transplant).

This study included data of all adult patients (age ≥ 21 years) from 2007 to 2012 with ESRF already on dialysis for at least 3 months. Incident dialysis modality was defined as the dialysis modality after 3 months as patients planned for PD might have been started on HD initially. In addition, this was also to obtain a relatively stable cohort of patients on dialysis as patients with multiple comorbidities may not survive beyond first 3 months of dialysis initiation. This methodology was adopted from the renal NRDO, based on the USRDS methodology. Analysis of outcomes were based on incident dialysis modality. Baseline demographics (ethnicity, age and sex), comorbidities including presence of diabetes mellitus (DM), ischaemic heart disease (IHD), cerebrovascular accident (CVA), peripheral vascular disease (PVD), hypertension and malignancy at time of dialysis initiation were obtained. Data were matched against the Singapore Myocardial Infarction Registry to obtain incidence of AMI post-initiation of dialysis.

Notification of AMI became mandatory for all public hospitals since 2007 and for all private hospitals in Singapore since 2012. This encompasses notifications from all hospitals via the inpatient medical records and cardiac biomarkers, from Ministry of Health's Mediclaim (health insurance) and subvention list, as well as the death registry. The International Classification of Diseases 9th Revision (ICD-9) Clinical Modification code 410 was used as AMI case definition from 2007 to 2011. From 2012 onwards, the ICD-10 American Modification codes I21 and I22 were used.

Death outcomes were evaluated through the National Registry of Births and Deaths. Accurate capture of death records is high as reporting of death is mandatory by law in Singapore within 24 hours of its occurrence.¹⁰

Statistical analysis

We performed bivariate comparisons between HD and PD with t-test for continuous variables and chi-square test for categorical variables. Continuous variables are reported as a mean with standard deviation (SD).

We constructed univariate and multivariable Cox regression models to assess the risk factors for all-cause death and ACS, respectively.

We excluded 33 patients who were lost to follow-up and those who had continued follow-up in other countries. We also excluded 116 patients who underwent renal transplant as numbers were small and outcomes of transplanted patients are known to be better. All analyses were performed in STATA 13 (StataCorp LLC, College Station, US).

RESULTS

Between 2007 and 2012, 4,449 out of a total of 5,309 patients in the Singapore NRDO renal registry were on haemodialysis and 860 on PD. Mean age was 61 (± 13) years and 2,339 (44.1%) were females. There were 3,538 (66.6%) Chinese, 1,313 (24.6%) Malays and 391 (7.4%) Indians.

Majority of the patients had pre-existing hypertension (5,222, 98.4%). There were 3,678 (69.3%) patients with DM and 2,296 (43.3%) had underlying IHD. PVD was present in 764 patients (14.4%), while 1,156 (21.8%) had a history of CVA (Table 1).

All-cause incident mortality was 34% (1,817), of which 35% (640) were cardiovascular related.

Predictive risk factors of mortality included older age more than 60 years (hazard ratio [HR] 2.00, 95% confidence interval [CI] 1.80–2.22, $P < 0.0001$), IHD (HR 1.46, 95% CI 1.31–1.61, $P < 0.0001$), DM (HR 1.68, 95% CI 1.47–1.91, $P < 0.0001$), CVA (HR 1.46, 95% CI 1.31–1.62, $P < 0.0001$), PVD (HR 1.77, 95% CI 1.57–1.98, $P < 0.0001$), malignancy (HR 1.77, 95% CI 1.51–2.07, $P < 0.0001$) and PD (HR 1.51, 95% CI 1.35–1.70, $P < 0.0001$) (Table 2). Presence of hypertension (HR 0.44, 95% CI 0.31–0.62, $P < 0.0001$) was found to be protective against death. In comparison with patients on HD, PD patients had lower survival rates during follow-up using logrank test ($P < 0.0001$) (Fig. 1).

There were 915 patients who developed AMI (5.6/100 person years). Predictive risk factors for AMI include an older age more than 60 years (HR 1.47, 95% CI 1.27–1.69, $P < 0.0001$), IHD (HR 2.27, 95% CI 1.97–2.62, $P < 0.0001$), DM (HR 1.75, 95% CI 1.45–2.10, $P < 0.0001$), CVA (HR 1.31, 95%

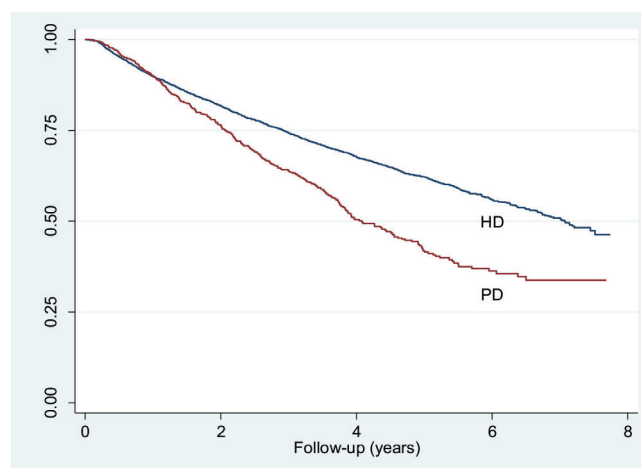


Fig. 1. Kaplan Meier survival curve for patients on haemodialysis (HD) and peritoneal dialysis (PD). Using logrank test, HD patients had significantly higher survival probability compared to PD patients ($P < 0.0001$).

CI 1.13–1.52, $P < 0.0001$), PVD (HR 1.55, 95% CI 1.32–1.83, $P < 0.0001$) and current/ex-smoker (HR 1.37, 95% CI 1.17–1.61, $P < 0.0001$) (Table 3).

DISCUSSION

Despite advances in clinical medicine, mortality rate of ESRF patients in our population-based study remains high.

Cardiovascular mortality plays a significant role in outcomes, but majority of deaths remain non-cardiovascular. This is reflected in a study of ESRF patients on dialysis who underwent transcatheter aortic valve replacement for severe aortic stenosis in Singapore; which shows high mortality rate of 16.7% at 1 year, majority of which were non-cardiovascular.¹¹ The high mortality rate mirrors that of ESRF patients in the Western population. In the Dialysis Outcomes and Patterns Study involving ESRF patients on dialysis in France, Germany, Italy, Japan, Spain, the UK and the US, 1-year mortality rates were 15.6% in the European countries and 21.7% in the US. These numbers contrast with the 1-year mortality rate of 6.6% observed in Japan. Differences were only partly explained by patient demographic factors and comorbidities.¹²

Patients on PD have increased rates of mortality compared to HD patients in our study. Studies in different countries comparing mortality outcome by different dialysis modalities have shown conflicting results. Our results mirror that of a prior single-centre study conducted in Singapore.⁷ This observational study comprised 871 patients newly initiated on dialysis from January 2005 to December 2010. Patients on PD had a higher mortality

Table 1. Baseline clinical characteristics of patients and their modality of dialysis

	Haemodialysis (n=4,449) No. (%)	Peritoneal dialysis (n=860) No. (%)	Total (N=5,309) No. (%)	P value
Mean age±SD, years	60±12.9	62±15.3	61±13.3	0.0078
Age >60, years	2,334 (52.9)	525 (61.1)	2,859 (54.2)	<0.0001
Ethnicity				0.0020
Chinese	2,929 (65.8)	609 (70.8)	3,538 (66.6)	
Malay	1,115 (25.1)	192 (22.3)	1,307 (24.6)	
Indian	348 (7.8)	43 (5.0)	391 (7.4)	
Others	57 (1.3)	16 (1.9)	73 (1.4)	
Female	1,882 (42.3)	457 (53.1)	2,339 (44.1)	<0.0001
Diabetes mellitus	3,063 (68.9)	615 (71.5)	3,678 (69.3)	0.12
Ischaemic heart disease	1,908 (42.9)	388 (45.1)	2,296 (43.3)	0.23
Cerebrovascular accident	931 (20.9)	225 (26.2)	1,156 (21.8)	0.0010
Peripheral vascular disease	638 (14.3)	125 (14.5)	763 (14.4)	0.88
Malignancy	329 (7.4)	26 (3.0)	355 (6.7)	<0.0001
Hypertension	4,369 (98.2)	853 (99.2)	5,222 (98.4)	0.037
Have never smoked	2,780 (63.7)	608 (72.0)	3,388 (65.1)	<0.0001

SD: standard deviation

rate compared to patients on HD. Studies in most other Asian countries have yielded similar results. Kim et al. conducted a population-based study involving 32,280 incident dialysis patients with median follow-up of 26.5 months using the Korean Health Insurance Review and Assessment Service database. Mortality rates in PD patients was found to be higher than HD patients.⁵ Similarly, a Taiwan study using data from the National Health Insurance Research Database of Taiwan showed worst survival in PD patients compared to HD patients. In this study, a total of 35,664 incident dialysis patients from 1997 to 2007 were studied for a mean follow-up period of 1,265.4±970.8 days. The authors found poorer survival in ESRF patients with DM or cardiovascular disease (CVD) who underwent PD compared to HD. On the other hand, in ESRF patients without DM or CVD, dialysis modality had no impact on survival.⁶ Conversely, a small prospective multicentre study conducted by Suzuki et al. in Japan between 2003 and 2008 did not show survival differences between ESRF patients on HD and PD. Prevalence of DM among the patients in this Japanese study was relatively low: 18.1% in PD patients and 27.7% in HD patients. This contrasts with higher rates of DM in other Asian studies. Prevalence of DM in our study was 68.5%.

In the single-centre study by Yang et al., 70% of patients had DM⁷ and in the Korean study by Kim et al., 62.5% were diabetic.⁵ In the Taiwan study, 46.3% of the HD patients and 34.2% of the PD patients had DM.⁶

Findings of poorer outcomes of PD patients in Asian studies contrasts with most Western studies, which show no difference between the 2 modalities or better survival of PD in the initial period of dialysis initiation.^{4,13-15} For example, in a study by Mehrotra et al. looking at 684,426 patients in the USRDS, there was no difference in mortality between HD and PD patients among incident dialysis patients.⁴ Approximately half of the patients in both the HD and PD group had DM. Allan et al. studied incident Medicare patients (99,048 patients on HD and 18,110 patients on PD) from 1994 to 1996 and found PD patients to have better survival outcomes compared to HD patients. The superior outcome of PD might have been contributed by shorter follow-up period of this study. Outcomes were studied were within 2 years of dialysis initiation.¹⁴

The difference has been thought to be possibly contributed by the increased prevalence of DM in Asian population studied compared to the Western

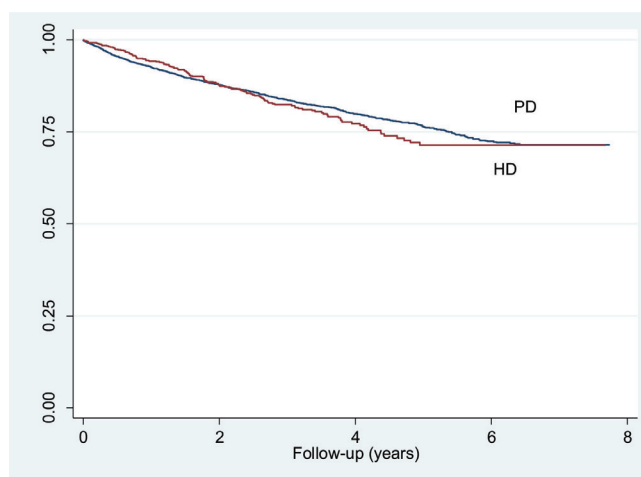
Table 2. Univariate and multivariate analysis of the risk factors for all-cause death

	Unadjusted hazard ratio (95% confidence interval)	P value	Adjusted hazard ratio (95% confidence intervals)	P value
Age >60 years	2.36 (2.13–2.60)	<0.0001	2.00 (1.80–2.22)	<0.0001
Ethnicity				
Chinese	1		1	
Malay	0.97 (0.87–1.08)	0.39	1.10 (0.99–1.24)	0.085
Indian	0.92 (0.77–1.11)	0.59	0.95 (0.78–1.14)	0.56
Others	1.16 (0.80–1.68)	0.45	1.40 (0.96–2.04)	0.080
Female sex	1.07 (0.98–1.18)	0.14	1.07 (0.96–1.20)	0.21
Comorbidities				
Diabetes mellitus	2.21 (1.97–2.49)	<0.0001	1.68 (1.47–1.91)	<0.0001
Ischaemic heart disease	1.90 (1.73–2.08)	<0.0001	1.46 (1.32–1.61)	<0.0001
Stroke	1.85 (1.67–2.04)	<0.0001	1.46 (1.31–1.62)	<0.0001
Peripheral vascular disease	2.07 (1.85–2.31)	<0.0001	1.77 (1.57–1.98)	<0.0001
Malignancy	1.81 (1.55–2.12)	<0.0001	1.77 (1.51–2.07)	<0.0001
Hypertension	0.78 (0.56–1.09)	0.15	0.44 (0.31–0.62)	<0.0001
Current/ex-smoker	1.14 (1.03–1.25)	0.0090	1.12 (1.00–1.25)	0.056
Dialysis modality				
Haemodialysis			1	
Peritoneal dialysis	1.56 (1.39–1.75)	<0.0001	1.51 (1.35–1.70)	<0.0001

population.^{16,17} The glucose load present in PD dialysate is thought to exert a deleterious effect in diabetic patients.⁶ In addition, higher levels of atherogenic substances (low-density lipoprotein, serum triglycerides and total cholesterol) have been observed in PD patients compared to patients on HD.¹⁸ Though requiring further validation, these metabolic factors coupled with diabetes may have synergistic effects leading to worse outcomes.

Furthermore, patients selected for PD may be those who are frailer, with cardiac comorbidity.⁷ Also, PD patients are reviewed less frequently by medical staff as PD is largely managed at home, when compared to dialysis patients who are reviewed more frequently by medical personnel when they get to dialysis centre. Finally, dialysis efficiency in PD may decline with time, resulting in poorer solute clearance that may contribute to increased mortality.¹⁹

Increased age and presence of cardiovascular risk factors increased risk of AMI. Dialysis modality (Fig. 2) and racial factors (Table 3) were not observed to have an effect on incidence of AMI in incident dialysis patients.



AMI: acute myocardial infarction

Fig. 2. Kaplan Meier Curve of haemodialysis (HD) and peritoneal dialysis (PD) patients showing probability of remaining free of AMI. Using logrank test, there were no significant differences between the 2 dialysis modalities.

Study limitations

Results of this study must be interpreted in the context of certain limitations. The initial reasons for selecting HD or PD cannot be ascertained in this retrospective

Table 3. Univariate and multivariate analysis of the risk factors for acute myocardial infarction

	Unadjusted hazard ratio (95% confidence interval)	P value	Adjusted hazard ratio (95% confidence interval)	P value
Age >60years	1.71 (1.49–1.96)	<0.0001	1.47 (1.27–1.69)	<0.0001
Ethnicity				
Chinese	1		1	
Malay	1.14 (0.98–1.32)	0.087	1.15 (0.99–1.35)	0.070
Indian	1.42 (1.13–1.78)	0.020	1.24 (0.99–1.56)	0.064
Others	0.89 (0.48–1.66)	0.71	1.00 (0.53–1.86)	0.99
Female sex	0.91 (0.80–1.04)	0.19	1.09 (0.93–1.28)	0.27
Comorbidities				
Diabetes mellitus	2.67 (2.24–3.18)	<0.0001	1.75 (1.45–2.10)	<0.0001
Ischaemic heart disease	2.96 (2.58–3.39)	<0.0001	2.27 (1.97–2.62)	<0.0001
Stroke	1.71 (1.48–1.98)	<0.0001	1.31 (1.13–1.52)	<0.0001
Peripheral vascular disease	2.11 (1.80–2.47)	<0.0001	1.55 (1.32–1.83)	<0.0001
Malignancy	0.99 (0.75–1.31)	0.96	1.02 (0.77–1.35)	0.91
Hypertension	2.10 (1.00–4.42)	0.050	0.92 (0.43–1.94)	0.82
Current/ex-smoker	1.49 (1.31–1.70)	<0.0001	1.37 (1.17–1.61)	<0.0001
Dialysis modality				
Haemodialysis	1		1	
Peritoneal dialysis	1.05 (0.88–1.26)	0.59	0.99 (0.82–1.18)	0.89

analysis. Traditionally, PD has been thought to have less haemodynamic fluctuations. For example, patients with poor cardiovascular status may have been preferentially chosen by their physicians to undergo PD. Certain variables such as socio-economic circumstances, frailty, nutrition status, blood pressure, left ventricular ejection fraction information and types of HD access (such as arteriovenous fistulae versus dialysis catheter) were not available in our analysis. These may have been important unmeasured co-variables influencing decision for dialysis modality. Crossovers from PD to HD and vice versa were also not considered in our analysis.

CONCLUSION

To our knowledge, this is one of the few studies in Southeast Asia looking at mortality and AMI outcomes in incident dialysis patients at a population-based level. It underscores the high incidence of mortality and ACS in ESRF patients in Singapore despite progress in clinical care, medications and dialysis facilities. PD patients were found to have poorer survival outcomes compared to HD patients. Inherent limitations associated with population-based epidemiological studies limits

elucidation of causalities of survival and ACS outcomes. We believe that this study has identified a group of patients in whom more aggressive treatment of underlying risk factors and monitoring may be appropriate, and could serve as a foundation for further studies.

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