Nephrol Dial Transplant (2011) 0: 1–6 doi: 10.1093/ndt/gfq835

Original Article



Long-term outcomes of end-stage renal disease patients admitted to the ICU

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Abstract

Background. End-stage renal disease (ESRD) patients admitted to the intensive care unit (ICU) have poor survival and high rates of readmission; however, little evidence exists on long-term outcomes. We set out to investigate the long-term (6 and 12 months) survival of ESRD patients admitted to the ICU and whether differential survival could be explained by dialysis modality and vascular access.

Methods. We compared the admission characteristics, outcomes and readmission rates of 619 ESRD [95 peritoneal dialysis (PD), 334 hemodialysis with a catheter (HD CVC), 190 hemodialysis with an AV fistula (HD AVF)] patients admitted to 11 ICU's in Winnipeg, Manitoba, Canada. Parametric and nonparametric tests were used as appropriate to determine differences in baseline characteristics. Multivariable Cox and logistic regression was used to assess outcomes between the groups.

Results. The 6- and 12-month crude survival was 62 and 52%, respectively. In a univariate model, modality and vascular access were associated with an increased hazard ratio (HR) of death [PD HR 1.60 95% confidence interval (CI) 1.20–2.13, HD CVC HR 1.55 95% CI 1.25–1.93] compared to patients on HD with an AVF. In three different multivariate adjusted models, this association persisted with HRs for death of 1.63–1.75 for PD and 1.50–1.58 for HD CVC.

Conclusions. Overall long-term survival of ESRD patients after admission to the ICU is poor. Being on PD or being dialyzed with a catheter was independently associated with an increased mortality.

Keywords: critical care; dialysis modality; end-stage renal disease; long-term mortality; vascular access

Introduction

Patients with end-stage renal disease (ESRD) have a high propensity for critical illness and require admission to ICU 25 times more frequently than patients in the general population without ESRD [1]. It has been estimated that 2% of all dialysis patients require admission to an intensive care

unit (ICU) every year. It is probable that as the ESRD population grows, the need for more intensive medical care will rise in parallel. Recent literature has begun to focus on ESRD outcomes after admission to the ICU [2–13]. Short-term ICU and in-hospital survival appears similar in ESRD patients and non-ESRD patients after adjustment for case mix, comorbidities and ICU admission characteristics [6]. Very few studies have focused on long-term outcomes of the ESRD ICU population [2, 3, 14]. Furthermore, there is little data regarding the impact of renal replacement modality and vascular access type on mortality in this population.

We set out to investigate the long-term mortality of ESRD patients admitted to the ICU and assess whether any differential impact on mortality occurred due to dialysis modality and vascular access.

Methods

Study population

The study population consisted of all adult ESRD patients who were admitted to any of the 11 ICUs serving the city of Winnipeg, Manitoba, Canada, (Population 675 000, catchments area 1 400 000) and has been described in detail elsewhere [1]. In brief, the study duration was over a 9.5-year period and included all patients admitted to an ICU between 1 January 2000 and 31 December 2006, and with follow-up to 30 June 2009. The 11 ICUs consisted of both primarily medical and surgical units in both academic and community settings. There was marked overlap in the patient characteristics between the surgical and medical units due to transfer of patients between units in accordance with bed availability. Only 2 of the 11 ICUs were dialysis capable; therefore, all patients requiring dialysis were transferred to one of the dialysis-capable units. This study was approved by the St Boniface General Hospital Research and Ethics Board, Winnipeg, Manitoba, Canada.

Data collection and validation

The electronic database for the ICUs is a regional prospectively maintained database of all patients admitted to any of the 11 ICUs in Winnipeg. The database tracks patients from ICU admission to death or hospital discharge. Data collection and entry is a mandatory part of the admission process and is performed by attending physicians and trained research staff. The database includes patient demographics, diagnoses, ICU admission physiologic and laboratory variables, APACHE II, Therapeutic Intervention Scoring System (TISS) scores, length of stay and outcomes. The TISS is a recognized measure of ICU resource utilization and was calculated and entered daily into the ICU database over the first 10 days of

admission. Data validation is by independent audit for completeness and if necessary, a chart review to identify missing data elements. Outcomes are adjudicated by the attending ICU physician. For the purposes of our study, we utilized an 'adjusted' APACHE II score where elements of the score involving renal function were removed.

Long-term survival, ESRD status, length of time on dialysis, dialysis modality and vascular access data were extracted from an administrative database for the Manitoba Renal Program (MRP). Data in the MRP registry is prospectively collected with respect to dates of dialysis initiation, modality transitions (i.e. switches from one form of renal replacement therapy to another), vascular access and outcomes (death). The outcomes are adjudicated at multidisciplinary weekly meetings attended by all renal health care providers (nephrologists, nurses and allied health professionals). All dialysis starts, modality changes and deaths are cross-validated with billing data which is captured separately and independently by the program. Modality and vascular access changes are updated weekly in the MRP database.

Cohort definitions

Chronic dialysis (ESRD) patients were defined as those patients receiving chronic peritoneal dialysis (PD) or hemodialysis (HD) for at least 6 weeks prior to time of admission to the ICU. ESRD status in the ICU database was cross-validated with the MRP database and discrepancies excluded from the analysis. For ESRD patients with repeated admissions to ICU, we included only the first admission in the analysis (see Figure 1).

In the MRP, there are roughly 1200 prevalent patients requiring dialysis therapies. We aim to start all suitable patients on PD as their first modality and roughly 20% of our ESRD cohort is on PD. Of those on HD, just >50% are dialyzed via a central venous catheter (CVC) often due to lack of suitable vessels for arteriovenous fistula (AVF) creation.

Dialysis modality or vascular access was defined as the last modality or access in the MRP database prior to ICU admission. For example, if a PD patient was admitted to ICU and then received a catheter for renal replacement therapy during the admission, they were still considered a PD patient. Patients were also classified as PD upon insertion of the PD catheter, which may not reflect actual time of PD initiation. Patients having both a central venous catheter and an AVF were included in the CVC for the purpose of analysis. The designation catheter included temporary (nontunneled, non-cuffed) or permanent (tunneled, cuffed) CVC.

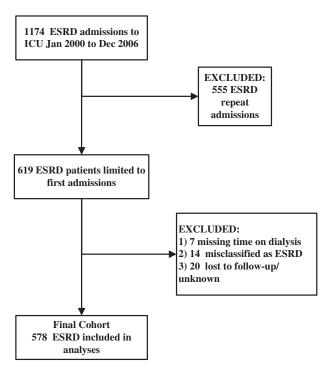


Fig. 1. Derivation of our study cohort.

Outcome definitions

The primary outcomes were mortality from the date of ICU admission. The ICU database tracks all patients from ICU admission to final discharge from hospital or death, so in-hospital outcomes were known for 100% of patients. Mortality after hospital discharge was extracted from the MRP database.

Data analysis

Continuous variables of interest were summarized as mean or medians with standard deviation or intra-quartile range as appropriate. Differences in baseline characteristics were determined by Student's *t*-test and analysis of variance for continuous variables and Mann–Whitney *U*-test and the Kruskall–Wallis test for dichotomous variables. The *Z*-test for proportions was used to compare continuous and dichotomous variables, respectively. All analyses were conducted using STATA v.10, College station, TX.

To examine the association of ESRD status with mortality, univariate analyses were performed with $P \leq 0.05$ considered significant. To examine the impact of modality and vascular access on outcomes, multivariate Cox proportional hazard models were performed with variables included in three predefined models. Adjustment variables were selected based on significance ($P \leq 0.05$) in univariate analyses and/or known importance based on the published literature. The hazards assumption was tested for proportionality and met. A sensitivity analysis was performed using multivariate logistic regression for mortality at three time points: in the ICU and by 6- and 12-month post-ICU discharge. All statistical tests were considered significant if P < 0.05. Logistic model fit and calibration were determined by the c-statistic and the Hosmer–Lemeshow test.

Results

During the study period, there were a total of 34 965 ICU admissions of which 1174 admissions were patients with ESRD and 619 were first admissions (Figure 1). Forty-one cases were excluded: 7 were missing data regarding time on dialysis, 14 were misclassified as ESRD and 20 were lost to follow-up or had unknown outcomes. Five hundred and seventy-eight (93.3% of total) ESRD ICU first admissions were included in the analyses.

Table 1 outlines the baseline characteristics based on dialysis modality and vascular access. A total of 483 (83%) were HD patients with 190 (32.9%) dialyzed by AVF and 293 (50.7%) by CVC. The remaining 95 (16.4%) patients were on PD prior to ICU admission. HD catheter patients were older, had shorter time on dialysis prior to ICU admission and had more coronary artery disease. PD and HD CVC patients were more commonly Caucasian, while the HD AVF group had significantly more First Nations people. HD AVF patients had been on dialysis the longest. There were no significant differences in sex, diabetic status, stroke, peripheral artery disease and malignancy between the groups.

The primary reason for ICU admission for all groups was sepsis. Upon admission to the ICU, the main differences observed were that HD patients were more likely to be admitted following cardiac arrest, and HD AVF patients had a slightly higher hematocrit (see Table 1). There were no differences in adjusted APACHE scores or requirement for mechanical ventilation between the groups.

Unadjusted mortality and readmission rate to ICU are presented in Figure 2. A total of 13.3% (77), 38% (218) and 48% (276) of all ESRD patients admitted to the ICU died in the ICU or after 6 and 12 months of follow-up, respectively. HD AVF patients were less likely to die in the ICU (10.5 versus 14.7 HD CVC or 14.7% PD), but inhospital mortality was not different between the groups.

Table 1. Baseline characteristics, comorbid illness and ICU admission characteristics of ESRD patients admitted to ICU by modality and vascular access^a

	Modality		
Characteristic	HD AVF (N = 190)	HD CVC (N = 293)	PD (N = 95)
Demographics			
Age (years)		$62.4 \pm 13.4^{\circ}$	59.1 ± 15.5
Female (%)	41.6 ^b	46.8 ^b	47.4 ^b
Ethnicity			
Caucasian (%)	45.8 ^b	59.4°	64.2°
Indigenous peoples (%)	43.2 ^b	27.3°	26.3°
Other (%)	11.1 ^b	13.3 ^b	9.5 ^b
Length of time on	$59.3 \pm 3.8^{\circ}$	44.3 ± 3.8^{b}	$48.3 \pm 6.6^{\circ}$
dialysis (months)			
Comorbidities			
Diabetes mellitus (%)	55.3 ^b	54.3 ^b	46.3 ^b
Coronary artery disease (%)	15.8 ^d	17.4 ^b	8.4°
Stroke (%)	11.6 ^b	9.9 ^b	7.4 ^b
Peripheral artery	25.8 ^b	33.8 ^b	30.5 ^b
disease (%)			
Cancer (%)	6.8 ^b	10.2 ^b	12.6 ^b
ICU admission			
characteristics			
Cardiac arrest (%)	11.6 ^b	11.1 ^b	4.2°
Sepsis (%)	15.3 ^b	16.5 ^b	14.7 ^b
Mechanical	43.2 ^b	42.2 ^b	38.9 ^b
ventilation (%)			
Medical (%)	81.6 ^b	86.2 ^b	78.9 ^b
Surgical			
Elective (%)	5.8 ^b	6.9 ^b	12.6 ^b
Emergent (%)	12.6 ^b	6.9 ^b	8.4 ^b
GCS	14 ± 1^{b}	13 ± 2^{b}	13 ± 2^{b}
Adjusted APACHE	19 ± 6^{b}	20 ± 7^{b}	19 ± 6^{b}
score			
MAP (mmHg)	80 ± 32^{b}	76 ± 30^{b}	74 ± 30^{b}
WBC	13 ± 8^{b}	14 ± 6^{b}	15 ± 7^{b}
Temperature (°C)	36.6 ± 1.2^{b}	36.7 ± 1.4^{b}	36.6 ± 1.2^{b}
Hematocrit (%)	30 ± 7^{b}	28 ± 7^{c}	28 ± 7^{c}

 $^{\rm a}$ In a row, means/proportions superscripted by differing letters have P <0.05; those sharing a common letter are not. All significance tests were corrected for multiple comparisons (Bonferroni). Analysis of variance, Wilcoxon scores Rank *t*-approximation test or Chi-square tests were used as appropriate. Values are presented as proportions when appropriate. Continuous variables are presented with standard deviations or variance dependent on distribution.

HD AVF patients had lower 6-month mortality (27.9 versus 42 HD CVC or 44.2% PD) and 12-month mortality (35.6% versus 54.7 HD CVC or 47.8% PD) compared to HD CVC or PD patients. Similarly, HD AVF patients were less likely to require readmission to the ICU during their hospitalization (4.7 versus 16.4 HD catheter or 13.7% PD).

Univariate associations between mortality and multiple variables of interest, including various admission characteristics are summarized in Table 2. PD and HD CVC use were associated with higher hazard ratios (HRs) compared to HD AVF. Among baseline demographics, only age was associated with increased mortality. A history of vascular disease (coronary artery disease, stroke and peripheral artery disease) was consistently associated with an increase in mortality. In general, ICU admission characteristics were strongly associated with long-term mortality. Cardiac arrest, sepsis, decreases in Glasgow coma scale (GCS) and mean arterial pressure (MAP) and increases in adjusted

APACHE and white blood cell count (WBC) were all independently associated with death. Measures of ICU resources requirements (TISS score) were also associated with mortality.

We explored the impact of adjustment for baseline characteristics (MODEL 1), comorbidities (MODEL 2) and ICU admission characteristics (MODEL 3), on the association between modality/access and mortality (see Table 3). Modality and vascular access, relative to the HD AVF, were associated with much higher mortality in all three models of adjustment. The odds of mortality at specific time points (ICU, 6 and 12 months) are presented in Figure 3. PD patients have similar survival to HD AVF patients in the ICU, however, by 6- and 12-month post-ICU discharge, the odds of death increases steadily to an odds ratio (OR) of 2.33 [95% confidence interval (CI) 1.35–4.01] and OR 2.62 (95% CI 1.54–4.48), respectively. Patients with a CVC had consistently increased mortality at all three time points.

Discussion

Our study assessed the long-term survival and differential impact of dialysis modality and vascular access on survival of ESRD patients after critical illness. Overall, we found that long-term survival of ESRD patients admitted to the ICU was poor. PD or undergoing HD with a CVC was independently associated with an increase in mortality even after adjustment for baseline characteristics, comorbid illnesses and ICU admission characteristics.

There is a paucity of data for comparison regarding longterm outcomes of ESRD patients after ICU admission [3, 7, 13, 14]. Six- and 12-month mortality rates have been previously reported ranging from 40 to 48% in small cohorts from Canada and Europe [2, 3, 7]. We found similar mortality rates in our cohort of 38 and 48% at 6- and 12months, respectively. Discrepancies between reported mortality rates could be accounted for by regional population differences and discrepancies in case mix. Of note, our ESRD ICU mortality rate of 13% was also consistent with previous reports [1–11, 14, 15]. Bell et al. [3] utilizing Swedish ICU registry data, reported 5-year mortality data for ESRD patients after ICU admission. Interestingly, the majority of deaths in this cohort did not occur during the critical illness itself. Mortality appeared to be the highest in the first 6 months after discharge with relatively stable rate of death afterward, a finding consistent with our data.

The adverse risk of long-term mortality in PD patients was unexpected. After adjustment, the HR for mortality in PD ranged from 1.63 to 1.75 in comparison to HD patients with an AVF. This was consistent in all three models after multivariate adjustment and in a sensitivity analysis employing logistic regression at specific time points. Mahnes *et al.* examined outcomes in 92 ESRD patients admitted to the ICU, 16 (17%) of whom were on PD. In that study, 7 of the 16 (44%) PD patients died in the ICU compared to 19/76 (25%) HD patients, although the number of patients was too small to detect statistical difference (P = 0.2) [7]. Our findings are congruent with this earlier observation and suggest that the adverse risk associated with PD may be real. It is unclear why PD patients experienced such poor

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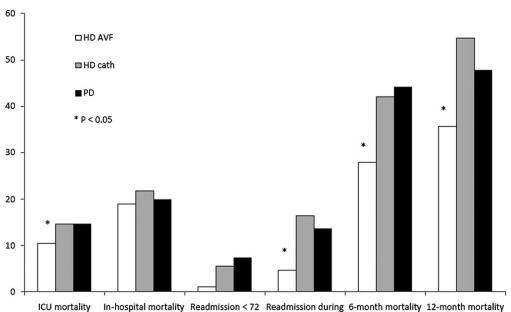


Fig. 2. Proportion of patients who experienced death or requirements for readmission by vascular access type and modality. *Denotes statistically significant P values (<0.05) when comparing HD CVC and PD to HD AVF (referent).

long-term survival after ICU admission. We can only speculate that it may be due to the impact of variables not captured in our analysis such as inflammation, delays in treatment, different potential sources of sepsis (peritonitis in PD), nutritional status and length of mechanical ventilation. It is plausible that HD patients may have their acute illnesses recognized and treated earlier than PD patients, by virtue of the fact they are assessed more regularly by MDs and nurses thrice weekly on their regular dialysis schedules. There are no reports to our knowledge individually examining long-term survival of PD patients after ICU admission. Further investigations to confirm this finding and to elucidate the responsible factors are warranted.

HD CVC use is associated with all-cause and infectionrelated mortality in chronic HD patients [16–23]. However, to our knowledge, the association between mortality and vascular access in the critically ill ESRD patient has not been previously examined. In this study cohort, vascular access was significantly associated with mortality. Patients dialyzed with a CVC had a higher crude mortality of 42 and 54% at 6 and 12 months, respectively, compared to patients dialyzed with an AVF (28 and 35% at 6 and 12 months, respectively). HD CVC use was independently associated with death even after adjustment for baseline characteristics, comorbid illness and ICU admission characteristics with HRs ranging from 1.50 to 1.58. The risk of death associated with catheters observed in this study is higher than the reported differences in the non-ICU chronic HD population, suggesting that the observed mortality difference was impacted by the ICU admission and not merely a reflection of expected background risk [20, 23]. We were also cognizant that cohort studies examining vascular access and outcomes suffer from confounding by indication (does the catheter cause mortality or is it a marker of poor health status).

Table 2. Univariate HR of mortality for modality, access, demographics, comorbidities and ICU admission characteristics

	Mortality	
Characteristics	HR	95% CI
PD	1.60	1.20-2.13
HD CVC	1.55	1.25-1.93
HD AVF	Referent	
Demographics		
Age	1.03	1.02 - 1.03
Length on dialysis	1.00	1.0-1.00
Female	0.95	0.79-1.15
Race		
Caucasian	0.96	0.71 - 1.28
Indigenous peoples	0.88	0.65 - 1.21
Other	Referent	
Comorbidities		
Diabetes mellitus	1.03	0.85 - 1.25
Coronary artery disease	1.51	1.18-1.93
Stroke	1.63	1.21-2.18
Peripheral artery disease	1.51	1.24-1.84
Cancer	1.57	1.16-2.13
ICU admission characteristics		
Cardiac arrest	1.60	1.19-2.15
Sepsis	1.55	1.21-1.99
Mechanical ventilation	1.14	0.94-1.38
Surgical		
Elective	0.65	0.44-0.97
Emergent	0.68	0.48 - 0.98
Medical	Referent	
TISS	1.02	1.01-1.03
GCS	0.90	0.87 - 0.92
Adjusted APACHE score	1.08	1.06-1.09
MAP	0.99	0.99-0.99
WBC	1.02	1.01-1.03
Temperature	0.99	0.91 - 1.07
Hematocrit	1.00	0.99-1.01

Table 3. Adjusted HR of mortality for ESRD patients by dialysis modality and vascular access^a

Cohort	HR	95% CI	P
Model 1			
PD	1.75	1.31-2.35	0.0002
HD CVC	1.58	1.26-1.97	< 0.0001
HD AVF	Referent		
Model 2			
PD	1.68	1.25-2.24	0.0005
HD CVC	1.50	1.21-1.85	0.0003
HD AVF	Referent		
Model 3			
PD	1.63	1.22-2.20	0.0011
HD CVC	1.55	1.24-1.93	< 0.0001
HD AVF	Referent		

^aMODEL 1 adjusted for ethnicity, age, sex and length of time on dialysis (days). MODEL 2 adjusted for diabetes, coronary artery disease, stroke, peripheral artery disease and cancer. MODEL 3 adjusted for cardiac arrest, sepsis, elective or emergent admission, GCS, adjusted APACHE score and length of intensive care unit stay (days).

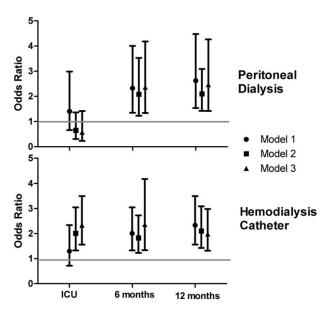


Fig. 3. Adjusted OR of ICU, 6- and 12-month mortality for ESRD patients by modality and vascular access. MODEL 1 adjusted for ethnicity, age, sex and length of time on dialysis (days). MODEL 2 adjusted for diabetes, coronary artery disease, stroke, peripheral artery disease and cancer. MODEL 3 adjusted for cardiac arrest, sepsis, elective or emergent admission, GCS, adjusted APACHE score and length of intensive care unit stay (days). HD AVF is the referent. Error bars represent 95% CI for point estimate.

Other characteristics associated with long-term mortality in our study included age, a history of vascular disease and several ICU admission variables: cardiac arrest, sepsis, mechanical ventilation, increased TISS score and ICU length of stay, lower GCS and MAP and higher temperature, adjusted APACHE score and WBC count. Previous reports in both the ESRD and non-ESRD populations have found these variables to be consistently associated with long-term mortality [2, 3, 7, 24, 25]. Interestingly, predictors of shortand long-term ICU mortality are consistent and heavily reliant on ICU admission characteristics such as physiological variables and reason for admission to the ICU [1, 4, 6,

8, 10, 11]. These findings could aid in providing both shortand long-term prognostication of ESRD patients admitted to the ICU.

The requirement for readmission differed based on vascular access and modality. Patients on PD or those with catheters experienced higher readmission during hospitalization compared to those with an AVF. Although not statistically significant due to a small number of events, this trend can be observed in patients who required early (<72 h) readmission. Whether these discrepancies are present with a larger number of events and after adjustment requires further investigation. It is suggestive of potential fragility in both PD and catheter patients, which may warrant longer ICU admissions or discharge to hospital wards with closer observation.

Our study was limited by the observational retrospective study design that does not allow for determination of causal associations. We attempted to overcome this by analyzing a large cohort size of 578 ICU admissions, adjusted for a high number of demographic, comorbid and ICU admission characteristics. Methodologically, our Cox and logistic regression models were consistent in effect and magnitude of the point estimates. Modality and vascular access were obtained from the MRP database (updated weekly) and not at the time of ICU admission. Patients were classified as PD upon PD catheter insertion and not date of PD initiation. In general, >90% of all patients initiate PD within 30 days of catheter insertion. Thus, if modality or access changes occurred between ICU admission and the MRP database being updated, a potential misclassification may occur. The mean length of time on dialysis was longer for HD AVF patients compared to HD catheter and PD patients. This may lead to the welldescribed 'survivor bias' as healthier HD AVF patients would likely experience less critical illness and if they do become ill, may transfer to HD with a catheter prior to critical illness [26, 27]. Time-adjusted categorization of vascular access and dialysis modality, limiting the study to include only incident dialysis patients (for example, who started dialysis within 1 year of ICU admission) or a prospective study design could minimize this bias [28, 29]. Lastly, further data such as cause of death and laboratory values were not available.

Long-term mortality of ESRD patients admitted to the ICU is high with an increased mortality being associated with PD and HD CVC. These findings require confirmation and further investigations should be directed toward elucidating underlying factors in both populations, which may contribute to this increase in mortality.

Acknowledgements. The authors would like to thank Dolores Friesen, Amanda Eng, Loretta Eng and the Manitoba Renal Program (MRP). This research was funded by a grant from the Renal Research and Development Committee.

Conflict of interest statement. None declared.

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Received for publication: 26.7.10; Accepted in revised form: 22.12.10