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ORIGINAL ARTICLE

In-hospital mortality among incident hemodialysis older patients in Peru

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Background: Understanding the pattern of mortality linked to end stage renal disease (ESRD) is important given the increasing ageing population in low- and middle-income countries.

Methods: We analyzed older patients with ESRD with incident hemodialysis, from January 2012 to August 2017 in one large general hospital in Peru. Individual and health system-related variables were analyzed using Generalized Linear Models (GLM) to estimate their association with in-hospital all-cause mortality. Relative risk (RR) with their 95% confidence intervals (95% CI) were calculated.

Results: We evaluated 312 patients; mean age 69 years, 93.6% started hemodialysis with a transient central venous catheter, 1.7% had previous hemodialysis indication and 24.7% died during hospital stay. The mean length of stay was 16.1 days (SD 13.5). In the adjusted multivariate models, we found higher in-hospital mortality among those with encephalopathy (aRR 1.85, 95% CI 1.21-2.82 vs. without encephalopathy) and a lower in-hospital mortality among those with eGFR $\leq$7 mL/min (aRR 0.45, 95% CI 0.31-0.67 vs. eGFR>7 mL/min).

Conclusions: There is a high in-hospital mortality among older hemodialysis patients in Peru. The presence of uremic encephalopathy was associated with higher mortality and a lower estimated glomerular filtration rate with lower mortality.

Keywords: mortality, renal dialysis, health services, epidemiology, Peru

Introduction

The number of patients with end-stage renal disease (ESRD) in renal replacement therapy has substantially increased worldwide, and it is expected to grow further.[1] In 2010, there were 2,618 million people with ESRD in the world, and it is projected to increase to 5,439 million people in 2030, hemodialysis being the main type of renal replacement therapy.[1, 2] One of the reasons for the increase in patients in hemodialysis is the growing inclusion of older adults in renal replacement therapy.[3]

The number of older people is increasing worldwide alongside chronic non-communicable diseases associated to ESRD such as diabetes and hypertension, conditions that are also very common in this age group, particularly in low- and middle-income countries (LMIC).[4] Kidney transplantation is the treatment of choice in ESRD irrespective of age, yet hemodialysis remains the most used therapy.[5]

Survival of older patients (i.e. >60 years old) in hemodialysis is poor, an effect of several factors including age and late referral to specialized nephrology care.[6, 7] In addition to individual clinical variables, inadequate pre-hemodialysis care is strongly associated with higher mortality in older patients in hemodialysis.[8] Most studies exploring the effect of pre-hemodialysis care on mortality and its associated factors have typically included prevalent rather than incident cases, thus limiting the evaluation of the effect on early mortality of pre-hemodialysis care on incident patients.[9]

Health systems in many in LMIC face major burdens, and their preparedness to serve patients in hemodialysis is not always optimal. Peru is a country with a high ageing index of 35.7%, which is the number of persons 60 years old or over per hundred persons under age 15,[10] and the public national health system does not have adequate and effective strategies for pre-hemodialysis care, including older adults.[11, 12] As such, characterizing the mortality of older patients in hemodialysis and its associated factors will inform and improve health system-level responses oriented to address the challenges imposed by ESRD and hemodialysis in resource limited settings.

Methods

Study design and setting

We analyzed a data set of incident hemodialysis older patients with ESRD, attending the 2 de Mayo General Hospital in Lima, Peru's capital with nearly 10 million inhabitants. Peru has a fragmented health care system where two institutions provide renal replacement therapy: The Ministry of Health, the largest public health care provider in the country, and the Social Security system managed by the Ministry of Labor. In 2014, the Ministry of Health offered hemodialysis to 1,983 individuals.[13] 2 de Mayo General Hospital is one of the tertiary care hospitals from the Ministry of Health, covering close to 0.5 million visits in the outpatient services annually.

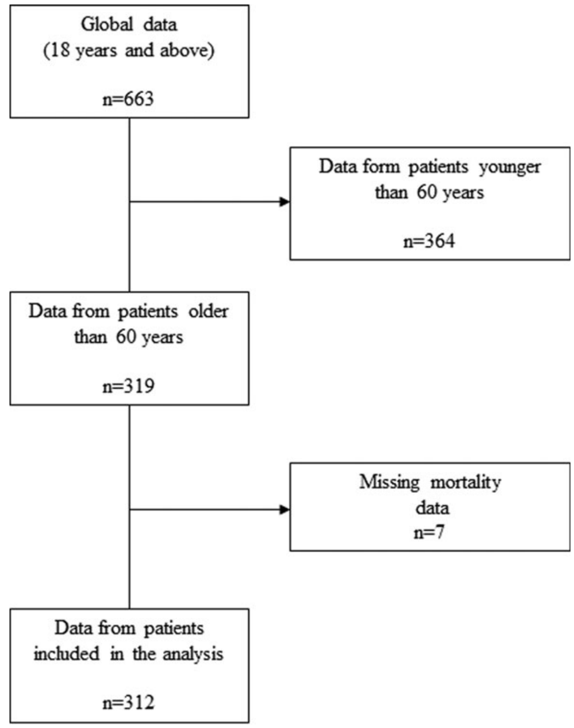

Figure 1. Flowchart of data included in the analysis.

Data source

The hemodialysis data set included 663 patients over 18 years old. Those over 60 years were 319. Were excluded 7 patients for missing mortality data; therefore, 312 patients were included in the analysis (Figure 1). This data set is an in-hospital registry of patients in hemodialysis of the 2 de Mayo General Hospital. While they remain hospitalized, patients receive hemodialysis exclusively in the nephrology service by nephrologists of the hospital. The data set includes demographics, date of admission and discharge, discharge status (dead or alive), etiology of ESRD and inpatient laboratory information. Individual's ≥60 years were defined as older adults, according to the World Health Organization.[14] Previous nephrologist consultation was defined as at least two assessments in the last year by any nephrologist.

We included data about time of ESRD diagnosis, if the patient started hemodialysis by using a transient catheter to dialyze, if had no previous nephrologist consultation and the presence of uremic symptoms as criteria to initiate hemodialysis. We also included pre-hemodialysis laboratory values: serum potassium, pH, bicarbonate, hemoglobin, calcium, phosphorus, and the estimated glomerular filtration rate. Estimated glomerular filtration rate (eGFR), calculated using the MDRD4 formula,[15] was categorized as follows:>7 mL/min, and ≤7 mL/min.[16] All patients started hemodialysis in different times in a period between January 2012 and October 2017. We considered in-hospital all-cause mortality as primary outcome.

Data analysis

Categorical data were summarized as frequencies and percentages. Continuous variables were summarized as mean and standard deviation (SD), except when the variable show skew distribution, we summarized as medians and interquartile ranges (IQR). Differences between two groups were tested with Chi square test for categorical variables, and the Wilcoxon rank sum test for continuous variables. We calculated the relative risk (RR) together with their 95% confidence intervals (CI) of independent predictors for in-hospital all-cause mortality using Poisson generalized linear models (GLM) with robust error standards. Independent predictor variables, established confounding variables for epidemiologic and clinical criteria were considered in the multivariable GLM model. Unadjusted and age, sex, and diabetes adjusted RR were reported. All the tests were 2-tailed, and the type 1 error rate was set at 5%. Analyses were performed with Stata 15.0 (Stata Corp, College Station, TX, USA).

Ethics statement

This study was conducted using non-identified data. The protocol of this study was approved by the Ethics Committee (Comité Institucional de Ética en Investigación) of the Universidad Peruana Cayetano Heredia in Lima, Peru; approval code number 096-05-17.

Results

We evaluated 312 patients, 195 (62.5%) males, mean age 69 years (SD±6.9, range 60-89). Diabetic nephropathy was the most common etiology of ESRD and the most common indication for hemodialysis was encephalopathy. Only six (1.9%) patients who start hemodialysis because of uremia symptoms had a previous planned hemodialysis indication. Only 179

Table 1. Bivariable association between patient characteristics and gender or in-hospital mortality in ESRD older adults with incident hemodialysis

	Male (n=195)	Female (n=117)	p-value*	Died (n=77)	Alive (n=235)	p-value**	Total (n=312)
General variables							
Male				50 (64.9)	145 (61.7)	0.611	195 (62.5)
Female				27 (35.1)	90 (38.3)		
Previous nephrologist consultation	47 (24.1)	34 (29.1)	0.334	20 (25.9)	61 (25.9)	0.998	81 (25.9)
Etiology of ESRD							
Diabetic nephropathy	76 (38.9)	65 (55.6)	0.004	37 (48.1)	104 (44.3)	0.561	141 (45.2)
HTA nephroangiosclerosis	26 (13.3)	20 (17.1)	0.364	12 (15.6)	34 (14.5)	0.81	46 (14.7)
Chronic glomerulonephritis	6 (3.1)	5 (4.3)	0.579	7 (3.0)	4 (5.2)	0.36	11 (3.5)
Obstructive nephropathy	44 (22.6)	3 (2.6)	0.001	7 (9.1)	40 (17.0)	0.091	47 (15.1)
Renal polycystic disease	2 (1.1)	3 (2.6)	0.295	1 (1.3)	4 (1.7)	0.807	5 (1.6)
Non-classified	3 (1.8)	1 (1.1)	0.634	14 (18.2)	40 (17.0)	0.815	54 (17.3)
Time of ESRD diagnosis							
Recent	93 (49.5)	38 (33.1)	0.019	36 (46.8)	95 (40.4)	0.657	131 (42.0)
1 to 6 months	44 (23.4)	28 (24.4)		15 (19.5)	57 (24.3)		72 (23.1)
6 to 12 months	16 (8.5)	18 (15.6)		9 (11.7)	25 (10.6)		34 (10.9)
>1 year	35 (18.6)	31 (26.9)		14 (21.9)	52 (26.0)		66 (25.0)
Criteria to initiate HD							
Encephalopathy	115 (58.9)	64 (54.7)	0.461	55 (71.4)	124 (52.8)	0.004	179 (57.4)
Uremic gastric affection	60 (30.7)	41 (35.1)	0.435	14 (18.2)	87 (37.0)	0.002	101 (32.4)
Pericarditis	2 (1.1)	1 (0.9)	0.881	1 (1.3)	2 (0.9)	0.727	3 (1.0)
Pulmonary edema	44 (22.6)	34 (29.1)	0.201	19 (24.7)	59 (25.1)	0.94	78 (25.0)
Acidosis	82 (42.1)	32 (27.4)	0.009	28 (36.4)	86 (36.6)	0.971	114 (36.5)
Hyperkalemia	60 (30.8)	15 (12.9)	0.001	18 (23.4)	57 (24.3)	0.876	75 (24.0)
Laboratory values at HD initiation							
eGFR <7 (mL/min)	154 (79.4)	90 (77.6)	0.709	48 (62.3)	196 (84.1)	<0.001	5.1 (2.9)
Potassium (mEq/L)	6.1 (0.1)	5.5 (0.1)	0.004	5.8 (1.4)	5.9 (1.5)	0.743	5.9 (1.5)
pH	7.2 (0.1)	7.1 (0.1)	0.269	7.16 (0.87)	7.16 (0.86)	0.991	7.16 (0.86)
Bicarbonate (mEq/L)	11.8 (0.6)	12.7 (0.5)	0.297	11.9 (5.7)	12.2 (8.4)	0.862	12.1 (7.8)
Hemoglobin (g/dL)	7.6 (0.2)	7.8 (0.2)	0.402	7.7 (1.9)	7.7 (2.3)	0.872	7.7 (2.2)
Calcium (mg/dL)	8.2 (0.5)	7.9 (0.2)	0.716	7.9 (1.3)	8.1 (5.6)	0.727	8.1 (4.9)
Phosphorus (mg/dL)	7.1 (0.2)	6.2 (0.2)	0.009	7.1 (2.5)	6.7 (2.7)	0.284	6.8 (2.6)

*p comparing sex, **p comparing survival
ESRD: end-stage renal disease, HD: hemodialysis, eGFR: estimated glomerular filtration rate

(57.4%) patients had a previous consultation by a nephrologist, and 292 patients (93.6%) were dialyzed through a transient central venous catheter. Table 1 shows the characteristics of the study participants.

The mean length of stay was 16.1 days (SD: 13.5), and a total of 77 (24.7%) patients died during the hospitalization period. The in-hospital all-cause mortality rate was 5.6 deaths per 1000 person-years (95% CI 4.5–7.0).

In the bivariable analysis, we found a strong association between in-hospital all-cause mortality and encephalopathy and uremic gastric affection as criteria to initiate hemodialysis and also with an eGFR <7mL/min (Table 1).

In the multivariable models, having uremic encephalopathy (vs. no) was associated with higher mortality, and a lower eGFR (≤7 vs.>7 mL/min) was associated with lower mortality (Table 2).

Discussion

We found that in-hospital all-cause mortality in older patients with incident hemodialysis was high, with one in four older people in hemodialysis dying during hospitalization. The presence of uremic encephalopathy was associated with an increased risk of death and an eGFR ≤7 mL/min was associated with a lower mortality risk in this population.

Our mortality rate was substantially higher than estimates reported in a systematic review showing a median survival time of 8–67 months;[6] however, only one study of this systematic review showed age ranges similar to our population and reported a mortality rate of 10.3% also below our own.[17] In our study, we included incident patients, whilst the systematic review[6] only considered prevalent cases, hence our mortality

Table 2. Unadjusted and adjusted HR of predictors of in-hospital all-cause mortality of older ESRD adults receiving hemodialysis

Variable	Categories	RR (95% CI)	*p* value	aRR (95% CI)	p value
Encephalopathy	No	Ref			
	Yes	1.15 (1.04–1.26)	0.004	**1.85 (1.21–2.82)**	**0.004**
eGFR	7+	Ref			
	≤7	0.45 (0.31–0.65)	<0.001	**0.45 (0.31–0.67)**	**<.001**

CKD: Chronic Disease Kidney; RR: Relative Risk; aRR: Relative Risk; 95% CI: Confidence Interval 95%.
eGFR: estimated glomerular filtration rate
GLM model with family poisson, link log, robust covariance and p value from Wald test

rate could be higher than estimates reported among prevalent cases. It has been reported that mortality within the first 3 months of initiating hemodialysis is higher, since it is a period of adaptation to therapy.[17–23] However, studying mortality among incident patients allows an evaluation of the clinical conditions in which the patient initiates hemodialysis which is indirectly linked to the structure and delivery of health care.[17–23]

Our data showed that pre-hemodialysis care in our patients was deficient, especially due to two predominant factors. First, several patients initiated hemodialysis in an emergency way using transient vascular access. Second, most patients did not receive specialized consultation by a nephrologist. Both factors have been reported to be associated with higher mortality in other studies.[24–31] However, the frequency of these factors is similar among both groups according to death status; therefore, there were no significant differences in the multivariate analysis.

Older adults who initiated hemodialysis have different health, socioeconomic and functional status, cognitive and affective level and different degrees of disease burden, malnutrition and frailty.[32] An adequate comprehensive geriatric assessment is the best way to identify these conditions in the pre-hemodialysis period to improve survival[33–36] and even provide tools to involve older people in the decision-making process to decide for hemodialysis or a conservative management.

In our population, a clinical aspect such uremic encephalopathy was related to higher mortality and other studies have also found this association.[22, 37] Uremic symptoms are more likely to present in the average eGFR of patients (4.8 mL/min)[38] and it is difficult to define[39] and explain the discrepancies found as mortality predictor.[39–41] However, the presence of this symptom is an indicator of the severity with our patients start hemodialysis and the explaination of the association with a higher mortality.

Our finding that an eGFR ≤ 7 mL/min was associated with a lower mortality risk may be contradicting our description about uremic encephalopathy. An explanation of this result is that a lower GFR is an expression of a higher creatinine value, which indirectly could be related to a greater muscle mass and therefore less malnutrition than the group that started hemodialysis with lower creatinine level and higher GFR.[42] The malnutrition has been associated with greater mortality in hemodialysis patients, which could be the reason for this association.[43–45]

There is a growing interest to determine the time to start dialysis by a GFR level and its association with mortality. In general population, the IDEAL study did not find that an early start to dialysis, defined by a GFR > 10 mL/min, was associated with lower mortality.[38] In older patients, there are no randomized studies addressing this aspect; however, observational studies had discrepant results. One study among patients older than 67 years of the US Renal Data System, found that starting dialysis with a GFR > 10 mL/min was associated with higher mortality.[46] In contrast, a study made in Singapore found that starting dialysis with a GFR > 10 mL/min was not associated with higher mortality in those over 65 years of age, unlike younger patients.[47]

Our study has some limitations. Our database did not include variables such as coronary disease, smoking, obesity; however, the all-cause mortality rate is mainly due to cardiovascular mortality and those risk factors are very prevalent in ESRD population.[48] The database did not include other geriatric variables such as functionality, cognitive level and frailty, all of them associated with morbidity and mortality in older adults who initiate hemodialysis but those conditions were associated with mortality in prevalent patients rather than in incident population.[36] In the analysis, we excluded some variables with a high number of missing data; for example, serum albumin, sodium and chloride as electrolyte balance, however, the rest of variables included had more than 80% of data capture. This database was derived at a national reference hospital with one of the largest nephrology units of the Ministry of Health in Peru, and thus affords a reasonable scoping of hemodialysis in Peru and similar LMIC health systems.

In conclusion, there is a high in-hospital all-cause mortality among older population attending public hospitals in Peru. Uremic encephalopathy is associated with higher mortality and an eGFR ≤ 7 mL/min is associated to lower in-hospital mortality in this population. A correct and complete assessment of pre-hemodialysis care in elderly people, a health system quality indicator, should be a priority in low- and middle-income countries. Policies for early detection and timely management of older ESRD patients considering a comprehensive assessment should be designed.

Author's contributions: PHA and PJO conceived the study. PHA, PJO, JEP, AVH and JJM contributed to the module material. AVH and JEP analyzed the data, and the data were interpreted by PHE, PJO, TT and FG. PHA and

PJO drafted the manuscript. TT, FG, and JJM critically revised the manuscript. All authors read and approved the final manuscript.

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