Factors associated with mortality in a population with acute kidney injury undergoing hemodialysis in Peru

Fatores associados à mortalidade em uma população com lesão renal aguda submetidos a hemodiálise no Peru

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Submitted on: 1/4/2016.
Approved on: 2/8/2017.

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DOI: 10.5935/0101-2800.20170029

Abstract

Introduction: Patients with acute kidney injury (AKI) in developing countries are described in a profile of young age, with less comorbidities, with unifactorial, and with a lower mortality compared to patients in developed countries. **Objective:** To assess mortality in patients with acute kidney injury undergoing hemodialysis (HD) and its associated factors in a developing country setting. **Methods:** Retrospective study. Demographic, clinical, and mortality variables were collected from patients who presented AKI and underwent HD between January 2014 and December 2015 at a national reference hospital in Lima, Peru. Risk ratios (RR) and 95% confidence intervals (95%CI) were estimated through Poisson regressions. **Results:** Data from 72 patients with AKI that underwent HD were analyzed, 66.7% of them were < 64 years old, and 40.2% of all patients died undergoing HD. Crude analysis showed higher mortality among those who used vasopressors, but lower mortality among those with creatinine values > 8.9 mg/dL. The adjusted analysis showed that having had a creatinine level of > 8.9 mg/dL, compared to a creatinine level of < 5.2 mg/dL at the time of initiating HD, was associated with 74% less probability of death. **Conclusion:** Four out of every ten AKI patients undergoing HD die. Higher levels of creatinine were associated with lower probability of mortality.

Keywords: acute kidney injury; intensive care units; mortality; renal dialysis.

Resumo

Introdução: Os pacientes com lesão renal aguda (LRA) nos países em desenvolvimento são descritos como jovens, com menos comorbidades, com LRA unifactorial e com menor mortalidade em relação aos pacientes nos países desenvolvidos. **Objetivo:** Avaliar a mortalidade em pacientes com LRA submetidos à hemodiálise (HD) e seus fatores associados num país em desenvolvimento. **Métodos:** Estudo retrospectivo. As variáveis demográficas, clínicas e de mortalidade foram coletadas de pacientes que apresentaram LRA e foram submetidos à HD entre janeiro de 2014 e dezembro de 2015 em um hospital nacional de referência em Lima, Peru. As razões de risco (RR) e os intervalos de confiança de 95% (IC 95%) foram estimados através da regressão de Poisson. **Resultados:** Analisaram-se os dados de 72 pacientes com LRA submetidos à HD, sendo 66,7% com idade inferior a 64 anos e 40,2% de todos os pacientes morreram durante a HD. A análise bruta mostrou maior mortalidade entre os que usaram vasopressores, mas menor mortalidade entre aqueles com valores de creatinina > 8,9 mg/dL. A análise ajustada mostrou que haver tido um nível de creatinina > 8,9 mg/dL, comparado com um nível de creatinina < 5,2 mg/dL no momento do início da HD, foi associado com uma probabilidade de morte 74% menor. **Conclusão:** Quatro em cada dez pacientes com LRA submetidos a HD morrem. Níveis mais elevados de creatinina foram associados com menor probabilidade de mortalidade.

Palavras-chave: diálise renal; lesão renal aguda; mortalidade; unidades de terapia intensiva.

Introduction

Acute kidney injury (AKI) is a frequent disease, with approximately 13 million people suffering from this worldwide and 1.7 million deaths every year.[1,2] AKI is associated with high expenditures in

healthcare systems, reaching 1.72 billion dollars per year in the UK.[3] Given the limitations in healthcare delivery, kidney diseases represent a major challenge in Peru.[4]

In Latin America, a recent systemic review found that AKI incidence is 29.6% with a general mortality of 38.9%, which varies depending on the place where it is evaluated, being higher amongst intensive care unit patients.[2] However, this systemic review evaluated studies executed in Brazil, thus its generalization to the other Latin American countries is limited. In Peru, between the years 2002 and 2004, a study conducted at a national hospital found that the incidence of AKI among hospitalized patients was 21 to 39 patients per year, with mortality estimates of 39%,[5] similar to the recent review reported.[2] Yet, the mortality estimations in those patients with AKI undergoing hemodialysis (HD) was not established.

According to the Kidney Disease: Improving Global Outcomes (KDIGO),[6] patients with AKI are divided in three stages depending on the AKI's severity, and those in Stage 3 are patients who would potentially require HD, in case there is a fluid overload or an alteration in the electrolyte, and life-compromising acid-base balance.[6] Although patients who need HD represent 2.3% of the total of AKI patients, its associated mortality has been reported to be very high reaching nearly 50%.[1,2]

It has been suggested that AKI cases in developing countries such as Peru could have a different epidemiological profile from those in developed countries.[1] Patients with AKI in developing countries tend to be younger, with unifactorial AKI have less comorbidities and tend to have a lower mortality rate.[1] Nearly 80% of published studies on the topic of AKI arise from high-income countries[2] and most of Latin American studies have explored factors associated with AKI in general[7-12] but not complications arising from required HD. Therefore, investigating the profile of AKI patients undergoing HD will expand the body of evidence linked to AKI in low-income settings, and contribute towards decision-making efforts in the region. The objective of this study was to assess mortality in patients with AKI undergoing HD from a developing country and its associated factors.

Methods

Type of study

Retrospective study of patients older than 18 with an AKI diagnosis that were admitted for HD at the Nephrology Department at the 2 de Mayo National Hospital (HN2M) in Lima, Peru, between the months of January 2014 and December 2015.

The HN2M is a reference national hospital with an HD unit equipped with 11 HD machines. One of them is portable so that patients who cannot attend the unit can also be treated. Treatment of AKI patients is generally covered by Peru's Integrated Healthcare System and all patients are provided with intermittent HD, which is the type of HD available at HN2M.

Participants

Given that this is a study focused on AKI patients, patients admitted for dialysis with a chronic kidney disease diagnosis and with poisoning susceptible to dialysis, e.g. methanol intoxication, were excluded. In addition, patients with an AKI diagnosis who were referred by other hospitals and who had already started HD before referral were excluded given that the required laboratory data before HD and the clinical criteria used by doctors to initiate HD were unknown.

Variables

Our main outcome was assessed death during hospitalization. Death was assessed based on the nursing records of the Nephrology Service Division at HN2M, which ascertains patients' events during their hospitalization.

Patients' demographic and clinical variables such as age, sex, place of origin within the hospital at the time HD was initiated - [postoperative recovery, hospitalization or Intensive Care Unit (ICU)], and use of mechanical ventilator and vasopressors at the time HD was prescribed, were collected from the epidemiology control record within the Nephrology Service Division. Patients were considered as coming from an ICU if they were previously at an ICU, intermediate care unit or shock trauma unit at the time they started HD.

Laboratory measurements such as creatinine, hemoglobin, bicarbonate (HCO_3) and potassium (K) were also collected from the patient records within

the Nephrology Service Division. Those laboratory measurements were categorized in tertiles. For the measurement of creatinine, the Jaffe method was used; for the measurement of electrolytes the dry chemistry technique was used; for the hemoglobin, the Sysmex sodium laurel sulfate (SLS) method was used, and for the measurement of arterial gases the potentiometry method with electrodes was used. Results from these tests were taken into account when making the decision to start HD. The decision to initiated dialysis was made by the in-service nephrologist who evaluated the patient.

AKI diagnosis was given according to the evaluation performed by the in-service nephrologist who cared for the patient and who indicated HD based on clinical criteria such as kidney function and ultrasound before the actual hospitalization took place.[6] To the same extent, the individual severity score was included, whether AKI was due to surgery or not, as well as the reason for dialysis indication, also defined by the evaluating nephrologist according to what was stated on the clinical history at the Nephrology Service Division. The individual severity score is calculated as follows and has been validated in our country, recording that a value higher than 0.74 is associated with greater death risk:[13]

Severity index = 0.032*(age in decades) - 0.086*(male sex) - 0.109*(nephrotoxic) + 0.109*(oliguria) + 0.116*(hypotension) + 0.122*(jaundice) + 0.15*(coma) - 0.154*(normal conscience) + 0.182*(Mechanical Ventilation) + 0.21.

Statistical analysis

The statistical analysis was performed using STATA v14.0 software. Variables were described through central tendency measures, dispersion measures, absolute and relative frequencies.

To evaluate factors associated with death, we performed crude and adjusted Poisson regressions with robust variances, and calculated Risk Ratios (RR) and its respective 95% Confidence Intervals (95% CI). For the adjusted analysis, all the variables that showed evidence of a strong association ($p < 0.10$) with mortality in the crude analysis were included.

This study used de-identified secondary data obtained from the epidemiological control records of the Nephrology Services Division at HN2M, which only include the clinical medical record number, without the possibility of personally identifying patients. Therefore, this study was not submitted to review to the hospital's ethics committee.

Results

During the years 2014 and 2015, 270 patients initiated HD at the HN2M, and 72 of them had AKI diagnosis.

Of those 72 patients, 66.7% were 63 years old or younger, 48.6% were female, 45.8% were admitted into an ICU, and 80.6% were non-surgical AKI cases. On the clinical characteristics, 48.6% of patients required mechanical ventilation, 43.1% required vasopressors at the time HD was prescribed, and 69.4% of them had an Individual Severity Score lower than 0.74. The main indication to initiate HD was fluid overload, followed by uremic encephalopathy. Additional demographic and clinical characteristics are described in Table 1.

Of all patients with AKI and HD, 29 (40.2%) died and 17 (58.6%) of those who died were into ICU. Of the deceased, 10 (34.5%) died during the first day of initiating HD and 22 (75.9%) had died 15 days after initiating HD (Figure 1).

The crude analysis showed strong association between having required vasopressors and death, doubling the risk of mortality, but this association became non-significant in the adjusted analysis. On the other hand, crude and adjusted analysis showed that having had a creatinine level > 8.9 mg/dL, compared to a creatinine level < 5.2 mg/dL at the time of initiating HD, was strongly associated with a lower AKI mortality (Table 2).

Discussion

Our study reveals that around 40% of patients with AKI undergoing HD died and, almost 60% of them died when they were previously admitted to an ICU. After controlling for potential confounders, a high value of creatinine level at the time of admission for HD was found to be a protecting mortality factor.

Given that Peru is currently in an economic transition and bears the double burden of chronic illnesses and infectious diseases, these findings derived from a national reference hospital mortality rates similar to those reported in developed-country settings.[2] From a healthcare provider perspective, our findings raise concerns linked to greater challenges for a health system that is ill prepared to provide services to both acute and chronic care, thus calling for greater efforts to strengthen it.

Table 1 General characteristics of the study patients, and crude analysis (N = 72)

Characteristics	Alive N = 43	Deceased N = 29	RR (95%CI)	*p*
Age (years)				
16 to 49	15 (57.7)	11 (42.3)	Ref	
50 to 63	16 (72.7)	6 (27.3)	0.64 (0.28 - 1.47)	0.295
≥ 64	12 (50.0)	12 (50.0)	1.18 (0.65 - 2.17)	0.589
Gender				
Female	20 (57.1)	15 (42.9)	Ref	
Male	23 (62.2)	14 (37.8)	0.88 (0.50 - 1.56)	0.667
Intensive Care Units				
No	27 (69.2)	12 (30.8)	Ref	
Yes	16 (48.5)	17 (51.5)	1.67 (0.94 - 2.99)	0.081
Cause of Acute Kidney Injury				
Non-Surgical	34 (58.6)	24 (41.4)	Ref	
Surgical	9 (64.3)	5 (35.7)	0.86 (0.40 - 1.87)	0.709
Mechanical Ventilation				
No	25 (67.6)	12 (32.4)	Ref	
Yes	18 (51.4)	17 (48.6)	1.50 (0.84 - 2.68)	0.173
Vasoactive Drug				
No	30 (73.2)	11 (26.8)	Ref	
Yes	13 (41.9)	18 (58.1)	2.16 (1.20 - 3.91)	0.011
Individual Severity Score				
< 0.74	32 (64.0)	18 (36.0)	Ref	
0.74 or more	11 (50.0)	11 (50.0)	1.39 (0.79 - 2.44)	0.252
Fluid Overload				
No	35 (59.3)	24 (40.7)	Ref	
Yes	8 (61.5)	5 (38.5)	0.95 (0.44 - 2.02)	0.885
Oliguria				
No	27 (69.2)	12 (30.8)	Ref	
Yes	16 (48.5)	17 (51.5)	1.67 (0.94 - 2.99)	0.081
Potassium (meq/L)				
less than 4.47	13 (54.2)	11 (45.8)	Ref	
4.47 to 5.86	14 (58.3)	10 (41.7)	0.91 (0.48 - 1.74)	0.773
5.87 or more	16 (69.6)	7 (30.4)	0.66 (0.31 - 1.42)	0.292
Creatinine (mg/dL)				
Less than 5.2	9 (37.5)	15 (62.5)	Ref	
5.2 to 8.9	13 (54.2)	11 (45.8)	0.73 (0.43 - 1.26)	0.258
More than 8.9	21 (87.5)	3 (12.5)	0.20 (0.07 - 0.61)	0.005
HCO_3 (meq/L)				
less than 9.7	13 (54.2)	11 (45.8)	Ref	
9.7 to 12.4	14 (58.3)	10 (41.7)	0.91 (0.48 - 1.74)	0.773
more than 12.4	16 (66.7)	8 (33.3)	0.73 (0.35 - 1.49)	0.385
Hemoglobin (gr/dL)				
less than 8.6	17 (70.8)	7 (29.2)	Ref	
8.6 to 10.2	15 (62.5)	9 (37.5)	1.29 (0.57 - 2.91)	0.546
more than 10.2	11 (47.8)	12 (52.2)	1.79 (0.85 - 3.75)	0.124

Figure 1. Survival function in acuye kidney injury in hemodialysis (95% CI).

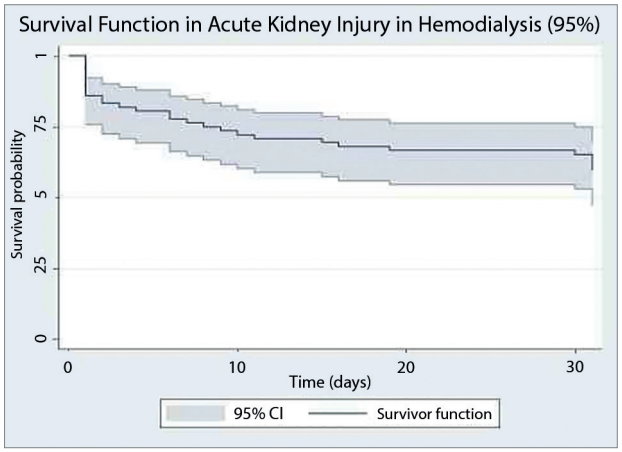

Table 2 Adjusted analysis of factors associated with death using Poisson regression

Characteristics	Adjusted RR (95%CI)	*p*
Intensive Care Units		
No	Ref	
Yes	1.03 (0.59 - 1.81)	0.912
Use of vasopressors		
No	Ref	
Yes	1.34 (0.61 - 2.94)	0.461
Oliguria		
No	Ref	
Yes	1.07 (0.59 - 1.93)	0.830
Creatinine (mg/dL)		
< 5.2	Ref	
5.2 to 8.9	0.89 (0.44 - 1.82)	0.753
> 8.9	0.26 (0.07 - 0.96)	0.044

Adjusted for all variables cited in the table.

Mortality in AKI patients

There is uncertainty whether mortality in AKI patients is due to the disease itself or to the general conditions of patients who develop this pathology.[1] It is also argued whether the epidemiological profile of AKI patients undergoing HD is associated with higher mortality. In this regard, the answer varies depending on whether those concerned correspond to developing or developed countries.[1] It is usually considered that AKI patients coming from developing countries like Peru are younger, their cause is unifactorial, they have less comorbidities and, as a result, have a lower mortality rate.[1]

In our study, even though most patients are younger than 64 and have an Individual Severity Score lower than 0.74, the general mortality is similar to the one reported in developed countries. This may be because despite AKI cases in developing countries may have the previously described characteristics (the cause of AKI is unifactorial and they have less comorbidities),[1] clinical characteristics of AKI patients undergoing HD at hospital level, which include other factors not evaluated in our study, are similar to those in developed countries; this has been suggested by other authors.[1]

This would also explain the high mortality amongst patients in ICU, although that is not a worldwide finding: for example, in a 5-year study in Nigeria,[14] mortality of AKI patients undergoing HD was 28%, which is quite lower than the reported mortality in this study. In the study of Nigeria it is important to mention that most of the deaths were related to non-surgical situations such as preeclampsia.[14]

Factors associated with mortality

Our results suggest that the use of vasoactive drugs and lower creatinine levels are associated with higher mortality. Studies made in Latin American populations that evaluate factors associated with mortality in AKI have focused on all AKI patients and not on those specifically requiring HD. However, the association between the use of vasoactive drugs and mortality coincide with the results from Moreno *et al.*[7] as well as the ones from Silva Júnior *et al.*[8] and Ponce D *et al.*[9] in a ICU in Colombia and Brazil, respectively.

A critical state or a hypercatabolic state can be translated in higher creatinine. A higher AKI stage according to the KDIGO classification, determined by a higher creatinine level, has been found associated with a higher mortality rate.[2,6,11] Nevertheless, the inverse association between higher creatinine level and mortality found in our study is similar to that found by Souza *et al.*[15] who suggest that a low creatinine value could underestimate the severity of AKI and delay the onset of HD in patients who could benefit from early therapy and increasing their mortality. Similarly, Wilson et al. in a study among patients with AKI who received continuous venovenous hemodialysis found that lower low-grade creatinine generation was independently associated with in-hospital mortality in

unadjusted analysis and after multivariate adjustment for severity of disease.[16] Finally, De Corte *et al.* did not find that urea and creatinine levels at the onset of HD are predictors of mortality among patients with AKI who initiate HD.[17]

Possible explanations for this inverse association between creatinine levels and mortality are fluid overload and malnutrition.[15,18-21] Fluid overload can alter the volume of creatinine distribution, producing artificially low creatinine values.[22] However, fluid overload is associated with higher mortality in critical patients,[23,24] so it is possible that the association between lower creatinine and higher mortality is actually an association between water overload and mortality. Similarly, persons with poor nutritional status will have low creatinine levels and higher mortality, which could also explain our results.[25]

Unfortunately, in this study we were not able to objectively evaluate fluid overload or malnutrition. Likewise, it has been suggested that critical patients have a lower creatinine formation rate,[16] which may explain the values found in our patients. A low creatinine value could underestimate the severity of IKA and delay the onset of HD and, therefore, explain their increased mortality.

Strengths and limitations

One of the strengths to be highlighted is the fact that this is one of the first studies that has evaluated the mortality in AKI patients undergoing HD in a Latin American country undergoing an economic transition. In this regard, this study opens up the possibilities of improvement of care for critical patients in hospital settings and in similar environments.

Our study has, however, some limitations that are worth mentioning. First, the limited samples could affect our ability to explore other variables potentially associated with mortality: etiology, AKI, and the Individual Severity Score. There was also a short follow-up period and we did not value other factors that may have influenced the inverse relationship between mortality and creatinine values. Second, this study has been developed in a single hospital; however, being a national reference hospital with one of the biggest nephrology and critical care units in the Peruvian Ministry of Health (MINSA), the institution that serves more than 60% of the Peruvian population, this hospital could serve as a reliable sample of the rest of hospitals from MINSA. Third, the care in this hospital is not interchangeable with the rest of institutions that offer healthcare to Peruvian patients, such as social security, armed forces hospitals and private care, where in some cases slow HD techniques are used in critical patients. Fourth, in the absence of an established protocol to admit patients for dialysis in case of AKI in our hospital, the time of admission for HD much depends on the criteria of the in-service nephrologist, which prevents the standardization of the sample. Lastly, the time of hospitalization was not recorded, information that would be useful in order to perform a finer analysis of time and event.

Conclusions

Four out of ten AKI patients undergoing HD died. In crude analysis, we found that those patients who used vasopressors doubled their probability of death; however, this association disappeared in the adjusted analysis. Additionally, a lower mortality is reported in those patients with higher creatinine values. Characterizing this profile will strengthen the early management of AKI patients.

Acknowledgements

To: Cecilia Aurora Cuevas de la Cruz, Rodrigo Geronimo Alcorta Proano, Rodrigo Martín Carrillo Larco and Gabriela Villarreal Romo

Key points

1- In Peru, a country undergoing an economic transition, mortality rates of AKI patients undergoing HD are similar to those reported in high-income countries.

2- Around 40% of AKI patients undergoing HD died and almost 60% of those who died were previously admitted to an ICU.

3- A higher creatinine level at the time of admission for HD was found to be a protecting factor for mortality.

Conflicts of interest

We declare no competing interests.

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