ORIGINAL ARTICLE

CLINICAL CHARACTERISTICS, OUTCOMES AND RISK FACTORS FOR DEATH AMONG CRITICALLY ILL PATIENTS WITH HIV-RELATED ACUTE KIDNEY INJURY

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SUMMARY

Background: The aim of this study is to describe clinical characteristics, outcomes and risk factors for death among patients with HIV-related acute kidney injury (AKI) admitted to an intensive care unit (ICU). **Methods:** A retrospective study was conducted with HIV-infected AKI patients admitted to the ICU of an infectious diseases hospital in *Fortaleza*, Brazil. All the patients with confirmed diagnosis of HIV and AKI admitted from January 2004 to December 2011 were included. A comparison between survivors and non-survivors was performed. Risk factors for death were investigated. **Results:** Among 256 AKI patients admitted to the ICU in the study period, 73 were identified as HIV-infected, with a predominance of male patients (83.6%), and the mean age was 41.2 ± 10.4 years. Non-survivor patients presented higher APACHE II scores (61.4 ± 19 vs. 38.6 ± 18, $p = 0.004$), used more vasoconstrictors (70.9 vs. 37.5%, $p = 0.02$) and needed more mechanical ventilation - MV (81.1 vs. 35.3%, $p = 0.001$). There were 55 deaths (75.3%), most of them (53.4%) due to septic shock. Independent risk factors for mortality were septic shock (OR = 14.2, 95% CI = 2.0-96.9, $p = 0.007$) and respiratory insufficiency with need of MV (OR = 27.6, 95% CI = 5.0-153.0, $p < 0.001$). **Conclusion:** Non-survivor HIV-infected patients with AKI admitted to the ICU presented higher severity APACHE II scores, more respiratory damage and hemodynamic impairment than survivors. Septic shock and respiratory insufficiency were independently associated to death.

KEYWORDS: HIV; AIDS; Acute kidney injury; Intensive care unit.

INTRODUCTION

According to the World Health Organization (WHO), more than 35 million people are living with HIV worldwide. The advent of the Highly Active Antiretroviral Therapy (HAART) has improved the mortality and morbidity profiles in these patients. As a consequence, they have similar life expectancies when compared to patients living with other chronic diseases[1-3].

There are several complications of HIV infection that can lead to admission to an Intensive Care Unit (ICU), such as association with infections, comorbid conditions and acute kidney injury (AKI). The establishment of HAART decreased the frequency of opportunistic infections and hospital admissions, but ICU admission rates remained stable, mostly due to non-HIV-related critical illnesses[1,4-6].

HIV infection is related to an increased incidence of AKI, a well described risk factor for mortality in ICU[7]. In this context, the main etiologies of HIV-related AKI include antiretroviral drugs, volume depletion, sepsis and hepatic disease[8]. Low CD4 count and elevated viral load were also associated to higher risks of dialysis-requiring AKI, but this association became less relevant in the post-HAART era[9,10].

Therefore, the aim of this study was to describe clinical characteristics, outcomes and risk factors for death among HIV-infected AKI patients in the ICU setting.

METHODS

Study population and design

This is a retrospective study conducted with HIV and AKI patients admitted to the ICU of *São José* Infectious Diseases Hospital, *Fortaleza*, Brazil. The medical records of all the AKI patients admitted to the ICU from January 2004 to December 2011 were evaluated. Among these, all the HIV-infected patients were included in the study. HIV diagnosis consisted of two positive serological tests (ELISA and Western Blot), as recommended by the Brazilian Ministry of Health. Patients with previous renal impairment, arterial hypertension, diabetes mellitus, nephrolithiasis and other co-morbidities that could affect the renal

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function were excluded.

The study protocol was approved by the ethical committee of the Institution.

Studied parameters

Patients' data included demographics, physiologic variables, treatments, and in-hospital survival. Laboratory evaluation included: hemoglobin, hematocrit, white blood cells count, platelets count, serum urea, creatinine, sodium, potassium, aspartate aminotransferase, alanine aminotransferase and arterial blood gas analysis (pH, bicarbonate, CO_2 partial pressure and inspired oxygen), as well as CD4 lymphocyte count and viral load of HIV when available. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated on admission for all the patients. A standardized case investigation form was used to complete demographical, epidemiological, clinical and laboratory data.

Definitions

AKI was defined and classified according to the RIFLE criteria ("risk", "injury", "failure", "loss" and "end-stage renal disease"), as presented in Table 1[11]. The baseline creatinine level was measured on hospital admission, or the lowest creatinine level before hospital admission was considered. The RIFLE criteria were calculated based on the highest creatinine level achieved by each patient during ICU stay.

The Acute Physiology and Chronic Health Evaluation (APACHE) II was used as the gold-standard severity score. Oliguria was defined as urinary output < 0.5 ml/kg/h, despite appropriate fluid replacement. Respiratory insufficiency was defined as the need of mechanical ventilation (MV). Opportunistic infections were defined as infectious conditions that happen more frequently in immunosuppressed individuals and are related to the CD4 count. On the other hand, 'associated infection' was used for infectious conditions that were not HIV-related.

Therapy with vasoconstrictors was initiated when the mean arterial blood pressure (MAP) remained lower than 60 mmHg, despite adequate intravenous fluids replacement. Dialysis was indicated in those patients that remained oliguric after effective hydration, when uremia was associated to hyper catabolism, hemorrhagic or severe respiratory failure and when hyperkalemia or refractory metabolic acidosis were diagnosed.

Patients were divided into two groups, survivors and non-survivors,

and a comparison of clinical and laboratory data was performed. Non-survivors were considered when death occurred after ICU admission but before hospital discharge.

Statistical analysis

Statistical analysis was performed using the SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The statistical analysis consisted of univariate and multivariate analysis of clinical and laboratory data. The Student's T test and the Mann-Whitney test were used to perform the comparison between the two groups (survivors and non-survivors). Correlations between death and categorized risk factors were analyzed using the Pearson's chi-squared test. A logistic regression model was used for quantitative variables. Adjusted odds ratios and 95% confidence intervals were calculated. Only factors considered statistically significant ($p \leq 0.05$) in the univariate analysis were included in the multivariate model. Variables with normal distribution were described as mean ± standard deviation (SD), while variables with non-normal distribution were described as median (range of distribution).

RESULTS

A total of 256 AKI patients were identified in the study period. Among these, all the HIV-infected patients (73) were selected. The mean age of HIV patients was 41.2 ± 10.4 years. Most of them (83.6%) were male. The median of hospital stay was 1 (0-27) day. Opportunistic infections were diagnosed in 19 patients (26%).

Comparison of demographic data from survivors and non-survivors did not find significant differences regarding age (39.5 ± 7.4 vs. 41.8 ± 11.2 years, $p = 0.429$), hospital stay (9.38 ± 5.6 vs. 5.56 ± 3.6 days, $p = 0.07$) and gender (males 81.8 vs. 88.8%, $p = 0.71$).

The need of mechanical ventilation was higher in non-survivors (92.7% vs. 33.3%, $p < 0.001$). The MAP and the Glasgow Coma Scale (GCS) on admission were lower (77 ± 17 vs. 89 ± 23 mmHg, $p = 0.017$, and 8 ± 5 vs. 12 ± 4, $p = 0.013$, respectively), and the admission APACHE II score was significantly higher in non-survivors (65 ± 17 vs. 42 ± 18, $p = 0.002$). The prevalence of sepsis, septic shock and the need of vasoconstrictors were significantly higher in the non-survivors group (69.0 vs. 27.7%, $p = 0.005$; 61.8 vs. 11.1%, $p < 0.001$; 70.9 vs. 38.8%, $p = 0.023$, respectively). The comparison of clinical characteristics, complications and treatment between groups is shown in Table 2.

Table 1
RIFLE criteria in AKI patients

	Cr	Urine Output
Risk	Cr increase by 25%	< 0.5 ml/Kg/h for 6 hours
Injury	Cr increase by 50%	< 0.5 ml/Kg/h for 12 hours
Failure	Cr increase by 75% or Cr > 4.0 mg/dL	< 0.3 ml/Kg/h for 24 hours or anuric for 12 hours
Loss	Persistent failure > 4 weeks	
ESRD	Persistent failure > 3 months	

Cr - Serum Creatinine; ERSD - End Stage Renal Disease

Table 2
Comparison of clinical data between survivor and non-survivor HIV patients admitted to the ICU

	Non-survivors N = 55	Survivors N = 18	*P*
Need of MV	51 (92.7%)	6 (33.3%)	<0.001
MAP (mmHg)	76.7 ± 16.8	89.1 ± 23.1	0.017
Systolic BP (mmHg)	104.3 ± 20.0	121.3 ± 29.0	0.007
APACHE II	65.1 ± 16.9	42.5 ± 18.1	0.002
Glasgow Coma Scale	7.9 ± 4.8	11.8 ± 4.2	0.013
Comorbid conditions			
Diabetes	2 (3.6%)	1 (5.5%)	1.000
Hypertension	3 (5.4%)	2 (11.1%)	0.591
Complications			
Sepsis	38 (69.0%)	5 (27.7%)	0.005
Septic Shock	34 (61.8%)	2 (11.1%)	<0.001
Metabolic Acidosis	41 (74.5%)	12 (66.7%)	0.322
Treatment			
Vasoconstrictor	39 (70.9%)	7 (38.8%)	0.023
Diuretics	21 (38.2%)	5 (27.8%)	0.573
ACEi	5 (9.1%)	4 (22.2%)	0.211

MV – mechanical ventilation; MAP - Mean Arterial Pressure; BP – blood pressure. ACEi – Angiotensin Converting Enzyme inhibitor. Pearson's chi-squared test, Student's t test and Mann-Whitney tests were used. Values were expressed as mean ± SD. *P* values ≤ 0.05 were considered statistically significant.

Regarding the laboratory tests, the non-survivors group presented significant lower arterial blood pH (7.24 ± 0.14 vs. 7.37 ± 0.11, *p* = 0.002) as well as higher PCO_2 (36.0 ± 14.3 vs. 24.6 ± 7.2 mmHg, *p* < 0.001) and fraction of inspired oxygen (69.2 ± 24.5 vs. 38.7 ± 25.8%, *p* = 0.002). The laboratory data evaluation is presented in Table 3.

Regarding the viral and immunological status, data were available in only 18 cases. There was no difference on the CD4 count and the viral load between the two groups (283.3 ± 277.6 vs. 214.4 ± 209.8, *p* = 0.624 and 147.2 ± 141.0 vs. 98.0 ± 165.4, *p* = 0.549, respectively).

Acute kidney injury was confirmed in all the HIV cases, since it was an inclusion criterion. The main causes of HIV-related AKI included sepsis and circulatory shock. Renal replacement therapy was required in 17 patients (22.9%). Regarding AKI distribution according to RIFLE criteria, the frequency of severe stages was not significantly higher in non-survivors (RIFLE F 38.2 vs. 50.0%, *p* = 0.549), as summarized in Table 4.

A total of 55 deaths were recorded (75.3%), most of them (53.4%) due to septic shock. Independent risk factors for mortality in the multivariate analysis were septic shock (OR = 14.2, 95% CI = 2.0-96.9, *p* = 0.007) and respiratory insufficiency with need of MV (OR = 27.6, 95% CI = 5.0-153.0, *p* < 0.001).

DISCUSSION

After the establishment of HAART, hospitalization and mortality rates of HIV patients have decreased considerably[5]. Due to an increase in their life expectancy, a higher prevalence of non-infectious diseases and comorbid illnesses have been observed, keeping the rate of ICU admission relatively constant. It is described that 4% to 12% of HIV-hospitalized patients require ICU care and a high number of admissions are due to causes that are not directly related to HIV, such as drug toxicity, co-infections with hepatitis B or hepatitis C virus, and general conditions like chronic pulmonary disease, renal insufficiency, cardiomyopathy and cirrhosis[5,12-17]. In the present study, most patients were admitted to the ICU due to an infectious cause, both opportunistic and associated to HIV.

There are few studies on HIV-critically ill patients in Brazil. In the present study, we observed that most patients presented high levels of bilirubin, especially the direct fraction. We also noticed that non-survivor patients presented significantly higher prevalence of respiratory acidosis and need of MV, as well as significantly higher APACHE II levels. The main mortality cause was septic shock, with markedly higher prevalence among non-survivors. Septic shock and respiratory insufficiency with need of MV were also independent risk factors for death.

Elevation of liver enzymes and bilirubin was noted in most patients. Liver disease is a common condition associated to HIV infection. Besides the direct liver injury caused by HIV itself, drug toxicity, co-infection with hepatitis B and C viruses and opportunistic infections may also justify increased bilirubin levels in HIV-infected patients[18]. In our cohort, it was not possible to identify one single cause of bilirubin, AST and ALT elevation, since most of these damaging factors could be observed.

Table 3
Laboratory tests of survivors and non-survivors HIV patients admitted to the ICU

	Non-survivors N = 55	Survivors N = 18	*P*
Hb (g/dL)	9.4 ± 2.5	9.8 ± 2.7	0.605
Hct (%)	28.1 ± 7.5	28.4 ± 7.9	0.869
WBC (/mm^3)	10,539 ± 7462	7,899 ± 5162	0.168
Platelets(10^3/mm^3)	150.8 ± 125.9	158.6 ± 89.9	0.808
AST (UI/L)	348.1 ± 811.1	215.0 ± 290.8	0.555
ALT (UI/L)	148.6 ± 319.1	149.2 ± 239.3	0.995
Creatinine (mg/dl)	2.8 ± 1.2	3.5 ± 2.0	0.163
Urea (mg/dl)	97.0 ± 48.4	93.1 ± 49.4	0.767
Sodium (mEq/L)	134.2 ± 9.9	133.6 ± 9.6	0.815
Potassium (mEq/L)	4.3 ± 1.0	4.1 ± 1.1	0.513
pH	7.24 ± 0.14	7.37 ± 0.11	0.002
HCO$_3$(mEq/L)	15.2 ± 6.7	15.4 ± 6.4	0.921
PCO$_2$(mmHg)	36.0 ± 14.3	24.6 ± 7.2	<0.001
Inspired oxygen fraction (%)	69.2 ± 24.5	38.7 ± 25.8	0.002

Hb – hemoglobina; Hct – hematocrit; WBC – white blood cells; AST – aspartate aminotransferase; ALT – alanine aminotransferase; HCO$_3$ - sérum bicarbonate; PCO$_2$ – CO$_2$ partial pressure. Values were expressed as mean ± SD. Student's t test and Mann-Whitney test were used. Values expressed as mean ± SD. *P* values ≤ 0.05 were considered statistically significant.

Table 4
Comparison of acute kidney injury and dialysis requirement between survivor and non-survivor HIV patients admitted to the ICU

	Non-survivors N = 55	Survivors N = 18	*P*
Dialysis	13 (23.6%)	4 (22.2%)	1.000
Oliguria	32 (58.2%)	7 (38.8%)	0.159
RIFLE			
Risk	4 (7.3%)	3 (16.7%)	NC
Injury	30 (54.5%)	6 (33.3%)	0.549
Failure	21 (38.2%)	9 (50.0%)	NC

Student's t test and Mann-Whitney tests were performed. Values expressed as mean ± SD. *P* values ≤ 0.05 were considered statistically significant. NC – not calculated

Acidosis was a common finding in the present cohort, especially the variant associated to respiratory etiology. This finding reflects the high prevalence of respiratory failure in non-survivors, and justifies the high percentage of patients who needed MV. Additionally, MV has been described as the main predictor of mortality in several studies with HIV-infected patients admitted to the ICU[19-21].

Respiratory failure remains the most common diagnosis at the time of ICU admission in HIV patients, and despite advances in medical therapy and intensive care, mortality rates among of these patients remain substantial[5]. In our cohort, the need of MV was markedly higher in the non-survivors group, mostly associated to respiratory failure of infectious etiology and sepsis. The association between infectious-related respiratory failure and mortality is well described[22].

Despite being a mortality-linked factor[23], the CD4 count was not significantly lower in non-survivors than in survivors. This might be explained by the fact that only 18 patients had CD4 and viral load data available in their medical charts. With so little data, it is less likely to notice significant differences related to CD4 count and mortality.

The APACHE II score has been described as a good predictor for mortality in ICU patients[24,25]. In the present study, we observed that non-survivor patients presented remarkably higher scores when compared to survivors. In a study performed in Atlanta, USA, with 125 HIV-infected patients presenting severe sepsis, the APACHE II was an independent predictor of mortality (OR = 1.15, 95% CI = 1.07 – 1.25, *p* < 0.001).

AKI is a frequent and potentially fatal complication in infectious diseases, including HIV. In a recent study conducted in our region with 256 AKI patients admitted to an ICU, HIV was the most prevalent infection associated to AKI (30%)[7]. According to RIFLE criteria, the overall prevalence of severe AKI in the present study (41%) was similar to previously reported rates[22]. Hemodialysis was indicated in 22.9% of patients, but it did not influence mortality, since it was similar in both groups.

Past studies have shown high mortality rates in HIV-infected patients admitted to ICUs. In the present study we observed a high mortality rate (> 70%). Medrano *et al*. in a large Spanish cohort study, evidenced that

among HIV patients, mortality rates in the first seven days were higher in all groups when compared to non-HIV patients (36.5 vs. 28.8%, $p <$ 0.001)[26]. In the present study, mortality was associated to sepsis and septic shock, the main overall causes of death in ICU patients[27-29].

In one of the few studies that have investigated critically ill HIV-infected patients in Brazil, Amâncio *et al.* found that mortality was associated to APACHE II scores, mechanical ventilation, tuberculosis treatment, antiretroviral therapy and septic shock[30]. Another recent Brazilian study has evidenced that HIV-positive patients had more severe sepsis, with higher inflammatory markers levels than HIV-negative ones[31]. Sepsis was also described as an important risk factor for death in HIV patients after ICU admission, even after the lapse of six months[27].

In summary, we observed that non-survivor HIV and AKI patients admitted to the ICU presented higher severity scores, more respiratory damage and need of MV. AKI was diagnosed in all the patients, which demonstrates a high prevalence of severe AKI in both groups. In addition, septic shock and need of MV were independent risk factors for mortality.

Study limitations

Most of the study limitations are due to its retrospective nature. Since information was obtained from the patient's medical records, some data were scarce or not available, such as the use of antiretroviral treatment and the time of HIV diagnosis. Most importantly, CD4 lymphocyte count and viral load data were available in only a few patients, therefore the evaluation of the previous immunological status was compromised. Another important limitation refers to the low number of survivors in the study, so that the amount of patients in the two groups was very discrepant.

CONFLICTS OF INTEREST

We declare we have no conflict of interest.

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