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Acute kidney injury in intensive care unit patients: A prospective study on incidence, risk factors and mortality

Injúria renal aguda em unidade de terapia intensiva: Estudo prospectivo sobre a incidência, fatores de risco e mortalidade

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ABSTRACT

Objective: To compare the clinical features and outcomes of patients with and without acute kidney injury in an intensive care unit of a tertiary university hospital and to identify acute kidney injury and mortality risk factors.

Methods: This was a prospective observational study of a cohort including 564 patients followed during their stay in the intensive care unit of Hospital das Clinicas da Faculdade de Medicina de Botucatu (Botucatu, São Paulo, Brazil) between May 2008 and May 2010. Patients were allocated to two different groups: with (G1) and without (G2) acute kidney injury.

Results: The incidence of acute kidney injury was 25.5%. The groups were different with respect to the reason for admission to the intensive care unit (sepsis, G1: 41.6% versus G2: 24.1%; $p < 0.0001$; neurosurgery, postoperative G1: 13.8% versus G2: 38.1%; $p < 0.0001$); age (G1: 56.8 ± 15.9 vs. G2: 49.8 ± 17.8 years; $p < 0.0001$); Acute Physiological Chronic Health Evaluation (APACHE) II score (G1: 21.9 ± 6.9 versus G2: 14.1 ± 4.6; $p < 0.0001$); use of mechanical ventilation (G1: 89.2% vs. G2: 69.1%; $p < 0.0001$) and use of vasoactive drugs (G1: 78.3% vs. G2: 56.1%; $p < 0.0001$). Higher rates of diabetes mellitus, congestive heart failure, chronic renal disease and use of non-steroidal anti-inflammatory drugs were more frequent in acute kidney injury patients (28.2% vs. 19.7%, $p = 0.03$; 23.6 vs. 11.6%, $p = 0.0002$; 21.5% vs. 11.5%, $p < 0.0001$ and 23.5% vs. 71.%, $p < 0.0001$, for G1 versus G2, respectively). Length of hospital stay and mortality were also higher for acute kidney injury patients (G1: 6.6 ± 2.7 days versus G2: 12.9 ±5.6 days, $p < 0.0001$ and G1: 62.5% versus G2: 16.4%, $p < 0.0001$). Multivariate analysis identified the following as risk factors for acute kidney injury: age above 55 years, APACHE II score above 16, baseline creatinine above 1.2 and use of non-steroidal anti-inflammatory drugs (odds ratio (OR) = 1.36, 95% confidence interval (95%CI): 1.22 – 1.85; OR = 1.2, 95%CI: 1.11 – 1.33; OR = 5.2, 95%CI: 2.3 – 11.6 and OR = 2.15, 95%CI: 1.1 – 4.2, respectively). Acute kidney injury was independently associated with longer hospital stay and increased mortality (OR = 1.18, 95%CI: 1.05 – 1.26 and OR = 1.24, 95%CI: 1.09 – 1.99, respectively). Analysis of the survival curve 30 days after admission showed 83.3% mortality for acute kidney injury patients and 45.2% for non-acute kidney injury patients ($p < 0.0001$).

Conclusion: The incidence of acute kidney injury was high in this intensive care unit; the independent risk factors associated with acute kidney injury were age > 55 years, APACHE II > 16, baseline serum creatinine > 1.2 and use of non-steroidal anti-inflammatory drugs. Acute kidney injury is an independent risk factor for longer intensive care unit stay and mortality.

Keywords: Acute kidney injury; Incidence; Risk factors; Mortality; Intensive care unit

INTRODUCTION

Acute kidney injury (AKI) is characterized by a rapid drop in glomerular filtration rate that may be accompanied by increased blood nitrogen and hydroelectrolytic disorders.[1,2] This is a complex syndrome with multiple and variable etiologies and is not clearly defined.[3,4] In 2007, Mehta et al.[5] proposed the following as AKI diagnostic and classification criteria: acute serum creatinine changes (absolute serum creatinine increase above 0.3 mg/dL or relative 50% increase from baseline values) or urinary output (below 0.5 mL/kg/minute for more than 6 hours; oliguria).

AKI is one of the most important complications in hospitalized patients. Its incidence is variable, depends on the patient's clinical status and is more frequent in the intensive care unit (ICU; 20 to 40%) and less frequent in intermediate care wards (1 to 7%). A multicenter trial by Uchino et al.[6] has shown that 5.7% of ICU-admitted patients progress to AKI requiring dialysis.

Additionally, AKI is an independent mortality risk.[6,7] The prognosis for these patients is poor, with mortality rates of approximately 50% in spite of technological advances and new dialysis techniques. However, in spite of its seriousness and increasing hospital rates, AKI mortality has dropped in recent years.[3,4,8]

Several aspects may contribute to AKI, including an inability to identify risk factors for developing AKI, delayed diagnosis and lack of information on mortality-associated factors.[9,10]

In our hospital, Hospital das Clínicas da Faculdade de Medicina de Botucatu (HC-FMB), AKI is seen in approximately 1.9% of the admitted patients.[11] However, in this hospital ICU, these figures increase to 30% with a 70% mortality rate. Overall, there is a consensus among the nephrologists that several AKI diagnoses are late. Therefore, studies assessing incidence and clinical features are necessary for appropriate prevention and early diagnosis.

This study's objectives were to compare the clinical features and outcomes of patients with and without AKI admitted to the ICU of the HC-FMB and to identify risk factors associated with AKI and mortality.

METHODS

Adult patients admitted to the ICU of HC-FMB from May 2008 to May 2010 were evaluated from their admission until discharge from the ICU to regular wards or death. The evaluation was only observational; no intervention was performed.

Daily, one of the investigators visited the ICU and recorded the patient's identification, admission-associated conditions and clinical and laboratory (serum creatinine, blood urea nitrogen and potassium) follow-up and renal function parameters; the time of the eventual AKI diagnosis was also recorded.

By the end of the follow-up patients were allocated to either:

- Group 1: patients with AKI acquired during the ICU stay
- Group 2: patients without AKI acquired during the ICU stay

AKI was defined according to the AKI criteria as a 50% increase in the creatinine value from baseline for 48 hours or urinary output below 0.5 mL/kg/hour for longer than 6 hours from the renal insult,[5] during the ICU stay.

Patients under 18 years old, with advanced chronic renal disease (CRD) with baseline serum creatinine > 4.0 mg/mL, or under chronic dialysis therapy as well as those that had previously received renal transplants and patients staying less than 48 hours in the ICU were excluded.

The variables analyzed were age, gender, cause for ICU admission, mechanical ventilation and vasoactive drug use, Acute Physiologic Chronic Health Evaluation (APACHE) II score, previous CRD (baseline creatinine above 1.5 mg/dL), diabetes, arterial hypertension, congestive heart failure (CHF), use of non-steroidal anti-inflammatory drugs (NSAIDs; defined as ingesting at least one NSAID tablet daily for 5 consecutive days in the month preceding the admission), and patient outcome.

To the extent possible, the intensive care team was not informed about the trial, except for the ICU chiefs.

Each patient or the legally acceptable representative signed an informed consent form. This study was approved by the FMB-UNESP Ethics Committee on September 3, 2007 under the registration number 1793/2007.

Statistical analysis

Data were analyzed using the STATA 8.0 (STATACORP, 2004) statistical software package. Descriptive statistics were prepared in order to assess AKI incidence during the study period.

Patients with or without AKI were allocated to groups for data analysis. Descriptive analysis was provided by calculating the central trend and dispersion for continuous variables and the frequency for categorical variables.

The statistical significance of the association between categorical variables and AKI was assessed using the Chi-squared test. The association of continuous variables with AKI diagnosis was tested using the Student's *t*-test.

Intergroup comparisons used the *t*-test to evaluate the parametric distribution of continuous data; the Mann-Whitney test was used for non-parametric data.

Logistical regression multivariate analysis was performed for identification of AKI risk factors, based on clinical and laboratory data presenting $p < 0.25$ on univariate analysis. Kaplan-Meyer survival curves were plotted for each group using a logrank test. Finally, outcomes for patients with and without AKI were compared in a multivariate analysis with a Cox model based on variables that had $p < 0.25$ in the univariate analysis.

For all tests, the statistical significance level was established as $p < 0.05$.

RESULTS

From May 2008 to May 2010, 564 patients were included in the study, with 66 excluded due to: ICU stay of less than 48 hours (30 patients), baseline creatinine above 4 mg/dL (16 patients) and use of chronic dialysis therapy or previous renal transplant (20 patients). Therefore, 498 patients were analyzed.

Overall, 144 patients were diagnosed with AKI (25.5%). The groups were different for age (G1: 56.8 ± 15.9 versus G2: 49.8 ± 17.8 years; $p < 0.0001$); APACHE II score (G1: 22.9 ± 6.9 versus G2: 14.1 ± 4.6; $p < 0.0001$) and reason for ICU admission as follows: sepsis, G1: 41.6% versus G2: 24.2%; $p < 0.0001$ and neurosurgery, postoperative, G1: 13.8 versus G2: 38.1%; $p < 0.0001$).

The groups were also different for oliguria (diuresis < 400 mL/24 hours), G1: 67.1% versus G2: 4.9%; $p < 0.0001$). Mechanical ventilation was required by 89.2% of G1 patients versus 69.1% of G2 patients; $p < 0.0001$), and vasoactive drugs were required by 78.3% versus 56.1% ($p < 0.0001$) of G1 versus G2 patients, respectively. The length of ICU stay was 12.9 ±5.6 days versus 6.6 ± 2.7 days ($p < 0.0001$), and mortality was 62.5% versus 16.4% ($p < 0.0001$) for G1 versus G2 patients, respectively.

Based on the analysis of AKI risk factors, the groups were different for diabetes mellitus (G1: 28.1% versus G2: 19.9%; $p = 0.03$), congestive heart failure (G1: 23.6% versus G2: 11.6%; $p = 0.0002$), chronic renal disease (G1: 21.5% versus G2: 11.5%; $p < 0.0001$), use of non-steroidal anti-inflammatory drugs (G1: 23.5% versus G2: 7.1%; $p < 0.0001$) and septic shock (G1: 68.7% versus G2: 14.2%; $p < 0.0001$). Table 1 summarizes the main clinical and laboratory data.

Table 1 – Distribution of patients with or without acute kidney injury acquired during stay in the intensive care unit, according to their main clinical and laboratory characteristics

	With AKI (N = 144)	Without AKI (N = 354)	p value
Age	56.8±15.9	49.8±17.8	< 0.0001
Male gender	55.7	57.3	0.13
Ethnic group			
White	22	19.5	0.14
Mixed-race	54	56	0.22
Black	24	24.5	0.33
APACHE II	21.9±6.9	14.1±4.6	< 0.0001
Reason for ICU admission			
Sepsis	41.6	24.1	<0.0001
PO neurosurgery	13.8	38. 1	<0.0001
Other PO	33.5	29.6	0.37
Other	13.1	8.2	0.18
Oliguria	68.5	4.9	< 0.0001
Mechanical ventilation	89.2	69.1	<0.0001
Vasoactive drugs	78.3	56.1	<0.0001
Septic shock	65.9	14.5	< 0.0001
DM	28.2	19.7	0.03
CHF	23.6	11.6	0.0002
CRD	21.5	11.5	<0.0001
NSAID use	23.5	7.1	<0.0001
Length of stay (days)	12.9±5.6	6.6±2.7	<0.0001
Mortality	62.5	16.4	<0.0001

PO - postoperative; APACHE - Acute Physiological Chronic Health Evaluation; DM - diabetes mellitus; CHF – congestive heart failure; CRD – chronic renal disease; NSAID – non-steroidal anti-inflammatory drug. Oliguria: urinary output < 400 mL/24 hrs. Values expressed as the mean ± standard deviation or number and %.

The multivariate analysis identified the following as AKI risk factors: age above 55 years (Odds Ratio

(OR) = 1.36; 95% Confidence Interval (95%CI) 1.22 – 1.85; p = 0.004), APACHE II > 16 (OR = 1.2, 95%CI: 1.11-1.33; p = 0.008), baseline serum creatinine > 1.2 mg/dL (OR = 5.2; 95%CI: 2.3-11.6; p < 0.0001), use of NSAIDs (OR = 2.1; 95%CI: 1.1-4.2; p = 0.001) and septic shock (OR = 2.61; 95%CI: 2.1-6.1; p = 0.001), as shown in table 2.

Table 2 – Multivariate analysis using logistic regression of acute kidney injury risk factors

Variables	OR (95%CI)	p value
Age > 55 years	1.36 (1.22 – 1.85)	0.004
APACHE 2 > 16	1.2 (1.11 – 1.33)	0.008
Mechanical ventilation	1.29 (0.98 – 1.38)	0.08
Vasoactive drugs	1.17 (0.94 – 2.17)	0.09
Septic shock	2.68 (2.2 – 6.8)	0.001
Baseline Cr > 1.2 mg/dL	5.2 (2.3 – 11.6)	< 0.0001
NSAID use	2.15 (1.1 – 4.2)	0.001
CHF	1.26 (0.92 – 2.31)	0.21
DM	1.14 (0.97 – 1.51)	0.11

APACHE - Acute Physiological Chronic Health Evaluation; DM - diabetes mellitus; CHF – congestive heart failure; NSAID – non-steroidal anti-inflammatory drug; OR- odds ratio; 95%CI: 95% confidence interval. Values expressed as %.

AKI was independently associated with prolonged length of stay (OR = 1.18; 95%CI: 1.05-1.26; p = 0.02) and increased mortality (OR = 1.24; 95%CI: 1.09-1.99; p = 0.001). Figure 1 shows the 60-day group survival curves.

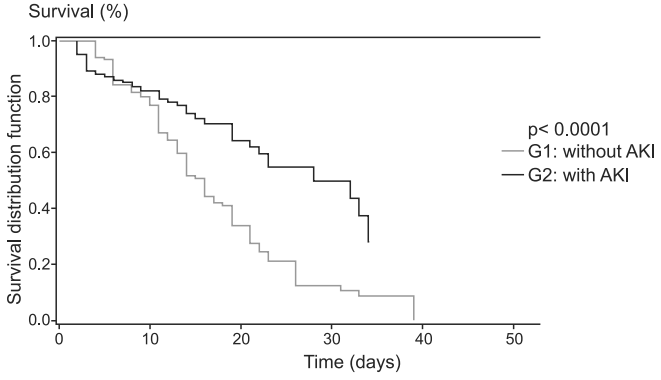

Figure 1 – 60-day survival of patients with or without acute kidney injury acquired during stay in the intensive care unit.

DISCUSSION

This study aimed to assess the incidence of AKI in a general ICU of a tertiary hospital, to identify AKI risk factors in critically ill patients and to compare the clinical characteristics and outcomes of patients who did or did not develop AKI during their stay at the ICU of HC-FMB.

AKI is one of the most serius complications in hospitalized patients. Its incidence is variable according to the patients' clinical condition and is higher in ICU patients, occurring in 20 to 40% of the patients.[12] In a recent study, Hsu et al.[13] have shown that the rate of AKI, requiring acute renal support (ARS) or not, has steadily increased during the past decade. From 1996 to 2003, the incidence of AKI not requiring ARS increased from 322.7 to 522.4/100,000 persons/year, while AKI requiring ARS increased from 19.5 to 29.5/100,000 persons/year. As discussed above, AKI is common in critically ill patients and additionally is an independent mortality risk factor.[1-4, 6-9]

In agreement with the literature, AKI was frequent in this ICU and was observed in 29.7% of the admitted patients. The literature reports that conditions determining renal hypoperfusion and ischemia are related to the development of AKI and that reduced renal reserve allows this condition to be develop with minor kidney insults.[14-17] Therefore, several risk factors are associated with AKI, such as advanced age, previous serum creatinine level, diabetes mellitus, high blood pressure and congestive heart failure, in addition to chronic NSAID use.[15-19]

In this study, AKI patients showed clinical characteristics similar to those described in the literature, such as advanced age and several associated comorbidities, especially arterial hypertension and CRD. In the multivariate analysis, the risk factors for AKI during the ICU stay included age above 55 years, APACHE II above 16, baseline serum creatinine above 1.2 mg/dL and previous NSAID use, in addition to septic shock.

There are many factors contributing to high AKI mortality, and the lack of identified risk factors and mortality-associated factors should be highlighted.[15]

Liaño et al.[17] have shown significant differences between AKI patients staying in the ICU (70 to 80%) and in intermediate-care wards (approximately 50%). A possible explanation for this would be ICU patients' epidemiological profile, with predominance of multiple-organ and systems failure. In this clinical condition, AKI is rarely an isolated condition but rather a complication observed in association with a large number of conditions.[18-23]

Therefore, complications during the ICU stay, such as infections, sepsis, bleeding, and the need for surgery or dialysis may increase the severity of AKI and are associated with mortality.[14-18]

In this study, AKI patient mortality was 62.1%, significantly above that observed in the group without AKI (16.5%; p < 0.0001). This can be explained by the severity of clinical and prognostic parameters found in AKI patients, for example, older, more oliguria, more sepsis, higher APACHE II scores, in addition to greater use of vasoactive drugs and a more frequent need for mechanical ventilation.

AKI was also observed to be independently associated with a prolonged length of stay and increased mortality. After 30 days' stay in the hospital, AKI patients' survival was significantly lower than that of patients without AKI.

CONCLUSION

In this study, AKI was frequently diagnosed in the ICU. The following were identified as risk factors: age above 55 years, APACHE II score above 16, baseline serum creatinine above 1.2 mg/dL, previous NSAID use and septic shock. Additionally, AKI was independently associated with prolonged ICU stay and higher mortality.

However, more prospective studies are necessary to confirm the identified risk factors associated with unfavorable outcomes in AKI, which would in turn allow for the development of prophylactics and measures for early diagnosis.

RESUMO

Objetivo: Comparar características clínicas e evolução de pacientes com e sem injúria renal aguda adquirida em unidade de terapia intensiva geral de um hospital universitário terciário e identificar fatores de risco associados ao desenvolvimento de injúria renal aguda e à mortalidade.

Métodos: Estudo prospectivo observacional com 564 pacientes acompanhados diariamente durante a internação em unidade de terapia intensiva geral do Hospital das Clínicas da Faculdade de Medicina de Botucatu por 2 anos consecutivos (de maio de 2008 a maio de 2010), divididos em 2 grupos: com injúria renal aguda adquirida (G1) e sem injúria renal aguda adquirida (G2).

Resultados: A incidência de injúria renal aguda foi 25,5%. Os grupos diferiram quanto à etiologia da admissão em unidade de terapia intensiva (sepse: G1:41,6% x G2:24,1%, p<0,0001 e pós operatório neurológico 13,8% x 38,1%, p<0,0001), idade (56,8±15,9 x 49,8± 17,8 anos, p< 0,0001), APACHE II (21,9±6,9 x 14,1±4,6, p<0,0001), ventilação mecânica (89,2 x 69,1%, p<0,0001) e uso de drogas vasoativas (78,3 x 56,1%, p<0,0001). Com relação aos fatores de risco e às comorbidades, os grupos foram diferentes quanto à presença de diabetes mellitus, insuficiência cardíaca congestiva, insuficiência renal crônica e uso de anti-inflamatórios não hormonais (28,2 x 19,7%, p=0,03; 23,6 x 11,6%, p=0,0002, 21,5 x 11,5%, p< 0,0001 e 23,5 x 7,1%, p<0,0001, respectivamente). O tempo de internação e a mortalidade foram superiores nos pacientes que adquiriram injúria renal aguda (6,6 ± 2,7 x 12,9± 5,6 dias p<0,0001 e 62,5 x 16,4%, p<0,0001). À análise multivariada foram identificados como fatores de risco para injúria renal aguda, idade>55 anos, APACHE II>16, creatinina (cr) basal>1,2 e uso de anti-inflamatórios não hormonais (OR=1,36 IC:1,22-1,85, OR=1,2 IC:1,11-1,33, OR=5,2 IC:2,3-11,6 e OR=2,15 IC:1,1-4,2, respectivamente) e a injúria renal aguda esteve independentemente associada ao maior tempo de internação e à mortalidade (OR=1,18 IC:1,05-1,26 e OR=1,24 IC:1,09-1,99 respectivamente). À análise da curva de sobrevida, após 30 dias de internação, a mortalidade foi de 83,3% no G1 e 45,2% no G2 (p<0,0001).

Conclusão: A incidência de injúria renal aguda é elevada em unidade de terapia intensiva, os fatores de riscos independentes para adquirir injúria renal aguda são idade >55 anos, APACHE II>16, Cr basal >1,2 e uso de anti-inflamatórios não hormonais e a injúria renal aguda é fator de risco independente para o maior tempo de permanência em unidade de terapia intensiva e mortalidade.

Descritores: Lesão renal aguda; Incidência; Fatores de risco; Mortalidade; Unidade de terapia intensiva

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