

Impact of acute kidney injury staging on prognosis of patients with cirrhosis

Fernando C SCHACHER¹, Angelo A MATTOS^{1,2}, Carolina M MULAZZANI³, Rafaela B DETANICO³, Bruna FAVERO³, Bárbara B FONSECA³, Patricia H FELIX³, Tales Henrique S PASE⁴, Carlos KUPSKI³, Marta B MACHADO³, Gabriela P CORAL^{1,2}, Denusa WILTGEN^{1,2} and Angelo Z MATTOS^{1,2}

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ABSTRACT – Background – Acute kidney injury (AKI) is a common and severe complication of cirrhosis. **Objective** – To evaluate the impact of AKI staging on 30-day mortality of patients with cirrhosis. **Methods** – We performed a retrospective cohort study of hospitalized patients with cirrhosis. Acute kidney injury (AKI) was diagnosed according to the International Club of Ascites recommendations and staged according to the European Association for the Study of the Liver guidelines. Comparisons between groups were made by one-way analysis of variance and Tukey test. Chi-square was calculated for dichotomous variables. Comparisons of renal impairment status among patients were performed using Kaplan–Meier statistics and differences between groups were analyzed using the log-rank test. A *P*-value <0.05 was considered to be statistically significant. **Results** – Two hundred and thirty-two patients were included in the study. The diagnosis of AKI was performed in 98 (42.2%) of them. The overall 30-day mortality was 19.8% (46/232). Mortality increased as the degree of AKI progressed. Among patients who did not have AKI, mortality was 5.2% (7/134). When compared to patients without AKI, patients diagnosed with AKI stage 1a had mortality of 12.1% (4/33, *P*=0.152); patients with AKI stage 1b had mortality of 45% (18/40, *P*<0.001); and patients with AKI stages 2 or 3 had mortality of 68% (17/25, *P*<0.001). Moreover, it is noteworthy that full response to treatment was associated to a decreased mortality when compared to patients who did not show complete recovery of renal function (14.3% vs 57.9%, *P*<0.001). **Conclusion** – AKI stages 1b or greater, but not AKI stage 1a, are associated to higher 30-day mortality of patients with cirrhosis.

HEADINGS – Liver cirrhosis. Acute kidney injury, mortality. Prognosis.

INTRODUCTION

Cirrhosis is the 13th leading cause of death globally⁽¹⁾ and liver diseases are the 8th cause of mortality in Brazil⁽²⁾, with cirrhosis being the most important cause. The development of renal impairment in patients with liver diseases usually occurs in the advanced stages of cirrhosis due to the progression of hemodynamic changes or is triggered by an acute event, such as an infection⁽³⁾. Acute kidney injury (AKI), which is estimated to occur in 20% of hospitalized cirrhotic patients⁽⁴⁾, is associated with more than 6-fold increase in the risk of death of such patients⁽⁵⁾.

The measurement of serum creatinine (sCr) is traditionally used to diagnose renal impairment in cirrhosis. Up to 2015, the criterium used to define AKI (at that time designated acute renal failure) in cirrhotic patients was an increase in sCr reaching at least a threshold of 1.5mg/dL^(6,7). However, there are some particularities in cirrhosis that affect the measurement of sCr: decreased production of creatinine from creatine in muscles, secondary to sarcopenia⁽⁸⁾; increased renal tubular secretion of creatinine⁽⁹⁾; increased volume of distribution in cirrhosis that may dilute sCr; and interference of elevated bilirubin with assays for sCr⁽¹⁰⁾. Thus, it was considered that using a fixed cutoff of sCr of 1.5 mg/dL to define AKI was problematic and that using dynamic criteria to establish AKI could lead to earlier diagnosis and, consequently, to better prognosis for patients.

In this context, in 2015, the International Club of Ascites (ICA) redefined diagnostic criteria for AKI, as well as its staging system⁽¹¹⁾. According to ICA, AKI should now be diagnosed in patients with cirrhosis who develop an increase in sCr of at least 0.3 mg/dL over the baseline within 48 hours or of 50% within one week⁽¹¹⁾. Regarding the staging system, ICA suggested that AKI in cirrhosis should be divided in three stages⁽¹¹⁾. More recently, the European Association for the Study of the Liver recommended that stage 1 should be further divided in two (1a and 1b)⁽¹²⁾. It is well recognized that the higher the stage of AKI, the worse the prognosis of the patients^(11,13-16). However, it is still controversial if mild AKI with sCr <1.5 mg/dL affects survival of patients with cirrhosis⁽¹⁷⁻²⁰⁾. Therefore, the aim of this study was to evaluate the impact of AKI staging on 30-day mortality of hospitalized patients with cirrhosis.

METHODS

Subjects

A total of 232 consecutive patients with cirrhosis who were admitted to two tertiary hospitals in Southern Brazil between January 2011 and December 2015 were enrolled in this retrospective cohort study and had their medical records reviewed. Cirrhotic patients with 18 years of age or more who had at least two measurements of sCr were considered eligible for the study. The diagnosis of

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¹ Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brasil. ² Universidade Federal de Ciências da Saúde de Porto Alegre, Programa de Pós-Graduação em Medicina: Hepatologia, Porto Alegre, RS, Brasil. ³ Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brasil. ⁴ Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brasil.

Corresponding author: Ângelo Zambam de Mattos, MD, MSc, PhD. E-mail: angmattos@hotmail.com

cirrhosis was based on histological examination or on clinical, biochemical, endoscopic and imaging findings. Patients with elective hospitalizations were excluded from the study. Clinical and laboratory data, the main reason for admission, as well as severity scores, such as Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh, were obtained for each patient at the time of admission. Serum creatinine was recorded as baseline sCr, peak sCr and sCr at the time of discharge or death.

Definition of acute kidney injury

AKI was defined according to the International Club of Ascites criteria⁽¹¹⁾, as an increase in sCr of ≥ 0.3 mg/dL from baseline within 48 hours or $\geq 50\%$ from baseline which is known or presumed to have occurred within the prior seven days. The baseline sCr was defined as the most recent stable sCr available in the previous 3 months before admission.

AKI stages were defined as:

- Stage 1: increase in sCr ≥ 0.3 mg/dL or increase of 1.5-fold to 2-fold from baseline
- Stage 1a: AKI stage 1 with sCr < 1.5 mg/dL
- Stage 1b: AKI stage 1 with sCr ≥ 1.5 mg/dL;
- Stage 2: increase in sCr of > 2 -fold to 3-fold from baseline;
- Stage 3: increase in sCr of > 3 -fold from baseline, or sCr ≥ 4.0 mg/dL with an acute increase ≥ 0.3 mg/dL, or initiation of renal replacement therapy.

Response to treatment was considered as:

- No response: no regression of AKI;
- Partial response: regression of AKI stage with a reduction of sCr to a value ≥ 0.3 mg/dL above the baseline;
- Full response: return of sCr to a value within 0.3 mg/dL of the baseline.

Ethical aspects

The study protocol was approved by the Institutional Review Boards of Pontifical Catholic University of Rio Grande do Sul and *Irmandade Santa Casa de Misericórdia de Porto Alegre*, in accordance with the Helsinki Declaration. A waiver of informed consent was granted for this study. All data were gathered from patient records and anonymously stored in a database.

Statistical analyses

Results are presented as mean and standard deviation (SD) or median and interquartile range for continuous variables and as proportions for categorical ones. Comparisons between groups were made by one-way analysis of variance followed by Tukey test. Log10 transformation was used to normalize distribution of non-Gaussian variables. Chi-square was calculated for comparisons of dichotomous variables. Comparisons of renal impairment status among patients were calculated using Kaplan–Meier statistics and differences between groups were analyzed using the log-rank test. A *P*-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS statistics software version 20.

RESULTS

From the 232 patients analyzed, 66.8% were men, and the mean age was 61.52 ± 9.7 years. The most common causes of cirrhosis were hepatitis C (39.7%) and alcohol abuse (24.6%). The mean MELD score was 15.8 ± 6.0 , and 46% of all patients were classi-

fied as Child-Pugh B. The average length of hospitalization was 10.34 ± 8.0 days. The main reason for hospital admission was acute decompensation of cirrhosis.

AKI was diagnosed in 98 (42.2%) patients. Due to the small number of patients with AKI stages 2 and 3, we decided to combine both groups for the analyses. Therefore, 33 (14.2%) patients were classified as having AKI stage 1a; 40 (17.2%) patients as having AKI stage 1b; and 25 (10.8%) patients as having AKI stages 2 or 3. There were no statistical differences among the groups regarding age, cause of cirrhosis, reason for hospitalization, presence of hepatocellular carcinoma (HCC) or length of hospitalization. Among patients with higher degrees of AKI, there was a trend towards higher frequency of ascites ($P=0.05$), hepatic encephalopathy was more severe ($P=0.01$), and MELD score was higher ($P<0.001$). TABLE 1 depicts the baseline characteristics of the patients according to the presence and stages of AKI.

The overall 30-day mortality rate was 19.8% (46/232 patients). Mortality rates according to the diagnosis and staging of AKI were: 5.2% (7/134) for patients without the diagnosis of AKI; 12.1% (4/33) for patients with AKI stage 1a; 45% (18/40) for individuals with AKI stage 1b; and 68% (17/25) for those with AKI stages 2 or 3 ($P<0.001$). FIGURE 1 demonstrates mortality rates according to AKI stages.

When comparing groups, there was no statistical difference between the odds of dying of patients with AKI stage 1a and that of patients without AKI (OR=2.5, 95% confidence interval – 95% CI=0.68–9.11, $P=0.152$). On the other hand, there was a significant difference between the odds of dying of patients with AKI stage 1b and that of those without AKI (OR=14.8, 95% CI=5.55–39.68, $P<0.001$). Similarly, there was also a significant difference between the odds of dying of patients with AKI stage 1b and that of patients with AKI stage 1a (OR=5.9, 95% CI=1.75–20.03, $P=0.002$). Finally, the odd of dying was the greatest when we compared patients with AKI stages 2 or 3 and patients without AKI (OR=38.5, 95% CI=12.40–119.78, $P<0.001$). FIGURE 2 shows the Kaplan-Meier curves for survival according the diagnosis and staging of AKI.

Another important finding of the present study regards the response to treatment of AKI. When AKI was detected and treatment led to its complete reversal, there was an impact on mortality. While patients with full response to treatment had 30-day mortality of 14.3%, those who did not achieve such response had 30-day mortality of 57.9% ($P<0.001$).

DISCUSSION

In this study, we have retrospectively evaluated a cohort of inpatients with cirrhosis with and without AKI diagnosed according to ICA criteria⁽¹¹⁾, and staged according to the current recommendations of EASL⁽¹²⁾. We were able to demonstrate that 30-day mortality significantly increased in patients with AKI stage 1b or greater, but not in patients with AKI stage 1a. Moreover, we demonstrated that patients with AKI who had full response to treatment also had lower mortality than those who did not achieve complete reversal of renal impairment.

We found an incidence of AKI of 42.2% in our sample. This is higher than it used to be described when using the traditional definition for renal impairment in cirrhosis⁽⁴⁾, but it is roughly what has been reported by other authors using the current definition of AKI, with the incidences ranging from 32.6%⁽²¹⁾ to 51%⁽²²⁾.

Besides confirming the high incidence of AKI among hospital-

TABLE 1. Baseline characteristics of the patients according to the diagnosis and staging of acute kidney injury.

	No AKI	AKI 1a	AKI 1b	AKI 2/3	P
Patients (n [%])	134 [57.8]	33 [14.2]	40 [17.2]	25 [10.8]	–
Age (years) ± SD	60.47±10.06	62.58±8.29	63.23±10.40	63.04±8.89	0.292
Sex (m/f [%m])	95/39 [70.8]	16/17 [48.4]	28/12 [70]	16/9 [64]	0.09
Etiology (n[%])					
Hepatitis C	54 [40.3]	17 [51.5]	11 [27.5]	10 [40]	0.312
Hepatitis B	1 [0.8]	0 [0]	0 [0]	0 [0]	
Alcohol	30 [22.4]	4 [12.1]	14 [35]	9 [36]	
NASH	9 [6.7]	1 [3]	2 [5]	1 [4]	
Virus + Alcohol	28 [20.9]	6 [18.2]	12 [30]	5 [20]	
Others	12 [8.9]	5 [15.2]	1 [2.5]	0 [0]	
Reason for admission (n[%])					
SBP	6 [4.5]	1 [3]	6 [15]	5 [20]	0.054
Pneumonia	4 [2.9]	1 [3]	4 [10]	4 [16]	
UTI	3 [2.3]	2 [6]	1 [2.5]	0 [0]	
Other infections	10 [7.4]	2 [6]	0 [0]	1 [4]	
Digestive bleeding	29 [21.6]	6 [18.3]	11 [27.5]	6 [24]	
Decompensation of cirrhosis	82 [61.3]	21 [63.7]	18 [45]	9 [36]	
Ascites (n[%])					
None	64 [47.8]	11 [33.3]	11 [27.5]	5 [20]	0.05
Mild	56 [41.8]	17 [51.6]	16 [40]	3 [12]	
Moderate/Severe	14 [10.4]	5 [15.1]	13 [32.5]	17 [68]	
Encephalopathy (n[%])					
None	97 [72.4]	20 [60.6]	21 [52.5]	8 [32]	0.01
Grade I-II	35 [26.1]	11 [33.3]	17 [42.5]	3 [12]	
Grade III-IV	2 [1.5]	2 [6.1]	2 [5]	14 [56]	
Presence of HCC (n[%])	32 [23.8]	7 [21.2]	16 [40]	6 [24]	0.188
Length of stay (days)	9.22	11.09	12.35	12.20	0.312
Child-Pugh A/B/C (n)	28/52/31	4/12/13	5/20/12	1/12/10	0.10
MELD (median ± SD)	13.5±5.839	14.5±5.326	17±5.528	21±5.478	<0.001

SD: standard deviation; AKI: acute kidney injury; NASH: non-alcoholic steato-hepatitis; SBP: spontaneous bacterial peritonitis; UTI: urinary tract infection; HCC: hepatocellular carcinoma.

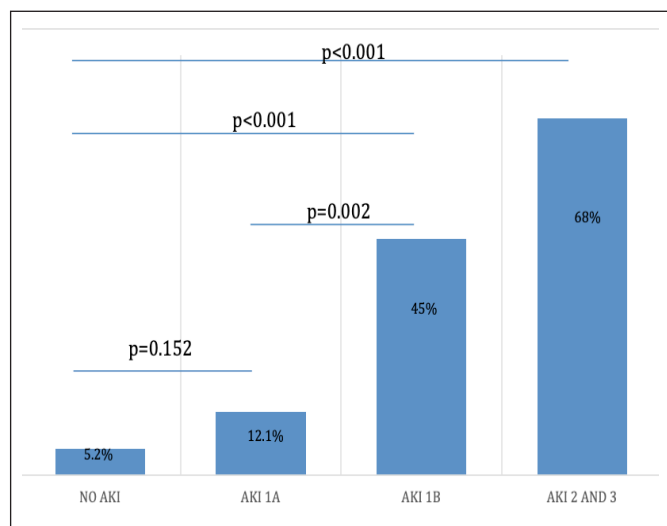


FIGURE 1. Mortality according to the diagnosis and staging of acute kidney injury.

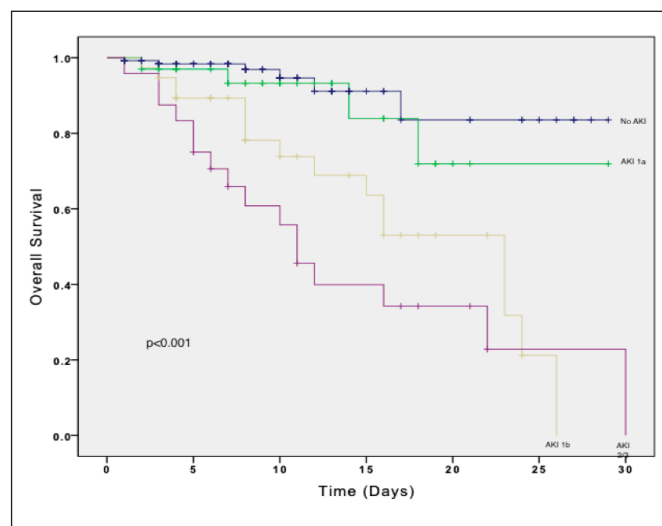


FIGURE 2. Kaplan-Meier curves for survival according to the diagnosis and staging of acute kidney injury.

ized patients with cirrhosis, our study supports that the development of AKI according to ICA criteria is a strong determinant of prognosis for patients with cirrhosis and that the higher the stage of AKI, the higher the mortality, except for AKI stage 1a. This is in contrast to other studies, in which there were worse outcomes in patients who had increases in sCr ≥ 0.3 mg/dL, even if the threshold of 1.5 mg/dL was not reached^(17,21,23). On the other hand, our results are in agreement with what had been previously found by Fagundes et al.⁽¹⁸⁾ and Piano et al.⁽¹⁹⁾. In a correspondence regarding these papers, Thalheimer et al.⁽²⁴⁾ suggested that the lack of impact of AKI stage 1a on mortality might be explained by the fact that, in the institutions where the studies were performed, there are protocols determining early interventions for patients with renal impairment, even when they have only mild increases in creatinine. The importance of a prompt intervention even for mild renal dysfunction has been corroborated by current guidelines⁽¹²⁾.

The present study also highlights the importance of the reversal of renal impairment in patients with cirrhosis. Participants who did not achieve full response to the treatment of AKI had much higher mortality than those who did.

Some considerations must also be made regarding the fact that, despite not statistically significant, there might be some differences among groups concerning risk factors recognizably associated to poor prognosis. For instance, spontaneous bacterial peritonitis and pneumonia were more frequent among patients with AKI stages 1b, 2 or 3 than in patients with AKI stage 1a or without AKI. On the other hand, infections commonly associated to a less severe course, such as urinary tract infection, were more frequent in patients without AKI or with AKI stage 1a than in those with higher degrees of AKI. It has already been demonstrated that infections in cirrhosis are highly heterogeneous and that some infections are associated to higher mortality rates than others⁽²⁵⁾. In this context, higher rates of spontaneous bacterial peritonitis and pneumonia could have led to more severe renal impairment and higher mortality rates.

Our study has some limitations. First, it is a retrospective evaluation and it is prone to all the possible biases of this kind of study, especially those related to incomplete medical records. For instance, due to the absence of clear information on the cause of AKI in most of the medical records, we were unable to adjust our analyses by etiology of AKI. We believe that the role of the etiology of AKI in this context could be evaluated by future prospective studies. On the other hand, we believe that the retrospective design of our study did not have other important impacts on our findings, since we did not have missing data regarding the main variables of the study.

Second, our sample size might not have been large enough to allow identifying small differences in mortality between the groups of patients without AKI and with AKI stage 1a. Moreover, our sample size did not permit that we analyzed AKI stages 2 and 3 separately. Finally, even if early-stage AKI does not have a significant impact on short-term prognosis of patients with cirrhosis, our study was not planned to evaluate its impact on longer-term outcomes. We believe that it would be important for future studies to analyze the impact of early-stage AKI on longer-term mortality, number of hospitalizations, recurrence of AKI and development of other complications of cirrhosis.

CONCLUSION

In conclusion, this study has demonstrated that AKI is a frequent complication of hospitalized patients with cirrhosis and that the higher the stage of AKI, the higher the odds of dying, except for AKI stage 1a, which was not associated to significantly increased mortality. Moreover, the full response to the management of AKI is associated to a decrease in mortality, which reinforces the importance of early and effective approaches to patients with cirrhosis and renal impairment.

Authors' contribution

Schacher FC: author responsible for the integrity of the work. All authors Mattos AM, Kupski C, Machado MB, Coral GP, Wiltgen D, Mattos AZ reviewed the project as well as provided intellectual contributions. The authors Mulazzani CM, Detanico RB, Favero B, Fonseca BB, Felix PH, Pase THS were involved in the development of the research as well as collection of data.

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Fernando Comunello Schacher: 0000-0002-6991-1174.
Angelo Alves de Mattos: 0000-0003-2417-9765.
Carolina Mattana Mulazzani: 0000-0001-7513-0238.
Rafaela B Detanico: 0000-0002-1007-1502.
Bruna Favero: 0000-0002-5618-7957.
Bárbara B Fonseca: 0000-0002-3520-1369.
Patrícia H Felix: 0000-0001-8783-7310.
Tales Henrique Pase: 0000-0001-7474-2048.
Carlos Kupski: 0000-0001-6206-7217.
Marta Brenner Machado: 0000-0002-8153-6688.
Gabriela P Coral: 0000-0003-4318-2871.
Denusa Wiltgen: 0000-0002-7334-2779.
Angelo Zambam de Mattos: 0000-0002-3063-0199.

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RESUMO – Contexto – A lesão renal aguda (LRA) é uma complicação comum e grave na cirrose. **Objetivo** – Avaliar o impacto dos estágios da LRA na mortalidade em 30 dias de pacientes com cirrose. **Métodos** – Realizou-se um estudo de coorte retrospectivo com pacientes com cirrose hospitalizados. LRA foi diagnosticada de acordo com as recomendações do *International Club of Ascites* e o estadiamento foi feito de acordo com as recomendações da *European Association for the Study of the Liver*. Comparações entre os grupos foram feitas por análise de variância unidirecional e teste de Tukey. O teste do qui-quadrado foi calculado para variáveis categóricas. Comparações quanto à lesão renal entre os pacientes foram realizadas com estatísticas de Kaplan–Meier, e diferenças entre os grupos foram analisadas pelo teste de log-rank. Um *P*-valor <0,05 foi considerado estatisticamente significativo. **Resultados** – Duzentos e trinta e dois pacientes foram incluídos no estudo. O diagnóstico de LRA foi realizado em 98 (42,2%) deles. A mortalidade geral em 30 dias foi de 19,8% (46/232). A mortalidade aumentou de acordo com a progressão dos estágios de LRA. Entre pacientes sem LRA, a mortalidade foi de 5,2% (7/134). Quando comparados aos pacientes sem LRA, pacientes diagnosticados com LRA estágio 1a tiveram mortalidade de 12,1% (4/33, *P*=0,152); pacientes com LRA estágio 1b tiveram mortalidade de 45% (18/40, *P*<0,001); e pacientes com LRA estágios 2 ou 3 tiveram mortalidade de 68% (17/25, *P*<0,001). Além disso, é importante ressaltar que a resposta completa ao tratamento associou-se à menor mortalidade quando comparada à ausência de recuperação completa da função renal (14,3% vs 57,9%, *P*<0,001). **Conclusão** – LRA estágios 1b ou superior, mas não estágio 1a, estão associadas à maior mortalidade em 30 dias de pacientes com cirrose.

DESCRIPTORIOS – Cirrose hepática. Lesão renal aguda, mortalidade. Prognóstico.

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