



Acute Kidney Injury at Admission Is a Better Predictor of Mortality than Its Persistence at 48 h in Patients with Acute-on-chronic Liver Failure

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Abstract

Background and Aims: Acute kidney injury (AKI) occurs commonly in patients with acute-on-chronic liver failure (ACLF). However, there are scant data regarding the impact of AKI on survival in ACLF. We performed a prospective study to evaluate the impact of AKI on survival in ACLF.

Methods: This study was conducted in ACLF patients hospitalized in the Gastroenterology Department of Sriram Chandra Bhanja Medical College (India) between October 2016 and February 2018. Demographic, clinical and laboratory parameters were recorded, and outcomes were compared between patients with and without AKI and between patients with persistent AKI and AKI reversal at 48 h.

Results: We screened 439 chronic liver disease patients as per the Asian Pacific Association for the Study of the Liver criteria and found that 113 (25.7%) of them had ACLF and 78 (69%) of them had AKI as per the Acute Kidney Injury Network criteria. ACLF patients with AKI had reduced 28-day survival (44.9% vs. 74.3%; $p = 0.004$) and 90-day survival (25.6% vs. 51.4%; $p = 0.007$), in comparison to ACLF patients without AKI. However, when comparison was made between AKI reverters and AKI persisters at 48 h, survival was comparable for both at 28 days and 90 days. Further, about one-tenth of ACLF patients with AKI died within 48 h of hospitalization. **Conclusions:** Over two-thirds of ACLF patients had AKI. Although ACLF itself is a predictor of reduced survival, a very small increase in serum creatinine further worsens survival. Importantly, AKI at admission is a better predictor of early mortality in ACLF patients since recovery from AKI at 48 h does not improve survival.

Citation of this article: Khatua CR, Panigrahi S, Mishra D, Pradhan S, Sahu SK, Barik RK, *et al.* Acute kidney injury at admission is a better predictor of mortality than persistence at 48 h in patients with acute-on-chronic liver failure.

Keywords: Acute kidney injury; Acute on chronic liver failure.

Abbreviations: AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; APASL, Asian Pacific Association for the Study of the Liver; CI, confidence interval; DC, decompensated cirrhosis; HR, hazard ratio; OR, odds ratio.

Received: 7 June 2018; Revised: 14 September 2018; Accepted: 3 October 2018

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J Clin Transl Hepatol 2018;6(4):396–401. doi: 10.14218/JCTH.2018.00035.

Introduction

Acute kidney injury (AKI) is a common complication (20%–50%)^{1,2} encountered in patients with cirrhosis and is associated with a high mortality rate.^{1–4} Because of the labile kidney circulation, it has been observed that patients with cirrhosis frequently experience small variations of serum creatinine levels that are readily reversible. These variations occur spontaneously or secondary to specific circumstances, such as diuretic therapy or episodes of moderate hypovolemia. However, the impairment of kidney function in cirrhosis occurs frequently in association with failure of other organs, a condition known as acute-on-chronic liver failure (ACLF), which may adversely impact the prognosis of these patients.^{5,6}

Studies have reported renal dysfunction in 22.8%–34% of patients with ACLF as per the Asian Pacific Association for the Study of the Liver (APASL) criteria; besides, AKI prevalence has been reported to be as high as 51% using the more sensitive Acute Kidney Injury Network (AKIN) criteria.^{7,8} AKI is defined as abrupt decline in renal function characterized by absolute increase in serum creatinine of 0.3 mg/dL within 48 h or by percentage increase in serum creatinine $\geq 50\%$ from baseline, which is known, or presumed, to have occurred within the previous 7 days.²

AKI progression has been shown in various studies to be associated with very high mortality in hospitalized patients with cirrhosis.^{9,10} However, there are very few studies on the outcome of ACLF patients having AKI at the time of hospitalization. The kidneys are differentially affected in patients with cirrhosis with or without liver failure. Patients with ACLF with AKI have more structural AKI, yet greater potential for reversibility despite higher progression, as well as higher mortality compared to patients with acute decompensated cirrhosis. Therefore, emphasis on prevention and early detection of AKI in patients with ACLF is of utmost importance.¹¹

We therefore conducted this prospective study to evaluate the impact of AKI at admission and at 48 h on survival of patients with ACLF and also the influence of reversal of AKI on survival. We also evaluated the baseline predictors of both early and late mortality in ACLF patients with AKI.

Methods

This study was conducted in ACLF patients whose diagnosis was defined according to the APASL definition: "an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease".^{7,12} Data were collected prospectively from in-patients admitted to the Gastroenterology Department, Sriram Chandra Bhanja Medical College between October 2016 and February 2018. Exclusion criteria included presence of chronic kidney disease, obstructive uropathy, hepatocellular carcinoma, and history of prior decompensation, cardiopulmonary diseases, or other malignancy.

For ACLF patients at admission, AKI was defined as per the AKIN criteria.^{7,8} Patients were managed according to the standard of care. Patients were assessed for precipitants for ACLF and risk factors causing AKI (i.e. nephrotoxic drugs: diuretics, nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, vasodilators and aminoglycoside antibiotics). Intravascular hypovolumic condition (i.e. dehydration) was corrected with intravenous saline, and variceal bleeding was treated with blood transfusion and intravenous terlipressin until endotherapy was complete.

Intravenous albumin was used for initial volume expansion for 48 h, and patients with volume-nonresponsive AKI and fulfilling the criteria for hepatorenal syndrome were treated with intravenous albumin and terlipressin or noradrenaline; hemodialysis was planned when required. Patients with bacterial infection received intravenous antibiotics, albumin and, later on, antibiotics, which were changed according to culture and sensitivity report. In septic shock patients, noradrenaline infusion was used.^{3,13,14}

AKI reverters were defined as patients with AKI in whom serum creatinine level decreased to the normal level, before hospitalization, and persistent AKI was defined in patients when serum creatinine increased from the admission serum level or did not decrease to a level that would not meet the criteria for AKI resolution after 48 h of admission.¹⁰

Primary and secondary outcomes

Survival at 28 days was defined as the primary end-point, while that at 90 days served as the secondary end-point for our survival analysis. Duration of hospital stay was the other secondary end-point for comparing ACLF patients with and without AKI at admission.

Statistical methods

Demographic, clinical, and laboratory parameters and outcome were compared between patients with and without AKI. Normally distributed continuous variables were reported as mean and standard deviation and compared using Student's *t*-test. Nonnormally distributed continuous variables were reported as median and interquartile range and compared using Mann-Whitney U test. Categorical variables were reported as proportions and compared by chi-square test or Fisher's exact test, as appropriate. The 28-day and 90-day survival were estimated by the Kaplan-Meier method and compared by means of log-rank test. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. All tests were two-tailed, and *p* values <0.05 were considered significant. The statistical analysis was performed using SPSS statistical package, version 20.0 (IBM Corp, Armonk, NY, USA).

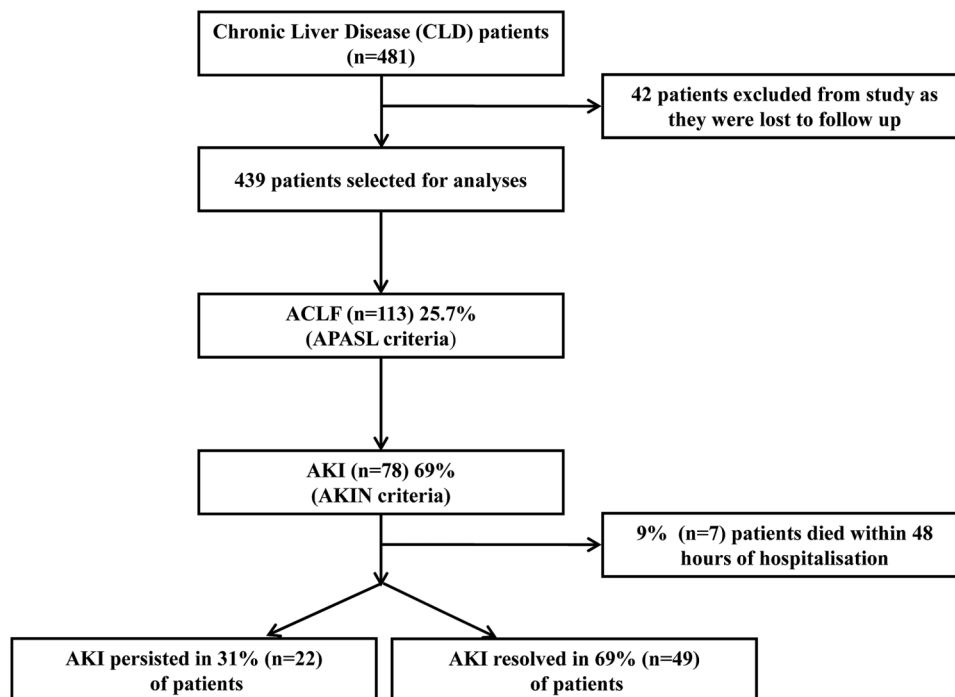


Fig. 1. Schematic flow diagram for the study.

Table 1. Comparison of baseline characteristics of ACLF patients with and without AKI

Sl No	Total ACLF patients (n = 113)	No AKI (n = 35)	AKI (n = 78)	p
1	Age	48.14 ± 11.22	44.51 ± 9.12	0.073
2	Gender (Male)	85.7%(30/35)	94.9%(74/78)	0.096
3	BMI (kg/mt ²)	22.35 ± 4.34	22.12 ± 3.52	0.386
4	MAP (mmHg)	84.70 ± 7.82	82.69 ± 12.62	0.637
5	Total leucocyte count (10 ³ cells/dL)	9000 (7200–10000)	10700 (8150–14000)	0.739
6	Serum bilirubin (total) (mg/dL)	6.60(5.50–12.40)	9.65(6.7–17.43)	0.038
7	Serum creatinine (mg/dL)	0.80(0.70–1.00)	1.90(1.48–3.02)	<0.001
8	Urea (mg/dL)	22.00(17.00–25.00)	56.00(35.25–91.50)	<0.001
9	Serum protein (g/dL)	6.61 ± 0.71	6.51 ± 0.99	0.552
10	Serum albumin (g/dL)	2.50 ± 0.39	2.49 ± 0.39	0.967
11	Serum sodium (mEq/L)	132.40 ± 5.46	129.53 ± 9.15	0.041
12	Serum potassium (mEq/L)	4.05 ± 0.59	4.29 ± 1.10	0.129
13	SAAG	2.08 ± 0.38	2.09 ± 0.45	0.951
14	INR	2.09 ± 0.49	2.84 ± 1.38	<0.001
15	MELD (UNOS)	22.60 ± 2.81	33.10 ± 8.03	<0.001
16	MELD (Na ⁺)	25.92 ± 3.16	34.25 ± 6.56	<0.001
17	CTP score	12.49 ± 1.12	13.08 ± 1.84	0.081
18	Duration of hospital stay (days)	5(3–5)	6(4–9)	0.001
19	28 days survival	74.3%(26/35)	44.9%(35/78)	0.004
20	90 days survival	51.4%(18/35)	25.6%(20/78)	0.007

Data are presented as mean (standard deviation), median (interquartile range), or frequency (%).

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; BMI, body mass index; CTP, Child-Turcotte-Pugh classification score; INR, international normalized ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; SAAG, serum-ascites albumin gradient.

Ethic committee clearance

Ethical clearance was obtained from the Institutional Ethics Committee, Sriram Chandra Bhanja Medical College (Cuttack-753007, Odisha), Registration No. ECR/84/Inst/OR/2013.

Results

We included 439 participants (372 males, 84.76%; 67 females, 15.24%) in the study. Of these, 113 (25.7%) patients had ACLF as per APASL criteria. Of the 113 ACLF patients,

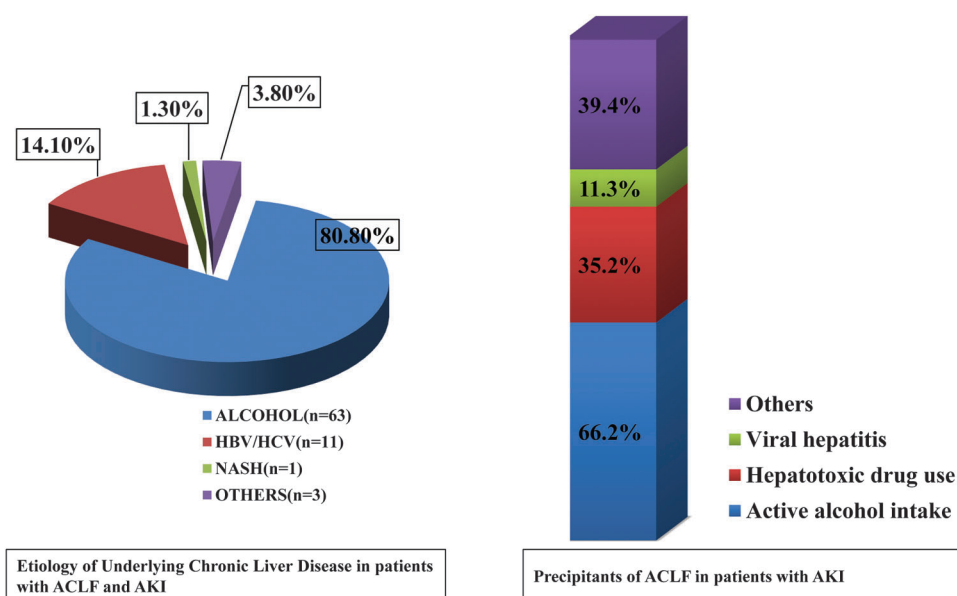


Fig. 2. Etiology of underlying chronic liver disease and the precipitants in ACLF patients with AKI.

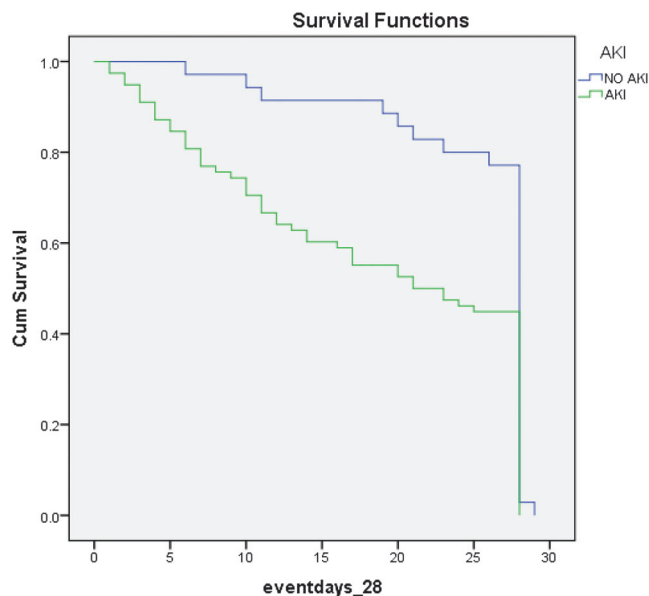


Fig. 3. Kaplan-Meier survival curves comparing survival at day 28 for participants with ACLF with and without AKI at admission.

78 (69%) had AKI as per AKIN criteria (Fig. 1). Table 1 shows the comparison of baseline characteristics of ACLF patients with and without AKI. ACLF patients with AKI and without AKI were comparable for age [mean age of patients 44.50 ± 9.19 vs. 48.14 ± 11.22 ; $p = 0.073$]. Among the etiologies of underlying chronic liver disease in the ACLF patients, alcohol was the predominant etiology, followed by viral hepatitis B or hepatitis C (Figs. 2 and 3). Active alcohol intake was the most common precipitant in ACLF patients (60.2%) as well as in ACLF with AKI (66.2%), followed by hepatotoxic drug use, variceal bleeding and viral hepatitis (Fig. 4).

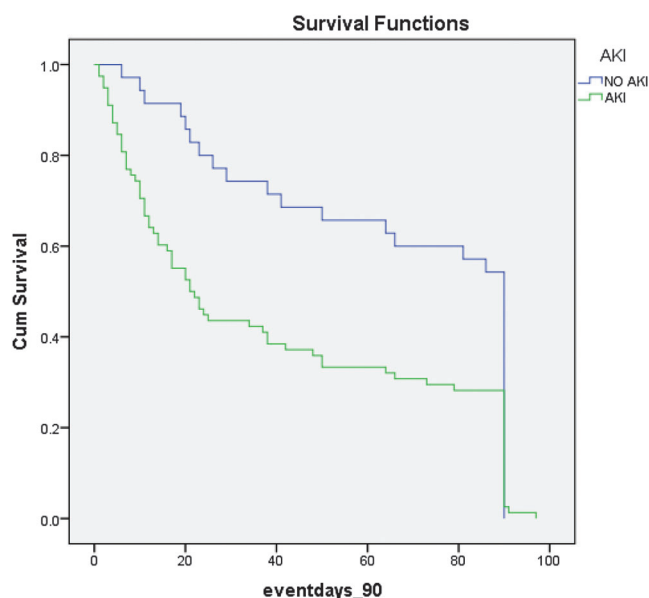


Fig. 4. Kaplan-Meier survival curves comparing survival at day 90 for participants with ACLF with and without AKI at admission.

AKI at admission among ACLF patients

At admission, AKI was found in 78 (69%) patients (males=74; females=4). Admission serum creatinine for AKI patients was 1.90 (interquartile range: 1.48–3.02) versus 0.80 (interquartile range: 0.70–1.00) mg/dL ($p < 0.001$) in ACLF without AKI. Significant differences were noted in admission serum urea level [56.00 (interquartile range: 35.25 - 91.50) vs. 22.00 (interquartile range:17.00–25.00) mg/dL; $p < 0.001$], model of end-stage liver disease score (UNOS) (33.10 ± 8.03 vs. 22.60 ± 2.81 ; $p < 0.001$), model of end-stage liver disease score (Na^+) (34.25 ± 6.56 vs. 25.92 ± 3.16 ; $p < 0.001$), duration of hospital stay (6 vs. 5; $p = 0.002$) days, 28-day survival (44.9% vs. 74.3%; $p = 0.004$) and 90-day survival (25.6% vs. 51.4%; $p = 0.007$). Kaplan-Meier survival curve showed significantly decreased survival in AKI patients both at 28 days and 90 days (log-rank p values of 0.001 and 0.004) (Figs. 3 and 4).

On Cox regression analysis (univariate), hazards of mortality were significant with admission serum creatinine, urea, sodium, bilirubin and international normalized ratio. But on multivariate analysis, the independent predictors of mortality at 28 days and 90 days were urea, bilirubin and international normalized ratio (Table 2).

Discussion

This study on ACLF with AKI was carried out in a resource-constrained region of South Asia, where liver transplantation facilities are not available. Due to lack of liver transplantation facilities, it was possible to study the natural history of ACLF patients with AKI at our center. Verdelho *et al.*¹⁵ too observed that patients having ACLF with renal dysfunction had an increased mortality. In our study, it was observed that ACLF was a very common occurrence in our cohort of hospitalized patients with decompensated cirrhosis (DC); over one-fourth (25.7%) of the DC patients had ACLF. Besides, AKI was also very common in these subjects with ACLF; over two-thirds (69%) of ACLF patients had AKI. This figure was much higher than the prevalence of 47% reported by the AARC group.¹⁶

The recent AARC study had concluded that AKI persistence at 48 h predicted worst outcome in patients with ACLF, thereby indirectly underplaying the importance of AKI at admission. This study from AARC gives a false impression that recovery of AKI at 48 h perhaps dramatically improves the outcome and survival. Our present study provided us an opportunity to critically examine this very issue, particularly the questions: How important is AKI at the point of hospitalization for ACLF patients? And, did reversal of AKI at 48 h improve the outcomes in these patients?

Our study showed that, while ACLF patients had significantly decreased early (28 days) and long-term (3 months) survival (Supplementary Table 1), AKI, which was present in 69% of the ACLF patients, further affected the survival of patients, both short-term and long-term survival (Table 1). Unlike the AARC study by Maiwall *et al.*¹¹ our study clearly showed that notwithstanding AKI at 48 h, AKI at admission itself was associated with equally poor prognosis. Besides, around 10% ($n = 7$) of patients died within 48 h of hospitalization (Table 3), and when comparison was made between AKI persisters and reverters, the survival was comparable both at 28 days and 90 days. Despite recovery from AKI, one-fourth of patients died by 28 days, and more than half

Table 2. Predictors of 28 days' and 90 days' mortality in ACLF patients with AKI

Univariate Cox regression analysis				
Parameters at admission	28 days		90 days	
	<i>p</i>	HR(95% CI)	<i>p</i>	HR(95% CI)
Serum creatinine	0.003	1.211(1.065–1.377)	<0.001	1.232(1.087–1.396)
Urea	<0.001	1.012(1.006–1.017)	<0.001	1.014(1.008–1.019)
Serum sodium	0.068	0.978(0.954–1.002)	0.059	0.978(0.955–1.001)
Serum bilirubin	0.006	1.038(1.011–1.066)	0.003	1.044(1.015–1.074)
INR	<0.001	1.317(1.134–1.528)	<0.001	1.299(1.117–1.511)

Multivariate Cox regression analysis				
Parameters at admission	28 days		90 days	
	<i>p</i>	AHR(95% CI)	<i>p</i>	AHR(95% CI)
Serum creatinine	0.117	0.801(0.607–1.057)	0.117	0.796(0.598–1.059)
Urea	0.002	1.014(1.005–1.023)	0.001	1.016(1.007–1.025)
Serum bilirubin	0.019	1.034(1.006–1.064)	0.027	1.035(1.004–1.067)
INR	0.006	1.3581.090–1.691)	0.015	1.312(1.053–1.635)

Abbreviations: ACLF, acute-on-chronic liver failure; AHR, adjusted hazard ratio; AKI, acute kidney injury; HR, hazard ratio; INR, international normalized ratio.

by 90 days. This suggests that in ACLF patients, AKI at admission is a better prognostic indicator than AKI at 48 h.

In our study, the median time of reversal of AKI in ACLF patients was 4 (range: 3–6) days. So, waiting for 48 h to see if there is reversal of AKI in these patients is not a worthwhile proposition, as it could delay intervention and prognostication of these patients. The published paper from the AARC study¹⁶ states, "AKI persistence at 48 h predicts mortality in patients with [ACLF]". The authors looked at the status of AKI at different time points with respect to day 1 and prediction of 1-month mortality, and they found increased odds ratio (OR) at day 6 (OR: 4.4) versus day 2 (OR: 3.7). However, surprisingly, they preferred day 2 instead of day 6, to enable early intervention.

In our study, since we found that admission AKI was as important as AKI persistence (at 48 h), we preferred to highlight this as a better prognostic predictor rather than delaying for 48 h to enable early triaging and intervention.

Table 3. Survival comparison at 48 h between AKI persisters versus AKI reverters in ACLF

Sl No	ACLF with AKI patients at 48 h (n = 71*)	AKI reverters (n = 49, 69.01%)	AKI persister (n = 22, 30.99%)	<i>p</i> [#]
1	28 days survival	77.55% (38/49)	68.18% (15/22)	0.502
2	90 days survival	48.98% (24/49)	45.45% (10/22)	0.772

* Seven ACLF with AKI patients died before 48 h.

[#]Survival comparison at 48 h between AKI reverters versus ACLF patients without AKI at admission.

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury.

So, without waiting for 48 h, patients with ACLF and AKI should be prognosticated from the beginning to enable early decision making regarding further intervention including liver transplantation.

Our study has a few limitations. It includes data from a single, resource-constrained region, and it might not be appropriate to extrapolate our conclusions regarding outcome to the population of other regions across the globe. Besides, the study also needs validation from other multi-centric studies with larger sample size.

Conclusions

Over one-fourth of DC patients had ACLF, and more than two-thirds of them had AKI. Presence of AKI in ACLF decreases both 28- and 90-day survival rates. AKI at admission is an important prognostic indicator. Strategically, AKI at admission is a more important prognostic indicator than AKI persistence at 48 h.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to the study design, analysis and interpretation of data, statistical analysis and manuscript writing (CRK, SPan, DM, SPra, SKS, RKB, PKP, SB, SPa, SPS).

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