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ORIGINAL ARTICLE

Comparison of clinical characteristics of acute kidney injury versus acute-on-chronic renal failure: Our experience in a developing country

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sepsis;
volume depletion

Summary *Background:* From developing countries, there is paucity of information regarding epidemiological characteristics of acute-on-chronic renal failure (ACRF) that differs from acute kidney injury (AKI).
Methods: In this prospective study, we analyzed and compared clinical characteristics and outcome of ACRF with AKI from January 2007 to August 2012.
Results: A total of 1117 patients with community-acquired AKI were included in study (AKI = 835; ACRF = 282). Patients with ACRF were older than patients with AKI ($p < 0.001$). Sepsis was the main cause of acute decline in renal functions in patients with ACRF in comparison to AKI ($p < 0.001$). Volume depletion/renal hypoperfusion was the most common cause of AKI and the difference was statistically significant as compared to ACRF (33.9% vs. 17.7%; $p < 0.001$). Need for dialysis was significantly less in patients with ACRF as compared to AKI (68% vs. 77.4%; p 0.002). Lower inhospital mortality was observed in ACRF in comparison to AKI (5% vs. 8.9%, $p = 0.04$), while no significant difference was noted in terms of duration of hospital stay between the two groups ($p = 0.67$). However, a significantly higher proportion of patients with ACRF did not recover and progressed to end-stage renal disease as compared to AKI (20% vs. 7.8%; $p < 0.001$).

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Conclusion: ACRF constituted an important cause (25%) of AKI. An episode of superimposed AKI is associated with significantly increased risk of progression to end-stage renal disease in patients with chronic kidney disease.

背景: 慢性腎病合併急性腎衰竭 (ACRF) 不同於急性腎損傷 (AKI)，然而在發展中國家，ACRF 的流行病學數據仍然相當有限。
方法: 在 2007 年 1 月至 2012 年 8 月期間，我們進行了一項前瞻性研究，分析並比較了 ACRF 與 AKI 的臨床特徵和治療後果。
結果: 研究對象為 1117 位社區性 AKI 患者 (AKI = 835；ACRF = 282)，其中 ACRF 患者較 AKI 患者年老 ($p < 0.001$)。相比於 AKI，ACRF 的急性腎功能下降較常歸因於敗血症 ($p < 0.001$)；相比於 ACRF，AKI 則較常歸因於容積匱乏/腎灌流不足 (33.9% vs. 17.7%；$p < 0.001$)；ACRF 患者比 AKI 患者較少需要接受透析療法 (68% vs. 77.4%；$p = 0.002$)；ACRF 患者的院內死亡率低於 AKI 患者 (5% vs. 8.9%；$p = 0.04$)，兩組間的住院期則無明顯差別 ($p = 0.67$)；然而，相比於 AKI 患者，明顯較多的 ACRF 患者無法康復並惡化成末期腎病 (ESRD) (20% vs. 7.8%；$p < 0.001$)。
結論: 慢性腎病合併急性腎衰竭是急性腎損傷的重要病因 (25%)；在慢性腎病患者間，AKI 的發生明顯增加惡化為 ESRD 的風險。

Introduction

Acute kidney injury (AKI) is defined as a rapid (over hours to weeks) and usually reversible decline in glomerular filtration rate (GFR) that can occur either in the setting of previously normal renal function ("classical" AKI) or in a patient with pre-existing chronic kidney disease (acute-on-chronic renal failure; ACRF).[1–3] In developed countries AKI primarily occurs in hospitalized patients, while AKI is mainly community acquired in developing countries.[3,4] ACRF forms an important group of AKI and is a significant cause of morbidity and mortality.[5] However, there is a paucity of information on the entity ACRF and its clinical outcomes are not well studied.[6] Available data suggest that epidemiological characteristics of ACRF differ from AKI. Patients with ACRF are of older age, have lower inhospital mortality, higher need for dialysis, and a significant number of these patients progress to end-stage renal disease (ESRD).[5,7] With this background, the aim of the present study was to compare the etiology, clinical features, and outcome of patients suffering from ACRF with AKI from a tertiary level hospital of eastern India.

Methods

In this prospective study, patients of both sexes with clinical diagnosis of community-acquired AKI or ACRF, attending the Department of Nephrology, Sir Sundar Lal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, from January 2007 to August 2012, were included for analysis. Patients with hospital-acquired AKI were excluded. Ethics committee approval was obtained prior to the study and written informed consent was taken from all patients. In patients with AKI and ACRF, detailed history, physical examination, and relevant laboratory investigations were undertaken with the purpose to identify etiology and precipitating factors responsible for the acute decline of renal functions. Patient and renal outcome were analyzed using the following parameters: need for renal replacement therapy, duration of hospital stay, recovery of renal functions, and inhospital mortality. The following definitions were used in this study. (1) AKI was defined as increase in serum creatinine (SCr) concentration $\geq$ 44 μM and baseline SCr $<$ 132 μM,[8] or SCr level at time of presentation was $\geq$177 μM,[9,10] when baseline levels were not known and during course of illness SCr returned to normal range (70.7—123.7 μM). (2) Chronic kidney disease (CKD) was defined as either kidney damage or GFR $<$ 60 mL/min/1.73 m^2 for $\geq$ 3 months. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.[11] However, we calculated estimated GFR (eGFR) using the Cockcraft—Gault formula in this study. (3) Patients were classified as ACRF if they made the criteria for CKD as defined above and had an acute rise in SCr $\geq$ 1.5 times over baseline value in a known case of CKD[5] or when underlying CKD[11] was diagnosed during course of treatment in patients with AKI. (4) Renal recovery[5]: the renal function status of all surviving patients with AKI and ACRF was evaluated at $\geq$ 3 months after AKI episode and these patients were categorized into fully recovered, partially recovered, or nonrecovered, defined as (a) full recovery: SCr concentration down to normal range (or to the baseline in case of ACRF); (b) partial recovery: SCr remains above 123.7μM (or remains above baseline in case of ACRF, or above 177μM when baseline not known); (c) failure to recover (nonrecovery): dialysis dependence after 3 months of AKI. (5) Sepsis was defined according to ACCP/SCCM consensus conference committee guidelines.[12]

Statistical analysis

Categorical variables are reported in the form of number (%) while continuous data are expressed as mean ± standard deviation. Chi-square test was used for dichotomous variables, while continuous data were analyzed using unpaired *t* test. A statistical value of $p < 0.05$ was considered significant. All the calculations were carried out using SPSS software version 16 (SPSS Inc., Chicago, IL, USA).

Results

From January 2007 to August 2012, a total of 1117 patients (679 males, 438 females) with community-acquired AKI

Table 1 Demographic features of patients with acute kidney injury (AKI) and acute-on-chronic renal failure (ACRF).

Parameter	AKI (n = 835)	ACRF (n = 282)	p
Mean age (y)	44 ± 19	54 ± 15	< 0.001
Male	498 (59.6)	181 (64.2)	0.18
Female	337 (40.4)	101 (35.8)	
Incidence per 1000 hospital admissions	3.2	1.1	
Number of patients with known baseline SCr prior to AKI	67 (8.0)	176 (62.4)	< 0.001
Peak SCr (μM)	724.9 ± 371.3	716 ± 362.4	0.73
Peak blood urea nitrogen (mM)	30.1 ± 13.1	30.6 ± 12.7	0.55
Comorbid conditions			
Hypertension	206 (24.7)	179 (63.5)	< 0.001
Diabetes mellitus	87 (10.4)	106 (37.6)	< 0.001
Coronary artery disease	50 (6.0)	74 (26.2)	< 0.001
COPD	11 (1.3)	39 (13.8)	< 0.001
Malignancy	72 (8.6)	26 (9.2)	0.80

Data are presented as n (%) or mean ± standard deviation.
COPD = chronic obstructive pulmonary disease; SCr = serum creatinine.

were studied. Patients with AKI and ACRF comprised 835 (75%) and 282 (25%) cases, respectively. The demographic and clinical profiles of both groups of patients are shown in Table 1. Mean age of AKI and ACRF patients was 44 ± 19 years (range, 15–92 years) and 54 ± 15 years (range, 20–85 years), respectively. The male patients were dominant in both AKI and ACRF groups (59.6% and 64.2% of cases, respectively). Baseline SCr value was available for only 67 (8%) patients with AKI and for 176 (62.4%) patients with ACRF before the development of acute renal failure. The mean eGFR of CKD patients was 37.2 ± 16.4 mL/min (range, 21.4–55.0 mL/min). In contrast to AKI, the majority of patients with ACRF had presence of various comorbid conditions. Prevalence of hypertension and diabetes were observed in 179 (63.5%) patients and 106 (37.6%) patients with ACRF, respectively (Table 1).

Diabetic nephropathy was the leading cause (n = 88; 31.2%) of CKD in patients with ACRF group. Obstructive nephropathy was the second most common cause of CKD, seen in 55 patients (19.5%). The other causes of CKD were: chronic interstitial nephritis (n = 41; 14.5%); chronic glomerulonephritis (n = 35; 12.4%); autosomal dominant polycystic kidney disease (n = 19; 6.7%), and hypertensive nephrosclerosis (n = 12; 4.3%). However, the cause of CKD was uncertain in 29 patients (10.3%). Diagnosis of CKD was already established prior to AKI in 176 patients (62.4%). In remaining 106 patients (37.6%), underlying CKD was diagnosed on the basis 2002 of Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[11]

In patients with AKI, the majority (n = 727; 87.1%) presented with intrinsic AKI, while prerenal and postrenal AKI constituted of 68 patients (8.1%) and 40 patients (4.8%), respectively. In patients with intrinsic AKI, acute tubular necrosis was the most common (n = 583; 70%) lesion. Acute glomerulonephritis, acute interstitial nephritis (AIN), and thrombotic microangiopathy were noted in 94 patients (11.3%), 45 patients (5.4%), and five patients (0.6%), respectively. The majority of cases of acute interstitial nephritis were due to drugs (rifampicin and ciprofloxacin). Volume depletion–hypoperfusion (n = 283; 33.9%) was the most common etiology of classical AKI, followed by sepsis (n = 181; 21.7%). Etiology of AKI was multifactorial in 147 patients (17.6%; Table 2). Renal biopsy was done in 103 AKI patients who had systemic or glomerular disease (n = 72), unexplained AKI (n = 18), and prolonged course of AKI (n = 13). Histopathology revealed: crescentic glomerulonephritis (n = 43: 39 pauci-immune and 4 anti-glomerular basement membrane disease), systemic lupus erythematosus (n = 23), AIN (n = 14), diffuse endocapillary proliferative glomerulonephritis (n = 10), Henoch–Schonlein purpura (n = 7), membranous glomerulonephritis with crescentic transformation (n = 2), and thrombotic microangiopathy (n = 2). Two patients in the ACRF group underwent renal biopsy at the time of AKI and they had lupus nephritis World Health Organization class IV.

In patients with ACRF, five each had prerenal and postrenal AKI, while intrinsic AKI was observed in 272 patients. Acute tubular necrosis was also the most common lesion (n = 270; 95.8%) in the ACRF group, while acute glomerulonephritis was observed in two cases only. In contrast to the AKI group, sepsis was the leading cause (n = 188; 66.7%) of acute decline in renal functions in patients with ACRF. Source of sepsis was diverse and urinary tract was the most common (34.4%) site of infection (Table 2). Volume depletion–hypoperfusion related AKI was seen in 50 patients (17.7%) with ACRF. There were multiple precipitating factors for AKI in 33 patients (11.7%) with ACRF. Drug-related AKI was observed in 19 cases of ACRF; nonsteroidal anti-inflammatory drugs were the MOST common culprit agents (n = 9), followed by contrast media (n = 6). We observed emphysematous pyelonephritis in three patients with ACRF (Table 2).

Table 3 shows comparative analysis of the outcome of AKI and ACRF patients. The ACRF group had lower inhospital mortality in comparison to the AKI group (5% and 8.9%, respectively, p = 0.04). Dialysis requirement was lower in the ACRF group as compared to AKI patients (68% vs. 77.4%, p = 0.002). We observed no significant difference regarding length of hospital stay (p = 0.67) and average number of dialysis sessions required (p = 0.18) between the two groups. The rate of recovery of renal functions was comparatively slow in the ACRF group. We observed full and partial recovery of renal functions in 38.8% and 41% of patients with ACRF, respectively, while, in AKI patients, full

Table 2 Causes of acute decline in renal function in patients with acute-on-chronic renal failure (ACRF) and acute kidney injury (AKI).

Causes	AKI ($n = 835$)	ACRF ($n = 282$)	p
Sepsis-related	181 (21.7)	188 (66.7)	< 0.001
Urinary tract infections	68 (8.1)	97 (34.4)	
Respiratory tract infections	60 (7.2)	34 (12.1)	
Cellulitis/cutaneous abscess	11 (1.3)	22 (7.8)	
Unknown	42 (5.0)	17 (6.0)	
Diabetic foot	0	16 (5.7)	
Acute cholangitis	0	2 (0.7)	
Volume depletion—hypoperfusion	283 (33.9)	50 (17.7)	< 0.001
Acute gastroenteritis	216 (25.9)	29 (10.3)	
Volume depletion (other than gastroenteritis)	67 (8.0)	21 (7.5)	
Drugs	61 (7.3)	19 (6.7)	> 0.99
Acute glomerulonephritis	94 (11.3)	2 (0.7)	< 0.001
Thrombotic microangiopathy	5 (0.6)	0	
Malarial AKI	78 (9.3)	3 (1.1)	< 0.001
Acute pancreatitis	49 (5.9)	1 (0.4)	< 0.001
Myeloma-related AKI	26 (3.1)	0	
Accelerated hypertension	0	11 (3.9)	
Miscellaneous	13 (1.6) [a]	3 (1.1) [b]	
Urinary tract obstruction (postrenal AKI)	40 (4.8)	5 (1.8)	0.02

Data are presented as n (%).
[a] Hepatorenal syndrome ($n = 5$); rhabdomyolysis ($n = 5$); snake bite ($n = 3$).
[b] One each of enteric fever, hepatorenal syndrome, and congestive cardiac failure.

and partial recovery was reported in 66.1% and 26.1% of cases, respectively ($p < 0.001$). At 3-month follow-up, a significantly higher proportion of patients in the ACRF group had nonrecovery of renal functions in comparison to AKI and progressed to ESRD (20% vs. 7.8%, $p < 0.001$).

Discussion

The present study compared the etiology, clinical features, and outcome of patients suffering from ACRF with those with AKI. ACRF constituted 282 (25%) of the total AKI cases in the present study. The reported incidence of ACRF of total AKI cases has a wide variation ranging from 12.7% to 35.5% (Table 4).[5,13–17,19] Patients with ACRF constituted 22% of total AKI cases in another Indian study.[13] Zhang et al[14] from China reported that ACRF accounted for the 104 (35.5%) of 293 biopsied acute renal failure cases. Similarly, in the BEST (Beginning and Ending Supportive Therapy for the kidney) cohort, 30% of patients had impaired kidney function (defined as "any abnormal serum level of creatinine or creatinine clearance before hospitalization"), whereas 15% had unknown baseline kidney function.[15] We had reported ACRF in 22.4% of patients of total AKI cases in our previous study.[16] Thus our results are similar to other reported studies.[13–19] It is intuitive that an already damaged kidney is more susceptible to acute injury.[6] Indeed, baseline renal dysfunction has been observed to be a risk factor for the development of AKI in a number of settings, such as radiocontrast administration, cardiac surgery, and sepsis.[5,6,20] The mean age of AKI patients was 49 ± 18 years in the present study. Male patients were dominant in both AKI and ACRF groups (59.6% and 64.2%, respectively). The similar pattern of males outnumbering females has been reported in other studies from developing countries.[4,9,21–24]

Table 3 Comparative analysis of outcome of patients with acute kidney injury (AKI) and acute-on-chronic renal failure (ACRF).

Parameter	AKI ($n = 835$)	ACRF ($n = 282$)	p
Need for dialysis	646 (77.4)	192 (68)	0.002
Sessions of dialysis (number)	3.9 ± 2.8	4.2 ± 3.2	0.18
Inhospital mortality	74 (8.9)	14 (5.0)	0.04
Length of stay (d)	11.9 ± 6.5	12.1 ± 5.3	0.67
Renal function status in survivors at 3 months after AKI episode	**($n = 761$)**	**($n = 268$)**	
A. Full recovery	503 (66.1)	104 (38.8)	< 0.001
B. Partial recovery (dialysis independent)	199 (26.1)	110 (41)	< 0.001
C. Nonrecovery (progression to ESRD)	59 (7.8)	54 (20.2)	< 0.001

Data are presented as n (%) or mean $\pm$ standard deviation.
ESRD = end-stage renal disease.

Table 4 Literature review: Percentage of patients with acute-on-chronic renal failure (ACRF) of total acute kidney injury (AKI) cases in different studies.

Authors	Place	Total no. of AKI cases	Distribution of ACRF of total AKI patients *n* (%)
Liaño and Pascual 1996 [19]	Spain	748	95 (12.7)
Kohli et al 2000 [13]	India	59	13 (22.0)
Silvester et al 2001 [17]	Australia	299	99 (33.1)
Uchino et al 2005 [15]	Multicenter	1738	512 (29.5)
Zhang et al 2005 [14]	China	293	104 (35.5)
Ali et al 2007 [5]	Scotland	562	88 (15.6)
Prakash et al 2011 [16]	India	775	174 (22.4)
Prakash et al (present study)	India	1117	282 (25.2)

Despite the term ACRF being familiar to most nephrologists, epidemiological data on ACRF are limited because this entity has not been extensively investigated. Our knowledge of the complex interactions between AKI and CKD continues to evolve. It is evident that baseline renal dysfunction is a strong risk factor for developing AKI, and, in turn, AKI *per se* may contribute to CKD progression and ESRD.[6,7] The epidemiological characteristics of ACRF from developing countries differ from developed countries in certain ways: (1) community-acquired AKI is predominant in developing countries, affecting a younger population and caused by single disease (e.g., diarrhea or malaria); (2) sepsis and volume depletion are the main precipitating factors for AKI in patients with CKD. Ali et al[5] reported that the median age of patients with acute on CKD was 80.5 years; similarly another study from the USA noted that the mean age of patients with ACRF was 66.6 ± 13.5 years.[7] In contrast to the developed world, the mean age of ACRF patients was lower (54 ± 15 years) in our study. Sepsis was the leading cause (66.7%) of AKI in patients with ACRF in the present study. Sepsis was the most frequent precipitating factor (47%) for AKI in study by Ali et al.[5] We reported that sepsis was the main cause (63.2%) of AKI in patients with CKD in our previous study as well, similar to the findings of others.[16] However, a hospital database study revealed that sepsis was the precipitating factor for ACRF in only 21% of patients, while 76% cases were due to decreased renal perfusion.[7] Volume depletion was the precipitating factor for ACRF in 17.7% of cases in the present study.

Clinical outcome of patients with ACRF differ from AKI in certain respects.[5,7] We observed a need for dialysis in 68.1% and 77.4% of patients with ACRF and AKI, respectively. Dialysis requirement was significantly higher in patients with AKI in comparison to ACRF cases ($p = 0.002$). Ali et al[5] reported that there was a need for renal replacement therapy in 7.8% and 12.5% of cases with AKI and ACRF only, respectively. The present study observed a significantly higher incidence of partial (41% vs. 26%, $p < 0.001$) or nonrecovery (20% vs. 7.8%, $p < 0.001$) of renal functions among surviving patients with ACRF as compared to AKI cases. Twenty percent of patients with ACRF progressed to ESRD in the present study. The findings are consistent with the literature showing high rates of progression to ESRD in patients with CKD following AKI.[5–7,24,25] In a study by Wu et al,[24] the incidence of recovery of renal functions was higher in postsurgery AKI patients in comparison to cases with pre-existing CKD (86.7 vs. 72.3%; $p < 0.01$).[24] In another study by Hsu et al,[7] the majority of survivors of ACRF (66.5%) went on to require long-term dialysis within 30 day of discharge. Furthermore, the episode of AKI in CKD patients was associated with a 30% increase in long-term risk for death or ESRD in their study.[7] The increase in incidence of AKI in the past 2 decades has coincided with an increase in the incidence of ESRD. Epidemiological studies have consistently shown that AKI is a risk factor for incident CKD, progression of CKD and incident ESRD.[26] Thus, AKI patients with previously diagnosed CKD are at a significantly increased risk of ESRD, suggesting that an episode of AKI may accelerate progression of renal diseases. Experimental studies have shown that AKI causes permanent damage to the microvasculature and subsequent abnormalities in kidney structure and function. In this regard, several animal models suggest that one isolated episode of AKI that is completely reversible, leads to CKD and renal fibrosis.[27] Recent studies revealed that nonrecovery of kidney functions after AKI is important for long-term prognosis rather than AKI *per se*.[2] Pannu et al,[28] in their retrospective analysis of 190,962 patients, concluded that renal recovery after AKI is associated with a lower risk of death or adverse renal outcome than nonrecovery of kidney functions. These findings should be confirmed in prospective studies of AKI.[28,29] Based on these observations, the 2012 Kidney Disease Improving Global outcome guideline for AKI recommended that patients with AKI should be evaluated 3 months after an episode of AKI to assess recovery, development of incident CKD, or worsening of pre-existing CKD.[30]

The patients with AKI had 8.9% inhospital mortality in the present study. The rate of AKI-associated mortality seems to be lower in developing countries and varies from 10% to 40%.[4,21,31] In contrast to developing countries, very high mortality rates of AKI are reported from developed countries, ranging between 37% and 81%.[15,18,19,32,33] The representations of a large part of AKI by younger individuals coupled with low incidence of comorbid conditions are the main reason for low mortality in AKI cases in developing countries.[31] The inhospital mortality of patients with ACRF was only 5% in the present study, which was significantly lower than the AKI group ($p = 0.04$). The available literature also suggests that patients with ACRF may have lower inhospital mortality than patients with AKI.[19,34] The Nationwide Inpatient Sample study revealed that 22% of patients with ACRF died in hospital as compared

with 30% of mortality in patients with AKI.[34] The Madrid acute renal failure study reported 35% mortality in patients with pre-existing renal dysfunction as compared to 47% mortality seen in AKI cases.[19] Several reasons could be postulated to explain the observed lower mortality following AKI, in patients with chronic kidney disease. Preclinical studies have shown that the presence of adaptive mechanisms such as high osmolar clearance per nephron and low fractional excretion of sodium seen in CKD can alter the course of AKI.[35] Similarly, ischemic preconditioning seems to be protective for AKI.[36] Also, in patients with underlying CKD, relatively less severe acute insult is required to manifest AKI, as compared to those with normal renal function.

There are certain limitations of the present study. Because of nonavailability of baseline SCr in the majority of patients, we did not use RIFLE (Risk, Injury, Failure, Loss of function, and End stage renal disease) or AKIN (Acute Kidney Injury Network) criteria for definition and staging AKI in this study. The Cockcroft—Gault formula was used to define eGFR, although this may underestimate true GFR in earlier stages of CKD. Similarly, hourly urine output monitoring was difficult task in overcrowded general ward. By applying the criterion of presenting SCr value of $\geq$ 177μM to define AKI, some patients of ACRF with unknown baseline SCr value might have been misclassified to the AKI group.

In summary, we observed that ACRF constitutes 25% cases of AKI in our clinical practice and clinical characteristics of ACRF differed from AKI with respect to the age, cause, outcome, and recovery of renal functions. Patients with ACRF were of older age than the patients with AKI. Sepsis was the commonest precipitating factor for ACRF, while AKI was mainly due to volume depletion—hypoperfusion. The need for dialysis and inhospital mortality were significantly lower in the ACRF group. With appropriate treatment, renal functions reverted to the predamaged state in 80% of cases with ACRF. We documented that the rate of recovery of renal functions was slower in ACRF patients in comparison to AKI patients and 20% of cases of ACRF progressed to ESRD after an AKI episode. Thus, superimposed AKI is a risk factor for progression to ESRD in patients with CKD.

Conflicts of interest

The authors declare no conflicts of interest.

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