Original Article

Risk Factors and Outcomes of Acute Decompensation in Patients with Chronic Kidney Disease

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ABSTRACT

Introduction: The occurrence of acute decompensation in patients with background chronic kidney disease (CKD) is very common and further worsens the patient's outcome. Because of the limited data on the risk factors and outcomes of acute-on-chronic kidney failure (ACKF), we sought to assess the common causes of acute decompensation in non-dialytic CKD patients necessitating emergency dialysis and to assess the relationship between these risk factors and outcomes.

Materials and Methods: We analysed the data of adults ACKF patients admitted to the Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, between December 2009 and March 2011. One hundred and sixty-three CKD patients with AKI were recruited. Laboratory data, including complete blood count, biochemical and microbiological analyses, were documented. Two-dimensional and Doppler echocardiography was performed where indicated. Multivariable logistic regression analysis was used to analyse the association between the risk factors for ACKF and in-hospital mortality.

Results: The median age was 39 (28–52) years, with male preponderance (76.7%). The common causes of acute decompensation of CKD identified were heart failure (41.7%), malignant hypertension (39.9%), sepsis (35.6%), nephrotoxins (20.9%) and hypovolemia (16. 9.8%). In-hospital mortality was recorded in 34.4% of the patients. Adjusted odds of in-hospital mortality were significantly increased in the presence of heart failure (odds ratio [OR], 2.93 [95%, 1.14–7.55]; $P = 0.026$) and malignant hypertension (OR, 3.69 [1.15–11.81]; $P = 0.028$).

Conclusion: The risk factors for ACKF such as heart failure and malignant hypertension are also the independent predictors of in-hospital mortality. Given the high mortality rates, aggressive management of these precipitants could be life-saving.

Key words: Acute kidney injury, acute-on-chronic kidney failure, chronic kidney disease, in-hospital mortality

INTRODUCTION

Acute-on-chronic kidney failure (ACKF), defined as a rapid decline in kidney function in patients with pre-existing kidney function, represents an important group of acute kidney injury (AKI) and is a major cause of morbidity and mortality.[1-5] It often presents acutely with attendant high mortality, so much so that, when severe enough to require urgent dialysis, associated in-hospital mortality could be as high as 30% or even more.[6]

Because ACKF confers greater risk for progression to end-stage renal disease (ESKD) and mortality,[6-8] we determined the common risk factors for ACKF and their impacts on the outcomes in chronic kidney disease (CKD) patients requiring dialysis.

MATERIALS AND METHODS

Study design and participants

We conducted a single-center, observational, prospective study of adult non-dialytic CKD patients managed at Renal Unit, Obafemi Awolowo University Teaching Hospital Complex (OAUTHC), Ile-Ife, Nigeria, between December 2009 and March 2011. The study participants included all adults CKD patients (≥18 years) admitted consecutively to the medical wards with a need for the emergency dialysis.

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The following patients were excluded from the study: Patients without baseline creatinine, with pre-existing end-stage kidney disease, those already on maintenance dialysis and those who had received kidney transplantation in the previous 3 months. The study was conducted in accordance with the declaration of Helsinki and conforms to the STROBE statement for reporting observational studies.

Data collection

We collected the information on the date of hospital admission and discharge from Renal Unit, demographics, etiology of CKD, clinical presentation, dialysis requirement and mortality using the case report form. Laboratory data, including packed cell volume (PCV), urinalysis, biochemical parameters and microbiological assays, were performed in the OAUTHC laboratory as part of the routine standard of care. Aetiology of CKD were defined based on our previously published clinical diagnostic criteria used in categorising aetiological factors for CKD.[9,10] Baseline serum creatinine (SCr) was defined as the lowest value in the 12 months before hospital admission.[11] Estimated creatinine clearance (at baseline, at discharge and 1-year follow-up) was calculated using Cockcroft-Gault equation, which estimates creatinine clearance on the basis of the serum creatinine, weight and gender.[12]

Definitions

AKI was defined according to the KDIGO definition using serum creatinine measurements and urine output criteria.[13] Sepsis was defined according to the American College of Chest Physicians and the Society of Critical Care Medicine consensus.[14,15] We defined sepsis as a condition in which the patient met the criteria for systemic inflammatory response syndrome (SIRS) and presented with either a documented (culture result) or suspected infection. Hypovolaemia was defined by medical history and physical examination of vital signs, skin turgor and central venous pressure measurement.[16] Heart failure was defined based on all of the following findings: (1) complaint of dyspnoea or presence of orthopnoea, (2) fine crepitation audible in both lungs, (3) radiographic findings consistent with pulmonary oedema and (4) depressed left ventricular ejection fraction on echocardiography. Malignant hypertension was diagnosed in patient with accelerated hypertension with the features of grade 3 or 4 hypertensive retinopathy on fundoscopy or microscopic haematuria. Nephrotoxicity was defined as any decline in baseline kidney function that is secondary to the use of a nephrotoxic agent (including drugs such as non-steroidal anti-inflammatory drugs [NSAIDs], aminoglycosides and herbal medications) and documented by a physician.

Outcomes

The primary outcome was in-hospital mortality from all causes. The secondary outcomes were recovery of kidney function following AKI diagnosis and progression to ESKD, defined as dialysis dependence for ≥3 months. Participants were adjudged to have met the criteria for kidney recovery if the last available creatinine fell within 50% of the baseline value

at admission, without requirement of haemodialysis (HD).[17] Participants were followed up for 1 year and follow-up began from the day of hospitalisation and ended at death, when the patient abandon the follow-up in the clinic or 31st March, 2011, which ever came first.

Statistical analysis

We expressed parametric data as mean ± standard deviation and non-parametric data as median (interquartile range). The Chi-square test was used to compare the categorical variables. The *t*-test and Mann–Whitney test were used to compare the parametric and non-parametric data, respectively. For the assessment of factors that are related to mortality, we performed unadjusted univariate analysis. Multivariable logistic regression analysis was then used to test significant univariate associations with in-hospital mortality by adjusting for age, gender, baseline estimated glomerular filtration rate (eGFR), number of sessions of HD, length of stay and PCV. Statistical analysis was carried out using the Statistical Package for the Social Sciences software, version 16 (SPSS, Inc., Chicago, IL, USA). $P < 0.05$ (two-tailed) was considered statistically significant.

Ethical approval for this study (Ethical Committee IRB/IEC 00005422) was provided by the Ethical Committee of Obafemi Awolowo University Teaching Hospital Complex, Ile-Ile, Nigeria, on 9th November 2009.

RESULTS

Patients' characteristics

One hundred and sixty-three previously diagnosed CKD patients were admitted for AKI-requiring HD during the study period. The median age of the study participants was 39 (interquartile range: 28–52 years, 125 (76.7%) were males, median baseline eGFR was 37 (32–45) ml/min/1.73 m[2], 112 (68.7%) had ≥2 proteinuria and 158 (96.9%) had anaemia (PCV <33%). Median systolic blood pressure and diastolic blood pressure were 160 (140–190) and 100 (90–120), respectively. The causes of CKD are outlined in Table I. The majority of patients had chronic glomerulonephritis (52.8%) and hypertension (28.2%) as the cause of CKD while aetiology was unknown in only 3.1%.

Causes of AKI in CKD patients

The common causes of acute decompensation of CKD identified among the study participants were heart failure (68, 41.7%),

Table I: Causes of chronic kidney disease (*n*=63)

Causes of CKD	*n* (%)
Glomerulonephritis	86 (52.8)
HT	46 (28.2)
Diabetes mellitus	15 (9.2)
Obstructive uropathy	7 (4.3)
Polycystic kidney disease	2 (1.2)
Chronic tubulointerstitial nephritis	2 (1.2)
Unknown	5 (3.1)

CKD: Chronic kidney disease, HT: Hypertension

malignant hypertension (65, 39.9%), sepsis (58, 35.6%) and nephrotoxins (34, 20.9%), of which majority were herbal remedies and hypovolaemia (16. 9.8%). Based on the cause of acute decompensation, patients were categorised into three groups: Group I (94, 57.7%) had only one acute precipitant, Group II had 2 precipitants (62, 38%) while Group III (7, 4.3%) presented with ≥3 causes of acute decompensation of CKD.

Table II showed the common causes of acute decompensation of CKD. Among patients with heart failure who had mandatory echocardiography, median ejection fraction and fractional shortening were 64.2 (59.2–68.3) % and 32.4 (28.3–36.3) %, respectively. The prevalence of systolic dysfunction was 16.6%, whereas diastolic dysfunction was 62.6%. Forty-five (43.3%) had impaired relaxation, whereas 18 (16.3%) had restrictive pattern. There was no evidence of coronary artery disease. Fifty-eight patients had sepsis on admission. The most common foci of sepsis were urinary tract and lower respiratory tract, whereas the common isolates were *Escherichia coli* (42.9%) and *Staph aureus* (21.4%), respectively.

Of the patients that had nephrotoxic agents, 22 (64.7%) received herbal medications and drug-related AKI was observed in 12 (35.3%) patients; NSAIDS were the most common culprit agents (*n* = 10).

Outcomes

Kidney function recovery and progression to end-stage renal disease

Kidney replacement therapy (KRT) offered was HD, and 107 (65.6%) patients were discharged from the hospital after median HD sessions and length of hospital stay of 3 (2–5)

Table II: Common causes of acute decompensation of chronic kidney disease

Precipitants	*n* (%)
HF	
Systolic dysfunction	27 (16.5)
Diastolic dysfunction	102 (62.6)
Impaired relaxation time (E/A<1)	45 (43.3)
Restrictive pattern (E/A>2)	18 (16.3)
Sepsis	
Escherichja coli	26 (44.8)
Staphylococcus aureus	13 (22.4)
Streptococcus pneumoniae	8 (13.8)
Klebsiella pneumoniae	4 (6.9)
Salmonella Spp.	3 (5.2)
Proteus Spp.	3 (5.2)
Pseudomonas Spp.	1 (1.7)
Malignant HT	
Grade 3	35 (53.9)
Grade 4	30 (46.1)
Nephrotoxins	
Herbal medication	22 (64.7)
Orthodox	12 (35.3)
Hypovolaemia	16 (9.8)

HF: Heart failure, HT: Hypertension, E/A: E wave/A wave

sessions and 2.5 (2.0–3.0) weeks, respectively. Of these 107 patients that survived, 95 (88.8%) recovered their kidney functions (median eGFR: 37 [31–43] ml/min/1.73 m² while 12 (11.2%) remained dependent on HD (median eGFR: 9.5 [6.5–11.5] ml/min/1.73 m². After 1 year of follow-up, 68 (41.7%) patients had stable kidney function without requiring KRT. Of the remaining patients, 61 (37.4%) deaths were recorded, 16 (9.8%) progressed to ESKD, whereas 18 (11.0%) patients were lost to follow-up.

Mortality

In-hospital mortality was recorded in 56 (34.4%) of the study cohort, of which 30 (53.6%) occurred within the first 2 weeks of hospitalisation. Table III shows the results of multivariable logistic regression analysis to assess the factors that were associated with in-hospital mortality. Adjusted odds of in-hospital mortality were significantly increased when CKD patients presented with heart failure (OR, 2.93 [95%, 1.14–7.55]; $P = 0.026$) and malignant hypertension (OR, 3.69 [1.15–11.81]; $P = 0.028$). One-year post-hospitalisation mortality occurred in only five (3.1%) patients, and this precludes further robust analysis of predictors of 1-year all-cause mortality in the present study.

DISCUSSION

Although most nephrologists are familiar with the term ACKF, there is, however, a paucity of epidemiological data on ACKF because ACKF patients have not been extensively studied. In the present study, we investigated the aetiology and outcome of patients who presented with ACKF at a tertiary centre in South-west Nigeria. The common causes of ACKF in this study were heart failure, malignant hypertension, sepsis and nephrotoxic agents. The findings are consistent with the results of a hospital-based study which revealed that decreased kidney perfusion (probably from heart failure and hypovolaemia) and sepsis were the common precipitating factors for ACKF in CKD patients.[18] Similarly, other studies in the literature showed that sepsis was the leading cause of AKI.[4,5,19,20] In contrast to a study by Prakash *et al.*[4] which reported that volume depletion was the precipitating factor for ACKF in 17.7% of their patients, hypovolaemia was diagnosed in 9.8% of cases in the present study. Our result corroborated finding by Prakash *et al.*[4] which showed that NSAIDs are the most common culprits drug precipitating ACKF.

Considering the clinical outcome of patients with ACKF, all our patients required dialysis and we observed dialysis-dependency in 7.4% of patients with ACKF. This is in contrast to the findings of Hsu *et al.*[18] that showed that more than 60% of patients became dialysis dependent within 30 days of discharge. Ali *et al.*[5] in their study showed that 12.5% of cases with ACKF needed permanent KRT. The present study observed that only 11.2% had non-recovery of kidney functions among surviving patients. Fifteen percent of our patients progressed to ESKD after the follow-up period, and this is consistent with previous reports suggesting the high rates of

Response	Variable	OR (95% CI)	P
Table III: Multivariable analysis of factors associated with in-hospital mortality in patients with acute-on-chronic renal failure			
In-hospital mortality	Age	1.017 (0.995-1.040)	0.124
	Sex (male vs. female)	0.915 (0.375-2.233)	0.846
	HF (yes vs. no)	2.928 (1.136-7.546)	0.026
	Malignant HT (yes vs. no)	3.686 (1.151-11.805)	0.028
	Sepsis (yes vs. no)	1.133 (0.415-3.094)	0.808
	HF + malignant HT (yes vs. no)	0.670 (0.155-2.886)	0.591
	Malignant HT + nephrotoxin (yes vs. no)	3.952 (0.272-57.365)	0.314
	Malignant HT + sepsis (yes vs. no)	0.180 (0.015-2.160)	0.176
	HF + malignant HT + nephrotoxin (yes vs. no)	0.101 (0.006-1.576)	0.102
	Baseline eGFR	1.029 (0.982-1.709)	0.226
	Number of HD session	1.149 (0.975-1.354)	0.097
	PCV	0.980 (0.903-1.064)	0.632
	Length of hospital stay	0.860 (0.729-1.015)	0.075

HF: Heart failure, HT: Hypertension, eGFR: Estimated glomerular filtration rate, HD: Haemodialysis, PCV: Packed cell volume, OR: Odds ratio, CI: Confidence interval

progression to ESRD in patients with acute decompensation of CKD.[11,18-22] Available evidence suggests that AKI is a risk factor for CKD, progression of CKD and ESKD.[23] Taken together, our findings suggest that AKI patients with pre-existing CKD have considerably higher risk of ESKD, signifying that occurrence of AKI may accelerate progression of CKD. In fact, the high incidence of recovery of kidney functions observed in this study and low post-hospitalisation mortality after 1-year follow-up further confirmed the report of a previous study which showed that kidney recovery after AKI is associated with a lower risk of death.[24] In the context of the 2012 kidney disease improving global outcome guideline for AKI, these data highlight the need to follow-up and evaluate AKI patients 3 months after an episode of AKI to assess for recovery, CKD development or worsening of pre-existing CKD.[13]

The patients with ACKF had 34.4% in-hospital mortality in the present study, and this is similar to the in-hospital mortality rate of 35% reported by the Madrid acute kidney failure study in patients with pre-existing kidney dysfunction but higher than the figure reported by the Nationwide Inpatient Sample study which showed that 22% of patients with ACKF died in the hospital.[25,26] The representations of the large part of our study cohort by uraemic patients requiring emergency dialysis coupled with late presentation and prolonged waiting time for dialysis may probably be the reason for high in-hospital mortality in this study. These factors have been well documented as the main reasons for high mortality in AKI[27,28] and chronic kidney failure patients[29-31] in the developing countries.

We found that two major risk factors for ACKF – heart failure and malignant hypertension – also were the independent predictors of in-hospital mortality. It was not surprising that heart failure and malignant hypertension were associated with mortality in this study because: First, the most common cause of death among CKD patients is cardiovascular disease, accounting for approximately half of the deaths;[32,33] second, the presence of congestive heart failure is strongly associated with early mortality in CKD patients, with the risk of cardiovascular death being much higher than the risk of progression to ESKD;[34] and third, malignant hypertension is an important cause of myocardial dysfunction and major adverse cardiovascular events. The West Birmingham Malignant Hypertension Registry revealed that the most common causes of death in patients with malignant hypertension were kidney failure, stroke, myocardial infarction and heart failure.[35] Even though dialysis can prevent death from uraemia, the presence of electrolyte derangement and fluid overload may adversely affect the prognosis in ACKF patients requiring emergency HD. Therefore, the control of fluid balance and hypertension is very crucial in the management of these patients because fluid overload result in persistent extravascular fluid volume expansion, hypertension and potential ventricular dysfunction.

The limitations of this study include the fact this is a single-centre study. While practice may vary across centres, comprehensive data collection from multiple centres increases generalisability. This is an observational study with the limiting ability to control for the confounders. The relatively smaller sample size prevented certain analyses, such as the predictors of long-term survival as well as the impact of CKD aetiology, which larger sample size would have allowed. Finally, Cockcroft–Gault equation was used to estimate creatinine clearance, and this may underestimate true creatinine clearance in earlier stages of CKD.

In summary, the common causes of acute decompensation in CKD were heart failure, malignant hypertension, infections and nephrotoxins. Our findings suggest that some of the risk factors for ACKF – such as heart failure and malignant hypertension – are also the independent predictors of in-hospital mortality, with 2-fold and 3-fold increase in adjusted odds of death in participants with heart failure and malignant hypertension, respectively. Given that ACKF is associated with high mortality rates, aggressive management of

these acute precipitants could be life-saving. With appropriate treatment, kidney recovery was achieved in 65% of cases of ACKF suggesting that kidney function could be sustained in these patients after initial salvage dialysis sessions.

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Conflicts of interest
There are no conflicts of interest.

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