

# Incidence and impact of Acute Cardio-Renal Syndrome on Acute Coronary Syndromes

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## ABSTRACT

**Background:** Acute cardiorenal syndrome (CRS-1) is one of the deleterious adverse outcomes in acute coronary syndrome (ACS). It is defined as an acute deterioration in cardiac function that secondarily results in acute kidney injury.

**Objectives:** Our study is focusing on the incidence and impact of acute cardiorenal syndrome on acute coronary syndrome regarding course of the disease, mortality and length of stay in intensive care unit (ICU).

**Methods:** This is a retrospective cohort study of patients of ACS with or without CRS-1 involving 210 consecutive patients admitted to Critical Care department - Cairo University over a year from 1 June 2013 to 31 May 2014

**Results:** 41.9% of study population had CRS-1 and had longer ICU stay and more association with other adverse outcomes especially hyponatremia and mechanical ventilation. All mortality cases (10.5%; 22/210) were CRS-1. CRS-1 predictors were: history of hypertension and dyslipidemia, Killip's class  $\geq$ II, acute myocardial infarction (AMI), higher serum creatinine level on admission,  $K^+$  and random blood sugar and lower  $Na^+$  values. Persistent kidney injury (KI) predictors were higher HR,  $K^+$  level and  $Na^+$ . Contrast induced-acute kidney injury (CI-AKI) and late AKI (after 48hours of admission) were found, also, to be risk factors for persistent KI.

**Conclusion:** CRS-1 is a frequent complication of ACS patients. It has a fatal impact on ACS regarding length of ICU stay, adverse outcomes and mortality. History of hypertension and dyslipidemia, AMI, Killip's class  $\geq$ II, higher serum creatinine level on admission,  $K^+$  and random blood sugar and lower  $Na^+$  values were found to be risk factors for CRS-1. Persistent KI predictors were higher HR,  $K^+$  level and  $Na^+$ . CI-AKI and late AKI (after 48 hours of admission) were found, also, as risk factors for persistent KI.

**Kew word:** acute cardiorenal syndromes, acute kidney injury acute coronary syndromes, STEMI, NSTEMI

## INTRODUCTION

Acute Kidney injury (AKI) has a fatal impact on critically ill patients. Some researches reveal not only its impact on disease course in intensive care unit (ICU), but also its hazards on post-discharge course and even unplanned 90-day hospital readmission <sup>(1)</sup>. Combined heart and kidney dysfunction is common <sup>(2)</sup>. A disorder of one organs often leads to dysfunction or injury to the other. This is the pathophysiological basis for cardiorenal syndrome (CRS) which is more common than many clinicians realize <sup>(3)</sup>

In 2008, the Acute Dialysis Quality Initiative (ADQI) Working Group proposed a consensus definition for cardiorenal syndrome as: *a complex pathophysiological disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or*

*chronic dysfunction in the other organ* <sup>(4)</sup>. There are 5 types of CRS:

- **CRS type 1 (Acute Cardiorenal Syndrome):** it is defined as an acute deterioration in cardiac function or acute cardiac injury that secondarily results in acute kidney injury (AKI).

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- **CRS type 2 (Chronic Cardiorenal Syndrome):** This syndrome is characterized by chronic abnormalities in cardiac function, leading to kidney injury or dysfunction.
- **CRS type 3 (Acute Renocardiac Syndrome):** This syndrome is characterized by acute worsening of kidney function that leads to acute cardiac injury and/or dysfunction.
- **CRS type 4 (Chronic Renocardiac Syndrome):** This CRS subtype refers to cardiac dysfunction and/or disease primarily occurring in response to chronic kidney disease.
- **CRS type 5 (Secondary Cardiorenal Syndrome):** this syndrome is characterized by acute or chronic systemic illnesses that concurrently induces both cardiac and kidney dysfunction.

Many studies have evaluated the development of AKI in acute decompensated heart failure and acute coronary syndrome (ACS) and have used the term 'worsening renal function' to describe changes in kidney function <sup>(5-7)</sup>.

Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) work group has published new definition of AKI <sup>(8)</sup>. With new criteria and classification, KDIGO new definition is harmonizing RIFLE and AKIN definitions, containing those individuals diagnosed as AKI but not by RIFLE or AKIN <sup>(9)</sup>. According to **Li et al** <sup>(9)</sup>, KDIGO criteria identified significantly more CRS-1 episodes than RIFLE or AKIN and AKI missed diagnosed by RIFLE or AKIN criteria was an independent risk factor for in-hospital mortality. It is of critical significance to determine the incidence of and outcomes associated with CRS-1 in ACS for understanding the overall burden of the disease as well as its natural history, morbidity, and mortality.

#### **Aim of the study:**

The objectives of our study are to determine the incidence and impact of acute CRS on ACS regarding course of the disease, mortality and length of stay in ICU. Other objectives are the AKI predictors in ACS and persistent KI predictors.

## **PATIENTS AND METHODS**

This is a retrospective cohort study of patients of ACS. The data were collected from department data base medic phase 4 of critical care department Cairo University hospital from 1 June 2013 to 31 May 2014 including 210 consecutive patients. Process of cases selection as in **Figure-1**.

### **1) Inclusion Criteria**

All patients who were admitted to The Critical Care Department - Cairo University Hospital within the period

from 1 June 2013 to 31 May 2014 and diagnosed on admission as ACS.

### **2) Exclusion Criteria**

1. Length of stay in ICU 48 hours or less.
2. Other causes of chest pain than ACS
3. Cardiac surgery prior admission to ICU.
4. Complicated elective PCI
5. ACS during ICU admission of other illness.
6. Not have complete ICU course in The Critical Care Department - Cairo University Hospital either referred from other units after acute phase to have PCI, or to other units or discharged against medical advice.
7. Renal replacement therapy.
8. Lack of documentation

### **3) Data Collected (Data Sets)**

#### **A. Demographic Data:**

Sex, age, weight, length of ICU stay and smoking status

#### **B. History Of Previous Illness:**

Hypertension, diabetes mellitus, ischemic heart disease, dyslipidemia, chronic kidney disease and cerebro-vascular accident.

#### **C. Hemodynamic Parameters And Ef:**

- a. Blood pressure, heart rate, central venous pressure, these parameters have 3 records: admission, maximum value, minimum value
- b. Left ventricle EF% by echocardiogram
- c. Killip's class.

#### **D. Laboratory:**

- a. Renal profile:
  - Maximum serum BUN level
  - eGFR (MDRD equation):  

$$eGFR = 186 \times (S.Cr.)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$
  - Serum creatinine (S. Cr.) level:  
Admission, Maximum, Minimum level and Last record before discharge
- b. Hemoglobin: lowest reading
- c. Electrolytes:
  - Serum sodium (Na+) level; maximum and minimum,
  - Serum potassium (K+) level; maximum and minimum.
- d. Random blood sugar: Highest reading

#### **E. Mortality and Adverse Outcomes**

- a. All-cause mortality,
- b. Survived-cardiac arrest,
- c. Cardiogenic shock,
- d. Heart failure (pulmonary congestion/ edema),
- e. Tachyarrhythmias
- f. Heart Block/Temporary Pace Maker,
- g. Chest infection,
- h. Mechanical ventilation

- i. Cerebrovascular accident,
- j. Major bleeding,
- k. Hyperglycemia,
- l. Na<sup>+</sup> disorders: hyponatremia, hypernatremia,
- m. K<sup>+</sup> disorders: hypokalemia, Hyperkalemia,
- n. Anemia.

The cohort population was categorized by existence or absence of AKI diagnosed by KDIGO,2012 (8)to determine risk factors and impact of AKI on ACS.

**Statistical Analysis:**

Statistical analysis of our study was conducted, by IBM SPSS statistics® version.24 and some add-ins of Microsoft excel® 2013 (XLSTAT® version 18.07.39066 and Real-Statistics Analysis Tool®). P value <0.05 was considered statistically significant.

- Categorical values were expressed as number and percentage and tested for association by chi-square test (χ<sup>2</sup>). While continuous values were expressed as mean ± standard deviation (SD) and tested for association between two groups by Student’s test (t test) or analysis of variance (ANOVA) if more than two groups.
- Multivariate analysis (binary logistic regression) was carried out in enter method (standard regression analysis). The results were expressed as odds ratio (OR) with its 95% confidence interval (95%CI) upper and lower limit.

**RESULTS**

The contribution of each type of ACS in total cohort is shown in (Table-1). The cohort population is divided into two groups:

**AKI Group:** includes 88 pts (41.9%) with AKI

**Non-AKI Group:** includes 122 (58.1%) non-AKI patients

**Table 1 Type of ACS and PCI in total cohort**

Variable	n (%)
STEMI	109 (51.91%)
NSTEMI	28 (13.33%)
Unstable angina	73 (34.76%)
PCI	159 (75.71%)

*NSTEMI= non-ST elevation myocardial infarction, PCI= percutaneous coronary intervention, STEMI= ST elevation myocardial infarction*

**Basic characteristics**

The basic characteristics of study population are shown in Table-2. The mean age in AKI group was 61.33±11.93, and in non-AKI group was 56.77±10.18 with high statistical significance (p=0.003). ICU-LOS was 7.60±5.56 in AKI group and 5.49±2.16 in non-AKI group (p=0.001) with high statistical significance. There was no statistical significance (p>0.05) between the two groups regarding: smoking, IHD and CKD. But there was a statistical significance in dyslipidemia (p=0.005),

hypertension (p= 0.010), diabetes mellitus (p=0.026) and cerebrovascular accident (p=0.012).

**Type of ACS and PCI regarding AKI**

Unstable angina was less likely to develop AKI with statistical significance of p=0.012. No statistical significance regarding PCI or multivessel disease was found between the two groups regarding AKI (p= 0.237, 0.093 respectively). (Figure-2, Table-2).

**Clinical data regarding AKI**

There was no statistical significance on admission between the two groups regarding mean arterial pressure (MAP) (p= 0.416), heart rate (HR) (p=0.554) & central venous pressure (CVP) (p=0.186). But it was of high significance in max. values of MAP (p=0.038), HR (p=0.004) and CVP (p= 0.002) as they were higher in AKI group. The minimum value of MAP was also of significance as it was lower in AKI Group than non-AKI Group (p=0.001). Killip’s class ≥ II was found significant between AKI group (n=43, 48.9%) & non-AKI group (n=20, 16.4%), p= 0.001. Ejection fraction (EF) was not significant between the two groups (p= 0.105).

**Laboratory data regarding AKI**

AKI Group tended to have lower value in hemoglobin level 11.50 ±2.44 and minimum value of Na<sup>+</sup> 129.78 ±7.59 indicating more risk of anemia and hyponatremia (p= 0.001), tended to have higher value in random blood sugar 235.99 ±140.91 and maximum value of K<sup>+</sup> 4.54 ±0.69 indicating that hyperglycemia and hyperkalemia were more frequent in AKI group. There was no significance between both groups regarding maximum value of Na<sup>+</sup> (p= 0.830) & minimum value of K<sup>+</sup> (p= 0.529).

**Mortality and adverse outcomes regarding AKI**

Total mortality was 22 pts who were all had AKI. 25% of AKI group died with high statistical significance in comparison to non-AKI group 0% (p=0.001). Most of included adverse outcomes had high significance between AKI group & non-AKI group; cardiogenic shock (33%, 9% respectively; p=0.001), acute heart failure (25%,4.9% respectively; p=0.001), Tachyarrhythmias (20.5%, 5.7% respectively; p= 0.001), chest infection (25%, 4.9% respectively; p= 0.001), mechanical ventilation (29.5%, 3.3% respecti-vely; p=0.001), hyperkalemia (15.9%, 4.1%; p=0.003) hyponatremia (69.3%, 52.5%; p=0.014), hyperglycemia (72.7%, 54.1%; p=0.006), survived-cardiac arrest (13.6%, 4.9; p=0.026) & anemia (63.6%, 46.7%; p= 0.015). (Table-3, Figure-3).

**AKI risk factors**

A logistic regression was performed to ascertain the effects of variables listed in Table 4 on the likelihood that participants would have AKI. The logistic regression model was statistically significant, p<.0001. The model correctly classified 77.6% of cases.

This regression test revealed the independent AKI risk factors in total cohort which are:

1. History of hypertension,
2. History of dyslipidemia,
3. Acute myocardial infarction,
4. Killip's classification  $\geq$  II
5. Level of S. Cr. on admission,
6. Low Na<sup>+</sup> level,
7. High K<sup>+</sup> level,
8. High random blood sugar level

Killip's class  $\geq$  II and AMI were highly associated to each other as 54% of AMI were classified as Killip's class  $\geq$  II in comparison to 23% of unstable angina ( $\chi^2= 18.31$   $p= 0.001$ ). Therefore, one of both variables was inserted into the model of regression alternatively.

**Table 4: AKI risk factors**

	OR	95% C.I.		P value
		Lower	Upper	
Age	1.019	0.982	1.057	0.316
Hypertension	2.826	1.195	6.681	<b>0.018*</b>
Diabetes mellitus	0.707	0.291	1.714	0.442
Dyslipidemia	5.021	1.219	20.680	<b>0.025*</b>
HR max	1.001	0.977	1.025	0.953
CVP max	0.978	0.908	1.053	0.557
S. Cr. admission	25.684	4.301	153.383	<b>0.001*</b>
eGFR admission	1.017	0.993	1.041	0.170
Hb	0.949	0.790	1.139	0.574
Na min	0.935	0.877	0.997	<b>0.039*</b>
K max	2.902	1.410	5.976	<b>0.004*</b>
RBS	1.006	1.001	1.010	<b>0.013*</b>
Alternatively inserted into the model				
Killip's class $\geq$ II	2.182	1.022	4.661	<b>0.044*</b>
AMI	2.562	1.062	6.182	<b>0.036*</b>

AMI= acute myocardial infarction, C.I. = confidence interval, CVP= central venous pressure, CVS= cerebrovascular stroke, eGFR= estimated glomerular filtration rate, HR= heart rate, MAP= mean arterial blood pressure, OR= odds ratio, RBS= random blood sugar, S. Cr. = serum creatinine.

### AKI recovery predictors

A logistic regression was performed to ascertain the effects of variables listed in **Table 5** on the likelihood that participants had AKI recovered. The logistic regression model was statistically significant,  $p < 0.001$ . The model correctly classified 80.7% of cases. CI-AKI and late AKI (after 48 hours of admission) were considered as risk factors for persistent KI. The lower HR, serum K<sup>+</sup> level and serum Na<sup>+</sup> level (within normal values), the more chance for favorable outcome -i.e. transient KI- was found.

**N.B.,** We tried to find out cutoff points for AKI risk factors and AKI recovery prediction but the AUC of their ROC curves were small ( $\leq 0.6$ ) and flattened.

### Serum creatinine level and mortality

S.Cr. admission and max values showed high statistical significance between mortality & survival groups (1.73 $\pm$ 0.67 vs 1.05 $\pm$ 0.49 & 4.35 $\pm$  2.52 vs 1.29  $\pm$ 0.73; respectively) (**Table 6**).

**Table-6. Renal profile data regarding total mortality**

	Mortality group mean $\pm$ SD	Survival group mean $\pm$ SD	P value
BUN max (mg/dl)	63.64 $\pm$ 35.69	19.53 $\pm$ 13.18	0.001*
S. Cr. Admission (mg/dl)	1.73 $\pm$ 0.67	1.15 $\pm$ 0.5	0.001*
S. Cr. max (mg/dl)	4.35 $\pm$ 2.52	1.29 $\pm$ 0.73	0.001*

BUN= blood urea nitrogen, eGFR= estimated glomerular filtration rate, S. Cr. = serum creatinine

In addition, there was a positive correlation of significance between mortality and max S. Cr. level ( $r = 0.66$ ,  $p < 0.001$ ) and S. Cr. level on admission ( $r = -0.32$ ,  $p < 0.001$ ) (**Figure-4**).

The AUC of admission S. Cr. was 0.779 (95%CI 0.645-0.913) and the best cutoff point was 1.3 mg/dl (sensitivity 81.8%, specificity 71.3% and accuracy 72.4%)

The AUC of max S. Cr. level was 0.961 (95%CI 0.927-0.996) and the best cutoff point was 1.8 mg/dl (sensitivity 90.9%, specificity 83.6% and accuracy 85.7%) (**Figure-5**).

## DISCUSSION

### AKI incidence, predictors & impact:

41.9% of all population in our cohort study had developed AKI and considered had CRS-1. This is higher than the proportion in the other studies which varies from 12.1%<sup>(10)</sup> to 36.6%<sup>(11)</sup>. This may be due to high prevalence of some AKI risk factors in Egypt as hypertension, dyslipidemia<sup>(12)</sup>, and diabetes mellitus<sup>(13)</sup>.

Our study showed 61.43% of patients had history of hypertension which is close to the result by Libório et al<sup>(14)</sup>, Neves et al<sup>(15)</sup>, Rodrigues et al<sup>(11)</sup> and Sun et al<sup>(16)</sup> (62% -69.7%).

History of diabetes mellitus in our study (43.33%) was higher than others (16.4% - 34.2%). This may be a projection of the fact that Egypt is ranked 8<sup>th</sup> country over world in number of people with diabetes (with age 20-79 years)<sup>(13)</sup>

84.8% of our study population were dyslipidemic or had a history of dyslipidemia which is higher than Rodrigues et al<sup>(11)</sup> (22.5%) and Neves et al<sup>(15)</sup> (58.5%).

### PCI and Type of ACS

In our study, unstable angina group was found less likely to develop AKI (25% of AKI group vs. 41.8% of non-AKI group) which matches the results revealed by



Neves *et al* <sup>(15)</sup> (3.2% of AKI group vs. 6.5% of non-AKI group).

Due to the heterogeneity of population among studies we cannot compare studies regarding ACS type. The type of ACS varied among studies from ST elevation myocardial infarction (STEMI) <sup>(14)</sup>, acute myocardial infarction (STEMI/ NSTEMI) <sup>(10, 11, 16)</sup>, NSTEMI-ACS with non-invasive management (NSTEMI/unstable angina) <sup>(17)</sup>.

PCI was less frequently performed in AKI group in studies mentioned previously with statistical significance, unlike our study which has no statistical significance.

### Clinical data

In our study, we recorded and considered admission, maximum and minimum reading regarding: MAP, HR and CVP. Admission readings of MAP, HR, or CVP showed no statistical significance. The significant readings were minimum of MAP and the max reading of MAP, HR and CVP during the ICU stay. While other studies considered admission reading only of HR, systolic and/or diastolic blood pressure. None of them considered CVP as a variable in their study

However; Neves *et al* <sup>(15)</sup>, Rodrigues *et al* <sup>(11)</sup> and Sun *et al* <sup>(16)</sup> revealed statistical significance regarding admission reading of systolic and/or diastolic blood pressure as AKI group tended to show lower readings than non-AKI group. HR on admission was found to be of statistical significance by Liao *et al* <sup>(10)</sup>, Neves *et al* <sup>(15)</sup> and Rodrigues *et al* <sup>(11)</sup>; as AKI group tended to higher HR than non-AKI.

Regarding Killip's classification, our study found high statistical significance between AKI (59.1% had Killip's class  $\geq$  II) and non-AKI group (32%);  $p=0.001$ . This matches the findings by Liao *et al* <sup>(10)</sup>, Neves *et al* <sup>(15)</sup>, Rodrigues *et al* <sup>(11)</sup> and Sun *et al* <sup>(16)</sup>.

#### AKI predictors

AKI predictors in our study were found to be: - history of hypertension, - dyslipidemia, AMI (STEMI/NSTEMI), Killip's class  $\geq$  II, S. Cr. level on admission, low  $\text{Na}^+$  level, high  $\text{K}^+$  and random blood sugar level. (Table 6)

Neves *et al* <sup>(15)</sup> stated that the incidence of AKI was associated with older age, history of hypertension, renal failure and stroke/ transient ischemic attack, Killip class  $> I$  on admission and LVEF  $<50\%$ .

Liao *et al* <sup>(10)</sup> reported that eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$ , baseline (admission) S. Cr. level and Killip class  $\geq$  III as absolute risk factors for AKI.

Moreover, in another study, Sun *et al* (16) found decreased baseline eGFR, increased fasting plasma glucose, use of diuretics and Killip grade IV were independent risk factors of AKI, while increased diastolic blood pressure on admission was a protective factor for patients in conservative treatment group (no PCI).

Those studies didn't report any data about electrolytes or CVP state.

### AKI and mortality predictors in ACS

AKI showed, in univariate analysis, a strong statistical significance regarding mortality ( $p < 0.001$ ); as all mortality were of AKI diagnosis. AKI patients were found to be 25% less likely to live than non-AKI (RR= 0.75, decreased risk 25%). Furthermore, we found a positive correlation between mortality and maximum S. Cr. level ( $r -0.66$ ,  $p < 0.001$ ) and S. Cr. level on admission ( $r -0.32$ ,  $p < 0.001$ ). This matches results of many studies.

Libório *et al* (14) reported that AKI and its stages individually were found as an absolute risk factors for mortality (any AKI OR 3.692, 95%CI 1.865–7.963; stage 1 OR 12.731, 95%CI 8.812–32.618; stage 2 OR 58.327, 95%CI 11.477–296.417 and stage 3 OR 5.454, 95%CI 1.875–15.867). Mortality risk according AKI stage was adjusted for GRACE risk and acute physiology and chronic health evaluation (APACHE)-II scores, both censored for renal function variables.

Correspondingly, Rodrigues *et al* (11) found that AKI diagnosed by KDIGO (2012) criteria was associated with an increased adjusted hazard ratio for 30-day death (3.99, 95%CI 2.59–6.15). the model was adjusted for age ( $>65$  years), gender (male), admission eGFR ( $<60\text{mL}/\text{min}/1.73\text{m}^2$ ), Killip class ( $> I$  at admission), systolic blood pressure ( $<100\text{mmHg}$  on admission), heart rate ( $>100\text{beats}/\text{min}$  on admission), value of creatine phosphokinase (CPK-MB), admission blood sugar, diabetes history, extracardiac vascular disease history, clopidogrel use during hospitalization, use of diuretics, coronary angiography during hospitalization, reperfusion therapy with primary PCI for STEMI, any type of revascularization with either PCI or CABG performed during hospitalization, reinfarction and severe systolic left ventricular dysfunction (LVD).

In this context, Liao *et al* (10) found that diminished eGFR ( $<60\text{ml}/\text{min}/1.73\text{m}^2$ ) and AKI at admission had the worst outcome with a mortality (OR 12.62, 95%CI 5.54-28.74). The multivariate analysis was adjusted to age, sex, history of hypertension, diabetes mellitus, stroke, prior MI, smoking status, systolic blood pressure, heart rate, anterior MI (or not), heart failure on admission, revascularization status and complications.

One more study by Neves *et al* (15) showed that AKI was also an independent predictor of in-hospital mortality (OR 4.72, 95% CI 2.94-7.56) adjusted to female gender, age, STEMI, valve disease, peripheral artery disease, Killip class on presentation (II, III, IV), multivessel disease and LVEF depression (mild, moderate, severe).

Additionally, Sun *et al* (16) reported that AKI presence and AKI staging in KDIGO were independent risk factors for mortality during hospitalization. Adjusted variables for multivariate logistic regression analysis were age, gender, diastolic blood pressure at admission, history of stroke, acute infection, serum albumin levels, baseline eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$ , hyperuricemia, fasting glucose, LVEF level and diuretics.

## CONCLUSION

CRS-1 is a frequent complication of ACS patients. Acute cardiorenal syndrome has a great impact on ACS regarding length of ICU stay, adverse outcomes and mortality. History of hypertension and dyslipidemia, AMI (STEMI/NSTEMI), Killip's class  $\geq$  II, S. Cr. level on admission, Na<sup>+</sup> minimum value, K<sup>+</sup> maximum value and random blood sugar highest value were found to be risk factors for CRS-1.

Persistent KI predictors were higher HR, K<sup>+</sup> level and Na<sup>+</sup>. CI-AKI and late AKI (after 48hours of admission) were found, also, as risk factors for persistent KI.

## Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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