Association of acute kidney injury defined with the AKIN criteria and poor outcome in acute respiratory distress syndrome patients

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Background Few studies have reported the deleterious association between acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI). We aimed to evaluate the association of AKI and poor outcome in ARDS patients and whether this association is related to fluid overload or not.

Patients and methods Sixty-four patients diagnosed with ARDS and had been mechanically ventilated were enrolled. AKI was diagnosed using the Acute Kidney Injury Network criteria. Patients were stratified into two groups according to the degree of renal impairment. All data were statistically analyzed.

Results The mean age of the studied patients was 47.23 ±10.12 years; 33 (51.6%) were men. In group 2, the follow-up Lung Injury Severity Score and length of hospital stay were significantly higher compared with group 1: 3.33±0.74 points and 19.11±6.37 days versus 2.84±0.57 points and 12.38 ±4.21 days (P=0.004 and $<$0.001, respectively). Also, they had higher need to use vasoactive (VA) agents, 21 (55.3%) versus 6 (23.1%) patients, and spent more days on mechanical ventilation, 14.18±4.59 versus 8.51±3.77 (P=0.019 and $<$0.001, respectively). In-patient mortality was higher in group 2 compared with group 1: 18 (66.7%) versus 6 (23.1%) (P=0.019). In-patient mortality was significantly correlated with the need to use VA agents and higher cumulative fluid balance (R=0.394 and 0.24, P=0.001 and 0.05, respectively). The need to use VA agents was the only independent predictor of mortality (odds ratio=4.18, P=0.022).

Conclusion AKI as defined on the basis of the Acute Kidney Injury Network criteria is associated with poor outcome in ARDS patients.

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Introduction

Acute respiratory distress syndrome (ARDS) is a leading cause of mortality and morbidity in critically ill patients [1]. The main pathological changes in ARDS patients are increased capillary permeability that lead to accumulation of proteinaceous fluid in the pulmonary interstitum [2].

Many studies have reported the possible deleterious interactions between lung and kidney dysfunctions [3]. Experimental studies suggest that acute kidney injury (AKI) with subsequent activation of proinflammatory and proapoptotic pathways because of renal ischemia/reperfusion may be associated with an increased risk of acute lung injury. [3–7]. Moreover, several lines of evidence point to the adverse effects of ARDS and mechanical ventilation on renal function through three main mechanisms. First, positive-pressure ventilation may reduce cardiac output and increase central venous pressure, with a subsequent decrease of renal blood flow, free water clearance, and glomerular filtration rate [8]. In addition, hypoxia and hypercarbia may affect renal vascular resistance, renal perfusion, and diuresis [9]. Finally, the release of inflammatory cytokines following ARDS may lead to further systemic inflammation [10,11]. In 2005, a new classification of AKI was proposed by the Acute Kidney Injury Network (AKIN) working group composed of nephrologists, critical care physicians, and other physicians specialized in AKI. The AKIN classification was published in March 2007 [12].

The aim of this study is to evaluate the influence of AKI defined by the AKIN criteria on the outcome of ARDS patients in an ICU and to determine whether this influence is related to fluid overload or not.

Patients and methods

This study was a prospective observational study carried out on 64 patients admitted to the Critical Care Department of Cairo University and diagnosed with ARDS from March to December 2014. The study has been approved by our local ethical committee. According to the Berlin Criteria, ARDS was defined by timing (within 1 week of clinical insult or onset of respiratory symptoms); radiographic changes (bilateral opacities not fully explained by effusions, consolidation,

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or atelectasis); origin of edema (not fully explained by cardiac failure or fluid overload); and severity on the basis of the PaO_2/FiO_2 ratio on 5 cm of continuous positive airway pressure [13]. All patients underwent a full clinical examination and laboratory investigation including assessments of blood gases and lactate levels. Acute Physiology and Chronic Health Evaluation II (APACHE II) and Lung Injury Severity (LIS) Scores were calculated upon admission. The LIS score was reassessed 1 week after admission for all patients.

All patients received mechanical ventilation through a commercially available ventilator (Puritan-Bennett=840) in the volume-controlled mode. Tidal volume was set to be 6–8 ml/kg. Predicted body weight in kg was calculated from the following formula: 2.3[height (inches)-60] +45.5 for women or 50 for men. The respiratory rate was set up to 35 breaths/min to deliver the expected minute ventilation requirement (generally, 7–9 l/min). Positive end-expiratory pressure and FiO_2 were set to maintain an arterial oxygen saturation of 88–95%. Ventilator adjustments were made to maintain the plateau pressure (measured during an inspiratory hold of 0.5 s) less than 30 cmH_2O and to maintain accepted blood gas parameters with permissive hypercapnea. If plateau pressures remained high after following the above protocol, tidal volume was further reduced to as low as 4 ml/kg by 1 ml/kg stepwise increments. All patients were lightly sedated to minimize ventilator–patient dyssynchrony.

During ICU stay, the degree of renal impairment was assessed using the AKIN criteria and categorized into grades 1, 2, and 3 [14]. Patients were stratified according to the degree of renal impairment into two groups:

Group 1 included patients with normal or near normal kidney function (AKIN 0,1).

Group 2 included patients with significantly impaired kidney function (AKIN 2,3).

Both groups were compared in terms of their outcomes. Patients who died within 24 h of admission, had a suggestive history or clinical evidence of congestive heart failure, or were younger than 18 years of age were excluded.

Statistical methods

Data were statistically described as mean±SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was performed using the Student *t*-test for independent samples. To compare categorical data, the χ^2-test was performed. The exact test was used when the expected frequency was less than 5. The correlation between various variables was assessed using the Spearman rank correlation equation. *P* values less than 0.05 were considered statistically significant. All statistical calculations were carried out using the computer program statistical package for the social science (SPSS Inc., Chicago, Illinois, USA), release 15 for Microsoft Windows (2006).

Results

The mean age of the studied patients was 47.23±10.12 years; 33 (51.6%) were men. The mean PaO_2/FiO_2, and LIS score on admission were 169.95±31and 3.06± 0.54, respectively. Apart from cumulative fluid balance, which was higher in group 2 compared with group 1 (2.8±3.1 vs. −1.2±2.88 l, *P*=0.02), patients in both groups had comparable general characteristic data (Table 1). In group 2 patients, 15 (23.3%) and 12 (18.7%) patients had AKIN grades 2 and 3, respectively. Patients in group 2 had worse outcome parameters compared with those in group 1 as the follow-up LIS and length of hospital stay were significantly higher in group 2 compared with group 1 patients: 3.3±0.7 points and 19.1±6.3 days versus 2.84±0.5 points and 12.3±4.1 days (*P*=0.004 and 0.001, respectively). Also, they had a higher need to use vasoactive (VA) agents, 21 (77.7%) patients versus 17 (45.9%) patients, and spent more days on mechanical ventilation, 14.1±4.5 versus 8.5±3.7 (*P*=0.019 and <0.001, respectively) (Table 2).

In the studied patients, in-patient mortality occurred in 30 (46.9%) patients, and it was significantly higher in the patients in group 2: 18 (66.7%) versus 12 (32.4%) (*P*=0.019). (Table 3) shows a comparison of surviving

Table 1 General characteristics of the studied patients

	All patients	Group 1 (*n*=37)	Group 2 (*n*=27)	*P* value
Age	47.2±10.2	47.2±9.4	47.4±11.3	0.99
Sex (female)	33 (51)	19 (51.3)	14 (51.8)	0.58
DM	31 (48)	17 (45.9)	15 (55.5)	0.30
HTN	32 (50)	16 (43.2)	14 (51.8)	0.41
Smoking	35 (54)	21 (56.7)	14 (51.8)	0.44
PaO_2/FiO_2	169.9±30.7	169.4±32.3	170.6±29.9	0.87
APACHE II	26.4±4.04	26.2±4.1	26.6 (4)	0.73
LISS 1	3.06±0.54	3.09±0.5	3.01±0.6	0.58
Cumulative fluid balance	0.52±3.59	−1.2±2.88	2.8±3.1	0.02*

Data are presented as mean±SD or *n* (%). APACHE II, Acute Physiology and Chronic Health Evaluation II; DM, diabetes mellitus; FiO_2, fraction of inspired oxygen; HTN, hypertension; LISS, Lung Injury Severity Score; PaO_2, arterial partial oxygen pressure, **P* value < 0.05.

Table 2 Comparison between two studied groups in different outcome parameters

	Group 1 (*n*=37)	Group 2 (*n*=27)	*P* value
LISS 2	2.84±0.5	3.3±0.7	0.004*
Need to vasoactive agents	17 (45.9)	19.1±6.3	0.019*
MV days	8.5±3.7	14.1±4.5	<0.001*
LOS	12.3±4.2	19.1±6.3	<0.001*
Mortality	12 (32.4)	18 (66.6)	0.019*

Data are presented as mean±SD or *n* (%). LISS, Lung Injury Severity Score; LOS, length of hospital stay; MV, mechanical ventilation, *P value < 0.05.

Table 3 Comparison between survivors and nonsurvivors in their general characteristics

	Survivors (*n*=34)	Nonsurvivors (*n*=30)	*P* value
Sex (male)	20 (58.2)	13 (43.3)	0.51
Age	49±10.1	45±9.6	0.96
Diabetes	14 (41.1)	18 (60)	0.50
HTN	12 (35.2)	19 (63.3)	0.50
Smokers	19 (55.8)	16 (53.3)	0.31
APACHE II	26.7±3.8	26.1±4.3	0.66
PaO_2/FiO_2	172.9±29.1	166.6±33.1	0.21
LISS 1	3.03±0.55	3.09±0.54	0.93
Cumulative fluid balance	–0.14±3.5	1.27±3.5	0.08
LISS 2	3.04 (0.66)	3.05±0.71	0.05
Need to vasoactive agents	14 (41.7)	24 (80)	0.02*
MV days	9.9±4.8	12.03±5.02	0.05
LOS	13.9±5.6	16.6±6.5	0.05

Data are presented as mean±SD or *n* (%). APACHE II, Acute Physiology and Chronic Health Evaluation II; DM, diabetes mellitus; FiO_2, fraction of inspired oxygen; HTN, hypertension; LISS, Lung Injury Severity Score; LOS, length of hospital stay; MV, mechanical ventilation; PaO_2, arterial partial oxygen pressure, *P value < 0.05.

and nonsurviving patients. Although it was not significant, we noted that the cumulative fluid balance was more positive in nonsurviving patients as opposed to a more negative fluid balance in those who survived. Spearman's correlation showed that in-patient mortality was significantly correlated with the need to use VA agents and cumulative fluid balance, but not admission/follow-up LIS or length of hospital stay (Table 4).

Univariate regression analysis showed that positive cumulative fluid balance is an independent predictor of higher follow-up LIS and length of hospital stay, but not for the need to use VA agents or mortality (Table 5).

In multivariate analysis, AKIN grade was not an independent predictor of in-patient mortality (odds ratio=0.797 and P=0.549). The need to use VA agents was the only independent predictor of mortality in our cohort (odds ratio=4.18 and P=0.022).

Table 4 Correlation between in-patient mortality and other variables

	In-patient mortality	
	R	*P* value
Admission LISS	0.05	0.69
Follow-up LISS	0.008	0.95
Need to vasoactive agents	0.394	0.001*
LOS	0.213	0.09
Cumulative fluid balance	0.24	0.05*

LISS, Lung Injury Severity Score; LOS, length of hospital stay, *P value < 0.05.

Table 5 Cumulative fluid balance as a predictor of outcome

	Cumulative fluid balance		
		95% confidence interval	
	P value	Lower	Upper
Follow-up LISS	<0.001*	0.108	0.174
Need to vasoactive agents	0.322	0.932	1.239
LOS	<0.001*	0.884	1.511
In-patient mortality	0.118	0.972	1.291

LISS, Lung Injury Severity Score; LOS, length of hospital stay, *P value < 0.05.

Discussion

There is growing evidence pointing to deleterious interactions between lung dysfunction and renal impairment in critically ill patients [3]. This study found a higher incidence of AKI in ARDS patients and its contribution toward poor outcome in these patients as our results indicate that 42% of ARDS patients developed significant renal impairment, that is, AKIN grades 2 and 3 during their hospital stay. Also, development of significant renal impairment was associated with increased mortality, in addition to other poor outcome parameters such as length of hospital stay, need to use VA agents, and number of days on mechanical ventilation. Multivariate regression analysis showed that AKI was not an independent predictor of mortality in our cohort.

The reciprocal risk of AKI and lung dysfunction in critically ill patients was similarly reported by Clemens *et al.* [15]. Unlike our study, they also reported that both AKI and ARDS are independent risks for subsequent death. This can probably be attributed to the different type of patients in their study; they studied burn patients.

The ARDSNet investigators [10] and Darmon *et al.* [16] reported an increased risk of development

of AKI in ARDS patients. Similarly, many investigators reported that biotrauma induced by mechanical ventilation with the subsequent release of inflammatory cytokines not only affects the lung but also leads to further systemic inflammation with subsequent kidney and other organ dysfunction [10,11,17]. However, these studies did not clearly evaluate the influence of development of AKI on the patients' outcome.

A recent meta-analysis suggested that both ARDS and mechanical ventilation were associated with a three-fold increase in the risk of AKI [18]. The studies included in this analysis were focused on specific types of patients such as trauma [19], postlung transplant [20], malignant [21], and advanced liver cell failure patients [22]. Thus, the general applicability of the findings is unclear.

In our results, positive cumulative fluid balance was an independent predictor of poor outcome parameters such as follow-up LIS score and length of hospital stay, but not in-patient mortality. This observation may postulate the possible mechanism of the association between AKI and poor outcome in our cohort. We believe that this observation could have therapeutic implications in the management of AKI in ARDS patients. In line with these results, a randomized, multicenter study [2] evaluated a strategy of fluid restriction in ARDS patients. Unlike our study, they excluded patients with renal failure. However, their results similarly showed that a conservative strategy significantly improved oxygenation in patients and decreased the number of days with mechanical ventilation, but did not influence mortality at 60 days. However, Prowle *et al.* [23] limiting the beneficial effect of fluid restriction in ARDS patients to whom the pulmonary edema is more pronounced but not in less severe form of lung injury. Moreover, they reported that fluid restriction may lead to tissue hypoperfusion with and renal injury. Seethala *et al.* [24] reported that higher volume of early fluid administration was associated with the development of ARDS, meaning that higher cumulative fluid balance is not only a predictor of outcome in ARDS patients but could also be a causative factor in septic patients.

Our results also showed that the need to use VA agents was the only independent predictor of mortality in our cohort. This confirms previous study results of Boyle *et al.* [25], who reported that the use of vasopressors was one of the predictors of mortality in their cohort.

Conclusion

AKI is associated with poor outcome in ARDS patients. Higher cumulative balance with subsequent volume overload could possibly be a poor prognostic factor.

In addition to a small sample size, this study had many limitations. As this was an observational study, we did not evaluate the influence of different AKI therapeutic modalities on the outcome in ARDS patients. Also, the value of early renal replacement therapy in these patients was not assessed.

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Conflicts of interest

There are no conflicts of interest.

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