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A Clinical Risk Scoring System of Acute Respiratory Distress Syndrome-Induced Acute Kidney Injury

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Statistical Analysis C
Data Interpretation D
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Background: This study investigated the risk factors affecting development and prognosis of acute kidney injury (AKI) in patients with acute respiratory distress syndrome (ARDS).

Material/Methods: A total of 501 ARDS cases were retrospectively enrolled (296 males and 205 females) admitted to the First People's Hospital of Lianyungang from Aug 2015 to Aug 2017. Multivariable logistic modeling was conducted to select significant variables, and the assigned integer score was proportional to the adjusted odds ratio (OR). Then, the sum of weighted variables was utilized to estimate the score in patients.

Results: Patients with ARDS who had unconsciousness (OR=2.778, 95% CI: 1.396–5.528), hypertension (OR=1.771, 95% CI: 1.089–2.881), ARDS (moderate–severe) (OR=1.630, 95% CI: 1.027–2.588), AST (OR=2.093, 95% CI: 1.251–3.499), and D-dimer (OR=2.372, 95% CI: 1.316–4.275) were more likely to also have AKI. The score was allocated in proportion to the corresponding adjusted OR, hypertension, ARDS (moderate–severe), aspartate aminotransferase (AST), D-dimer (2 points each), and unconsciousness (3 points). The incidences of AKI in group A (score 0–2, n=9), group B (score 3–4, n=16), group C (score 5–6, n=33), and group D (score ≥7, n=72) were 10.98%, 16.00%, 31.13%, and 49.66%, respectively ($P<0.001$). Higher scores were associated with higher prevalence of AKI, and the trend was statistically significant ($P<0.001$).

Conclusions: This scoring system may provide a risk-integrative evaluation for AKI in patients with ARDS.

MeSH Keywords: **Acute Kidney Injury • Adult • Respiratory Distress Syndrome • Risk Factors**

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Background

Acute kidney injury (AKI) is a serious complication with high mortality and morbidity rates, and is characterized by sudden loss of kidney function [1–3]. Studies have demonstrated the application of specific therapies to alleviate AKI or accelerate rehabilitation [4–9], but the prognosis of patients with AKI is still poor due to various and complicated causes [10,11]. Therefore, it is necessary to establish a risk factor scoring system for AKI to improve the prognosis of patients with AKI.

Acute respiratory distress syndrome (ARDS), a severe form of acute respiratory failure, is characterized by disruption of the endothelial barrier of capillaries lining the alveoli with increased permeability, leading to an intense inflammatory insult, alveolar epithelial injury, and influx of protein-rich edema fluid into the alveoli, causing impaired gas exchange, decreased lung compliance, and increased work of breathing [12–14]. Previous studies have reported that the incidence of AKI is up to 35% among ARDS patients in the intensive care unit (ICU), revealing the relationship between patients with acute respiratory failure such as ARDS and the growing mortality rates in patients who developed AKI [15–17]. Multicenter studies show that the ARDS mortality rate in China is 68.5% in adult ICUs, and when AKI was complicated by acute lung injury (ALI), the mortality rate is as high as 80% [18]. To the best of our knowledge, however, the relationship of different levels of ARDS and AKI in patients with milder diseases have been rarely reported.

In this study we investigated the risk factors associated with development and prognosis of AKI in hospitalized ARDS patients, and established a scoring system based on these risks.

Material and Methods

Patients

A total of 501 patients with ARDS were (296 males and 205 females) admitted to the First People's Hospital of Lianyungang from Aug 2015 to Aug 2017. This study was approved by the Institutional Review Board of the First People's Hospital of Lianyungang (approval number LW20190125001).

Inclusion and exclusion criteria

Patients who met the following criteria were included: (1) met Berlin diagnostic criteria for ARDS, (2) at least 18 years old, and (3) admission to the respiratory intensive care unit or general ward.

Excluded criteria were: (1) tumors, (2) chronic kidney disease (CKD) stage 5 or undergoing renal replacement therapy

(peritoneal dialysis or hemodialysis) before hospitalization, (3) incomplete clinical data and unclear basal serum creatinine, and (4) admission time ≤ 48 h.

Diagnosis criteria

The following Berlin diagnostic criteria for ARDS [13] were used: (1) the new or pejorative respiratory symptoms with clear clinical symptoms or injuries within 1 week, (2) infiltrates in both lungs cannot be completely exuded through the lungs, lung collapse, or pulmonary nodules, (3) respiratory failure cannot be fully explained via heart failure or excessive volume load, and (4) oxygenation index classified as (a) mild: $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$, and $\text{PEEP or CAPA} \geq 5 \text{ cmH}_2\text{O}$; (b) moderate: $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$, and $\text{PEEP} \geq 5 \text{ cmH}_2\text{O}$; and (c) severe: $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$, and $\text{PEEP} \geq 5 \text{ cmH}_2\text{O}$.

Diagnostic criteria for patients with AKI conformed to the revised AKI diagnosis criteria of the 2012 Kidney Disease Improving Global Outcomes (KDIGO) [19], in which presence of any 1 of the following characteristics can lead to diagnosis of AKI: (a) suddenly decline in renal function within 48 h, (b) an increasing absolute value in serum creatinine not less than 0.3 mg/dL ($\geq 26.4 \text{ mmol/L}$), (c) blood creatinine at least 50% above than the baseline value, and (d) decreased urine output (urinary volume $< 0.5 \text{ mL/kg/h}$) for more than 6 h. The base creatinine concentration was the 3-month creatinine level before admission or minimum creatinine after admission.

Clinical risk scoring system

Logistic regression analysis was used to establish a clinical risk scoring for AKI, which was refined by Takagi et al. [20]. The multivariable logistic model was constructed to select significant variables which were assigned scores proportional to the adjusted OR. The variables with no statistical significance were explicitly defined as 1 point. The predictors with statistical significance were assigned an integer fraction which was proportional to OR. Then, the sum of weighted variables was used to estimate a patient's score. The 4 risk categories were determined based on quartile of total score: group A (score 0–2), group B (score 3–4), group C (score 5–6), and group D (score ≥ 7).

Statistical analysis

Statistical analysis was performed using SPSS 24.0 (SPSS, Inc., Chicago, IL). Count data were presented as n (%) with chi-square test or logistic regression. The risk factors were screened by multivariable logistic regression analysis. $P < 0.05$ were considered to be a statistically significant difference.

Table 1. Comparison for sociological characteristics between the 2 groups.

Variable	Classification	Group n (%)		χ^2	P
		N-AKI (n=353)	AKI (n=148)		
Sex	Male	203 (57.51)	93 (62.84)	1.226	0.268
	Female	150 (42.49)	55 (37.16)		
Age	<60	50 (14.16)	19 (12.84)	1.233	0.540
	60–75	148 (41.93)	56 (37.84)		
	>75	155 (43.91)	73 (49.32)		
Smoke	No	237 (67.14)	110 (74.32)	2.529	0.112
	Yes	116 (32.86)	38 (26.03)		
Respiratory failure	I	179 (50.71)	76 (51.35)	0.053	0.974
	II	171 (48.44)	71 (47.97)		
	Normal	3 (0.85)	1 (0.68)		
Blood glucose	Anomaly	202 (57.22)	95 (64.19)	2.096	0.148
	Normal	151 (42.78)	53 (35.81)		
PA	Normal	237 (69.10)	105 (70.95)	1.157	0.740
	Mild	54 (15.74)	20 (13.51)		
	Moderate	33 (9.62)	12 (8.11)		
	Severe	19 (5.54)	11 (7.43)		
Encephalopathy	No	277 (78.47)	105 (70.95)	3.260	0.071
	Yes	76 (21.53)	43 (29.05)		

N-AKI – non-acute kidney injury; AKI – acute kidney injury; PA – pulmonary arterial.

Results

Study population

As shown in Table 1, the parameters of sex, age, smoke, respiratory failure type, blood glucose, pulmonary arterial (PA), and encephalopathy were no significantly different between the 2 groups ($P>0.05$).

Factors analysis of AKI

The single and multiple factors analyses of AKI are presented in Tables 2 and 3, respectively. There were statistically obvious differences between the N-AKI and AKI groups in diabetics, consciousness, hypertension, ARDS, AF, pleural effusion, heart disease, aspartate aminotransferase (AST), and D-dimer (Table 2) ($P<0.05$). Patients with ARDS who had unconsciousness (OR=2.778, 95% CI: 1.396–5.528), hypertension (OR=1.771, 95% CI: 1.089–2.881), ARDS (moderate–severe) (OR=1.630, 95% CI: 1.027–2.588), AST (OR=2.093, 95% CI: 1.251–3.499), or D-dimer (OR=2.372, 95% CI: 1.316–4.275) were more likely to also have AKI (Table 3).

Model scoring

The assigned score of the correlative predictors are displayed in Table 3. Five significant predictors selected from the multi-variable logistic model were assigned integer scores proportional to the OR. The variables with no significant differences (bronchial disease, diabetes, AF, pleural effusion, and heart disease) were assigned 1 point. Ultimately, these 12 predictors were integrated into the risk scoring system.

The distribution of the points and correlated prevalence of AKI is shown in Figure 1. The incidences of AKI were 10.71% (score 0), 10.53% (score 1), 11.43% (score 2), 10.71% (score 3), 22.73% (score 4), 35.42% (score 5), 27.59% (score 6), 37.50% (score 7), and 54.29% (score ≥ 8).

Correlation analysis of different scoring groups

The prevalence of AKI was significantly different in the different scoring groups ($\chi^2=50.183$, $P<0.001$). Higher scores were associated with higher prevalence of AKI ($P_{trend}<0.001$) (Table 4).

Table 2. Single-factor analysis of AKI.

Variable	Classification	Group n (%)		OR	95% CI	P
		N-AKI (n=353)	AKI (n=148)			
Diagnosis	COPD	188 (53.26)	60 (40.54)	1	–	
	Bronchial disease	47 (13.31)	11 (7.43)	0.733	0.358–1.503	0.397
	Pneumonia	100 (28.33)	68 (45.95)	2.131	1.395–3.254	0.001
	Others	18 (5.10)	9 (6.08)	1.567	0.669–3.670	0.301
Diabetes	No	309 (88.03)	115 (77.70)	1	–	
	Yes	42 (11.97)	33 (22.30)	2.112	1.276–3.494	0.003
	Miss	2	0	–	–	
Consciousness	No	23 (6.52)	31 (20.95)	1	–	
	Yes	330 (93.48)	117 (79.05)	0.263	0.147–0.469	<0.001
Hypertension	No	239 (76.36)	74 (23.64)	1	–	
	Yes	114 (60.64)	74 (39.36)	2.097	1.417–3.102	<0.001
ARDS	Mild	202 (57.22)	57 (38.51)	1	–	
	Moderate–severe	151 (42.78)	91 (61.49)	2.121	1.420–3.170	<0.001
AF	No	327 (92.63)	122 (82.43)	1	–	
	Yes	26 (7.37)	26 (17.57)	2.680	1.497–4.796	0.001
Pleural effusion	No	259 (73.37)	89 (60.14)	1	–	
	Yes	94 (26.63)	59 (39.86)	1.827	1.218–2.739	0.003
Heart disease	No	215 (66.56)	72 (53.33)	1	–	
	Yes	108 (33.44)	63 (46.67)	1.742	1.157–2.624	0.008
	Miss	30	13	–	–	
AST	Normal	292 (82.72)	92 (62.16)	1	–	
	Abnormal	61 (17.28)	56 (37.84)	2.914	1.892–4.487	<0.001
D-dimer	Normal	137 (40.90)	23 (16.08)	1	–	
	Abnormal	198 (59.10)	120 (83.92)	3.610	2.197–5.931	<0.001
	Miss	18	5	–	–	

N-AKI – non-acute kidney injury; AKI – acute kidney injury; COPD – chronic obstructive pulmonary disease; ARDS – acute respiratory distress syndrome; AF – atrial fibrillation; AST – aspartate aminotransferase.

In this study, 4 risk categories were determined based on the scoring points: group A (score 0–2, n=9), group B (score 3–4, n=16), group C (score 5–6, n=33), and group D (score ≥7, n=72). As shown in Figure 2, the incidences of AKI in groups A, B, C, and D were 10.98%, 16.00%, 31.13%, and 49.66%, respectively ($P<0.001$).

The results of correlation analysis between the 3 risk groups and prognosis showed that less improvement was significantly associated with higher risk ($\chi^2=23.057$, $P<0.001$) (Table 5, Figure 3).

Discussion

The present study established a risk scoring system for patients with ARDS who developed AKI. Our results determined that this AKI risk score, in which 5 predictive factors based on the multiple-factor logistic regression were analyzed, displayed an obvious correlation with the development and prognosis of AKI. According to the score, 4 risk levels were defined and used to develop explicit risk stratification of AKI, and risk prediction was performed using the risk scoring system in the internal validation. To the best of our knowledge, it is the first published clinical risk scoring system for AKI patients.

Ashbaugh et al. first performed risk scoring for ARDS in 1967 [21], which is characterized by diffuse lesions of pulmonary

Table 3. Multivariable logistic analysis of AKI.

Variable	β	S.E.	Wald	P	OR	95% CI		Assigned score
						Lower	Upper	
Constant	-2.578	0.311	68.908	<0.001	-	-	-	-
Diagnosis (bronchial disease)	-0.100	0.421	0.057	0.812	0.905	0.397	2.063	1
Diagnosis (pneumonia)	0.156	0.266	0.342	0.558	1.168	0.694	1.968	1
Diagnosis (others)	0.156	0.521	0.089	0.765	1.168	0.421	3.244	1
Diabetes (yes)	0.359	0.314	1.301	0.254	1.431	0.773	2.651	1
Consciousness (no)	1.022	0.351	8.464	0.004	2.778	1.396	5.528	3
Hypertension (yes)	0.572	0.248	5.299	0.021	1.771	1.089	2.881	2
ARDS (moderate-severe)	0.489	0.236	4.292	0.038	1.630	1.027	2.588	2
AF (yes)	0.469	0.356	1.733	0.188	1.598	0.795	3.211	1
Pleural effusion (yes)	0.089	0.253	0.124	0.725	1.093	0.666	1.793	1
Heart disease (yes)	0.213	0.251	0.721	0.396	1.237	0.757	2.022	1
AST (abnormal)	0.738	0.262	7.925	0.005	2.093	1.251	3.499	2
D-dimer (abnormal)	0.864	0.301	8.258	0.004	2.372	1.316	4.275	2

ARDS – acute respiratory distress syndrome; AF – atrial fibrillation; AST – aspartate aminotransferase.

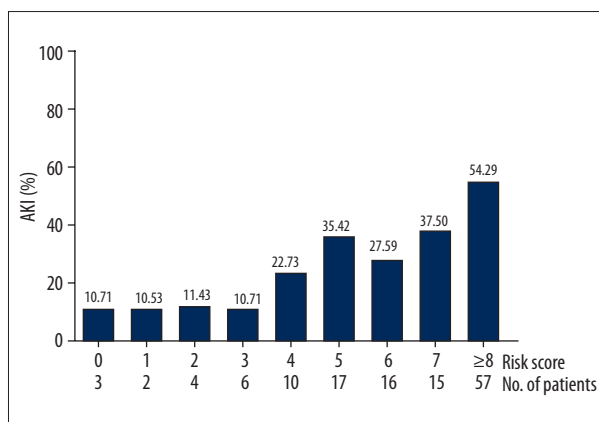


Figure 1. The distribution of the scoring points and associated prevalence of AKI.

endothelial and alveolar epithelium cells, resulting in alveolar and interstitial tissue flooding and edema, reduced lung compliance, imbalanced lung ventilation flow ratio, decreased lung volume, and refractory dyspnea [22–24]. The literature shows that AKI can lead to the release of various inflammatory factors and cytokines *in vivo* and promote the expression of pro-inflammatory genes in healthy lungs [25]. AKI is an important cause of mortality and morbidity in critically ill patients in ICUs [26]. A study demonstrated that IL-6, soluble TNF receptors, and plasminogen activator inhibitor-1 are associated independently with

AKI during mechanical ventilation [27]. Use of positive-pressure ventilation was reported to be associated with activation of the renin-angiotensin system, the sympathetic nervous system, and hemodynamic changes, which may reduce renal blood flow (RBF), glomerular filtration rate (GFR), and free water clearance [17]. It was reported that hypoxemia can affect renal vascular resistance and increase diuresis [17,28]. An experimental model of ARDS verified that renal end-organ injury can be induced through the high-volume ventilation [29,30]. Previous data analyses of ARDS co-occurring with AKI was mostly from ICU cases who had serious illness, many complications, and multiple-organ damage [17,31], and the survival rate was obviously decreased. In the present study, therefore, we developed and assessed a risk scoring system to predict development of AKI and prognosis for patients with ARDS.

In this work, a risk scoring system for AKI, which included multiple risk factors and assessed adverse events, was developed in AKI patients. The relevant clinical data required for this scoring system can be easily obtained, which would help predict prognosis of AKI patients. Furthermore, the prognostic stratification may inform individualized management involving assessment of the need for intensive medical therapy and close follow-up. Thus, it is of clinical significance to improve the compliance of high-risk patients by enhancing awareness using the risk scoring system.

Table 4. The relationship between the 4 risk groups and the prevalence of AKI.

Group	Group		χ^2	P	P _{trend}
	N-AKI	AKI			
A	73 (89.02)	9 (10.98)	50.183	<0.001	<0.001
B	84 (84.00)	16 (16.00)			
C	73 (68.87)	33 (31.13)			
D	73 (50.34)	72 (49.66)			

443 cases were included in this scoring system based on the logistic regression analysis. N-AKI – non-acute kidney injury; AKI – acute kidney injury. A – score 0–2; B – score 3–4; C – score 5–6; D: score ≥ 7 .

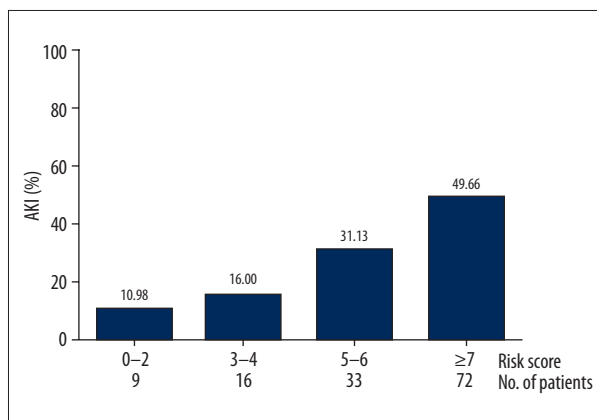


Figure 2. The 4 risk strata and corresponding prevalence of AKI.

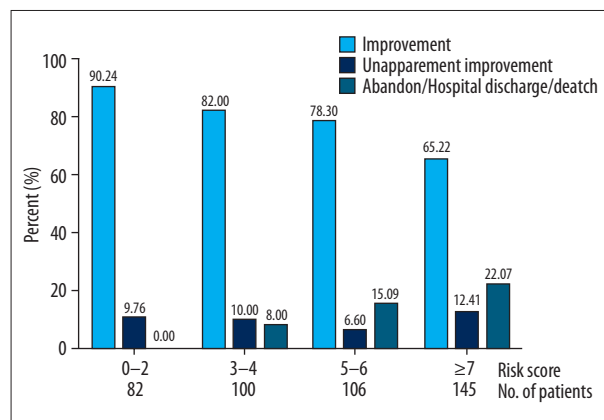


Figure 3. The prognosis in different scoring groups and associated prevalence of AKI.

Table 5. Correlation analysis of the 4 risk groups and prognosis.

Group	Prognosis n (%)			χ^2	P
	Improvement	Unapparent improvement	Abandon/hospital discharge/death		
A	74 (90.24)	8 (9.76)	0 (0.00)	23.057	<0.001
B	82 (82.00)	10 (10.00)	8 (8.00)		
C	83 (78.30)	7 (6.60)	16 (15.09)		
D	95 (65.22)	18 (12.41)	32 (22.07)		

443 cases were included in this scoring system based on the logistic regression analysis. A – score 0–2; B – score 3–4; C – score 5–6; D – score ≥ 7 .

A limitation of the present study is that the scoring system is only appropriate for AKI patients, and whether it would be applicable for other patients needs further study. The scoring system was developed and assessed at 2 hospitals, and whether it is applicable in other settings is unknown. As with all retrospective studies, there may have been some incompletely collected data and some missing values, and there was only 1 indicator of liver function. Thus, multicenter studies with larger samples and including

multiple diseases and hemodynamic indicators are needed for further verification of this scoring system in clinical practice.

Conclusions

We analyzed risk factors in the development and prognosis of AKI in patients with ARDS, and developed a clinical risk

prediction scoring system for AKI patients. The scoring system may provide risk-integrative evaluation and prognostic stratification for AKI patients.

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Conflicts of interest

None.