Acute Respiratory Distress Syndrome and Risk of AKI among Critically Ill Patients

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Abstract
Background and objectives Increasing experimental evidence suggests that acute respiratory distress syndrome (ARDS) may promote AKI. The primary objective of this study was to assess ARDS as a risk factor for AKI in critically ill patients.

Design, setting, participants, & measurements This was an observational study on a prospective database fed by 18 intensive care units (ICUs). Patients with ICU stays >24 hours were enrolled over a 14-year period. ARDS was defined using the Berlin criteria and AKI was defined using the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease criteria. Patients with AKI before ARDS onset were excluded.

Results This study enrolled 8029 patients, including 1879 patients with ARDS. AKI occurred in 31.3% of patients and was more common in patients with ARDS (44.3% versus 27.4% in patients without ARDS; \( P < 0.001 \)). After adjustment for confounders, both mechanical ventilation without ARDS (odds ratio [OR], 4.34; 95% confidence interval [95% CI], 3.71 to 5.10) and ARDS (OR, 11.01; 95% CI, 6.83 to 17.73) were independently associated with AKI. Hospital mortality was 14.2% (\( n = 1140 \)) and was higher in patients with ARDS (27.9% versus 10.0% in patients without ARDS; \( P < 0.001 \)) and in patients with AKI (27.6% versus 8.1% in those without AKI; \( P < 0.001 \)). AKI was associated with higher mortality in patients with ARDS (42.3% versus 20.2%; \( P < 0.001 \)).

Conclusions ARDS was independently associated with AKI. This study suggests that ARDS should be considered as a risk factor for AKI in critically ill patients.


Introduction
AKI is common in critically ill patients and remains associated with poor outcomes (1–3). The main known risk factors for AKI in critically ill patients are absolute or relative hypovolemia, nephrotoxic drug exposure, sepsis, and comorbidities (4–8).

An increasing body of evidence points to deleterious interactions between kidney and lung dysfunctions (9). Experimental studies suggest that AKI may increase the risk of lung injury, chiefly via the activation of proinflammatory and proapoptotic pathways because of renal ischemia/reperfusion (9–13). Several lines of evidence suggest that mechanical ventilation and acute respiratory distress syndrome (ARDS) may have adverse effects on kidney function via three main mechanisms. First, positive-pressure ventilation may reduce cardiac output and increase central venous pressure, thereby diminishing renal blood flow, free water clearance, or the GFR (14–17). In addition, changes in arterial blood \( O_2 \) or \( CO_2 \) may influence renal vascular resistance, renal perfusion, or diuresis (18–22). Finally, emerging data suggest that ventilator-induced lung injury may not only affect the lung, but may also lead to further systemic inflammation via the release of inflammatory cytokines (23–26).

Few studies have specifically addressed the association between respiratory failure and AKI (27–32). In addition, most of these studies were performed in specific patient populations and failed to adequately address the effect of ARDS on renal function (27,29–32).

The primary objective of this study was to assess the influence of ARDS on subsequent AKI in unselected patients in the intensive care unit (ICU).

Materials and Methods
Study Design and Data Source
We conducted an observational study on a prospective multicenter database (OutcomeRea; http://www.outcomerea.org) to assess influence of refractory hypoxemia on subsequent AKI. The database, fed by 18 French ICUs, collects prospective data on daily disease severity, iatrogenic events, and nosocomial infections. Each year, each ICU includes a random sample of at least 50 patients who have ICU...
stays >24 hours. Each ICU can choose to obtain patients’ samples by taking either consecutive admissions to selected ICU beds throughout the year or consecutive admissions to all ICU beds for 1 month.

**Study Population and Definitions**

This study was approved by the institutional review board of the Clermont Ferrand University Hospital, which waived the need for informed consent in compliance with French law on database studies. This study was conducted in accordance with the Declaration of Helsinki.

We included consecutive patients aged >18 years who were entered into the database between January 1997 and April 2011. Patients with preexisting chronic kidney failure (defined as an eGFR<60 ml/min per 1.73 m²), with pre-renal dysfunction (transient AKI) as the main mechanism of AKI, with AKI predating ARDS, treatment-limitation decisions, left ventricular dysfunction, or ICU stays <24 hours (and were thus unlikely to develop AKI after ARDS onset) were excluded.

AKI was defined according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria (33) and ARDS was defined as a PaO₂/FiO₂ ratio<300 mmHg in the absence of cardiogenic pulmonary edema (Table 1) (34). Because the 6- and 12-hour urine outputs were not recorded in the database, AKI definition and maximum renal severity were based upon changes in serum creatinine.

Baseline creatinine values were assessed using the four-variable Modification of Diet in Renal Disease (MDRD) equation. As recommended by the Acute Dialysis Quality Initiative Group, a normal eGFR of 75 ml/min per 1.73 m² before ICU admission was assumed (35).

CKD was either defined according to the Acute Physiology and Chronic Health Evaluation II definition or was identified through a specific code according to data extracted from the medical record. Transient AKI and left ventricular dysfunction were extracted from medical records and identified through a specific code in the database.

**Data Collection**

Data were collected daily by senior physicians and/or specifically trained study monitors in the participating ICUs and all of the collected data were extracted from medical records. For each patient, the investigators entered the data into a computer case-report form using data-capture software (RHEA; OutcomeRea) and imported all records into the OutcomeRea database. All codes and definitions were established before study initiation. The data quality checking procedure was described elsewhere (36). The following information was recorded: age, sex, admission category (medical, scheduled surgery, or unscheduled surgery), and origin (home, ward, or emergency department). Severity of illness was evaluated on the first ICU day using the Simplified Acute Physiology Score II (SAPS II), the Sequential Organ Failure Assessment (SOFA) score, and the Logistic Organ Dysfunction score (37–39). Knaus scale definitions were used to record pre-existing chronic organ failures including respiratory, cardiac, hepatic, renal, and immune system failures (40). Finally, the McCabe scoring system was assessed to obtain comparisons regarding the importance of host factors on the basis of the severity of the underlying disease, ranging from 1 (no fatal underlying disease) to 3 (rapidly fatal underlying disease) (41).

**Quality of the Database**

For most of the study variables, the data-capture software immediately ran an automatic check for internal consistency, generating queries that were sent to the ICUs for resolution before incorporation of the new data into the database. In each participating ICU, data quality was checked by having a senior physician from another participating ICU review a 2% random sample of the study data every other year. A 1-day data-capture training course held once a year was open to all OutcomeRea investigators and study monitors. All qualitative variables used in the analyses had k coefficients>0.8 and all variables had inter-rater coefficients in the 0.67–1 range, indicating good to excellent reproducibility.

**Statistical Analyses**

Categorical variables are presented as n (%) and continuous variables are medians (interquartile ranges). Comparisons of patients with and without AKI relied on chi-squared tests for categorical data and on the t test or Wilcoxon’s test, as appropriate, for continuous data. Risk factors associated with AKI were assessed using a multivariate logistic regression model. The potential link between ARDS and the subsequent development of AKI was assessed after adjusting for clinically pertinent confounding factors and for factors significant in the univariate analysis. These factors were baseline comorbidities (diabetes mellitus, immunodeficiency, chronic cardiac and pulmonary dysfunction, and myeloma), sepsis, administration of nephrotoxic drugs (aminoglycosides, glycopeptides, and/or iodinated contrast media), nonrenal organ failures (defined as the relevant specific SOFA component score>2), and age. Each of these variables was included in a stepwise logistic regression conditional model in which variables were selected according to their P value. Variables with a P value <0.05 were maintained in the final model. Goodness of fit and discrimination of the model were determined using the Hosmer–Lemeshow statistic and the C statistic (area under the curve), respectively. Results are reported as adjusted odds ratios (ORs) with their 95% confidence intervals (95% CIs).

All P values are two tailed, and P values <0.05 are considered significant. Statistical analyses were performed using the SAS 9.1 software package (SAS Institute, Cary, NC).

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**Table 1. Severity of ARDS**

<table>
<thead>
<tr>
<th>ARDS Severity</th>
<th>PaO₂/FiO₂ Ratio (mmHg)</th>
<th>PEEP (cmH₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>200–PaO₂/FiO₂≤300</td>
<td>≥5</td>
</tr>
<tr>
<td>Moderate</td>
<td>100–PaO₂/FiO₂≤200</td>
<td>≥5</td>
</tr>
<tr>
<td>Severe</td>
<td>100≤PaO₂/FiO₂</td>
<td>≥5</td>
</tr>
</tbody>
</table>

Severity is according to the Berlin definition (34). ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.
Results

Study Population

Of the 10,865 patients entered into the database during the study period, 2836 were excluded for the following reasons: history of CKD \((n=672)\), transient AKI \((n=130)\), AKI before ARDS onset \((n=46)\), treatment-limitation decisions \((n=1378)\), and evidence of left ventricular dysfunction \((n=610)\) (Figure 1). The remaining 8029 patients fulfilled the inclusion criteria and were enrolled in the study (Figure 1).

Table 2 reports the main patient characteristics at ICU admission. Overall, patients with AKI were older and were more often men; their acute illnesses were more severe as assessed on the basis of the SAPS II score or organ failures at ICU admission, and they had larger numbers of comorbidities.

ARDS and AKI

Overall, ARDS developed in 1879 patients (23.4%). AKI occurred after study inclusion in 832 patients with ARDS (44.3%) and in 1683 patients without ARDS (27.4%) \((P<0.001)\). The median delay between ARDS and AKI was 2 days (interquartile range, 1–9).

We assessed AKI severity among patients with and without ARDS using the RIFLE criteria. Among patients without ARDS, AKI severity was R in 736 patients (43.7% of patients with AKI), I in 455 patients (27.0% of patients with AKI), and F in 492 patients (29.3% of patients with AKI). Among patients with ARDS, AKI severity was R in 171 patients (20.5% of patients with AKI), I in 276 patients (33.2% of patients with AKI), and F in 385 patients (46.3% of patients with AKI) \((P<0.001)\).

Of the patients with ARDS, the severity of ARDS according to the Berlin classification was mild in 975 patients (51.9%), moderate in 379 patients (20.2%), and severe in 525 patients (27.9%).

Overall hospital mortality was 14.2% \((n=1140)\) and was higher in patients with ARDS (27.9% versus 10.0% in patients without ARDS; \(P<0.001)\) and in patients with AKI (27.6% versus 8.1% in patients without AKI; \(P<0.001)\).

Among the patients with ARDS, those who subsequently developed AKI had a higher hospital mortality rate than those without AKI (42.3% versus 20.2%; \(P<0.001)\). Changes in AKI and ARDS rates during the study period are reported in the Supplemental Appendix.

Risk Factors for AKI

After adjustment for confounders, both mechanical ventilation without ARDS (OR, 4.34; 95% CI, 3.71 to 5.10) and ARDS (OR, 11.01; 95% CI, 6.83 to 17.73) were independently associated with AKI (Table 3). Other factors independently associated with AKI were shock, myeloma, age, diabetes mellitus, immunodeficiency, chronic liver or cardiac disease, and multiple myeloma. The model was well calibrated and the C statistic was 0.77. Figure 2 reports the cumulative incidence of AKI in patients with and without ARDS. Finally, a sensitivity analysis was performed to assess the influence of ARDS duration on AKI incidence before and after adjustment (Supplemental Appendix).

The incidences of AKI before adjustment in patients with mild, moderate, and severe ARDS were 40%, 75.7%, and 29.5%, respectively. After adjustment for confounders, mild ARDS (OR, 2.42; 95% CI, 1.52 to 3.83), moderate ARDS (OR, 2.22; 95% CI, 1.38 to 3.55), and severe ARDS (OR, 2.58; 95% CI, 1.57 to 4.25) were significantly associated with AKI compared with patients without ARDS (Hosmer–Lemeshow goodness of fit \(P=0.30\); C statistic, 0.74).

Discussion

We found a significant independent association between ARDS and subsequent AKI. Although several studies point to physiologic mechanisms responsible for a deleterious effect of ARDS on other organs, little information was available on the clinical effect of ARDS on kidney function. Our results support the addition of ARDS to the list of risk factors for AKI in critically ill patients.

The growing evidence pointing to deleterious interactions between kidney and lung dysfunctions suggests a

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**Figure 1.** Flow chart of patients admitted during the study period. ARDS, acute respiratory distress syndrome; FLST, decision to forgo life-sustaining therapies.
partial explanation for the natural history of multiple organ dysfunctions in critically ill patients (9). In experimental studies in animals or healthy volunteers, acute lung injury adversely affected kidney function. The three main underlying mechanisms were positive-pressure ventilation, hypoxemia, and systemic inflammation. Positive-pressure ventilation may modify the cardiac preload and has been associated with systemic hemodynamic changes leading to decreases in the GFR, renal blood flow, and free water clearance (16,17,42). Moreover, activation of the sympathetic and renin-angiotensin systems, together with suppression of atrial natriuretic peptide release, observed during positive pressure ventilation further decreases glomerular perfusion, GFR values, urine output, and sodium excretion.

### Table 2. Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>AKI (n=2515)</th>
<th>No AKI (n=5514)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>65.9±16</td>
<td>55.1±18.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>1472 (58.5)</td>
<td>3431 (62.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>SAPS II score</td>
<td>50.1±19.8</td>
<td>33.6±16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfer from ward</td>
<td>1214 (48.3)</td>
<td>2390 (43.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>McCabe score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1507 (59.9)</td>
<td>3928 (71.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>826 (32.9)</td>
<td>1314 (23.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>182 (7.2)</td>
<td>272 (4.9)</td>
<td></td>
</tr>
<tr>
<td>Admission category</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical</td>
<td>1747 (69.5)</td>
<td>3885 (70.5)</td>
<td></td>
</tr>
<tr>
<td>Scheduled surgery</td>
<td>471 (18.7)</td>
<td>769 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Unscheduled surgery</td>
<td>297 (11.8)</td>
<td>860 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Chronic comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>364 (14.5)</td>
<td>393 (7.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>313 (12.5)</td>
<td>822 (14.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Liver disease</td>
<td>170 (6.8)</td>
<td>283 (5.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>416 (16.5)</td>
<td>669 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>401 (15.9)</td>
<td>519 (9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myeloma</td>
<td>30 (1.2)</td>
<td>20 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARDS</td>
<td>832 (33.1)</td>
<td>1047 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemodynamic failure</td>
<td>1127 (44.8)</td>
<td>1576 (28.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>848 (33.7)</td>
<td>1102 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1265 (49.3)</td>
<td>2841 (51.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Nephrotoxic drugs</td>
<td>1316 (52.3)</td>
<td>3108 (56.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>543 (21.6)</td>
<td>291 (5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>693 (27.6)</td>
<td>448 (8.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are reported as the mean ±SD or n (%) unless otherwise specified. SAPS II, Simplified Acute Physiology Score version II (which can range from 0 to 155); ICU, intensive care unit.

### Table 3. Factors independently associated with AKI after adjustment for confounders (stepwise logistic regression)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory status&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No MV (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV, no ARDS</td>
<td>4.34 (3.71 to 5.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARDS</td>
<td>11.01 (6.83 to 17.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (per yr)</td>
<td>1.04 (1.03 to 1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic cardiac dysfunction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.54 (1.30 to 1.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic liver disease&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.41 (1.14 to 1.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immunodeficiency&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.68 (1.45 to 1.76)</td>
<td>0.002</td>
</tr>
<tr>
<td>Shock</td>
<td>4.23 (3.38 to 5.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.62 (1.38 to 1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.91 (1.01 to 3.61)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Hosmer–Lemeshow statistics were as follows: $\chi^2=11.8; P=0.16; C$ statistic: 0.77. OR, odds ratio; 95% CI, 95% confidence interval; MV, mechanical ventilation.

<sup>a</sup>Respiratory status was inserted as the dummy variable.

<sup>b</sup>Underlying comorbidities (chronic liver disease, chronic cardiac dysfunction, or immunodeficiency) were defined according to the Knaus definition (40).
Moreover, hypoxemia and hypercapnia were previously shown to modify renal vascular resistances (18,19,21) and to increase diuresis (20,44,45). Interestingly, similar effects were reported in patients with chronic obstructive pulmonary disease (19,21), as well as in renal transplant recipients (18) and critically ill patients with refractory hypoxemia (22). None of these studies, however, evaluated the long-term consequences of these physiologic alterations. Finally, systemic inflammation and biautrauma have been implicated in systemic organ dysfunction during ARDS. Thus, several lines of evidence indicate that biautrauma induced by mechanical ventilation not only affects the lung, but also leads to further systemic inflammation and organ dysfunction via the release of inflammatory cytokines (23–26). Thus, in studies evaluating protective ventilation, higher tidal volumes were associated with not only higher levels of TNF-α, IL-1β, IL-6, and IL-8, but also with higher rates of AKI or higher numbers of days with AKI (23–26).

Despite this large body of evidence suggesting an interaction between respiratory failure and AKI, few studies have evaluated the effect of respiratory failure on renal function by clearly assessing the time of mechanical ventilation initiation relative to the onset of AKI (27–32). A recent meta-analysis of these studies suggested that both ARDS and mechanical ventilation were associated with a 3-fold increase in the risk of AKI (46). Most of the studies included in this analysis were observational studies, however, and focused on specific populations such as trauma patients (27), lung transplant recipients (29), cancer patients (30), or patients with hepatic failure (32). Thus, the general applicability of their findings is unclear. Furthermore, these studies were not specifically designed to assess the influence of respiratory failure on AKI, and they did not separate the effect of mechanical ventilation from that of ARDS (46). In this study, both ARDS and mechanical ventilation were found to be independently associated with usual and well described risk factors for AKI, namely, shock, diabetes mellitus, age, underlying cardiac or hepatic dysfunction, and myeloma. Our study provides valid data supporting the addition of both ARDS and mechanical ventilation to the list of risk factors for AKI in unselected ICU patients.

Our study has several limitations. First, the observational design and lack of information on ventilator settings preclude conclusions about factors that may have promoted the development of AKI. Additional studies are needed to further assess the influence of ventilator settings, blood O2 and CO2 alterations, and systemic inflammation on the occurrence of AKI. In addition, data regarding the mechanism of AKI, fluid balance management across groups, or diuretics use in patients with ARDS were unavailable. Whether some differences regarding fluid management or type of fluid used in each of the studied groups might have accounted for the observed difference regarding AKI rate remains to be evaluated. Furthermore, although we adjusted for the main nephrotoxic agents (e.g., contrast media and antimicrobial agents), we must acknowledge the lack of information regarding other nephrotoxic agents, such as angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists. In this study, and in accordance with current guidelines, baseline creatinine was back calculated from the MDRD assuming a 75 ml/kg per 1.73 m² GFR (35,47). Although this imputation was validated in previous works (48), it may overestimate the incidence of AKI by nearly 10% and may misclassify severity of AKI in up to 30% (49). Finally, the observational study design only allows us to conclude
that ARDS was independently associated with AKI. No conclusions can be drawn about the causal nature of this association, despite the numerous experimental studies suggesting causality. Further studies are needed to address this issue more specifically and to evaluate the influence of ventilator settings on renal function.

In conclusion, the independent association demonstrated in our study between ARDS and subsequent AKI indicates that ARDS should be added to the list of risk factors for AKI in critically ill patients. Although no conclusions about causality can be drawn from our data, the strong experimental evidence suggesting causality supports the need for further studies in this field aimed at confirming our findings and evaluating the mechanisms underlying the ARDS-AKI association, most notably ventilator settings, in unselected ICU patients.

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References

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