ORIGINAL ARTICLE

Incidence and Outcomes of Acute Lung Injury

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ABSTRACT

BACKGROUND
Acute lung injury is a critical illness syndrome consisting of acute hypoxemic respiratory failure with bilateral pulmonary infiltrates that are not attributed to left atrial hypertension. Despite recent advances in our understanding of the mechanism and treatment of acute lung injury, its incidence and outcomes in the United States have been unclear.

METHODS
We conducted a prospective, population-based, cohort study in 21 hospitals in and around King County, Washington, from April 1999 through July 2000, using a validated screening protocol to identify patients who met the consensus criteria for acute lung injury.

RESULTS
A total of 1113 King County residents undergoing mechanical ventilation met the criteria for acute lung injury and were 15 years of age or older. On the basis of this figure, the crude incidence of acute lung injury was 78.9 per 100,000 person-years and the age-adjusted incidence was 86.2 per 100,000 person-years. The in-hospital mortality rate was 38.5 percent. The incidence of acute lung injury increased with age from 16 per 100,000 person-years for those 15 through 19 years of age to 306 per 100,000 person-years for those 75 through 84 years of age. Mortality increased with age from 24 percent for patients 15 through 19 years of age to 60 percent for patients 85 years of age or older (P<0.001). We estimate that each year in the United States there are 190,600 cases of acute lung injury, which are associated with 74,500 deaths and 3.6 million hospital days.

CONCLUSIONS
Acute lung injury has a substantial impact on public health, with an incidence in the United States that is considerably higher than previous reports have suggested.

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Acute lung injury is a syndrome consisting of acute hypoxemic respiratory failure with bilateral pulmonary infiltrates that is associated with both pulmonary and nonpulmonary risk factors and that is not primarily due to left atrial hypertension.[1] Despite recent advances in our understanding of the pathophysiology, treatment, and long-term outcome of acute lung injury, prospective, population-based data on the incidence and outcome of acute lung injury in the United States have not been available.[2-7] There has, however, been a prospective, population-based study of patients with acute respiratory distress syndrome (ARDS), a subtype of acute lung injury characterized by more severe hypoxemia.[8] That study, which estimated the incidence of ARDS as 8.3 per 100,000 person-years, was performed in 6 of the 40 hospitals in Utah in 1989, before the availability of current definitions of acute lung injury.

On the basis of these and other data suggesting an incidence of acute lung injury and ARDS of 1.5 to 8.3 per 100,000 person-years, these syndromes are considered rare.[9,10] However, the studies on which these estimates are based were limited by several factors, including extrapolation from less than a complete year of observation or from a subgroup of the hospitals in a region, use of inaccurate administrative coding, an absence of procedures to ensure reliable case identification, use of obsolete definitions, and use of observations from countries where differences in the availability and utilization of intensive care services may limit the applicability of the data to the United States.[11-15] The King County Lung Injury Project (KCLIP) was designed to address some of the limitations of previous studies and to answer questions about the incidence and outcomes of acute lung injury and ARDS.

METHODS

STUDY DESIGN AND SETTING

We conducted a prospective cohort study to determine the incidence and outcome of acute lung injury. The study was conducted in 21 hospitals, which included all 18 hospitals in King County, Washington, that care for patients undergoing mechanical ventilation, as well as three hospitals in adjacent counties that also care for this group of patients.

King County is the 12th most populous county in the United States, covering 5700 km^2 (2200 mi^2) and encompassing the urban areas around Seattle and the surrounding rural areas. Because it is bounded on the west by water and on the east by mountains, it is unlikely that residents would seek health care outside the county. In comparison with the total U.S. population, the 1.74 million persons living in King County in 2000 were wealthier (with a median annual family income of $53,000, as compared with $42,000 for the United States), were younger (with 10.5 percent 65 years of age or older, as compared with 12.4 percent for the United States), and had a different racial distribution (with 5.4 percent black and 10.8 percent Asian, as compared with 12.3 percent and 3.6 percent, respectively, for the United States).[16] In 2000, the cause-specific mortality rates in King County for diseases related to acute lung injury (pneumonia, trauma, and septicemia) were comparable to or lower than those for the United States as a whole.[17] According to the Washington State Comprehensive Hospital Abstract Reporting System (CHARS) database, 96.4 percent of King County residents who underwent mechanical ventilation in Washington State in 2000 received their care at one of the 21 KCLIP study hospitals. Four of these hospitals are primary teaching affiliates, where all critically ill patients receive care from resident physicians; these are classified as academic hospitals in the analysis. Data were obtained from each hospital for 12 consecutive months during the period from April 1999 through July 2000.

IDENTIFICATION OF CASES

Using data routinely obtained during clinical care of the patients, we identified patients with acute lung injury according to the definition of the American–European Consensus Conference on ARDS.[18] The criteria are the presence of acute hypoxemia with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FIO_2) of 300 mm Hg or less (for acute lung injury) or of 200 mm Hg or less (for ARDS); bilateral infiltrates (including very mild infiltrates) seen on a frontal chest radiograph that are consistent with pulmonary edema; and no clinical evidence of left atrial hypertension or (if it is measured) a pulmonary-artery wedge pressure of 18 mm Hg or less. If a patient had more than one episode that met the criteria, only the data from the first episode were included in the study.

All patients who were undergoing mechanical ventilation in an intensive care unit (ICU) through either an endotracheal tube or a face mask were screened for enrollment. To ensure that patients were not missed, we examined data from at least two sources at each hospital, including logs of patients undergoing mechanical ventilation, billing records, and other hospital databases. Patient records were cross-checked among hospitals to ensure that transferred patients were counted only once in the study. Patients were excluded from the study if they were not residents of King County (as determined by the ZIP Code of their primary residence), if they were less than six months of age (to exclude patients with neonatal respiratory distress syndrome), or if they had undergone mechanical ventilation for less than 24 hours after an operative procedure.

Only arterial blood gas measurements obtained while the patient was intubated were assessed. The arterial blood gas values with the worst PaO_2:FIO_2 ratio, regardless of the positive end-expiratory pressure, were used to assess oxygenation for each 24-hour period, and the values obtained on the first day on which the PaO_2:FIO_2 ratio was 300 mm Hg or less and other criteria were met were used to classify patients as having either acute lung injury or ARDS. Because the PaO_2:FIO_2 ratio becomes an increasingly unreliable assessment of shunt when the FIO_2 is below 0.40, the ratio was used to assess oxygenation only when the FIO_2 was 0.40 or more.[19]

The study used a standardized protocol to identify patients who met the enrollment criteria for acute lung injury. We used respiratory therapists and research nurses who had been trained in the reliable identification of chest radiographs that met the study criteria for acute lung injury and to collect data on clinical risk factors for acute lung injury. Trained medical-record abstractors collected other data from the medical records. Because our chest-radiography protocol was not designed to distinguish between chronic and acute abnormalities, radiographs showing bilateral parenchymal opacities in patients with a diagnosis of chronic pulmonary disease, such as asbestosis, pulmonary fibrosis, lymphangitic carcinoma, and bronchiectasis, were set aside for separate analysis. To exclude pediatric patients, the analysis included only patients who were at least 15 years old. We chose this age cutoff on the basis of U.S. Census tables, which classify adolescents and young adults into age categories of 10 through 14, 15 through 19, and 20 through 24 years.

Patients were assessed for the presence of any risk factors for acute lung injury during the four days before the onset of acute lung injury.[20] These risk factors included severe sepsis,[21] which was divided into sepsis with a suspected pulmonary source (pneumonia) and sepsis with a suspected nonpulmonary source or an unidentified source; severe trauma (with an Injury Severity Score[22] above 15 [possible scores range from 0 to 75, with higher scores indicating more severe injury]); witnessed aspiration, transfusion of more than 15 units of blood within a 24-hour period, drug overdose, pancreatitis, near-drowning, and inhalation injury. For this analysis, no attempt was made to assign a primary risk factor, and therefore the risk-factor categories are not mutually exclusive.

Patients with diagnoses of acute myocardial infarction or congestive heart failure on admission to the ICU and with no identifiable risk factors for acute lung injury were considered to have clinical evidence of left atrial hypertension, as were patients with a pulmonary-artery wedge pressure greater than 18 mm Hg on all days on which other criteria for acute lung injury were met (Fig. 1).

VALIDATION OF SCREENING PROTOCOL

Over a two-month period (from May 1 through June 30, 1999), we compared the results obtained by screening with the use of our protocol with the results obtained by clinical screening of 382 patients undergoing mechanical ventilation at Harborview Medical Center.[23] Each group of screeners was blinded to the results obtained by the other group. After adjudication of discordant cases by two clinicians (an intensivist and a chest radiologist), who were also blinded to the results of case assignment by the two groups of screeners, our screening protocol had a kappa value of 0.91 and an agreement of 96 percent with the adjudicated diagnosis of acute lung injury.

QUALITY CONTROL

Extensive efforts were made to ensure the quality of the data collected throughout the study. At each site, the data from a randomly chosen 5 percent of screened patients and from all patients about whom the screeners had questions were reviewed by the study physicians, including review of the chart and chest radiographs. Data from a random sample of 7 percent of cases were abstracted and entered into the database twice, with an error rate of less than

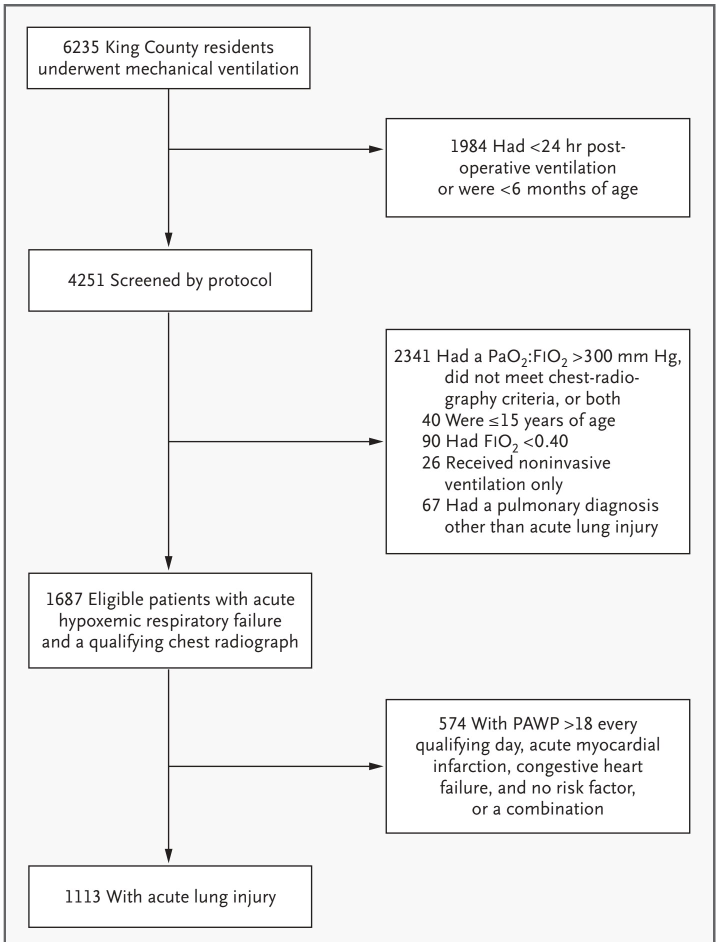

Figure 1. The Study Cohort in the King County Lung Injury Project.
PaO_2 denotes the partial pressure of arterial oxygen, FIO_2 the fraction of inspired oxygen, and PAWP the pulmonary-artery wedge pressure.

0.25 percent. The charts were reevaluated until the final notes, laboratory test results, and other results were complete. Complete data were available for 98.3 percent of the patients.

STATISTICAL ANALYSIS

The results are presented as percentages for categorical variables and as medians with interquartile ranges or as means with standard deviations for continuous variables. Depending on the distribution of the data, the Pearson chi-square test, the Mann–Whitney test, or Student's t-test was used to compare groups. Rates per 100,000 person-years were age-adjusted to the U.S. population in 2000. Statistical analyses were performed with SAS software (version 9).

The study was approved by the University of Washington institutional review board and, when required, by the institutional review boards at the individual sites.

RESULTS

During the study period, 6235 residents of King County underwent mechanical ventilation at the study hospitals, and 4251 were screened for the study. Of these, 1687 eligible patients (40 percent of the screened patients) met the criteria for acute hypoxemic respiratory failure and had a qualifying chest radiograph. Five hundred seventy-four of these 1687 patients (34 percent) had left atrial hypertension according to the clinical diagnosis or (when available) data from echocardiography or measurement of pulmonary-artery wedge pressure. The remaining 1113 patients met the criteria for acute lung injury, with an initial $PaO_2:FIO_2$ of 300 mm Hg or less (Fig. 1). Eight hundred twenty-eight of these (74 percent) had an initial $PaO_2:FIO_2$ of 200 mm Hg or less, meeting the criteria for ARDS, and 61 patients (21 percent of the 285 patients with a $PaO_2:FIO_2$ greater than 200 mm Hg and equal to or less than 300 mm Hg) progressed on either day 3 or day 7 of acute lung injury to a $PaO_2:FIO_2$ of 200 mm Hg or less. According to these data, the incidence of acute lung injury in King County was 78.9 cases per 100,000 person-years, and the incidence of ARDS was 58.7 cases per 100,000 person-years.

The in-hospital mortality rate was 38.5 percent (95 percent confidence interval, 34.9 to 42.2 percent) for patients with acute lung injury and 41.1 percent (95 percent confidence interval, 36.7 to 45.4 percent) for those with ARDS. Patients who presented with a $PaO_2:FIO_2$ greater than 200 mm Hg and equal to or less than 300 mm Hg and who progressed on day 3 or day 7 to a $PaO_2:FIO_2$ of 200 mm Hg or less had a mortality rate of 41.0 percent, similar to that of patients who presented with ARDS ($P=0.5$). Patients who presented with a $PaO_2:FIO_2$ greater than 200 and equal to or less than 300, and who did not progress on day 3 or day 7 to a $PaO_2:FIO_2$ of 200 or less, had a lower mortality rate (28.6 percent) than did patients with ARDS ($P=0.001$).

The most common risk factor for acute lung injury was severe sepsis with a suspected pulmonary source (46 percent), followed by severe sepsis with a suspected nonpulmonary source (33 percent). In this cohort, mortality varied according to the risk factor from 24.1 percent (95 percent confidence interval, 13.2 to 34.9 percent) among patients with severe trauma, to 40.6 percent (95 percent confidence interval, 35.1 to 46.1 percent) among patients with severe sepsis with a suspected pulmonary source, to 43.6 percent (95 percent confidence interval, 31.9 to 55.2 percent) among patients with witnessed aspiration. Extrapolating the age-adjusted incidence and mortality to the United States population leads to an estimate of 190,600 cases of acute lung injury per year, with an associated 74,500 deaths and 2.2 million days in ICUs (Table 1). The incidence and mortality increased with age (Fig. 2). The lowest age-specific incidence was in those 15 through 19 years of age (16 cases per 100,000 person-years); the incidence increased with age to a peak of 306 cases per 100,000 person-years in persons 75 through 84 years of age. Mortality also increased with age from a minimum of 24 percent among those 15 through 19 years old to 60 percent among those 85 years of age or older (P<0.001 for trend).

Table 1. Incidence of Acute Lung Injury and ARDS and Mortality from These Conditions.*

Variable	Acute Lung Injury	ARDS
Cases — no.	1,113	828
Crude incidence — no. per 100,000 person-yr	78.9	58.7
Age-adjusted incidence — no. per 100,000 person-yr†	86.2	64.0
Mortality (95% CI) — %	38.5 (34.9–42.2)	41.1 (36.7–45.4)
Estimated annual cases — no.†	190,600	141,500
Estimated annual deaths — no.†	74,500	59,000
Estimated annual hospital days — no.†	3,622,000	2,746,000
Estimated annual days in ICU — no.†	2,154,000	1,642,000

* ARDS denotes acute respiratory distress syndrome, and CI confidence interval.
† U.S. estimates, age-adjusted to the 2000 Census, are shown.

The majority (59 percent) of patients with acute lung injury were not cared for at one of the four academic sites where residents care for all critically ill patients. As compared with patients in the academic hospitals, patients in the community hospitals were older, had a different racial distribution, had shorter lengths of stay in the ICU and in the hospital, had higher Acute Physiology and Chronic Health Evaluation scores, had higher unadjusted in-hospital mortality rates, and had a different distribution of risk factors. Patients in the community hospitals also were more likely to be

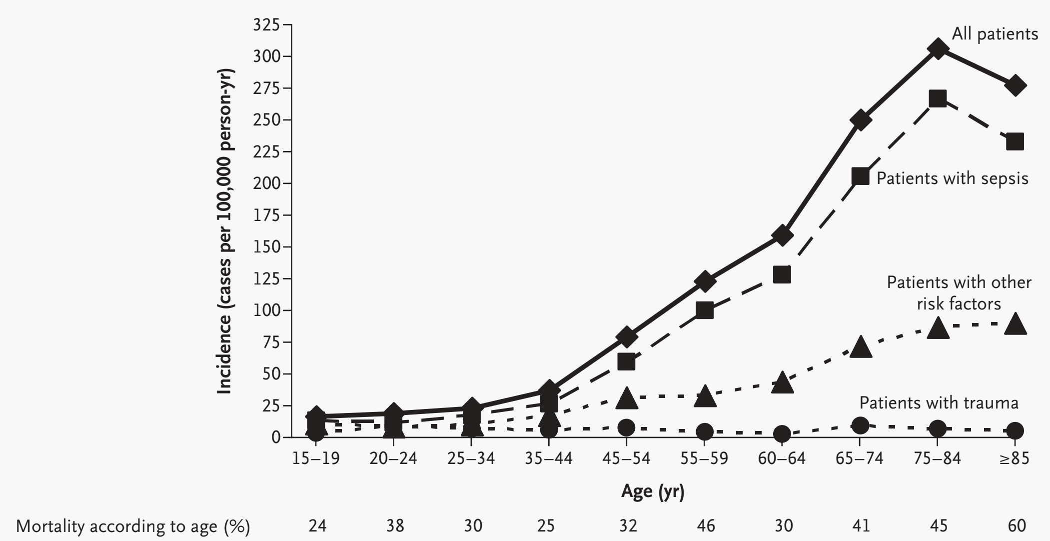

Figure 2. Age- and Risk-Specific Incidence of and Age-Specific Mortality from Acute Lung Injury.
Risk-factor categories are not mutually exclusive; P<0.001 for trend for the comparison of age-specific mortality rates.

admitted from a nursing home or institution, less likely to be admitted by transfer from another hospital, and less likely to have recently undergone surgery (Table 2).

DISCUSSION

Our data suggest that the incidence of acute lung injury in the United States is between 2.5 and 5 times as high, and the incidence of ARDS is between 2 and 40 times as high, as previous studies have indicated.[10] According to these findings, 74,500 persons die of acute lung injury in the United States each year, a figure that is comparable to the number of adult deaths attributed to breast cancer or human immunodeficiency virus disease in 1999.[6,24] It is equally important to note that more than 100,000 patients survive acute lung injury each year, many of whom require care for cognitive abnormalities, weakness, depression, or post-traumatic stress disorder.[2,25,26] In our study, only 34 percent of the survivors were well enough to be discharged directly home, a figure that probably reflects the fiscal pressures to shorten hospital stays and the degree of impairment after acute lung injury. Because the risk of acute lung injury and the mortality attributed to it increase with age, our results have important implications for the planning of services for critical care, mechanical ventilation, and rehabilitation in the future. On the basis of the age-specific incidence and mortality rates that we observed and projections of the future demographic characteristics of the U.S. population, we estimate that in 25 years the annual incidence of acute lung injury will be 335,000 cases, with 147,000 deaths per year.[16]

Several lines of reasoning support these results and suggest that the incidence of acute lung injury in the United States has been substantially underestimated in the past. By combining recent data on the incidence of severe sepsis and severe trauma (defined by Injury Severity Scores above 15) with data on the incidence of ARDS among patients with these conditions, the incidence of ARDS in the United States can be calculated as 56 to 82 cases per 100,000 person-years.[20,27-30] Another estimate, extrapolated from screening data from the ARDS Network clinical trial, was based on the conservative assumption that cases of acute lung injury are observed only in large ICUs with more than 20 beds; according to this estimate, the incidence of acute lung injury was 64.2 cases per 100,000 person-years.[31] Finally, it is of historical interest that an expert consensus in 1972 estimated that there were 150,000 cases of ARDS per year in the United States,[32] which is similar to the estimates we project.

There are a number of important limitations to this study. First, the study was conducted in a single region in which the epidemiology of acute lung injury may differ from that elsewhere in the United States. However, regional studies, most notably those from Olmsted County in Minnesota and Framingham, Massachusetts, have provided invaluable epidemiologic data for many diseases.[33,34] Children less than 15 years of age were excluded from this analysis, and therefore we cannot comment on the burden of pediatric acute lung injury.

The demographic features of King County are not identical to those of the United States as a whole. Although we present an age-adjusted analysis, the numbers of patients of certain races (for example, black patients) were too small to allow us to present reliable race-adjusted figures. The limited data that are available suggest that the younger age, higher socioeconomic status, and unrepresentative racial distribution of King County residents should bias our study toward underestimation of the true incidence of, and mortality from, acute lung injury in the United States.[35] Some of the differences between the academic and community sites may be explained by local differences in care procedures; for example, nearly all patients in the region with severe trauma are sent to an academic trauma center. Finally, patients may have been misclassified because of deficiencies in our protocol, missing documentation, or a lack of available clinical tests. We tried to minimize the risk of misclassification by validating the protocol against the results of clinical-trial screening conducted at an institution with experience in the investigation of acute lung injury and by supplementing screening with extensive quality control, which included central review of cases and chest radiographs.

Our approach reflects current practice for enrolling patients in clinical trials of acute lung injury; this practice does not require a specific diagnostic protocol to exclude clinical evidence of left atrial hypertension or to establish the presence of risk factors for acute lung injury. Recent studies suggest that elevated left atrial pressure and acute lung injury frequently coexist, and therefore some misclassification may be unavoidable until better biomarkers of acute lung injury are developed.[36]

Table 2. Demographic Characteristics of Patients and Outcomes of Acute Lung Injury According to Hospital Type.*

Variable	Acute Lung Injury	Academic Hospital (N=4)	Community Hospital (N=17)	P Value†
Cases (no.)	1113	459	654	
Age (yr)				<0.001
Median	62.0	51.8	68.7	
Interquartile range	48.3–74.9	42.2–64.9	55.4–78.5	
Male sex (%)	61	71	54	<0.001
Race (%)‡				<0.001
White	69	70	68	
Black	9	14	6	
Asian	5	7	4	
Other or unknown	17	9	22	
Hospital stay (days)				<0.001
Median	14.0	17.0	13.0	
Interquartile range	8.0–24.0	9.0–30.0	7.0–21.0	
ICU stay (days)				0.005
Median	7.8	8.6	7.0	
Interquartile range	3.7–14.3	4.2–15.8	3.6–13.3	
Mechanical ventilation (days)				0.04
Median	5.3	5.7	4.9	
Interquartile range	2.1–10.8	2.2–11.9	2.0–10.0	
APACHE II score on admission (mean ±SD)	26.1±8.5	25.2±8.7	26.7±11.0	0.004
Hospital mortality (%)	38.5	31.8	43.3	<0.001
Risk factors§				
Severe sepsis				
Pulmonary source (%)	46	40	51	<0.001
Other source (%)	33	30	36	0.04
Severe trauma (%)	7	16	0.5	<0.001
Witnessed aspiration (%)	11	10	12	0.24
Blood transfusion (%)	3	5	1	<0.001
Drug overdose (%)	3	5	2	0.05
Pancreatitis (%)	3	3	3	0.94
Other or no risk (%)	14	17	11	0.003
Admission source				<0.001
Home (%)	75	74	76	
Other hospital (%)	9	14	5	
Nursing home or institution (%)	16	12	19	
Postoperative patients (%)	22	29	17	<0.001
Disposition of surviving patients				<0.001
Home (%)	34	37	31	
Other hospital (%)	13	9	17	
Rehabilitation facility (%)	12	15	10	
Skilled nursing facility (%)	39	36	40	
Other (%)	2	3	2	

* APACHE II denotes Acute Physiology and Chronic Health Evaluation.
† P values are for the comparison between academic and community hospitals.
‡ Race was determined by a review of the medical records.
§ Risk factors are not mutually exclusive.

Table 3. Comparison of KCLIP Cohort with Other Population-Based Cohorts in Studies of Acute Lung Injury.*

Variable	KCLIP	Scandinavia	Australia
Acute lung injury incidence (cases per 100,000 person-yr)	78.9	17.9	34
Acute lung injury cases (no.)	1113	287	168
Observation period	12 mo, 1999–2000	2 mo, 1997	2 mo, 1999
ICU beds (no.)	430	NA	253
Population denominator (millions)	1.74	11.74	2.9
APACHE II score (mean ±SD)	26.1±8.5	18.7±8	20±9
Mean age (yr)	60.6	59.8	62
Mortality from acute lung injury (%)†	38.5	41.4	32
Mortality from ARDS (%)†	41.1	41.2	34
Ratio of cases of ARDS to cases of acute lung injury (%)	74	77	64
Ratio of cases of acute lung injury to cases of acute respiratory failure (%)	26	23	NA

* KCLIP denotes King County Lung Injury Project, APACHE II Acute Physiology and Chronic Health Evaluation, ARDS acute respiratory distress syndrome, and NA not available.
† Mortality figures represent hospital mortality for KCLIP, 90-day mortality for Scandinavia, and 28-day mortality for Australia.

Finally, with the notable exception of the incidence of acute lung injury, the cohort we studied is similar to other population-based cohorts in studies of acute lung injury with regard to a number of factors, a finding that supports the external validity of our case-identification protocol (Table 3).

On the basis of our results, acute lung injury and ARDS occur with a higher incidence than previously reported and therefore have a substantial impact on public health in the United States. Data from population-based epidemiologic studies of critical illnesses are essential for understanding the mechanism, trends, and burden of these diseases.

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