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A 12-month clinical survey of incidence and outcome of acute respiratory distress syndrome in Shanghai intensive care units

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Abstract *Objective:* To investigate incidence, causes, and outcome of acute respiratory distress syndrome (ARDS) in adult patients admitted to intensive care units (ICU) in Shanghai. *Design:* A prospective 12-month survey during 2001–2002 of the predispositions, clinical management strategies, complications, and 90-day survival rates of patients with ARDS. *Patients and setting:* Fifteen ICU in 12 university hospitals in Shanghai. All ICU admissions ≥15 years of age in the 12-month period were assessed. Patients fulfilling diagnostic criteria of ARDS, as defined by the American–European Consensus Conference, and having a continuous treatment period ≥24 h, were recruited. *Measurements and results:* Of 5320 adult patients admitted to ICUs, there were 108 (2%) with ARDS. At inclusion, ARDS patients had a mean PaO_2/FiO_2 value of 111.3±40.3 mmHg and a mean acute physiology and chronic health evaluation score (APACHE II) of 17.3±8.0; 33 patients had a lung injury score >2.5. Forty-one and 67 patients had ARDS associated with diseases of pulmonary and extrapulmonary origin, respectively. The most common predisposing factors for ARDS were pneumonia (34.3%) and nonpulmonary sepsis (30.6%). The overall ICU mortality was 10.3%. In-hospital and 90-day mortalities of ARDS patients were 68.5 and 70.4%, respectively, and accounted for 13.5% of the overall ICU mortality. For ARDS patients, multiple organ dysfunction syndrome was a major risk factor associated with death (59.5%). *Conclusion:* The high morbidity and mortality of ARDS in the ICUs in Shanghai require reassessment of respiratory and intensive care management and implementation of effective therapeutic interventions.

Keywords Acute respiratory distress syndrome · Respiratory therapy · Risk factors

Introduction

The acute respiratory distress syndrome (ARDS) has a high morbidity and mortality in adult patients admitted to intensive care units (ICUs), and its pathogenesis is in most circumstances related to acute injury and inflammation in the lungs due to intra- or extra-pulmonary causes [1]. Clinically, ARDS is characterized by arterial hypoxemia, bilateral lung infiltrates seen on the chest radiograph, dependence on mechanical ventilation with high levels of airway pressure and inspired oxygen, and pulmonary artery occlusion pressure insufficient to explain the clinical findings [2]. Several recent clinical epidemiological studies have reported the incidence rates of ARDS as 16–28 per 10^5 persons per annum with mortality ranging from 30 to 61% [3, 4]. Recent results from various clinical trials suggest that mortality of ARDS may be as low as 40%, with further reduction associated with a lung-protective ventilation strategy using small tidal volumes [5].

In China, with economic growth in the past decades, levels of respiratory care have been raised significantly in ICUs of level-III municipal and general hospitals [6]. While pulmonary infection and sepsis remain major causes of severe respiratory failure and ARDS, the incidence of multiple organ dysfunction syndrome (MODS), trauma, and immunosuppression are increasing considerably in these hospitals due to various causes, including natural disaster, traffic and construction accidents, organ and tissue transplantation, and chemotherapy. To date, no systematic study in multicenters has been conducted prospectively in major cities in China to determine the incidence, risk factors, clinical management, and outcome of ARDS; therefore, we performed a prospective, multicenter study to survey the incidence, predispositions and outcome of ARDS. Cases were defined using the American–European Consensus Conference (AECC) criteria [2], and we performed the study in 12 months period in 15 ICUs from 12 university-affiliated general hospitals and hospitals for chest diseases in Shanghai. Part of our results has previously been presented in abstract form at an international meeting [7].

Methods

The study protocol was approved by the scientific and ethics committees of the participating hospitals. Fifteen ICUs in 12 university-affiliated general hospitals and hospitals for chest diseases with resources to treat adult patients with conventional mechanical ventilation (CMV) participated in the study. Of the 15 ICUs, there were 8 for respiratory, 4 for surgical, 1 for medical, and 2 for interdepartmental care. Relatives agreed to the participation of the patients in the survey. All ICU admissions $\geq$15 years of age in 1 March 2001 and 28 February 2002 were surveyed. Patients fulfilling diagnostic criteria for ARDS and treated continuously in the ICU for $\geq$24 h were recruited. Patient diagnoses involved common surgical and medical disorders including immunosuppression, but patients admitted for burn treatment were excluded.

The diagnostic definition of ARDS proposed by the AECC was used [2]. All ICU patients admitted were examined daily for the development of ARDS. To ensure accuracy of the diagnosis of ARDS, the following steps were applied. Firstly, to obtain accurate values for PaO_2/FiO_2 for 27 patients treated without endotracheal intubation, we used a three-way connector and tight-fitting face mask to provide inhalation of 100% oxygen for 20 min at study entry. For 81 patients subjected to CMV via an endotracheal tube, or a bilevel-positive airway pressure (Bi-PAP) face-mask ventilator (BiPAP Vision, Respironics, Murryville, Pa.), PaO_2/FiO_2 was calculated directly from the blood gas values and ventilator generated FiO_2. Secondly, the chest radiographs of all patients were evaluated by experienced radiologists to assure bilateral infiltration as compliance with ARDS criteria. Thirdly, cardiac function of all included patients was assessed using clinical judgment or echocardiography, and there was no evidence of left atrial hypertension in any patient. The lung injury score (LIS) of Murray et al. [8] was applied at study entry to describe the severity of lung injury in ARDS using three or more score components (PaO_2/FiO_2, chest radiograph, PEEP value, and respiratory system compliance), and a score >2.5 was used to grade a patient as having severe lung injury. To predict hospital mortality risk for ARDS patients, we used the acute physiology and chronic health evaluation (APACHE II) score [9] in all ICUs. The MODS was determined daily using the following criteria established for specific organ failures [10]:

1. Renal failure: serum creatinine >2.0 mg/dl or patient requiring dialysis or urine output <20 ml/h for over 6 h
2. Cardiovascular failure: mean arterial blood pressure <50 mmHg, ventricular fibrillation, II–III degree atrioventricular block, or cardiac arrest
3. Coagulopathy: platelet count $<50\times10^9$/l or prothrombin time or partial thromboplastin time >3 s compared with the control, or hemorrhagic diathesis
4. Hepatic failure: bilirubin >34.2 μmol/l or serum glutamic pyruvic transaminase two times higher than the control level, or hepatic encephalopathy.
5. Central nervous system failure: absence of response to sound and pain stimulation (not attributable to a sedative drug effect or a primary central nervous system event)
6. Gastrointestinal failure: ileus lasting >24 h or bleeding from stress ulcer requiring transfusions

Sepsis and septic shock were diagnosed according to the criteria reported elsewhere [11].

Study monitoring procedure and validation of study inclusion

To monitor compliance with study inclusion criteria, we organized a steering committee and a task force group. The latter group consisted of one attending or senior resident physician from each ICU and was responsible for data capture. The total ICU admissions were used to calculate the study inclusion rate, and the daily reports of included patients were later reviewed for completeness. The steering committee discussed all the included cases at the end of every month to verify compliance with AECC criteria and resolve inconsistencies. A 24-h telephone service was established to provide immediate answers to questions regarding study procedure.

Data collection

Data were collected at the times of screening and study inclusion, and daily until discharge or death. Recorded demographic data included age, gender, body weight, and height. Left atrial hypertension was determined by transthoracic echocardiography or by clinical judgment. Severity of disease was based on calculation of LIS and APACHE II score at the time of ARDS diagnosis. The APACHE II score included an assessment of chronic diseases and a Glasgow Coma Score; if the patient was sedated, the best estimate of the pre-morbid Glasgow Coma Score was used. Each investigator was asked to identify the principal cause or causes for the development of ARDS from a list suggested by Lewandowski et al. [12]. To distinguish between pulmonary and non-pulmonary causes for the development of ARDS, we defined the former as a disease process confined to the lung with the pleura as the outer perimeter. Development of ARDS after elective or acute surgery was also noted. Ventilatory mode and settings were recorded. Survival to 90 days after inclusion was determined by telephone inquiry for all of the patients discharged.

Statistical analysis

Continuous variables were compared using Student's *t*-test. Chi-square test was used to compare categorical variables. Multivariate Cox regression model was used to independently assess variables that, in a univariate analysis (using multiple-logistic-regression model), were associated with mortality or that were considered to be predictive factors of clinical importance. Differences with a

value of $p<0.05$ were considered statistically significant. The statistical software SPSS (version 10.0; SPSS, Chicago, Ill.) was used for all statistical calculations. Values are presented as mean±SD unless otherwise noted.

Results

Patient inclusion

During the 12-month period there were 5320 ICU admissions, of which 548 died in the hospitals. ARDS was diagnosed in 108 patients, representing approximately 2.0% of all the ICU admissions. The patient age was 58.8±16.4 years, and 64 men and 44 women were included (Table 1). The ARDS patients were diagnosed at 3 days (median; range 1–36 days) after admission. Twelve patients were first subjected to Bi-PAP face-mask ventilation, and then converted to CMV. Seventeen patients were mechanically ventilated for a median of 2 days (range 1–8 days) before inclusion. At the time of diagnosis of ARDS, PaO_2/FiO_2 values for intubated and nonintubated patients were 111.6±41.3 and 110.5±37.7 mmHg, respectively. The temporal distribution of new cases during the 1-year period is shown in Fig. 1. There were statistically significant differences in the monthly frequencies of new ARDS cases (χ^2 square test, $p=0.001$).

Table 1 Clinical characteristics of patients with acute respiratory distress syndrome (*ARDS*) at study entry

	ARDS patients
Age (years)	58.8±16.4
Female/male	44/64
APACHE II score	17.3±8.0
PaO_2/FiO_2 (mmHg)	111.3±40.3
Pulmonary origin/nonpulmonary origin	41/67

Causes of ARDS

One or more causes for ARDS were noted for each of the 108 ARDS patients, and 41 patients (38%) had ARDS of pulmonary origin. The underlying diseases and major predispositions associated with the development of ARDS are presented in Table 2. Patients with pulmonary ($n=1$) or extrapulmonary ($n=5$) malignant tumors were diagnosed with ARDS after surgery. Emergent or elective surgery preceded the development of ARDS in 13.9% ($n=15$) or 7.4% ($n=8$) of the patients, respectively. Sepsis was the major cause for ARDS in patients after renal transplantation ($n=10$), with immunologic diseases ($n=7$), or with hematologic diseases ($n=3$), and was ascribed to immunosupression due to prolonged use of steroids or other immunosuppressive drugs. Pneumonia was the most common cause of direct ARDS ($n=37$, 34.3%). Extrapulmonary predispositions mainly consisted of nonpulmonary sepsis ($n=33$, 30.6%), acute pancreatitis ($n=15$, 13.9%), surgical insult ($n=12$, 11.1%), and trauma ($n=8$, 7.4%).

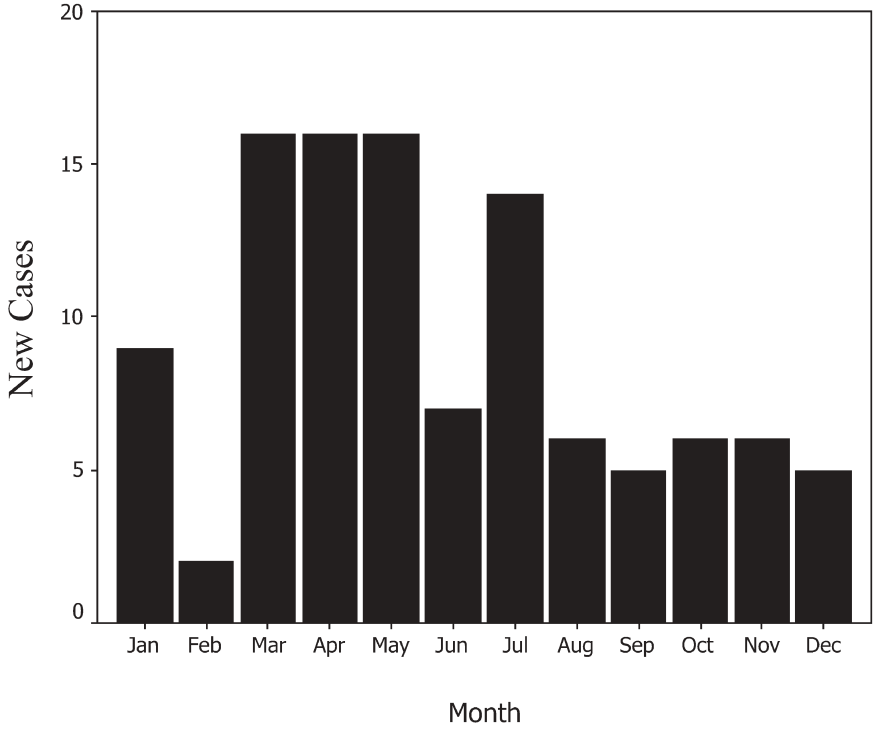

Fig. 1 Monthly distribution of new cases of ARDS among 15 intensive care units from 12 hospitals in Shanghai

Table 2 Underlying diseases and principal predispositions for development of ARDS and corresponding outcome in 108 patients with ARDS

	ARDS patients (*n*=108)	Died (*n*=74)
Pulmonary origin	41	32
Aspiration	2	1
Near drowning	1	1
Surgery for lung cancer	1	1
Pneumonia (bacteria, viruses, protozoa)	37	29
Extrapulmonary origin	67	42
Cardiovascular system		
Vascular surgery	3	3
Infection associated with cerebrovascular accident	4	4
Digestive system		
Surgery for esophageal or cardiac neoplasms	3	–
Pancreatitis	15	7
Peritonitis	6	4
Surgery for liver cancer	1	1
Bacterial colitis	1	1
Urogenital system		
Urinary sepsis	1	–
Renal transplantation	10	7
Ureterostenosis surgery	1	–
Blood system		
Acute leukemia	2	1
Idiopathic thrombocytopenic purpura	1	1
Skeletal system		
Traumatic bone fracture	3	1
Others		
Multisystem trauma	5	4
Immunologic disorder	7	5
Sepsis of unknown origin	1	1
Sublingual gland surgery	1	–
Herniorrhaphy	1	1
Epilepsy with infection	1	1

Lung injury score

Lung injury score (LIS) was measured at study inclusion for 69 ARDS patients who were subjected to CMV. Thirty-three intubated patients with LIS score >2.5 had the following characteristics: age 59.3±18.0 years; mean PaO_2/FiO_2 101.2±33.2 mmHg; APACHE II 19.0±6.4; and mean LIS 3.13±0.47. Thirty-six intubated patients with LIS $\leq$2.5 (mean value 1.85±0.49) had the following characteristics: age 62.3±13.9 years; mean PaO_2/FiO_2 120.4±46.6 mmHg; APACHE II 19.2±9.7. No significant differences in these values or in in-hospital and 90-day mortality were observed between patients with LIS $\leq$2.5 and those with LIS >2.5. In another 12 ARDS patients, Bi-PAP was provided for 24–72 h and subsequently converted to CMV through tracheotomy (*n*=3) or endotracheal intubation (*n*=9). The LIS was not applied and 6 of them died.

Respiratory support

Twenty-seven patients were not intubated; of these, 13 (12.4% of total) were treated with supplemental oxygen and continuous positive airway pressure or Bi-PAP, 8 (7.4%) were given supplemental oxygen via mask, and 6 (5.6%) received supplemental oxygen via nasal cannulae. The CMV was provided to all 31 (28.7% of total) tracheotomized, and 50 (46.3% of total) endotracheally intubated, ARDS patients. The median duration of mechanical ventilation was 9 days (range 1–80 days). During the treatment period of ARDS in ICU, the most commonly used ventilatory mode was synchronized intermittent mechanical ventilation (26 of 81, 32.1%) followed by volume control (24 of 81, 29.6%) and Bi-PAP (11 of 81, 13.6%). The values for the highest tidal volume and positive end expiratory pressure in patients during treatment were 8.1±1.7 ml/kg (range 4.4–13.2 ml/kg) and 8.5±2.9 cmH_2O (range 5–20 cmH_2O), respectively. The peak inspiratory pressure during the first day after inclusion was 27.1±8.7 cm H_2O.

Mortality

During the 1-year period, the overall mortality in all 15 ICUs was 10.3% (548 of 5320). Mortality rate in patients with ARDS represented 13.5% of all nonsurvivors in these ICUs. In-hospital mortality of patients with ARDS was 68.5%. The highest mortality rate (88.2%) was found in patients aged 75 years or older. No statistically significant difference in mortality was found between those age >65 years and $\leq$65 years (72.7 vs 65.6%, p=0.435). The MODS was the leading cause of death in patients

Table 3 Major causes of death in 74 ARDS patients during hospitalization. *MODS* multiple organ dysfunction syndrome

Cause	Nonsurvivors
MODS	44 (59.5)
Respiratory failure	17 (23.0)
Septic shock	9 (12.2)
Others	4 (5.4)

Numbers in parentheses are percentages

with ARDS (59.5%), and intractable respiratory failure and septic shock were the second and third most common causes of death (23 and 12.2%, respectively; Table 3). The 90-day mortality for patients with ARDS was 70.4%. The in-hospital and 90-day mortalities for patients with LIS >2.5 (n=44) were 61.4, and 63.6%, respectively. In-hospital mortalities in intubated and non-intubated patients were 72.8 and 55.6%, respectively (difference not significant). The in-hospital mortalities in respiratory, surgical, medical, and interdepartment ICUs were 75.5, 45.8, 70.8, and 81.8%, respectively.

S1 (see table in electronic supplementary material) show both uni- and multivariate analyses for determination of factors contributed independently to the mortality. In the multivariate model, causes of pulmonary origin, total APACHE II score >15, and chronic cardiovascular diseases were marginally significant in predicting mortality. Six patients with chronic respiratory disease were included as a result of acute onset of respiratory failure, but chronic respiratory diseases per se had no significant value for predicting mortality (S1B, see table in electronic supplementary material).

Discussion

We prospectively surveyed admissions to 15 ICUs in Shanghai during a 12-month period, and found an incidence of ARDS of approximately 2%, which is similar to that reported by Baumann et al. [13], Webster et al. [14], and Fialkow et al. [15]. Shanghai is a metropolitan city of 13 million permanent residents and 4 million transients. The medical care system, especially that found in ICUs at university teaching hospitals in Shanghai, represents the highest service quality of the country. We initiated this study based on ICU admissions in view of the incompleteness of data for estimating the population-based incidence of ARDS in Shanghai.

In a previous study, Baumann et al. [13] found a 2% incidence of ARDS among high-risk patients arriving at a large metropolitan hospital emergency room. Their criteria for ARDS included an arterial/alveolar PO_2 ratio <0.2 in intubated patients, or $PaO_2 \leq 50$ mmHg for non-intubated patients breathing oxygen at FiO_2>0.6. In a retrospective study, an ARDS incidence of 2.5% of all admissions to intensive therapy units in the UK in 1985, in which most ICUs used a figure for PaO_2/FiO_2 of less than 120 mmHg was described [14].

Definition of ALI and ARDS using the AECC standards is utilitarian and has been applied frequently. Two French studies reported that of all ICU admissions, approximately 7% met the AECC criteria for ARDS [16, 17]. The ARDS was reported in 6.1% of 6522 admissions to ICUs in 78 European countries [18]. Recently, in a 4-month prospective multicenter cohort of mechanically ventilated patients admitted to four ICUs in Argentina, 235 (7.7%) of 3050 patients met the AECC criteria of ARDS [19]. An incidence of 2.3% was reported in a 2-month prospective cohort study in the ICU of a Brazilian general university hospital [15]. Bersten et al. [3] reported an ARDS incidence of 7.5% in 21 adult ICUs in Australia and New Zealand, and an even higher incidence (8.1%) was reported recently in Scottish ICUs [4]. Our findings of an incidence of 2% ARDS in ICU admissions in Shanghai is somewhat lower than these figures. Geographical variations, differences in diagnostic definitions and type, and strength of the study designs may have contributed to the variations observed among these different studies.

In a 1991 prospective multicenter 2-month study in Berlin using LIS >2.5 as a criteria for ARDS [12], survey of adult patients from 72 ICUs indicated a population incidence of 3.2 per 10^5 persons per year. Luhr et al. [20] showed that the incidence was 13.5 patients per 10^5 persons per year for ARDS in Sweden, Denmark, and Iceland in 1997. In a retrospective study, the incidence of ARDS in an adult population in Kaiser Permanente of northeast Ohio from April 1996 to March 1999 was 15.3 per 10^5 persons per year [21], which is comparable to other reports [4, 20]. The incidence of acute lung injury (ALI) in the United States is estimated at 64.2 cases per 10^5 persons per year [22]. It appears that the various methodologies for identifying patients with ARDS are all imperfect, as they may be influenced by many factors that may, or may not, be controlled during investigation.

In this study, the in-hospital mortality and 90-day mortality of the ARDS patients were 68.5 and 70.4%, respectively, which contrast with the results of some recent studies in which mortality was approximately 40% [5, 20]. Our results showed that an APACHE II score >15 was marginally significant in predicting mortality. Since the APACHE II scoring system is based on very old data (1979–1982), those data may not predict the patient outcomes achieved by modern medical practice, and thus APACHE II may no longer be considered an appropriate, accurate, or contemporary method for risk-adjusted mortality prediction for ICU patients (http://www.apache-msi.com/solutions/Alert. 15 May 2004).

Zilberberg and Epstein [23] found similar mortality in patients with PaO_2/FiO_2 <300 mmHg compared with those <200 mmHg at the time of first recognition of ALI. Doyle et al. [24] found similar mortality rates in patients with PaO_2/FiO_2 <300 mmHg compared with those

<150 mmHg. Luhr et al. [20] found the same mortality in ARDS, ALI, and patients ventilated for 24 h or more. Bone et al. [25] also found that PaO_2/FiO_2 at early stage of ARDS did not affect outcome, but reported that improvement in PaO_2/FiO_2 was correlated with survival [26]. Krafft et al. [27], in a meta-analysis of 101 publications on ARDS, found no correlation between PaO_2/FiO_2 and mortality. Furthermore, in a multivariate analysis of patients with ARDS, Luhr et al. [20] found that an independent association with mortality could be shown by a PaO_2/FiO_2 <100 mmHg. In contrast to these reports, Brun-Buisson et al. [18] reported that the crude ICU and hospital mortalities were 22.6 and 32.7% ($p<0.001$), and 49.4 and 57.9% ($p=0.0005$), respectively, for mild ALI ($200<PaO_2/FiO_2<300$) and ARDS, suggesting an influence of oxygenation impairment severity on mortality.

Clinical management may significantly affect the fatality rates in patients with ARDS. A quarter of our ARDS patients were ventilated noninvasively. ARDS patients have impaired pulmonary mechanics and severe hypoxemia, which frequently necessitate intubation. The outcome for patients with ARDS is not improved by the use of noninvasive ventilation [28]. Other interventions, including lower volume ventilation, have been shown to significantly improve survival [5]; however, high-frequency oscillation [29], combined respiratory care, and life support using extracorporeal membrane oxygenation (ECMO) and inhaled nitric oxide [30], and prone position ventilation [31], have not been shown rigorously to improve overall mortality, and were not administered to the patients in this study. Suchyta et al. [32] reported that for ARDS patients meeting the criteria for ECMO, mortality was in the range of 60% or higher. Luhr et al. [20] found the 90-day mortality for ARDS in Sweden, Denmark, and Iceland in 1997 was 41.2%. The latest mortality of patients with ARDS in the ICUs of Argentina [19] and Brazil [15] was 58 and 46.7%, respectively. The differences between our results and those of the previous reports are likely due to inadequate respiratory care, such as standardized CMV and appropriate fluid management, and other therapeutic approaches necessary for mitigation of persistent hypoxemia, and intractable respiratory failure and lung injury. We believe that with improved respiratory care and targeted respiratory therapies, including use of a lower tidal volume, ventilation strategy a substantial reduction in mortality of our ARDS should be expected.

As MODS is the most common cause of death in patients with ARDS, to alter significantly the mortality of ARDS, a treatment must also be effective against MODS. Most studies have shown that nonsurvivors of ARDS usually die of nonrespiratory causes. Montgomery et al. [33] showed that only 16% of deaths were caused by respiratory failure. In a series of 129 patients with ARDS, 50% of the nonsurvivors died of sepsis/multiple organ failure, while 16% died of respiratory failure [34]. Roupie et al. [17] found that septic shock accounted for 45% of the mortality of patients with hypoxemic respiratory failure. There was also a trend toward higher mortality for immunosuppressed patients. Similarly, Bersten et al. [3] found that, while pulmonary failure contributed to the death of 24% patients, multiple organ dysfunction was the commonest single cause, accounting for 50%. Our study demonstrated that pneumonia (34.3%) was the most common direct insult, and sepsis (30.6%) was by far the most common indirect insult. Due to long-term use of steroids or chemotherapy, patients after renal transplantation or with malignant tumors were apt to develop infection, and the rates of ARDS in these patients are similar to observations elsewhere [1, 35]. The MODS was the leading cause associated with the mortality in patients with ARDS, while 23% of the patients died of intractable respiratory failure. The overriding influence of nonpulmonary organ dysfunction in determining mortality was evident. This suggests that the mechanisms by which ARDS develops and death occurs should be explored, and effective interventions be applied to mitigate or abolish lung injury and extra-pulmonary organ system dysfunction and failure; therefore, we favor establishment of an ARDS network among local ICUs to facilitate collaborative studies and to conduct clinical trials to combat ARDS.

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