Original Article

Incidence of acute lung injury and acute respiratory distress syndrome in the intensive care unit of a university hospital: a prospective study*

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ABSTRACT

Objective: To establish the incidence of acute lung injury and acute respiratory distress syndrome, as well as related risk factors and mortality in an intensive care unit. To compare patients developing lung injury with at-risk patients not presenting acute lung injury or acute respiratory distress syndrome. **Methods:** The study was conducted in the intensive care unit of the Ribeirão Preto Hospital das Clínicas Emergency Room. All patients admitted between May 2001 and April 2002 were monitored prospectively. Clinical data, Acute Physiologic and Chronic Health Evaluation II score, complications, length of stay in the intensive care unit and lung injury data were recorded. **Results:** Of the 524 patients admitted, 175 (33.4%) presented risk factors for acute lung injury and acute respiratory distress syndrome, 33 (6.3%) developed acute respiratory distress syndrome, and 12 (2.3%) developed acute lung injury. The main risk factors were pneumonia (37.7%), shock (32.0%), multiple trauma (24.6%) and sepsis (21.1%). Patients developing acute lung injury had higher Acute Physiologic and Chronic Health Evaluation II scores ($p < 0.05$), more frequently presented sepsis ($p = 0.001$), developed more complications ($p = 0.001$) and presented greater mortality ($p = 0.001$). The main cause of death was multiple organ failure (38.5%). **Conclusion:** The incidence of acute lung injury and acute respiratory distress syndrome was 2.3% and 6.3%, respectively.

Keywords: Respiratory distress syndrome, adult/epidemiology; Respiratory distress syndrome, adult/mortality; Risk factors; Hospitals, University

*Study conducted in the Emergency Room of the Universidade de São Paulo (USP, University of São Paulo) at Ribeirão Preto School of Medicine Hospital das Clínicas, Ribeirão Preto, São Paulo, Brazil

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) was first described in 1967 in twelve patients presenting acute respiratory failure that was refractory to oxygen therapy, together with decreased pulmonary compliance and diffuse infiltrate on chest X-ray.[1] Although this syndrome was given a name (at that time, "adult respiratory distress syndrome"), there were no well-established criteria for its diagnosis. In 1988, a lung injury score was created in order to diagnose and evaluate ARDS severity, taking into account four parameters: chest X-ray, hypoxemia through the arterial oxygen tension/fraction of inspired oxygen ratio, pulmonary compliance and positive end-expiratory pressure (PEEP).(2 It was not until 1994 that the American European Consensus Conference on ARDS established diagnostic criteria for ARDS, defining it as a "syndrome of inflammation and increased pulmonary capillary permeability accompanied by a large number of clinical, radiological and physiological abnormalities, which are not caused by pulmonary capillary hypertension but may coexist with it".[3] On that occasion, acute lung injury (ALI) was defined as a clinical profile of acute respiratory failure with bilateral infiltrate on chest X-ray, no left atrial hypertension (pulmonary capillary pressure less than or equal to 18 mmHg) and hypoxemia presenting an arterial oxygen tension/fraction of inspired oxygen ratio less than or equal to 300. If this ratio is less than or equal to 200, the patient is considered to have ARDS (Chart 1). Correlations between ARDS and several conditions or risk factors that lead to the inflammatory reaction and lung injury, be they direct (as is the case for pneumonia, aspiration of gastric content and chest trauma) or indirect (as are those found for sepsis, pancreatitis, shock and multiple trauma), were also established.[3-12]

The incidence of ARDS and ALI is still uncertain, even in the USA, where the National Institute of Health estimated it to be 75 cases/100,000 inhabitants for the year 1972. However, more recent studies have found considerably lower numbers, ranging from 1.5 to 15/100,000 inhabitants/year.[3-5,8-16] Since the 1994 American-European Consensus Conference on ARDS, at which the diagnostic criteria were redefined, the number of epidemiological studies has been steadily growing. In intensive care units (ICUs), ARDS is seen in 2% to 26% of all hospitalized patients, and the highest rates are observed among patients on mechanical ventilation.[8-12,17] In Brazil, no population studies have been conducted. To date, only two studies of ARDS and ALI frequency have been carried out in Brazil. In one of those studies, which was conducted in the Federal University of Rio Grande do Sul at Porto Alegre Hospital das Clínicas, the frequency of ALI was found to be 3.8%, compared with 2.3% for ARDS.[18] The other study was carried out at the Sírio Libanês Hospital in the city of São Paulo (state of São Paulo).[19] The authors of that study found the frequencies of ALI and ARDS to be 1% and 2%, respectively.[19]

The objectives of the present study, conducted in the ICU of a university hospital, were to determine the incidence of ALI and ARDS using the criteria established by the American-European Consensus Conference on ARDS, to describe the principal related risk factors, to calculate mortality among patients presenting lung injury, and to compare the outcomes in patients developing lung injury (group 1) with those seen in at-risk patients presenting no ARDS/ALI (group 2).

METHODS

The present study was conducted in the ICU of the Ribeirão Preto Hospital das Clínicas Department of Emergency Medicine between May of 2001 and

Chart 1 - Diagnostic criteria for ALI and ARDS according to the American-European Consensus Conference on ARDS held in 1994

	Chest X-ray	Beginning	Oxygenation	OPAP
ALI	Bilateral infiltrate	Acute	$PaO_2/FIO_2 \leq 300$	≤ 18 mmHg No left atrial hypertension
ARDS	Bilateral infiltrate	Acute	$PaO_2/FIO_2 \leq$" 200	≤ 18 mmHg No left atrial hypertension

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; OPAP: occluded pulmonary artery pressure; .PaO_2/FIO_2: arterial oxygen tension/fraction of inspired oxygen ratio

April of 2002, after being approved by the ethics in research committee of the institution. This ICU a referral center for trauma treatment and operates under the auspices of the State of São Paulo XVIII Regional Health Directorate, which serves 25 municipalities. It has 163 beds divided among clinical medicine, surgery, neurology, orthopedics, pediatrics, gynecology, burn treatment, pediatrics and general medicine. The present study was conducted on the general medicine ward, which has 16 beds divided into two units. The attending physicians who work full time in the ICU were aware of the fact that an observational study on ARDS was being conducted, whereas the attending physicians who work night or weekend shifts, as well as resident physicians specializing in intensive care medicine or other areas, might not have been.

All patients admitted with one or more risk factors for lung injury, as established by Ware et al. in 2000,(4) and remaining in the ICU for more than 24 hours were monitored prospectively, on a daily basis, in order to detect the development of lung injury. All other patients were observed daily in order to detect the onset of risk factors during the stay in the ICU.

The ARDS/ALI diagnosis was made according to the criteria established at the 1994 American-European Consensus Conference on ARDS[3] (Chart 1). In order to systematize the ARDS/ALI diagnosis, all chest X-rays were evaluated by the same researcher, who had experience in the area. The exclusion criterion was remaining in the ICU for less than 24 hours. For each patient, a form was used to collect personal data, as well as data regarding the Acute Physiologic and Chronic Health Evaluation (APACHE II) score,[20] diagnosis, presence of chronic disease, reason for admission to the ICU, complications and outcome (discharge or death in the ICU). Cardiac function was evaluated using either a pulmonary artery catheter or an echocardiogram. The choice between the two was made by the treatment team, and there was no interference with the treatment routine of the patients.

We studied the following risk factors[4]: pneumonia; sepsis (defined using the criteria established at the 1992 Society of Critical Care Medicine Consensus Conference)[21]; aspiration of gastric content (in the presence of a medical team) or tracheal tube aspirate; prolonged hypotension or shock; pulmonary contusion; multiple trauma (defined as fracture of one or more long bones or pelvic fracture); isolated chest trauma; isolated skull-brain trauma; multiple transfusions (defined as transfusion of at least 10 units of packed red blood cells within 24 hours); fat embolism; acute pancreatitis; drowning; and smoke inhalation injury. Since no surgical procedures using extracorporeal circulation are performed in this department of emergency medicine, this risk factor was not added.

Patients were divided into two groups: Group 1 was composed of patients who developed ARDS/ALI, and Group 2 was composed of at-risk patients who did not.

We also analyzed the characteristics of the lung injury of the patients in Group 1, categorizing it as pulmonary or extrapulmonary in origin. In addition, the Murray severity score[2] was determined. Data regarding pulmonary function and hemodynamics were collected on the day the lesion was diagnosed or on the day the patient was admitted to the ICU. All patients were monitored until discharge from or death in the ICU.

The results are expressed as means ± standard deviation. The variables were analyzed using the Kolmogorov-Smirnov normality test. The comparison between the groups was carried out using Fisher's exact test for nominal variables and the Student's t test for continuous variables. The Graphpad Instat® statistical program was used, and values of $p < 0.05$ were considered statistically significant.

RESULTS

In the period studied, there were 524 ICU admissions, and 175 patients (33.4%) presented one or more risk factors for the development of lung injury. Of those, 25 developed ARDS, and 12 developed ALI. Table 1 shows the characteristics of the patients studied.

The most frequent risk factors were pneumonia (in 66 patients, 37.7%), shock (in 56, 32.0%), multiple trauma (in 43, 24.6%), sepsis (in 37, 21.1%) and multiple transfusion (in 27, 15.4%). In some cases, more than one risk factor was identified for the same patient. Eighteen patients developed risk factors after being admitted to the ICU. Of those, 15 presented nosocomial pneumonia, and 3 developed sepsis. A total of 92 patients presented only one risk factor, 56 presented two, 25 presented three, and 2 presented four. The percentage of patients with lung

TABLE 1

Characteristics of patients admitted to the ICU presenting risk factors for lung injury, divided into Group 1 (with ARDS/ALI) and Group 2 (without ARDS/ALI)

Characteristic	GROUP 1 ARDS (N = 25)	ALI (N = 12)	GROUP 2 (N = 138)
Age (years)	46.3 ± 19.6	37.5 ± 21.3	44.9 ± 20.5
Gender (male)	17 (68%)	10 (83%)	102 (74%)
APACHE II score	19.2 ± 5.4*	17.0 ± 5.3	16.8 ± 0.47
Presence of comorbidities	14 (56.0%)	6 (50.0%)	67 (48.5 %)
Clinical admission	16 (64.0%)	7 (58.3%)	39 (59%)
Risk factors			
Pneumonia	12 (48%)	4 (33.3%)	50 (36.2%)
Shock/hypotension	9 (36%)	5 (41.6%)	32 (30.4%)
Sepsis	11 (44%)**	6 (50%)	20 (14.5%)
Multiple trauma	5 (20%)	2 (16.7%)	31 (22.5%)
Multiple transfusions	6 (24%)	1 (8.3%)	20 (14.5%)
Length of ICU stay (days)	11.2 ± 15	11.1 ± 7.8	11.9 ± 0.9
Time on mechanical ventilation (days)	9.3 ± 12.3	8.2 ± 4.6	9.2 ± 0.9
Complications	19 (76%)**	5 (41.6%)	56 (40.6%)
Death in the ICU	21 (84%)**,#	6 (50%)	51 (37%)
Cause of death			
MOF	11 (52.4%)	3 (50%)	16 (31.4%)
Septic shock	6 (28.6%)	3 (50%)	10 (19.6%)

ICU: intensive care unit; ARDS: acute respiratory distress syndrome; ALI: acute lung injury; APACHE II: acute physiologic and chronic health evaluation(20); MOF: multiple organ failure. z'*p < 0.05 between ARDS and Group 2; **p < 0.001 between ARDS and Group 2; #p <0.05 between ARDS and ALI

TABLE 2

Percentage of lung injury in patients admitted to the intensive care unit presenting at least one risk factor for ARDS/ALI*

Risk factor	Total	Lung injury	%
Pneumonia	66	16	24,2
Shock	56	14	25,0
Multiple trauma	43	7	16,3
Sepsis	37	17	45,9
Multiple transfusion	27	7	25,6
BST	23	1	04,3
Chest trauma	10	1	10,0
Pancreatitis	7	2	28,6
Pulmonary contusion	6	4	66,7
Aspiration of gastric content	4	2	50,0

*Risk factors assessed(4): pneumonia, sepsis,(21) aspiration of gastric content, prolonged hypotension or shock, pulmonary contusion, multiple traumatism, isolated chest trauma, isolated brain-skull trauma, multiple transfusion, fat embolism, acute pancreatitis, drowning, inhalation injury; ARDS: acute respiratory distress syndrome; ALI: acute lung injury; BST: brain-skull trauma.

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injury by number of risk factors was 13%, 28.6%, 32% and 50% for those presenting one, two, three and four risk factors, respectively. The percentage of patients who developed ARDS/ALI according to each risk factor is shown in Table 2. The risk factors associated with the highest rates of lung injury were sepsis, pulmonary contusion and aspiration of gastric content. However, the last two were present in a lower number of patients. Figure 1 shows the frequency of the principal risk factors in each group studied.

Group 1 comprised 37 patients (25 with ARDS and 12 with ALI), accounting for 4.7% of the total ICU admissions for ARDS and of 2.3% of those for ALI. Eight patients with ALI developed ARDS, raising the frequency of the latter to 6.3%. Only 4 patients presented ALI as the sole finding. In the population of patients with at least one risk factor (n = 175), the frequency of ARDS was 18.9% and the frequency of ALI was 6.9%. Data regarding pulmonary function on the day the lung injury was diagnosed are shown in Table 3. Of the 37 patients, 20 were monitored using a pulmonary artery catheter. Patients were ventilated in accordance with the ICU routine: tidal volume between 6 and 8 mL/kg of body weight (as

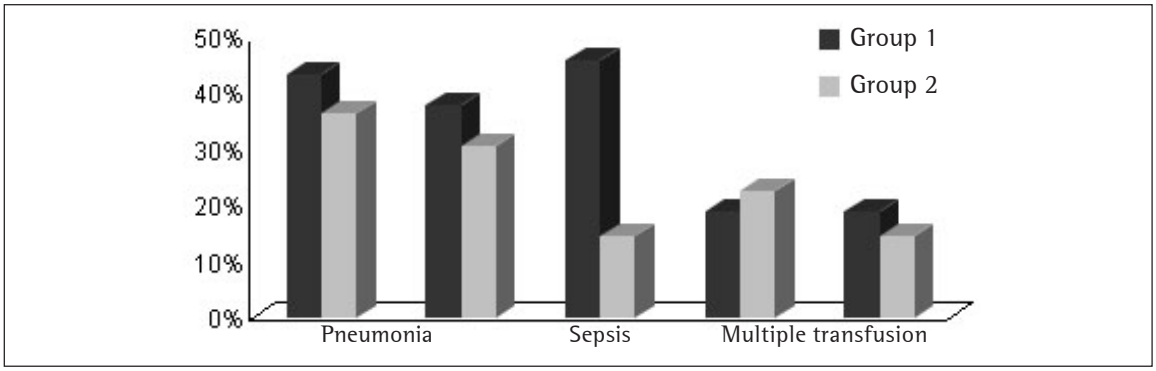

Figure 1- Frequency of the principal risk factors for acute lung injury in group 1 (patients with acute respiratory distress syndrome or acute lung injury) and group 2 (patients without lung injury)

measured upon admission), PEEP corresponding to the best compliance or (if not contraindicated) equal to 16 cmH_2O. Despite presenting hypoxemia (arterial oxygen tension/fraction of inspired oxygen ratio lower than 200), 16 patients were excluded from Group 1 and placed in Group 2. This was done because 5 of those patients presented evidence of cardiac dysfunction on the echocardiogram, 10 presented increased occluded pulmonary artery pressure, and 1 presented chronic respiratory disease with a history of hypoxemia.

Comparison between the groups revealed no statistically significant differences regarding age, gender, type of admission (clinical or surgical), presence of comorbidities, length of hospital stay or time on mechanical ventilation. However, the APACHE II scores, the frequency of sepsis and the rate of complications among ARDS patients were significantly higher than those observed among Group 2 patients: APACHE II score: 19.2 vs. 16.8 (p = 0.04); sepsis: 44% vs. 14.5% (p = 0.001); complications: 76% vs. 40% (p = 0.001) (Table 1). Mortality in the ICU was 84% among ARDS patients, 37% among Group 2 patients, 84% vs. 37% and 50% among ALI patients. There were statistically significant differences between ARDS-related mortality rates and those seen in the other two groups (ARDS vs. Group 2: p = 0.0001; ARDS vs. ALI: p = 0.048). The most frequent comorbidities were systemic arterial hypertension, alcoholism and diabetes mellitus, with frequencies of 13.5%, 13.5% and 5.4% in Group 1, and frequencies of 18.8%, 10.95 and 7.2% in Group 2. There was no difference between the groups. The most frequent complications were sepsis, acute renal failure and the need for tracheotomy, with rates of 21.6%, 16.2% and 13.5%, respectively, in Group 1 and 4.3%, 9.45 and 25.4%, respectively, in Group 2. Only 1 patient (a Group 2 patient) developed pneumothorax during the hospital stay. The leading causes of death were multiple organ failure and septic shock.

TABLE 3

Data regarding pulmonary function on the day the lung injury was diagnosed in the patients admitted to the intensive care unit presenting at least one risk factor for ARDS/ALI (n = 37)

Variable	ALI (N = 12)	ARDS (N = 25)
PaO_2/FIO_2	226.5 ± 39.7	97.8 ± 38.1
PEEP cmH_2O (day 1)	8.7 ± 0.7	10 ± 3.7
Lung injury score	2.27 ± 0.52	3.0 ± 0.5
Compliance (n = 33)	33.0 ± 12.9	28.5 ± 7.2
Direct lung injury	6 (50%)	17 (68%)

ARDS: acute respiratory distress syndrome; ALI: acute lung injury; PaO_2/FIO_2: arterial oxygen tension/fraction of inspired oxygen ratio; PEEP: positive end-expiratory pressure.

DISCUSSION

The principal risk factors for development of lung injury that have been identified since the first studies on ARDS were carried out are sepsis, pneumonia, aspiration of gastric content, multiple trauma and shock due to multiple transfusions.[2-11] This finding has been confirmed in more recent studies.[10-12,14] In a study of 217 ARDS cases in Argentina,[22] sepsis, pneumonia, shock and trauma were found to be

the most frequent risk factors. A study carried out in the city of São Paulo yielded similar results.[19] The present study confirms the significance of pneumonia, sepsis, multiple trauma, shock and multiple transfusion as the most common risk factors in the intensive care setting. The high frequency of multiple trauma is due to the fact that the facility studied is a referral center for the treatment of trauma in the region. However, the percentage of patients with multiple trauma who developed lung injury was much lower than that of those presenting pulmonary contusion, aspiration or sepsis (Table 2). As previously demonstrated in a study conducted in 1998,[6] The combination of risk factors progressively increased the frequency of ARDS/ALI, the rates being 13%, 28,6%, 32% and 50% for the presence of one, two, three and four risk factors, respectively.[6]

The findings that ARDS accounted for 6% and ALI for 2% of the total admissions are within the range reported in the literature (2% to 26% of all ICU admissions). However, these frequencies are higher than those found in national epidemiological studies conducted in the cities of Porto Alegre and São Paulo.[18-19] Comparison with other epidemiological studies is difficult due to methodological differences and, principally, due to the population studied. In a study carried out in Australia, 168 cases of ARDS (8.5%) and 148 cases of ALI (7.5%) were found among a total of 1977 patients admitted to 21 ICUs over a two-month period.[16] In another study, ARDS was identified in 8% of 5183 patients on mechanical ventilation in 361 ICUs over a one-month period, although the objective of that study was not to analyze ALI exclusively.[17] In an eight-week prospective study of 132 ICUs in Northern Europe, the incidences of ARDS found were 1.6% of the total number of admissions and 18% of the patients on mechanical ventilation.[14] In another study, the incidences reported were 7.7% of the total admissions and 20% among patients on mechanical ventilation, in 4 ICUs over a fifteen-month period.[22] In the Acute Lung Injury Verification of Epidemiology (ALIVE) study, a prospective multicenter study involving 78 ICUs in Europe, the frequency of ARDS was 6.1% of the 6522 patients admitted over two months.[23] In Brazil, the authors of a study of acute respiratory failure involving 87 beds designated for intensive care at the University of São Paulo School of Medicine Hospital das Clínicas reported that 14% of the 802 patients evaluated developed ARDS/ALI over the course of the eleven-month study.[24]

Among the patients who presented a risk factor for the development of lung injury (the 175 studied), the frequencies of ARDS and ALI found were 18.8% and 6.9%, respectively. This implies that approximately one out of four patients admitted with a risk factor will develop lung injury.

The frequency of ARDS varies according to each risk factor. Those with the highest rates (20%-40%) are pneumonia, sepsis and aspiration of gastric content.[6-7,11-12] In the present study, the highest rates of lung injury occurred in patients presenting pulmonary contusion (67%), aspiration of gastric content (50%), sepsis (46%) or pancreatitis (28.5%), results that are similar to the high rates found in these groups in previous studies.

The population of the two groups studied comprised young adults, predominantly male. The patients in Group 1 were more critically ill than those in Group 2 and were characterized by a significantly higher APACHE II score as well as by a higher frequency of sepsis, which could explain the high mortality and the development of complications in this group.

Clinical trials conducted over the years have shown that mortality due to ARDS has been progressively decreasing, from 70% in the first studies to a current rate of approximately 36%.[4,10,25] However, because critically ill patients with terminal illnesses are excluded from clinical trials, such trials do not reflect the heterogeneity and severity of the cases seen in the population of an actual ICU. In a clinical trial of the protective ventilatory strategy developed in Brazil in the early 1990s, mortality in the control group was 71%.[26] In a recent observational study of Argentine patients with lung injury, the mortality rate was found to be 58%,[22] similar to the 55% found in the ALIVE study.[23] The high mortality found in the present study might reflect the local reality. Since the hospital in which the study was conducted is a tertiary-care hospital, all patients come from basic health clinics or from other cities. In addition, patients with respiratory failure occasionally have to wait for an ICU bed, which delays the initiation of appropriate ventilatory support. The length of time spent waiting for ICU admission directly correlates with mortality.[24] Despite the large number of patients who are victims of

trauma, who typically present lower mortality,[12,27] many of the patients with lung injury presented sepsis (nearly 50%) or shock (38%), both of which are extremely lethal conditions. Reflections of this fact are the high APACHE II scores of the patients in Group 1 and the causes of death of the patients, mainly multiple organ failure and septic shock.

The limitations of the present study converge with the difficulties in establishing a diagnosis of ARDS. The daily monitoring of patients was performed in an extremely careful manner regarding the onset of lung injury or the appearance of risk factors (such as aspiration and nosocomial pneumonia) so as to prevent the loss of patients. All cases were individually evaluated by the main researcher in order to ensure that the diagnosis would be always made in consonance with the team that treated the patients. According to the literature, the ideal interpretation of chest X-rays would involve a consensus between two physicians who are not participating in the study. Since the present study was observational, we depended on the exams requested by the team for the evaluation of each patient. This might have delayed the diagnosis of lung injury, as was actually observed in some cases of patients presenting ALI without significant hypoxemia. The delay would not reduce the total number of cases, although the less severe ones might have been underestimated. There was no standardization of the ventilator settings used in the evaluation of the arterial oxygen tension/fraction of inspired oxygen ratio. The patients admitted with a diagnosis of lung injury had already been intubated, and PEEP levels were typically above 5 cmH_2O (mean of 10 cmH_2O in Group 1). These patients could have presented poorer oxygenation with lower PEEP levels, and this would not have changed the diagnosis. Only 4 patients with ALI did not develop ARDS and, of those, only 1 was being ventilated using a PEEP level above 5 cmH_2O (8 cmH_2O). That patient might have met the criteria for ARDS if lower PEEP levels had been used.

With regard to the patients in Group 2, 15 individuals with hypoxemia presented ventricular dysfunction or occluded pulmonary artery pressure above 18 mmHg. Of those, 6 died of septic shock or multiple organ failure, and it was not possible to rule out the presence of concomitant lung injury.

The incidence of ARDS and ALI in the heath facility studied was 6.3% and 2.3% of the total number of admissions, respectively, with a mortality of 84% for ARDS and 50% for ALI. The principal related risk factors were pneumonia, sepsis, shock, multiple trauma and multiple transfusions. The APACHE II scores and the mortality of patients with ARDS/ALI were higher than those of the other patients who presented risk factors for the development of lung injury. The leading causes of death were septic shock and multiple organ failure.

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