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Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients

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Abstract *Objective*: To evaluate the prevalence and outcome of the acute respiratory distress syndrome (ARDS) among patients requiring mechanical ventilation.
Design: A prospective, multi-institutional, initial cohort study including 28-day follow-up.
Settings: Thirty-six French intensive care units (ICUs) from a working group of the French Intensive Care Society (SRLF).
Patients: All the patients entering the ICUs during a 14-day period were screened prospectively. Hypoxemic patients, defined as having a PaO_2/FIO_2 ratio (P/F) of 300 mmHg or less and receiving mechanical ventilation, were classified into three groups, according to the Consensus Conference on ARDS: group 1 refers to ARDS (P/F: 200 mmHg or less and bilateral infiltrates on the chest X-ray); group 2 to acute lung injury (ALI) without having criteria for ARDS ($200 < P/F \leq 300$ mmHg and bilateral infiltrates) and group 3 to patients with P/F of 300 mmHg or less but having exclusion criteria from the previous groups.
Results: Nine hundred seventy-six patients entered the ICUs during the study period, 43 % of them being mechanically ventilated and 213 (22 %) meeting the criteria for one of the three groups. Among all the ICU admissions, ARDS, ALI and group 3 patients amounted, respectively, to 6.9 % (67), 1.8 % (17) and 13.3 % (129) of the patients, and represented 31.5 %, 8.1 % and 60.2 % of the hypoxemic, ventilated patients. The overall mortality rate was 41 % and was significantly higher in ARDS patients than in the others (60 % vs 31 % $p < 0.01$). In group 3, 42 patients had P/F less than 200 mmHg associated with unilateral lung injury; mortality was significantly lower (40.5 %) than in the ARDS group. In the whole group of hypoxemic, ventilated patients, septic shock and severity indices but not oxygenation indices were significantly associated with mortality, while the association with immunosuppression revealed only a trend ($p = 0.06$).
Conclusions: In this survey we found that very few patients fulfilled the ALI non-ARDS criteria and that the mortality of the group with ARDS was high.

Key words Acute lung injury · Acute respiratory distress syndrome · Mechanical ventilation

Introduction

Thirty years have elapsed since the first description of the acute respiratory distress syndrome (ARDS) [1]. The actual incidence and the mortality rate of this syndrome are still debated. Significant differences in incidence and mortality rates among studies may be attributed to differences in the type and strength of study designs, as well as to the wide variety of definitions used for this syndrome [2, 3].

Recent reports indicate a trend toward a decreasing mortality rate in ARDS [4]. Because of the frequent modifications of the definition, however, historical comparisons remain difficult [5]. An American-European Consensus Conference on ARDS proposed new definitions, with the aim of having a universally accepted definition to allow more objective comparisons [6]. These definitions tried to include a gradation in the level of hypoxemia, in order to differentiate the various stages of acute respiratory failure [7]. To date, however, only a few studies have used this definition [8, 9, 10, 11, 12]. We thus have little information about the prevalence of this syndrome, using these definitions.

The purpose of our study was prospectively to evaluate the prevalence, characteristics and outcome of ARDS among mechanically ventilated patients within French ICUs, using the most recent definitions proposed by the Consensus Conference. The clinical characteristics of the patients, including etiologies and underlying diseases, and the incidence of associated organ failures were collected. Mortality rate at 28 days and risk factors of deaths were analyzed.

Methods

Study design

A prospective initial cohort study was conducted involving patients admitted during a 14-day period from May 20th to June 2nd, 1996, in 36 (24 medical and 12 mixed medical-surgical) intensive care units (ICUs) (representing 665 ICU beds), participating in a working group of the French Language Society of Intensive Care Medicine (*Société de Réanimation de Langue Francaise;* including Swiss, Belgian and Tunisian members*)*. The 36 ICUs belonged to hospitals with 350–2673 beds (median: 925 ± 609). They were located in university hospitals (25 ICUs), non-university affiliated referral hospitals (6 ICUs) or private institutions (5 ICUs).

For all the patients entering these ICUs during the 2-week period of the study, a daily screening was performed over 7 days after admission to assess inclusion criteria to the study. Patients fulfilling the entry criteria within this 1-week period were prospectively followed for 28 days after their inclusion in the study. The three main entry criteria were: (1) the need for mechanical ventilation either through endotracheal intubation or with non-invasive ventilation for at least 6 h per day, (2) hypoxemia defined as PaO_2/FIO_2 ratio of 300 mmHg or less and (3) an acute onset of respiratory failure. Three groups of hypoxemic, mechanically ventilated patients with acute respiratory failure were defined prospectively. Bilateral infiltrates on frontal chest radiograph and a capillary wedge pressure of 18 mmHg or less or no clinical evidence of elevated left atrial pressure were necessary to meet the criteria for groups 1 and 2 [6]. Group 1 corresponded to the acute respiratory distress syndrome (ARDS) definition and included patients with PaO_2/FIO_2 ratio of 200 mmHg or less regardless of positive end-expiratory pressure (PEEP) level. Group 2 corresponded to patients meeting the acute lung injury (ALI) definition but not having ARDS (PaO_2/FIO_2 ratio of 201–300 mmHg, regardless of PEEP level). Group 3 included patients with PaO_2/FIO_2 ratio of 300 mmHg or less regardless of PEEP level, but not having other inclusion criteria for ALI or ARDS or having exclusion criteria for these groups. Patients having a PaO_2/FIO_2 ratio of 200 mmHg or less, but in whom the exclusion criterion from the ARDS group was the presence of unilateral injury, were included in group 3 and constituted a particular sub-group (group 3*unil*). This latter group was isolated to see whether it differed from patients included as ARDS [6].

Data collection

Protection of the privacy of personal data satisfied the provisions of French laws on "Informatique et Liberté". For each patient included in the study, demographics and previous health status (Mac Cabe score) [13] were recorded, as well as their general classification as medical, scheduled or non-scheduled surgical patients. Immunosuppression was defined by one of the following: recent chemotherapy, radiation, leukemia, metastatic cancer, immunosuppression therapy for organ transplant, AIDS or corticosteroids (long course of treatment and/or high dosage). The mode of ICU referral was notified, including duration and location of hospital stay before ICU admission. The Simplified Acute Physiology Score II (SAPS II) [14] was calculated after admission to the ICU (day 1 = SAPSa), and at the time of inclusion in one of the groups (SAPSi). Because the PaO_2/FIO_2 ratio is part of SAPS II calculation, we calculated a corrected score without this value (SAPSi'). An organ failure score (ODIN score) [15] was also calculated on admission to the ICU (ODINa) and at the time of inclusion when different (ODINi). ODINi and SAPSi were calculated on the worst values observed during the 24 h surrounding the patient's inclusion.

The causes of acute hypoxemia were notified using standardized definitions in all the centers. Criteria for aspiration of gastric contents included a strongly suspected aspiration based on predisposing factors (difficult intubation, altered mental status, etc.) and the evidence of vomiting and/or gastric contents in the oropharynx at the time of intubation, or actually witnessed aspiration [8, 16]. Pneumonia was defined as clinical evidence of primary lung infection from bacterial, viral, fungal or parasitic infection with positive blood cultures or Gram's stain and/or culture of distal protected samples or bronchoalveolar lavage specimens. The etiologies of hypoxemia were grouped in six mutually exclusive categories: left cardiac failure, chronic obstructive pulmonary disease (COPD) exacerbation, abdominal sepsis, extra-abdominal sepsis, direct pulmonary injury (whatever the etiology) and others. Because of the very small number of cases, acute pancreatitis was included in "abdominal sepsis".

The presence of the systemic inflammatory response syndrome (SIRS), of the sepsis syndrome or of septic shock were collected at inclusion using previously defined criteria [17]. Arterial blood gas values, ventilator settings and all data used to calculate the lung injury score (LIS) [18], were collected at inclusion.

Evolution

After the first 24 h of inclusion, episodes of sustained worsening in ventilatory status, defined as a 20% decrease in PaO_2/FIO_2 ratio, were recorded, as well as possible changes from the initial group of inclusion (i.e., group 2 to group 1). Suspected causes for this worsening were chosen among a list of 65 previously defined items.

Outcome

Acute respiratory distress syndrome patients (group 1) were compared to other hypoxemic non-ARDS, patients (groups 2 and 3). Groups 1 (ARDS) and 3unil (unilateral lung injury with PaO_2/FIO_2 ratio of 200 mmHg or less) were also compared. The final outcome was assessed at day 28 after inclusion. Survivors and non-survivors were compared to determine the mortality risk factors among the entire population of hypoxemic patients.

Statistical analysis

Medical records were reviewed in each center by a member of the Collaborative Group. A test to ensure the quality of the data was performed by the team of our Medical Information Unit, using gatekeeper values for extreme values, along with the confirmation that the entry criteria were truly met in all cases. The quality control process was reinforced by a daily control performed in each center by a member of the Collaborative Group. The member of the Collaborative Group was contacted in cases of any abnormality, inconsistency or outlier values in the patient's files. Moreover, investigators' meetings were organized in an attempt to ensure a homogeneous quality of recording.

Continuous data are presented as means ± standard deviations. Non-categorical and categorical variables were compared using unpaired *t*-tests and a chi-square test, respectively. The survival rate was analyzed using logistic regression allowing for the effects of the inclusion group (ARDS compared to non-ARDS). The effects of the following prognostic factors found to influence survival by univariate analysis ($p < 0.2$) were explored: age, PaO_2/FIO_2, LIS, $PaCO_2$, pH, PEEP, immunosuppression, septic shock, number of infiltrates, chemotherapy, SIRS, AIDS, SAPS II score at inclusion and ODIN score at inclusion. The results are presented as odds ratio for mortality effect (survivors compared to non-survivors), the 95% confidence limits for the odds ratio and associated probability value. The same parameters were included in the logistic regression model for patients included in the ARDS group and unilateral lung injury group.

Survival curves were estimated using the product-limit method of Kaplan-Meier and were compared using the log-rank test. A probability value (p) of less than 0.05 was accepted as indicating statistical significance. All statistical tests were two-tailed.

Results

Overall characteristics

The characteristics of the 36 ICUs participating in the study are reported in Table 1. During the 14-day inclusion period, 976 patients were admitted, 424 (43%) received mechanical ventilation and 213 (152 males and 61 females; 22% of all admissions) fulfilled the study criteria for acute hypoxemia (PaO_2/FIO_2 ratio of 300 mmHg or less). Sixty-seven patients entered the ARDS group (group 1), amounting to 6.9% of the entire screened population, 15.8% of the mechanically ventilated patients and 31.5% of the hypoxemic, ventilated patients. This prevalence of ARDS varied from 0% (in nine centers accounting for 18% of all ICU admissions) to 18.75% (in two centers accounting for 3% of all ICU admissions). Seventeen patients fulfilled criteria for acute lung injury (ALI) without ARDS (group 2). Among the 129 remaining hypoxemic, ventilated patients constituting group 3, 41 had left ventricular failure and 42 patients did not meet the ARDS criteria despite a PaO_2/FIO_2 ratio of 200 mmHg or less because of unilateral infiltrate (group 3*unil*).

More than 80% of the patients met the inclusion criteria within the first 48 h of their admission in the ICU, as shown on Fig. 1, no patient entering after day 5. Sev-

Table 1 Main characteristics of the 36 Intensive Care Units involved in the study

	Mean ± SD	Median	Extreme values
Number of ICU beds	18 ± 8	15	8–45
Acute care	15 ± 6	12	6–30
Intermediate care	7 ± 7	6	0–22
Number of ICU admissions (6 months)*	419 ± 305	308	153–1362
ICU mortality rate (%)*	18 ± 12	16	4–68
Modes of ICU referral (% of admissions)*			
Direct admission	37 ± 23	37	1–87
Other units, same hospital	37 ± 24	30	3–83
Other hospital	26 ± 18	20	2–63

* Calculated for the period from January 1th to June 30th, including the study period

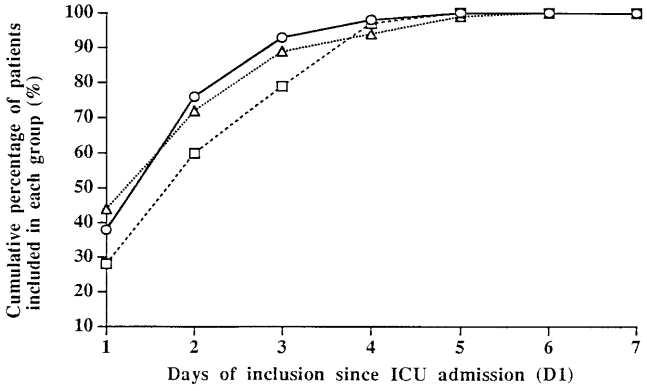

Fig. 1 Delay between admission in the ICU and inclusion into the study (D1). *Circles*, *triangles* and *squares* refer to groups 1, 2 and 3, respectively

Table 2 Patients' location prior to ICU and distribution of the patients according to different length of hospital stay (days) prior to their ICU admission

	ARDS (Group I) (n = 67)	Others (Groups II and III) (n = 146)	Overall (n = 213)
Direct admission	15 %	16 %	16 %
Emergency Room	23 %	20 %	21 %
Hospital ward	46 %	50 %	49 %
Other ICU	6 %	14 %	14 %
LOS prior to ICU (days)			
≤ 1	50 %	49 %	49 %
1–2	8 %	15 %	13 %
2–7	22 %	16 %	18 %
> 7	20 %	20 %	20 %

Abbreviations: LOS: Length of hospital stay

Table 3 Distribution of patients according to the etiology of respiratory failure in each group of patients

	Group I (ARDS) n (%)	Group II (ALI) n (%)	Group III (Others) n (%)
Left cardiac failure	0 (0)	0 (0)	41 (32)
COPD exacerbation	2 (3)	3 (17)	31 (24)
Direct lung injury with:	33 (49)	10 (56)	34 (26)
– infectious pneumonia	16	10	16
– Aspiration	13	0	15
– Others	4	0	3
Abdominal sepsis	21 (31)	4 (22)	1 (1)
Extra abdominal sepsis	3 (5)	0 (0)	2 (1)
Other etiologies	8 (12)	0 (0)	20 (16)
Total	67 (100)	17 (100)	129 (100)

enty-seven per cent of the patients were admitted for medical reasons, 9 % after a scheduled surgery and 14 % after emergency surgery, with no differences in the distribution among the three groups. As shown in Table 2, 63 % of all hypoxemic patients were hospitalized prior to their ICU admission. In those, the length of prior hospital stay was not significantly different among the three groups. At inclusion, 17 patients were ventilated non-invasively (12 in group 3 and 1 in group 2). Four (24 %) of them eventually required endotracheal intubation.

Causes of respiratory failure

The etiologies of hypoxemia are reported in Table 3. In the ARDS, as in the ALI, group there were two main categories: direct lung injury and abdominal sepsis. By contrast, in group 3 left cardiac failure, exacerbation of COPD and direct lung injury represented approximately one-third of the diagnosis each.

Table 4 Comparison between patients with ARDS and other hypoxemic patients

	Group I (ARDS) (n = 67)	Groups II and III (n = 146)	P value
Age (years)	55 ± 17	61 ± 16	0.008
PaO_2/FiO_2	117 ± 41	179 ± 65	0.001
LIS	3.1 ± 0.8	2.2 ± 0.5	0.001
$PaCO_2$ (mm Hg)	48 ± 14	50 ± 12	0.06
pH	7.36 ± 0.08	7.38 ± 0.05	0.17
PEEP (cm H_2O)	8 ± 4	6 ± 3	$< 10^{-3}$
VE (L/mn)	11 ± 7	11 ± 7	0.62
SAPSa	55 ± 22	46 ± 20	0.02
SAPSi	58 ± 21	47 ± 20	0.01
SAPSi′	48 ± 21	39 ± 19	0.01
ODINa	2.8 ± 1.3	1.9 ± 1.0	0.03
ODINi	6.0 ± 4.5	3.6 ± 3.1	0.003
SIRS	8 %	13 %	0.01
Severe sepsis	20 %	25 %	$< 10^{-4}$
Septic shock	51 %	14 %	$< 10^{-4}$
Immunosuppression n (%)	14 (21)	22 (15)	0.33
Mac Cabe score	1.7 ± 0.8	1.7 ± 0.7	0.53
Mortality rate at day 28	60 %	31 %	0.0001

(Abbreviations: PEEP: positive end-expiratory pressure, VE: expired minute volume, LIS: lung injury score, SAPS: simplified acute physiology score, ODIN: organ dysfunction and/or infection score; a and i after SAPS and ODIN refer to the score calculated at admission for a and at inclusion for i; SAPSi′ refers to SAPS value without PaO_2/FiO_2 ratio value for calculation, SIRS: systemic inflammatory response syndrome) Mean values are given ± SD

Comparison of ARDS and non-ARDS patients

Differences between ARDS (group 1) and non-ARDS patients (groups 2 and 3) are shown in Table 4. ARDS patients were younger, had lower values of oxygenation and were ventilated with a higher PEEP. SAPSa and SAPSi did not statistically differ within each group, but were significantly higher in ARDS compared to others, even when the PaO_2/FIO_2 ratio was excluded from the calculation (SAPSi'). The organ dysfunction score at inclusion (ODINi) was significantly higher than at the time of ICU admission (ODINa) in the two groups. A significant difference was observed between ARDS and others for both scores (ODINa and ODINi). Twelve ARDS patients only (18 % of all ARDS cases) were included without any other organ dysfunction, compared to 53 patients (31 %) in the other two groups ($p < 0.01$). The distribution and the number of non-pulmonary organ dysfunctions at inclusion are shown in Figs. 2 and 3. Lastly, septic shock was more frequently observed in ARDS patients (51 %).

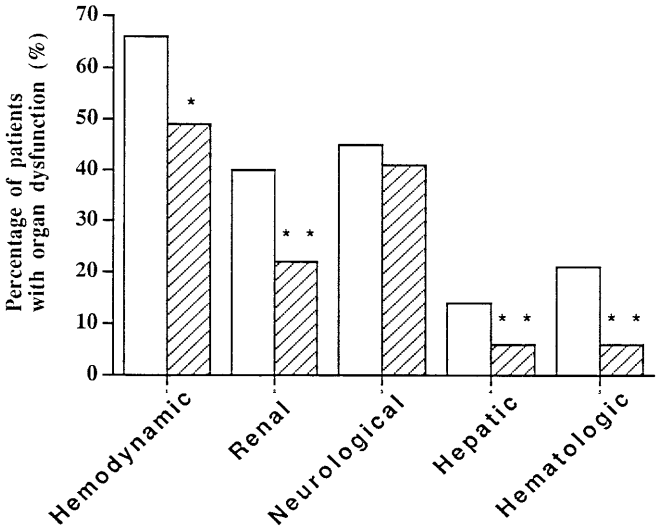

Fig. 2 Relative percentage of patients demonstrating at least one organ dysfunction, other than the lung, in the ARDS group (*open bars*) and in the other groups of hypoxemic patients (groups 2 and 3) (*dashed bars*). $*p < 0.01$, $**p < 0.001$

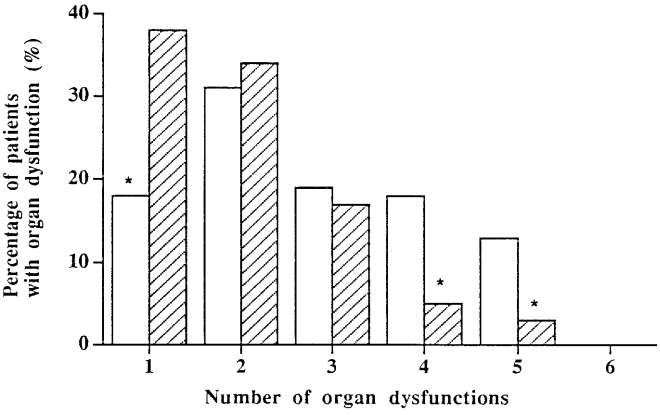

Fig. 3 Distribution of patients according to the number of organ dysfunctions in the group of ARDS patients (*open bars*) and in the other groups of hypoxemic patients (groups 2 and 3I) (*dashed bars*). A single organ dysfunction means lung injury only. $*p < 0.01$

Evolution after inclusion in the study

After initial inclusion in a non-ARDS group, four patients secondarily fulfilled ARDS criteria (1 from group 3 and 3 from group 2). These four patients were included in the ARDS group for analysis. Eighty-five episodes of worsening of the ventilatory status were recorded in 51 patients, including 71 episodes in 44 ARDS patients. These episodes were primarily explained by septic shock (39%), nosocomial infection (24%) and blood transfusion (22%). Other causes of ventilatory worsening were found among ARDS patients (cardiac arrest in 8 patients and dysfunction of the endotracheal tube in 3). Septic shock following a nosocomial infection was the cause of the change in group of inclusion in the four patients mentioned above.

Table 5 Clinical characteristics of the hypoxemic patients: Comparisons of survivors and non survivors

	Survivors (n = 128)	Nonsurvivors (n = 85)	P value
Age (years)	58 ± 17	61 ± 17	ns
Medical patients	77%	77%	ns
Scheduled surgery	8%	9%	ns
Unscheduled surgery	15%	14%	ns
LOS prior to ICU (days)	6 ± 12	6 ± 13	ns
Mac Cabe score	1.63 ± 0.9	1.90 ± 0.8	< 0.01
SAPSa	40 ± 15	61 ± 22	< 0.01
SAPSi	41 ± 14	64 ± 21	< 0.01
SAPSi′	32 ± 14	55 ± 20	< 0.01
ODIN a	1.8 ± 0.9	2.7 ± 1.4	< 0.01
ODIN i	1.8 ± 0.4	2.7 ± 1.4	< 0.01
LIS	2.6 ± 1.6	2.3 ± 1.5	ns
Number of quadrants	2.0 ± 1.4	2.6 ± 1.3	0.06
PEEP (cm H_2O)	3 ± 7	3 ± 4	ns
PaO_2/FiO_2	175 ± 21	138 ± 65	< 0.01
$PaCO_2$ (mm Hg)	48 ± 38	52 ± 36	0.06
pH	7.40 ± 0.09	7.30 ± 0.15	0.001
VE (L/mn)	11 ± 9	10 ± 3	ns
SIRS	8%	6%	0.08
Severe sepsis	39%	19%	< 0.01
Septic shock	12%	45%	< 0.01
Immunosuppression (n)	15	27	0.07
ARDS/Non ARDS (%)	21/79	45/55	< 0.01

(Abbreviations: PEEP: positive end-expiratory pressure, VE: expired minute volume, LIS: lung injury score, SAPS: simplified acute physiology score, ODIN: organ dysfunction and/or infection score; a and i after SAPS and ODIN refer to the score calculated at admission for a and at inclusion for i; SAPSi′ refers to SAPS value without PaO_2/FiO_2 ratio value for calculation, SIRS: systemic inflammatory response syndrome) Mean values are given ± sd

Risk factors for mortality

The overall mortality rate of the patients included in the study was 40%. Mortality at day 28 was significantly higher among ARDS patients than others (60% versus 31%; $p < 0.001$) (Fig. 4). A comparison of clinical characteristics between survivors and non-survivors is shown in Table 5. In a multivariate analysis using the whole population of hypoxemic, ventilated patients the following variables were found to be independently associated with mortality (Table 6): (1) septic shock ($p < 0.002$), (2) SAPS II ($p < 0.001$) and (3), close to significance, immunosuppression ($p = 0.06$). The mortality rate of patients who demonstrated septic shock at inclusion was 73% (40/55).

Comparison between patients with ARDS (group 1) and patients having unilateral lung injury and a PaO_2/FIO_2 ratio less than 200 (group 3*unil*) is shown in Ta-

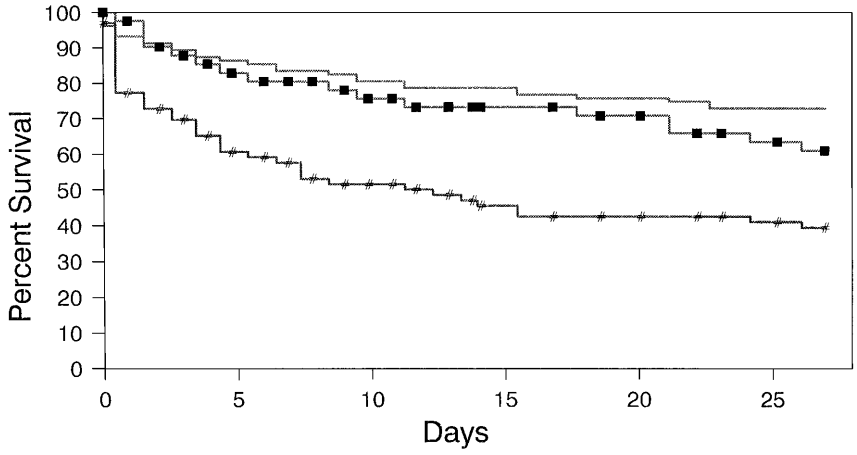

Fig. 4 Kaplan-Meier survival curves for time of ICU stay up to day 28 for patients with ARDS (group 1, $n = 67$) (*lower curve*, -#-), patients with oxygenation criteria for ARDS but unilateral lung injury (group 3*unil*, $n = 42$) (*middle curve*, full squares), and all other patients (groups 2 and 3 except 3*unil*, $n = 104$) (*upper curve*). $p < 0.05$ for ARDS vs group 3*unil*, $p < 0.01$ for ARDS vs other hypoxemic patients

Table 6 Multivariate model of variables associated with mortality in 213 patients with acute hypoxemia ($PaO_2/FiO_2 \leq 300$ mm Hg)

Variable	Odds Ratio	95 % CI	p Value
Septic Shock	4.32	1.88–9.95	< 0.001
Immunosuppression	2.31	1.05–5.72	0.06
SAPSII $\leq$ 40	1		
41 $\leq$ SAPSII < 60	2.38	1.01–5.63	< 0.001
SAPSII $\geq$ 60	19.2	7.16–51.50	

(Abbreviations: SAPS: simplified acute physiology score)

Table 7 Comparisons between ARDS patients (GI) and patients having an unilateral lung injury with PaO_2/FiO_2 ratio $\leq$ 200 mm Hg (Group III unil)

	GI (ARDS) (n = 67)	Group III unil (n = 42)	P value
Age (years)	55 ± 17	60 ± 19	0.06
PaO_2/FiO_2	117 ± 41	148 ± 39	0.05
LIS	3.1 ± 0.8	1.8 ± 0.8	0.01
$PaCO_2$ (mm Hg)	45 ± 14	44 ± 14	0.21
pH	7.36 ± 0.08	7.37 ± 0.08	0.72
PEEP (cm H_2O)	8 ± 4	6 ± 5	0.04
VE (L/mn)	9 ± 2	9 ± 1	0.59
SAPSi	58 ± 21	46 ± 20	0.09
SAPSi′	48 ± 21	37 ± 19	0.01
ODINa	2.8 ± 1.3	1.9 ± 1.0	0.06
ODINi	6.0 ± 4.5	3.5 ± 2.8	0.01
Mac Cabe score	1.7 ± 0.8	1.5 ± 0.7	0.16
Mortality rate (%) at day 28	60 %	40.5 %	0.05

(Abbreviations: PEEP: positive end-expiratory pressure, VE: expired minute volume, LIS: lung injury score, SAPS: simplified acute physiology score, ODIN: organ dysfunction and/or infection score; a and i after SAPS or ODIN refer to the score calculated at admission for a and at inclusion for i; SAPSi′ refers to SAPS value without PaO_2/FiO_2 ratio value for calculation). Mean values are given ± sd

ble 7. In ARDS patients the LIS score (number of quadrants), and the level of PEEP applied were higher, whereas the mean PaO_2/FIO_2 was lower. SAPSi' (calculated without PaO_2/FIO_2) and ODINi were also different between the two groups. At day 28, a difference in mortality was observed ($p = 0.05$). As shown in Fig. 4, death occurred significantly earlier in the ARDS group ($p < 0.05$). A multivariate analysis, shown on Table 8, indicates that the differentiation between ARDS and unilateral lung injury was an independent factor of mortality. Lastly, the 41 patients excluded from the ARDS group due to left heart failure had a 36 % mortality rate, which again significantly differed from ARDS mortality ($p < 0.01$).

Discussion

The prevalence of ARDS in this study was 6.9 % of all ICU admissions and 15.8 % of all mechanically ventilated patients. The mortality rate of this group was 60 % and was significantly higher than for the other hypoxemic patients. SAPS II and septic shock were independently linked to the risk of death, while the association with immunosuppression revealed a trend ($p = 0.06$). The prevalence of ARDS amounted to 7 % among ICU patients in this study, which is higher than the prevalence of 2–3 % reported by others using a similar definition of ARDS [9, 19].

One of the limitations of this study is the relatively short period of time (3 weeks) over which it was conducted. This was counterbalanced by the large number of ICUs included. Previous incidence studies on this syndrome found totals of 17 [20], 30 [21]and 48 patients [19] with severe forms of acute respiratory failure and/or ARDS. As such, our study constitutes one of the largest published databases of patients with this syndrome and without being selected for intervention trials. Another limitation comes from the imprecise nature of the

Table 8 Multivariate model of variables associated with mortality in ARDS (Group I) and Group III unil. (n = 109 patients)

Variable	Odds Ratio	95 % CI	p Value
Septic Shock	2.99	1–10	< 0.05
Immunosuppression	18.8	2.5–139	< 0.01
SAPSII ≤ 40	1		
41 ≤ SAPSII < 60	4.62	1–20	< 0.001
SAPSII ≥ 60	29.2	5.6–152	
ARDS vs Group III unil	8.5	1–77	< 0.05

(Abbreviations: SAPS: simplified acute physiology score)

radiographic definition of ARDS. This, however, is inherent in all the published definitions of this syndrome. Whether more precise guidelines or the use of computed tomography scanning to define ARDS will be of some help in the future, needs further investigation. Recent data suggest that a more stringent chest radiograph definition did not lead to a different outcome [22].

Using the definition of ALI and ARDS proposed by the American-European Consensus Conference on ARDS, very few patients were classified in the ALI non-ARDS group, contrary to what was expected. Sloane et al. have previously shown, however, that a more liberal definition of ARDS, such as the definition used for ALI, resulted in identification of the same patients, but earlier in their clinical course [23]. A similar follow-up was used in this study, but most of the patients entered the study with ARDS criteria, and patients with ALI non-ARDS (PaO_2/FIO_2 between 200 and 300 mmHg) were poorly represented in our study; only three of these patients secondarily fulfilled the criteria for ARDS. It must be emphasized, however, that 68 % of the patients were already hospitalized before ICU admission, and their previous respiratory status before ICU admission was not evaluated. It is possible that most patients meeting the ALI, but not the ARDS, criteria were still located in the ordinary wards, receiving additional oxygen and no mechanical ventilation. Some patients may not be identified because of the need for mechanical ventilation to measure the PaO_2/FIO_2 ratio in this study. Differences in the prevalence of ALI/ARDS observed in the literature may thus also result from differences in ICU admission policies. These results, however, question the interest in an ALI/non-ARDS definition, in the light of the low number of patients entered in this group. The classification proposed may not represent a realistic gradation of the different stages of acute respiratory failure. Other have also suggested that a threshold of 150 mmHg for PaO_2/FIO_2 may better identify the most severe patients [8].

The mortality rate of the ARDS patients was 60 %, which contrasts with the results of some recent studies claiming a marked improvement in ARDS mortality, nearing 40 % [4, 24]. Others, however, have reported similar results. Doyle and colleagues, defining ARDS with a PaO_2/FIO_2 ratio less than 150, reported a mortality rate of 56 % [8]. Lewandowski and colleagues reported a mortality of 58.8 % using the score described by Murray and co-workers (LIS) to diagnose ARDS [18, 20]. Until this study, only a few reports had strictly adhered to the Conference Consensus criteria for ARDS definition, so making it difficult to ensure the adequacy of comparisons between the different series [9, 10, 11]. Moreover, patients in this survey were mostly recruited among medical ICUs and did not include trauma patients, who usually have a much lower mortality [9, 12].

Although patients with ARDS had a significantly higher mortality than other hypoxemic, ventilated patients (61 % vs 35 %; $p < 0.001$), ARDS per se did not appear as a significant factor associated with mortality. When the entire population of hypoxemic patients was considered, only three variables were independently linked to mortality: SAPS II score at inclusion (with and without PaO_2/FIO_2 ratio), septic shock and, close to reaching statistical significance, immunosuppression. Different predictive criteria for mortality in ARDS have been described, including age [4, 19, 20, 23], non-pulmonary organ system dysfunction [8, 19, 21, 25, 26, 27, 28, 29], sepsis [29, 30, 31] or the severity of acute respiratory failure itself [18, 20, 25]. Most of these studies did not include a score of severity in their analysis, however, except for Knaus et al., who demonstrated the accuracy of an APACHE III stratification to predict the risk of mortality in ARDS [19]. These scores include age, which probably explains why it did not appear as an independent predictor in the present study, as found in other reports [4, 19, 20, 23]. Besides, one recent report has challenged this criteria in ARDS patients, suggesting that age could be a bias influencing decisions to withdraw support [32].

We found that patients with ARDS had significantly more non-pulmonary organ dysfunctions than the other hypoxemic patients. This finding has been considered as a predictor of mortality in ARDS [8, 19, 21, 25, 26, 27, 28, 29]. Although 82 % of the ARDS patients had at least one other non-pulmonary organ dysfunction, this did not appear as an independent predictor of mortality. However, organ dysfunction criteria are, at least partially, included in the SAPS II score and are closely linked with the presence of septic shock.

The severity of acute respiratory failure has often been shown to predict mortality [18, 20, 25]. In our study, non-survivors exhibited a lower PaO_2/FIO_2 than survivors at inclusion, but the PaO_2/FIO_2 ratio did not appear as an independent variable associated with mortality, when all hypoxemic patients were considered. Thus, the initial severity of the oxygenation defect appears to have little prognostic value; this finding is consistent with those in other series [8, 9, 22]. However, the other factors influencing oxygenation, such as the PEEP level, cardiac output, mixed venous oxygen satu-

ration and time, are not taken into account, which may totally mask some real associations of oxygenation with prognosis. In addition, only hypoxemic patients were included, which makes it more difficult to find the degree of hypoxemia that has a significant prognostic impact.

Immunosuppression appears independently associated with the risk of mortality. Although it has been demonstrated that ARDS increases the mortality rate in immunosuppressed patients [28, 33], only one earlier series, to our knowledge, has demonstrated that immunosuppression is, *per se,* a factor of mortality in a non-selected population of ARDS [34]. It must be emphasized that most of the published studies on ARDS mortality did not include immunocompromised patients. Our study, however, cannot give a definitive conclusion because of the borderline statistical significance of the test ($p = 0.06$), which may be explained by the low number of patients involved ($n = 36$).

The other main predictor of mortality in this series was septic shock at inclusion. The role of sepsis in this population is illustrated by the large number of patients demonstrating the criteria for sepsis, along with the frequent role of sepsis that was observed in a worsening of ventilatory status. These results are consistent with previous studies showing the influence of septic shock on ARDS mortality [9, 29, 35, 36, 37, 38]. ARDS patients in this study seemed to have a similar mortality rate to that usually reported in septic shock patients (60%) [39, 40, 41].

Panelists of the American-European Consensus Conference discussed whether patients with severe unilateral disease and severe hypoxemia (group 3*unil*) should be included in the ARDS group. In this study, these two groups differed markedly. Using the same oxygenation criteria, we found that patients with unilateral versus bilateral lung disease differed in the number of dysfunctional organs , which probably explains the significant difference in mortality (Fig. 4). We also found, however, that this classification was an independent predictor of mortality, suggesting that it may well represent two different syndromes. This also shows that using the PaO_2/FIO_2 ratio alone, and not taking into account the other factors influencing oxygenation, may not be a sufficient means with which to classify patients.

In summary, we found that ARDS patients represented 6.9% of all admissions to the ICUs, and had a 28-day mortality rate of 60%. The ALI non-ARDS group was poorly represented in this study and only a few patients from this particular group secondarily fulfilled the criteria for ARDS. Indices of severity and septic shock correlated with mortality, in contrast to oxygenation criteria, which did not. Future prospective randomized trials on ARDS should consider stratification for severity indices as well as sepsis and immunosuppression.

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