

Incidence and Mortality after Acute Respiratory Failure and Acute Respiratory Distress Syndrome in Sweden, Denmark, and Iceland

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To determine the incidence and 90-d mortality of acute respiratory failure (ARF), acute lung injury (ALI), and the acute respiratory distress syndrome (ARDS), we carried out an 8-wk prospective cohort study in Sweden, Denmark, and Iceland. All intensive care unit (ICU) admissions ($n = 13,346$) ≥ 15 yr of age were assessed between October 6th and November 30th, 1997 in 132 of 150 ICUs with resources to treat patients with intubation and mechanical ventilation (I + MV) ≥ 24 h. ARF was defined as I + MV ≥ 24 h. ALI and ARDS were defined using criteria recommended by the American-European Consensus Conference on ARDS. Calculation to correct the incidence for unidentified subjects from nonparticipating ICUs was made. No correction for in- or out-migration from the study area was possible. The population in the three countries ≥ 15 yr of age was 11.74 million. One thousand two hundred thirty-one ARF patients were included, 287 ALI and 221 ARDS patients were identified. The incidences were for ARF 77.6, for ALI 17.9, and for ARDS 13.5 patients per 100,000/yr. Ninety-day mortality was 41.0% for ARF, including ALI and ARDS patients, 42.2% for ALI not fulfilling ARDS criteria, and 41.2% for ARDS. Luhr OR, Antonsen K, Karlsson M, Aardal S, Thorsteinsson A, Frostell CG, Bonde J, and the ARF Study Group. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland.

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Epidemiological studies that evaluate the incidence and mortality of acute respiratory failure (ARF), acute lung injury (ALI), and the acute respiratory distress syndrome (ARDS) are few. Knowledge about incidence and risk factors associated with these syndromes is mandatory in the process of developing new therapeutic interventions that aim to improve clinical outcome. There is a variation in the reported ARDS incidence that may be attributed to differences in both the type and strength of study design as well as different definitions of ARDS (1). The mortality rate in patients with ARF exceeds 40% (2, 3), and the mortality after ARDS is considered to be in excess of 50% (4). Recent data, however, suggests a significant decrease in ARDS mortality, although the explanation for this observation remains unclear (5). The problem with the lack of a uniform definition of ARDS has

been addressed by the American-European Consensus Conference on ARDS (6) which has provided a definition for ALI and ARDS for future research. The primary objective of this study was to determine the incidence and 90-d mortality of ARF, defined as intubation and mechanical ventilation (I + MV) ≥ 24 h, and ALI/ARDS using the Consensus Conference definition in Sweden, Denmark, Norway, and Iceland using a population-based prospective cohort design. A secondary objective was to examine the extent of congruency between respiratory insufficiency evaluated by the lung injury score (LIS) as suggested by Murray and colleagues (7) and the ARDS definition given by the Consensus Conference.

METHODS

Local ethics committee approval was sought and granted for all participating intensive care units (ICUs) and the need for informed patient consent was waived from the regional ethics committee in the respective country.

Screened Hospitals

All adult ICUs in the respective country with resources to treat patients with I + MV ≥ 24 h were asked to participate in the study.

Participating ICUs. In Sweden, Denmark, and Iceland 132 of 150 eligible ICUs participated. The 132 ICUs consisted of 116 multidisciplinary units of varying size, six thoracic and four neuro-surgical ICUs in large referral hospitals, two ICUs that exclusively treat patients with

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burns, and four medical ICUs. Due to unforeseen problems in Norway only a limited number of ICUs (11 of 42) participated. Because of geographical considerations, most hospitals in Norway have resources to treat patients with I + MV \geq 24 h. A large number of small to medium-sized hospitals lack regular ICU physicians and no ICU investigators could be enrolled for the study period in a large number of centers. Because of this limited participation, the primary objective of determining incidence rates for ARF, ALI, and ARDS could not be fulfilled for this country and all Norwegian data are therefore omitted from the present data analysis. All participating ICUs are listed in the APPENDIX.

Nonparticipating ICUs. The nonparticipating ICUs consisted of eight small multidisciplinary units each serving a population of 39,500 to 75,000, five thoracic and four neurosurgical ICUs in large referral hospitals, and one interdisciplinary referral secondary/tertiary university ICU.

Definition of ARF

ARF was defined as a condition of respiratory insufficiency requiring I + MV \geq 24 h, regardless of fraction of inspired oxygen ($F_{I_{O_2}}$) (2).

Definition of ALI/ARDS

To define ALI and ARDS we have used the definition proposed by the American-European Consensus Conference on ARDS (6). The definition is based on the following criteria: (1) acute onset; (2) $P_{a_{O_2}}/F_{I_{O_2}} \leq 300$ mm Hg for ALI and $P_{a_{O_2}}/F_{I_{O_2}} \leq 200$ mm Hg for ARDS; (3) bilateral infiltrates seen on a frontal chest radiograph (CXR); and (4) pulmonary artery wedge pressure ≤ 18 mm Hg or no clinical evidence of left atrial hypertension.

LIS

Murray and colleagues (7) in 1988 proposed a LIS to be used as a quantitative index of the severity of lung injury in ARDS. They recommend using the term ARDS for those patients who collectively yield a score > 2.5 . Using this composite four-point scoring system we quantified the severity of lung injury.

Incidence Calculation

All reported incidences are calculated as "first incidence," i.e., for each patient the first ICU admission during the study period is counted. All patients included in the study received a unique identification number that made it possible to follow the patient in the event of readmissions to the ICU or transferral to other ICUs. All incidence figures are calculated with correction for unidentified patients as specified.

Study Populations

In this prospective cohort study we assessed all ICU admissions ≥ 15 yr of age between October 6th and November 30th, 1997. The inclu-

sion criteria were defined as a continuous treatment period ≥ 24 h of one or a combination of the following techniques: (1) administration of oxygen with an intended $F_{I_{O_2}} \geq 0.4$. Patients administered oxygen other than by oxygen delivery masks (e.g., nasal catheters) were not included in the data analysis; (2) patients treated with noninvasive ventilation with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BIPAP) or breathing spontaneously via an endotracheal tube with CPAP; (3) I + MV. Continuous treatment was defined as an uninterrupted intention to treat a persistent hypoxemia with one or a combination of the treatments defined in the inclusion criteria. These criteria were specifically designed to also include patients treated with noninvasive ventilatory support. The earliest possible inclusion time would be 24 h after admission to the ICU, although patients were eligible for inclusion in the study at any time during the ICU stay when such a 24-h treatment period was fulfilled. From the included patients we isolated three subpopulations for incidence calculations (Figure 1): (1) patients with ARF, (2) patients with ALI, and (3) patients with ARDS defined by the American-European Consensus Conference on ARDS. To compare patients with ARDS and patients with a LIS > 2.5 , we isolated this subpopulation together with patients not filling the ARDS definition.

Reference Population

We obtained the values for the populations in Sweden, Denmark, and Iceland including the value for the population < 15 yr of age from the File of National Registration in each respective country. Vital status for each patient (dead or alive 90 d after inclusion) was also obtained. The File of National Registration is continually updated and survival data were obtained > 30 d after the study endpoint (120 to 180 d after inclusion).

Correction for In- or Out-migration from the Area of Study

Correction for nonresidents of the three countries meeting inclusion criteria was not possible. To estimate the impact on the ARDS incidence rate of out-migration from the area of study we used the estimate given by Thomsen and Morris (8) in a study of the incidence of ARDS in the state of Utah.

Correction for Unidentified Patients in the Incidence Calculation

Correction was made for nonparticipating ICUs in Sweden and Denmark (Table 1). Four of the nonparticipating smaller multidisciplinary ICUs registered the number of patients requiring I + MV ≥ 24 h ($n = 31$) during the study period and this number was used to estimate the ARF incidence for these ICUs. We then calculated the ratio-identified ALI/ARF and ARDS/ARF patients from participating ICUs of similar size and used this to estimate the number of unidentified ALI/ARDS patients.

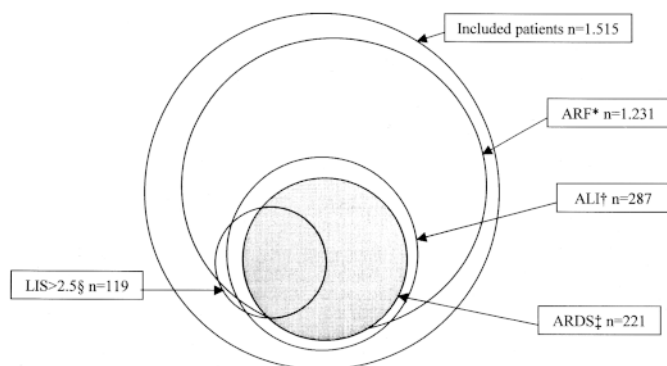


Figure 1. Included patients and isolated subpopulations: *ARF defined as I + MV ≥ 24 h; †ALI defined according to the American-European Consensus Conference on ARDS; ‡ARDS defined according to the American-European Consensus Conference on ARDS; §LIS defined according to Murray and coworkers (7).

TABLE 1
CALCULATED CORRECTIONS FOR UNIDENTIFIED PATIENTS IN THE INCIDENCE CALCULATION

Nonparticipating ICUs Type of ICU	Calculated Number of Missing Patients			
	ARF	ALI*	ARDS*	LIS > 2.5
Small interdisciplinary (n = 8)	38 [†]	9	6	1
Interdisciplinary referral (n = 1)	30	9	6	4
Neurosurgical (n = 4)	64	12	6	1
Thoracic (n = 5)	35	6	4	3
Total	167	36	22	9
Included in the study	1,231	287	221	127
Corrected total for the incidence calculation	1,398	323	243	136

* ALI and ARDS defined according to the American-European Consensus Conference on ARDS.

[†] Four of eight ICUs registered the number of patients fulfilling ARF criteria throughout the study period.

For the remaining four nonparticipating smaller interdisciplinary ICUs, the number of unidentified patients was calculated using the mean number of identified ARF and ALI/ARDS patients from participating ICUs of similar size. The same calculation method was used for the nonparticipating thoracic and neurosurgical ICUs. To calculate the number of unidentified patients from the large interdisciplinary referral secondary/tertiary university ICU, we used data from similar referral university ICUs. The numbers of unidentified patients were for ARF estimated to $n = 167$, for ALI to $n = 36$, for ARDS to $n = 22$, and for patients with a LIS > 2.5 to $n = 9$.

Study Monitoring Procedure and Validation of Study Inclusion

To monitor study inclusion we required a daily facsimile transmission from each ICU with a record of all ICU admissions during the previous 24 to 48 h. The patients were categorized into one of the following groups: (1) discharged within 24 h of admittance, (2) dead within 24 h of admittance, (3) fulfilling study inclusion criteria, (4) not fulfilling inclusion criteria. In addition, a list of all patients enrolled in the study with the date of inclusion and date when the patient left the study was also required. The total ICU admissions were used to validate study inclusion rate and the daily reports of included patients were later used to confirm that all included patients' case record forms (CRF) were collected at the end of the study period. The daily communication via facsimile also served as a control function to ensure that the participating centers remained active and screened patients throughout the study period. All data were captured on special registration forms, containing exact explanations and definitions of the requested data. The principal ICU investigator was responsible for validation of the data recorded on completion of the CRF when the patient left the study. A 24-h telephone service was established to provide immediate answers to questions regarding study procedure and inclusion of patients. No site reviews were made during the study period.

Data Collection

The requested data were to be recorded from the patient chart to correspond to the time when the patient met inclusion criteria. The data were to be recorded during working hours and if the patient fulfilled inclusion criteria outside this time period, no later than the following day or the first work day following a weekend. The charts of all patients who were discharged from the ICU outside regular working hours were kept or copied for later assessment. The following data were collected when inclusion criteria were met:

Demographics. Age, sex, weight, and height together with information if the patient participated simultaneously in other studies.

Left atrial hypertension. Presence of left atrial hypertension and whether this assessment was made clinically, using echocardiography, or by measuring pulmonary artery wedge pressure.

CXR. Scoring of unilateral/bilateral infiltrates together with number of quadrants engaged and whether the CXR was taken before, within, or after the 24-h inclusion period. Also, it was recorded if the CXR was evaluated by a radiologist or by the investigator in the ICU.

Severity of disease. A calculation of an Acute Physiology and Chronic Health Evaluation II (APACHE II) score for the 24-h period prior to fulfillment of inclusion criteria. The APACHE II score include an assessment of chronic diseases and a Glasgow Coma Score.

Ventilatory support. Patients were categorized into three groups: (1) mechanical ventilation (MV), (2) treatment with CPAP or BIPAP, (3) continuous oxygen delivery by other delivery systems intended to deliver a $FI_{O_2} \geq 0.4$. For MV, the ventilatory mode was noted: volume control ventilation (VCV), pressure control ventilation (PCV), synchronized intermittent mandatory ventilation (SIMV), pressure support ventilation/assisted spontaneous breathing (PSV/ASB), or pressure regulated volume control (PRVC) and also whether the patient was intubated or nonintubated.

Arterial blood gas data. Arterial pH, Pa_{O_2} , Pa_{CO_2} , base excess (BE), standard bicarbonate (StBic).

Ventilatory data. FI_{O_2} , minute ventilation, respiratory rate (RR), peak inspiratory (PIP), mean and plateau pressures, PEEP/CPAP, and inspiratory to expiratory time ratio (I:E).

Special techniques used. Note was made if any special technique had been used to improve oxygenation during the 24-h inclusion period.

Cause for the acute respiratory failure. In an effort to standardize, each investigator was asked to assess the principal cause or causes for the development of ARF from a list suggested by Lewandowski and coworkers (2). We have chosen to present the principal cause as either pulmonary or nonpulmonary origin in the statistical analysis of data and defined pulmonary origin as a disease process confined to the lung with the pleura as the outer perimeter. If more than one cause was noted, an option to clarify the diagnosis with a written statement was offered in the CRF, and all recorded data from these patients were examined by the principal investigator in order to decide if the development of ARF or ARDS was due to a pulmonary or nonpulmonary origin. The proportion of patients with a specific cause to the respiratory failure is shown in Table 2. Information whether the ARF was developed in the postoperative period after elective or acute surgery was also obtained.

For patients included after fulfillment of inclusion criteria 1 or 2 who later were intubated and mechanically ventilated, an additional data set with arterial blood gas and ventilatory data was collected 24 h after the intubation in order to correctly assess the total number of patients fulfilling criteria for ARF (I + MV) during the study period. An additional CXR was scored and an APACHE II score was calculated for the 24 h after the intubation. These patients were all included as ARF patients in the subsequent analyses.

The physicians in charge of the patient recorded all data on CRF. After the study period the forms were collected centrally in each country and manually entered into a computerized database (Microsoft Access 2.0) for subsequent analysis.

Statistical Analysis

Results of the descriptive statistics are expressed as mean \pm standard deviation or median and range as indicated. To compare frequency distributions in categorized variables we used Pearson's chi-square test and for continuous variables the Mann-Whitney U test. To analyze survival data we used Kaplan-Meier survival plots together with log-rank test for significance testing (9). In the ARF and ARDS subgroups, a multivariate Cox regression model was used to independently assess variables that in a univariate analysis were associated with mortality together with factors that we felt were clinically important. Consequently, we included age, gender, pulmonary/nonpulmonary origin, acute physiology score (APS) points, chronic comorbidities, Pa_{O_2}/FI_{O_2} ratio, PEEP, and number of quadrants with infiltrates on the frontal CXR. The continuous variables were analyzed both as continuous and dichotomized to age > 65 yr, APS > 15 , number of quadrants > 2 , PEEP > 5 together with P/F ratio > 200 for patients with ARF and P/F ratio > 100 for patients with ARDS. The reason to dichotomize these variables was to enable expression of the results as risk ratios. For the multivariate analysis a difference was considered significant if $p < 0.05$. For all other analyses a difference was considered significant if $p < 0.01$. The statistical software STATISTICA (1996; StatSoft Inc., Tulsa, OK) and JMP 3.2 (1997; SAS Institute Inc., Cary, NC) were used for all statistical calculations.

RESULTS

Included Patients

During the 8-wk period there were 13,346 reported ICU admissions. Of these 5,825 (43.6%) were discharged and 303 (2.3%) died within the first 24 h after admission. 1,515 patients (11.3%), 891 males and 624 females, with a mean age of 62.8 ± 16.0 fulfilled inclusion criteria. The remaining 5,570 patients (41.7%) stayed ≥ 24 h but did not meet criteria. The proportion of patients not fulfilling entry criteria on admission who later (> 24 h after ICU admission) fulfilled criteria was 12.7% (calculated from the 789 patients included in Sweden and Iceland). Of the included patients 240 (15.9%) received oxygen by mask, 62 (4.1%) were nonintubated and treated with CPAP/BIPAP, 24 (1.5%) were intubated and spontaneously breathing with CPAP at the time of inclusion, and 1,188 (78.5%) were I + MV ≥ 24 h. Of the nonintubated patients ($n = 302$), 43 were later intubated. Age, the presence of left

TABLE 2
PROPORTION OF PATIENTS WITH A SPECIFIC CAUSE REGISTERED FOR THE DEVELOPMENT OF ARF

	ARF Patients Including Patients with ALI and ARDS (<i>n</i> = 1,231) (%)	Subpopulations		
		ALI Patients Not fulfilling ARDS Criteria (<i>n</i> = 66) (%)	ARDS Patients (<i>n</i> = 227) (%)	Patients with LIS > 2.5 (<i>n</i> = 119) (%)
Pulmonary origin	52.1	60.0	77.9	76.4
Upper airways				
Laryngeal obstruction	2.8	—	1.8	0.8
Lower airways				
Tracheal obstruction	1.1	3.0	—	—
Acute bronchitis	1.2	—	0.5	—
Chronic bronchitis and chronic obstructive pulmonary disease	13.7	9.1	10.0	8.4
Asthma	2.4	4.5	0.9	—
Lung parenchyma				
Aspiration	5.7	9.1	11.3	8.4
Near drowning	0.2	—	0.5	0.8
Inhalation agents, pulmonary burns	0.3	—	—	—
Intrapulmonary bleeding	0.3	1.5	0.9	0.8
Pulmonary contusion	3.6	9.1	5.4	2.5
Neoplasms of lung parenchyma, intrapulmonary metastasis	0.6	—	1.8	2.5
Pneumonia (bacterial, viral, opportunistic)	23.7	33.3	46.2	41.2
Miliary tuberculosis	0.2	—	0.5	—
Atelectasis	15.4	18.2	20.4	10.9
Lung circulation				
Pulmonary hypertension	2.5	—	3.2	5.0
Pulmonary embolism	0.8	—	0.5	2.5
Lung edema—cardiogenic	9.2	—	2.7	13.4
Lung edema—noncardiogenic	4.9	7.6	10.4	12.6
Nonpulmonary origin	47.9	40.0	22.1	23.6
Pleura				
Pneumothorax	1.9	—	2.7	1.7
Pleural effusion	7.0	10.6	6.8	4.2
Chest				
Trauma and flail chest	2.3	3.0	3.2	2.5
Mediastinal emphysema	0.5	—	0.9	0.8
Ventilatory regulation system				
Central hypoventilation syndrome	0.8	3.0	—	—
Drug overdose	2.4	1.5	0.9	0.8
Cerebrovascular accident	8.9	4.5	4.1	1.7
Head/brain trauma	5.1	9.1	3.2	—
Cardiovascular system				
Hypovolemic shock	4.2	7.6	3.2	1.7
Polytransfusion	1.4	1.5	2.3	0.8
Cardiogenic shock	5.4	1.5	0.9	2.5
Abdominal disease				
Pancreatitis	2.4	3.0	3.6	4.2
Digestive necrosis	2.4	3.0	2.3	2.5
Abdominal sepsis	7.2	7.6	5.4	7.6
Peritonitis	6.4	6.1	3.6	2.5
Urogenital system				
Uremia	2.4	9.1	3.2	5.0
Urinary sepsis	1.0	1.5	0.9	—
Endocrinologic system				
Diabetic ketoacidosis	1.0	3.0	—	1.7
Anaphylaxis	0.2	1.5	—	—
Skeletal system				
Traumatic bone fracture	3.6	12.1	1.4	3.4
Neurologic disease				
Nontraumatic neurological disease including spinal trauma	2.5	6.1	2.3	—
Other				
Multisystem trauma	3.3	9.1	3.6	3.4
Burns	0.3	1.5	0.5	0.8
Immunologic disorder	1.6	3.0	4.1	5.9
Sepsis of unknown origin	4.1	6.1	6.3	8.4

atrial hypertension, number of quadrants with infiltrates, LIS, APACHE II score, and data regarding oxygenation and ventilatory measurements in patients with ARF, ALI not fulfilling ARDS, and ARDS are shown in Table 3.

Correction for In- or Out-migration from the Area of Study

For a total of 61 patients, data establishing whether the patient was dead or alive at 90 d were unavailable. Of these, six fulfilled criteria for ARDS. The patients comprised both patients who were not properly identified when included in the study and also foreign citizens who were nonresidents of the three countries. Using the same estimate used by Thomsen and Morris (8) to assess the number of residents leaving the area of study to receive ARDS care outside the studied countries, we estimated that seven patients per year could have been missed. For the given study period, this would amount to one missed ARDS patient. In the incidence calculation, we have refrained from correction of out-migration and further estimation of in-migration due to foreign citizens included, because we believe these figures to approximately counterbalance each other.

Reference Population

On December 31st, 1997 the population in Sweden was 8,847,625 with 1,654,506 persons (18.7%) < 15 yr of age. The corresponding numbers for Denmark were 5,294,860 with 952,188 (18.0%) < 15 yr and for Iceland 272,064 with 68,933 persons (25.3%) < 15 yr of age. The total reference population for the incidence calculation was 11,738,922.

Incidence of ARF

A total of 1,231 patients, 724 males and 507 females, fulfilled the definition of I + MV ≥ 24 h within the first week after ICU admission. The mean age was 62.3 ± 16.1 yr, Pa_{O₂}/F_{I_{O₂}} ratio 209 ± 102 mm Hg, and the APACHE II score 19.0 ± 7.9 points. The incidence was 77.6 per 100,000/yr.

Incidence of ALI and ARDS

Two hundred eighty-seven patients fulfilled the definition for ALI (Pa_{O₂}/F_{I_{O₂}} ratio < 300 mm Hg) and 221 patients fulfilled the definition of ARDS (Pa_{O₂}/F_{I_{O₂}} ratio < 200 mm Hg). Of the

221 patients with ARDS, 39 were nonintubated. Of these, 16 were treated with CPAP and 23 given oxygen via an oxygen mask with a reported F_{I_{O₂}} between 0.4 and 1.0. The incidence for ALI was 17.9 and for ARDS 13.5 per 100,000/yr. The mean age in the ARDS group was 61.3 ± 16.5, Pa_{O₂}/F_{I_{O₂}} 130.7 ± 37.5 mm Hg, APACHE II 19.2 ± 7.9 points, and the mean LIS was 2.4 ± 0.5 with a range of 1.0 to 3.7. For patients with ALI but not fulfilling ARDS (n = 66) the corresponding figures were age 55.0 ± 19.8, Pa_{O₂}/F_{I_{O₂}} 239.8 ± 27.1, APACHE II 17.2 ± 7.9, and mean LIS 1.8 ± 0.5 (Table 3). The CXR that is part of the definition of ARDS was evaluated by a radiologist in 91% of the patients and 83% were taken in the 24-h period just prior to inclusion. The remaining CXRs were taken > 24 h before inclusion.

LIS

One hundred nineteen patients had a LIS score > 2.5 (range 2.7 to 3.5) and this corresponds to an incidence for this patient group of 7.6 per 100,000/yr. The mean age was 60.1 ± 16.7, Pa_{O₂}/F_{I_{O₂}} 107.5 ± 38.9 mm Hg, and APACHE II 22.0 ± 8.3 points. Of the 119 patients only 71 simultaneously fulfilled ARDS criteria.

Severity of Disease

We used an APACHE II score, calculated for the 24 h prior to inclusion, to describe the general severity of disease. To describe the severity of pulmonary disease we used the LIS. An APACHE II score was calculated in all and a LIS in 79% of the patients. There was no significant difference in the APACHE scores between patients with ARF (19.0 ± 7.9), ALI (18.7 ± 8.0), or ARDS (19.2 ± 7.9). Both age and total APACHE II score were significant predictors for 90-d mortality. The cumulative proportion of surviving patients with ARF stratified with respect to different APACHE II scores and age is shown in Figures 2 and 3. The proportion of ARDS and non-ARDS patients with respect to APACHE II scores is shown in Figure 4.

For ARF patients, the presence of chronic diseases other than chronic respiratory disease as defined in the APACHE II score was correlated to subsequent mortality at Day 90 in the univariate analysis (Figure 5). Patients with chronic respiratory disease had the same mortality at Day 7, 14, 21, 30, 60,

TABLE 3
SUMMARY OF DATA FOR ARF, ALI, AND ARDS PATIENTS

	ARF (I + MV ≥ 24 h) All Patients Fulfilling Criteria for ARF Including Patients with ALI and ARDS	Subpopulations	
		ALI Patients Not Fulfilling ARDS Criteria	ARDS Patients
n	1,231	66	221
Age, yr	62.3 ± 16.1	55.0 ± 19.8	61.3 ± 16.5
Presence of left atrial hypertension	23.9%	0%	0%
Number of quadrants with infiltrates on a frontal CXR	1.3 ± 1.4	2.8 ± 0.8	3.0 ± 0.9
Pulmonary origin to the ARF	52.1%	60.0%	77.9%
LIS	1.4 ± 0.8	1.8 ± 0.5	2.3 ± 0.5
APACHE II score	19.0 ± 7.9	17.2 ± 7.9	19.2 ± 7.9
PIP, cm H ₂ O	25.7 ± 6.9	25.8 ± 5.1	28.5 ± 7.0
PEEP, cm H ₂ O	5.2 ± 3.0	5.8 ± 3.5	6.1 ± 3.3
F _{I_{O₂}}	0.50 ± 0.18	0.43 ± 0.11	0.61 ± 0.18
Pa _{O₂} , kPa	12.3 ± 4.2	13.6 ± 3.0	10.0 ± 2.2
Pa _{CO₂} , kPa	5.5 ± 2.1	5.5 ± 1.2	5.7 ± 1.3
Pa _{O₂} /F _{I_{O₂}} , mm Hg	209.3 ± 101.7	239.8 ± 27.1	130.7 ± 37.5
Ventilation, ml/kg	8.1 ± 2.3	8.3 ± 2.9	8.3 ± 2.7

Definition of abbreviations: I + MV = intubation and mechanical ventilation; LIS = lung injury score; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure.

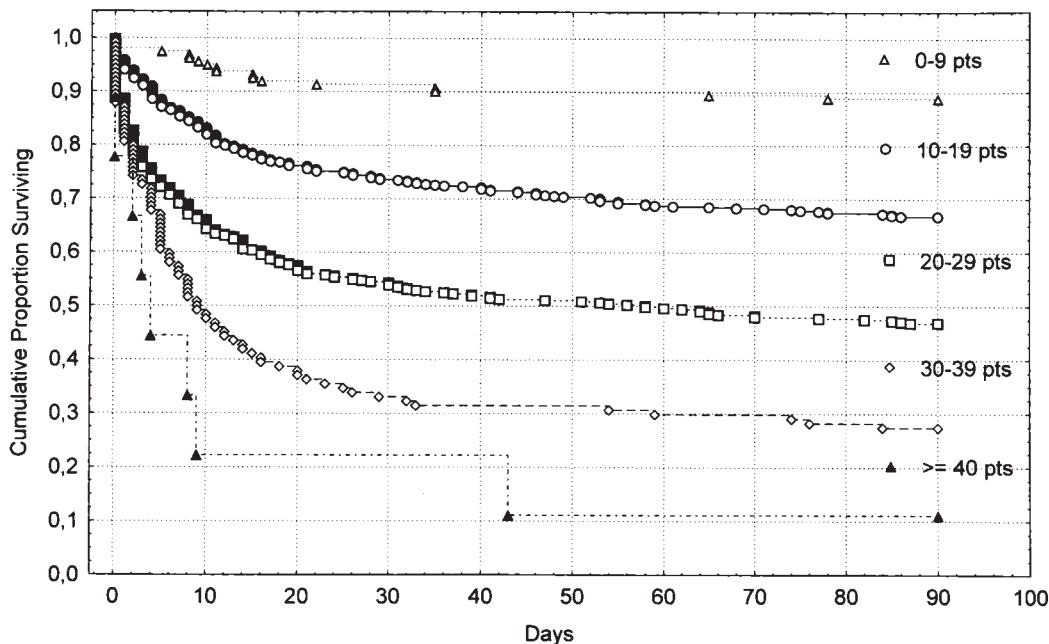


Figure 2. Cumulative proportion of surviving ARF patients. APACHE II score intervals: open triangles: 0 to 9 points, n = 129; open circles: 10 to 19 points, n = 551; open squares: 20 to 29 points, n = 409; open diamonds: 30 to 39 points, n = 114; closed triangles: ≥ 40 points, n = 8.

and 90 as previously healthy patients. However, when comorbid conditions were tested independently in ARF patients using a Cox regression analysis, only immunosuppression reached significance with mortality as the dependent variable. Chronic liver disease showed an independent association with mortality in patients with ARDS. A significant difference was found in the total APACHE II score between patients with ARDS

and patients with a LIS > 2.5. The latter group had significantly higher APS of 14.0 ± 6.5 versus 11.9 ± 5.6 and chronic disease points 2.1 ± 2.4 versus 1.0 ± 2.0 . Similarly, 38 of 119 patients with a LIS > 2.5 had evidence of left atrial hypertension (established clinically in 71%, echocardiographically in 16%, and by wedge pressure measurement in 13%). There was also a significant difference in LIS between the groups, $2.1 \pm$

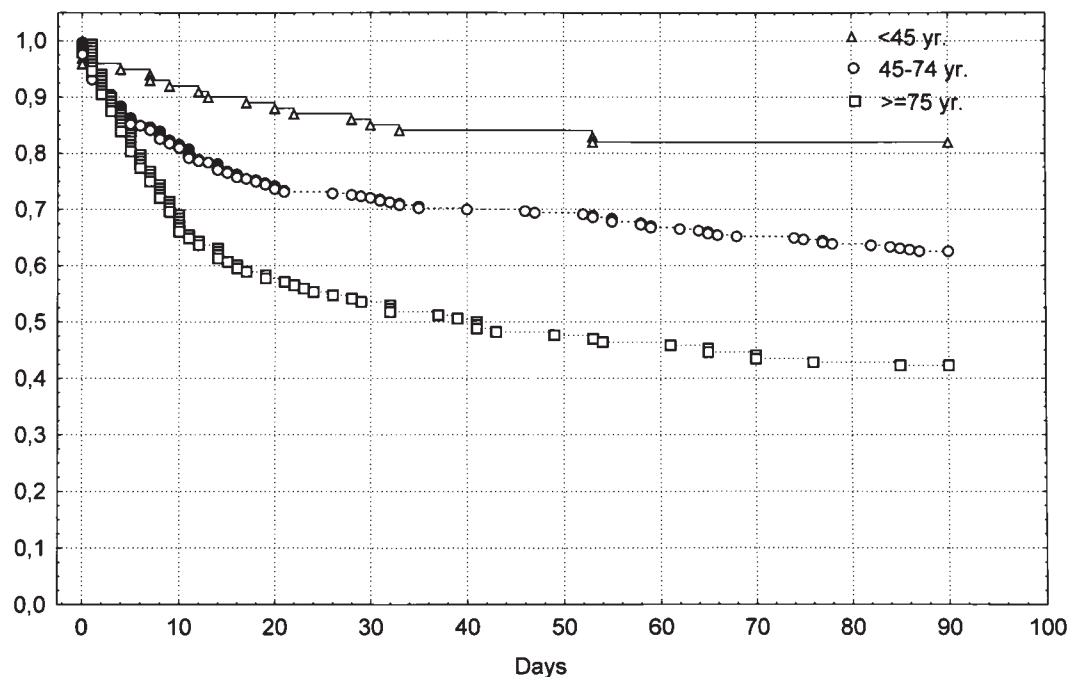


Figure 3. Cumulative proportion of surviving ARF patients. Age intervals: open triangles: < 45 yr, n = 179; open circles: 45 to 74 yr, n = 701; open squares: ≥ 75 yr, n = 277.

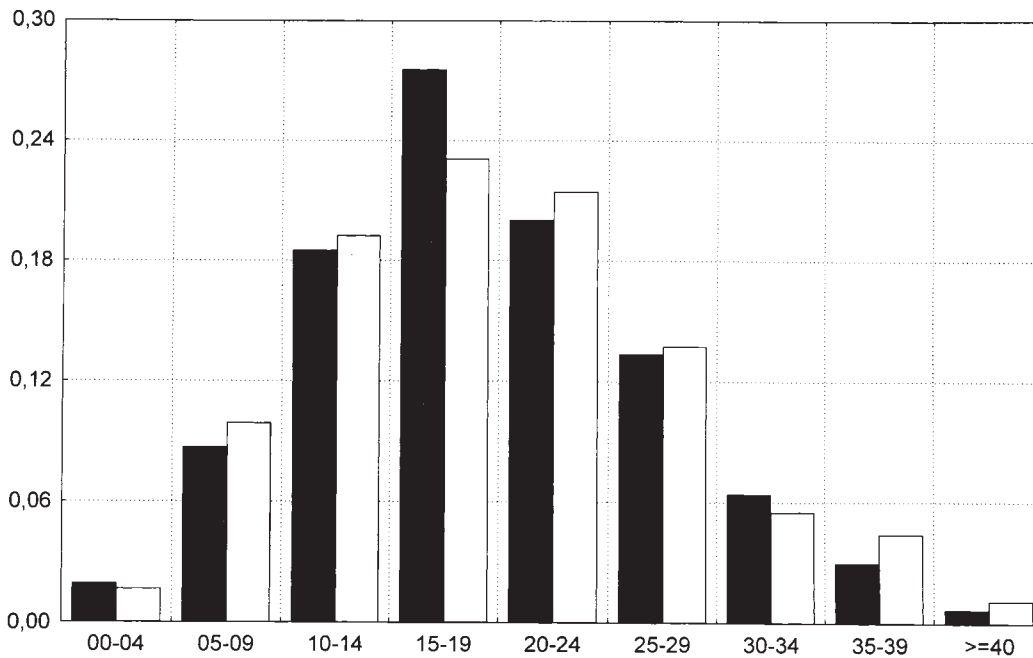


Figure 4. Fraction of the total number of patients with respect to APACHE II scores in ARDS and non-ARDS patients. The APACHE II score was calculated for the 24 h prior to inclusion in the study. *Solid bars = non-ARDS; white bars = ARDS.*

0.4 and 2.7 ± 0.3 , respectively. LIS, measured at study inclusion, could not be shown to be a significant predictor for survival in any of the groups. The cumulative proportion of surviving patients with ARF, stratified with respect to different LIS scores, is shown in Figure 6.

Ventilatory Treatment

At the time of inclusion the most commonly used ventilatory mode in patients with ARF was VCV (48%) followed by PCV (23%) and PRVC (14%). The corresponding figures for ARDS were VCV 34%, PCV 28%, and PRVC 11%. Within the 24 h

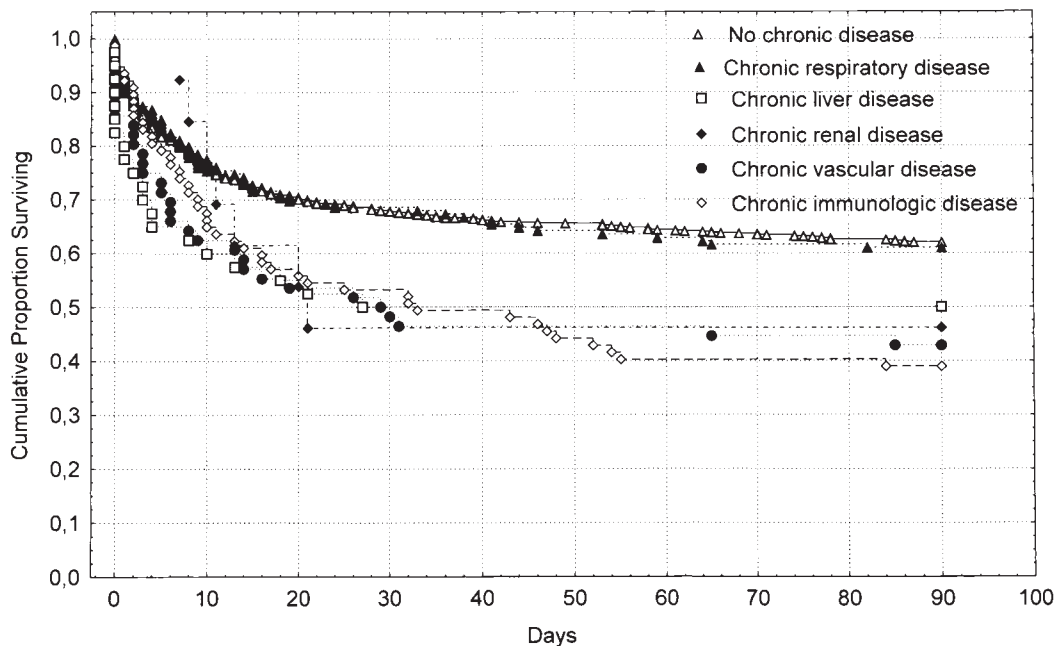


Figure 5. Cumulative proportion of surviving ARF patients. Patients with chronic diseases (other than chronic respiratory disease) as defined in the APACHE II score versus patients with no chronic diseases. *Open triangles:* no chronic disease, n = 1,081; *closed triangles:* chronic respiratory disease, n = 196; *open squares:* chronic liver disease, n = 46; *closed diamonds:* chronic renal disease, n = 19; *closed circles:* chronic cardiovascular disease, n = 81; *open diamonds:* chronic immunologic disease, n = 78.

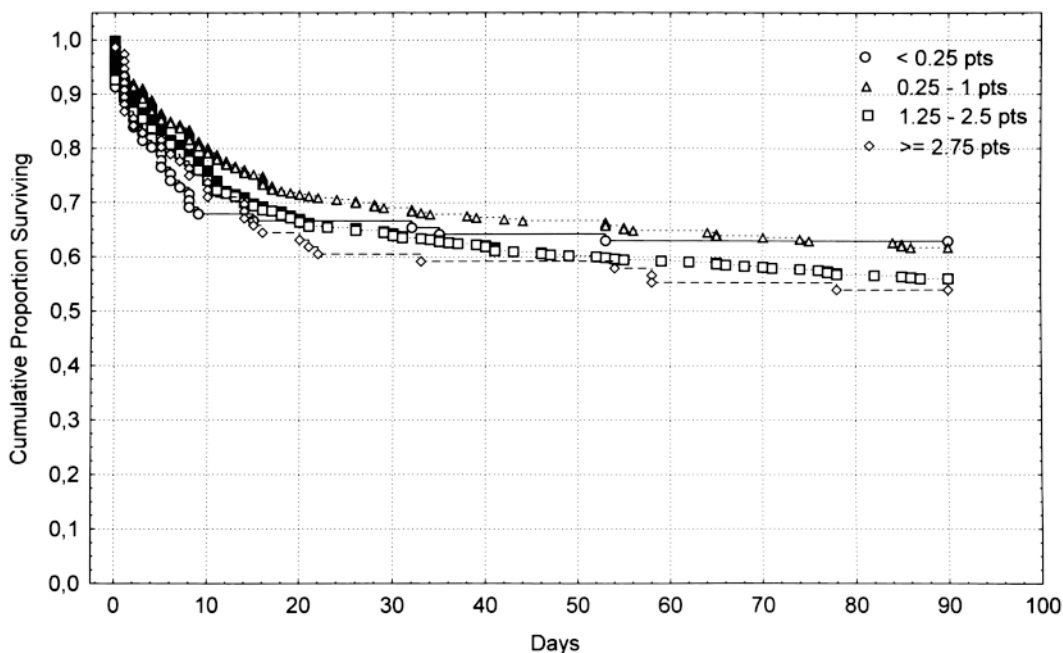


Figure 6. Cumulative proportion of ARF patients. LIS intervals: open circles: < 0.25 points, $n = 82$; open triangles: 0.25 to 1.0 points, $n = 334$; open squares: 1.25 to 2.5 points, $n = 537$; open diamonds: ≥ 2.75 points, $n = 80$.

prior to inclusion the use of extracorporeal membrane oxygenation (ECMO) was reported in two, inhaled nitric oxide (INO) in four, and prone positioning (PP) in 17 patients.

90-d Mortality

Data to show whether the patient was alive or dead at the time of follow-up were found in the Files of National Registration in 96% of all patients. There was no significant difference in mortality between patients with ARF, ALI, or ARDS at 7, 14, 21, 30, 60, or 90 d. The 90-d mortality for patients with ARF including ALI/ARDS was 41.0%. For ALI patients ($n = 66$) not fulfilling ARDS the corresponding mortality was 42.2% and for ARDS ($n = 221$) 41.2%. The mortality for patients with LIS > 2.5 ($n = 119$) was 46.5%.

Principal Reason for the Development of ARF/ARDS

For 1,438 (95%) of the 1,515 included patients one or more causes for the ARF were noted. A pulmonary cause was noted for 77.9% of the ARDS patients versus 49.1% for the non-ARDS group. For ARF, the corresponding figure was 52.1%. In 8.1% of the ARDS patients a traumatic cause (multisystem trauma, traumatic bone fracture, traumatic brain injury, or flail chest) was noted. Acute surgery had preceded the development of ARDS in 15.4% of the patients whereas the same figure for elective surgery was 5%. For the non-ARDS group, the corresponding figures were 20.3% and 9.6%. All reported etiologies of respiratory failure are presented in Table 2 for patients with ARF, ALI not fulfilling ARDS criteria, ARDS, and LIS > 2.5 .

Factors Independently Contributing to Mortality in ARF and ARDS

In the multivariate analysis of patients with ARF both age, APS points > 15 , a nonpulmonary origin to the respiratory failure, more than two quadrants with infiltrates, and immunosuppression were independently associated with subsequent out-

come (Table 4). An impaired oxygenation as manifested by a P/F ratio < 200 mm Hg was not significantly associated with mortality. For outcome in the ARDS group, an independent association could be shown between age, presence of chronic liver disease, and a P/F ratio < 100 mm Hg. The results remained consistent regardless of whether the continuous variables were analyzed as continuous or dichotomized.

DISCUSSION

This is the first epidemiological multicenter study in Scandinavia determining the incidence and 90-d mortality from ARF, ALI, and ARDS in an adult population of 11.74 million. We have used the criteria for ALI and ARDS proposed by the American-European Consensus Conference on ARDS and have identified 1,231 patients with ARF, corresponding to an incidence of 77.6 patients per 100,000/yr with a 90-d mortality of 41.0%. 287 patients fulfilled criteria for ALI and 221 patients criteria for ARDS. The incidence for ALI was 17.9 per 100,000/yr and for ARDS 13.5 per 100,000/yr. The 90-d mortality was 41.1% and 41.2%, respectively.

To determine the true incidence of a disease with a low anticipated frequency, a large study population has to be observed. This can be accomplished either by performing a large multicenter study during a short period of time or by using a restricted number of study centers and expanding the observation period. Drawbacks associated with a multicenter study include inhomogeneity of the studied population and practical problems with the study monitoring.

We considered our reference population to be homogeneous due to the similarity in health care system and provision, socioeconomic status, and pattern of disease within the three countries. The population size could be easily determined from each File of National Registration. Unfortunately no correction of the population size for in- or out-migration from the area of study could be made. However, the daily monitoring

TABLE 4

MULTIVARIATE MODEL OF VARIABLES ASSOCIATED WITH MORTALITY IN PATIENTS WITH ARF AND ARDS			
Term	Risk Ratio	95% Confidence Interval	Significance $p < 0.05$
ARF patients (n = 1,231)			
Age > 65 yr (n = 350)	1.31	1.18–1.44	< 0.001*
Sex 724 M/507 F	1.05	0.95–1.16	0.353
Pulmonary (n = 606)/nonpulmonary (n = 557) origin	0.89	0.80–0.99	0.025*
APS points > 15 (n = 265)	1.30	1.16–1.44	< 0.001*
Chronic liver disease (n = 46)	1.22	0.92–1.55	0.151
Chronic cardiovascular disease (n = 81)	1.06	0.84–1.29	0.626
Chronic respiratory disease (n = 196)	1.02	0.87–1.18	0.821
Chronic renal disease (n = 19)	1.15	0.77–1.59	0.450
Immunocompromised (n = 78)	1.22	1.01–1.44	0.040*
P/F ratio > 200 (n = 542)	0.93	0.84–1.03	0.146
PEEP > 5 cm H ₂ O (n = 461)	0.93	0.84–1.02	0.129
Number of quadrants with infiltrates on a frontal CXR (n = 232)	1.14	1.01–1.28	0.036*
ARDS patients (n = 221)			
Age > 65 yr (n = 67)	1.91	1.47–2.51	< 0.001*
Sex 148 M/73 F	1.16	0.90–1.53	0.259
Pulmonary (n = 162)/nonpulmonary (n = 46) origin	1.15	0.86–1.60	0.347
APS points > 15 (n = 60)	1.26	0.97–1.63	0.083
Chronic liver disease (n = 8)	2.04	1.16–3.27	0.016*
Chronic cardiovascular disease (n = 2)	N/A	N/A	N/A
Chronic respiratory disease (n = 20)	0.91	0.44–1.56	0.766
Chronic renal disease (n = 3)	0.67	0.16–1.47	0.375
Immunocompromised (n = 19)	1.29	0.84–1.87	0.223
P/F ratio > 100 (n = 170)	0.74	0.56–0.98	0.039*
PEEP > 5 cm H ₂ O (n = 103)	0.93	0.73–1.19	0.546
Number of quadrants with infiltrates on a frontal CXR (n = 135)	0.98	0.75–1.28	0.870

Definition of abbreviation: N/A = not available.

* $p < 0.05$.

of all ICU admissions and study inclusions guaranteed that all patients fulfilling inclusion criteria were included in the 132 participating ICUs during the study period. The disadvantage with this type of intense monitoring is the extensive resources that have to be utilized limiting the observation time. Hence, a possible seasonal variation in the incidence may pass undetected. In spite of the inherent problems with a multicenter approach, we considered the advantages with this design to outbalance potential shortcomings.

An additional problem is how to correct for unidentified patients in the incidence calculation. Two correction methods may be applied: (1) correction of the reference population, and (2) correction of the studied sample. An additional problem is in- and out-migration, something that we were not able to correct for. The three studied countries have a very similar structure of the health care system that enables patients to seek medical care regardless of permanent residency. Hence, it is difficult to establish a true reference population for each nonparticipating ICU. We have instead chosen to calculate the number of unidentified patients using the number of included patients from participating ICUs of similar type and size, a method described previously (8), because we believed that this method would render a more correct estimate.

Our intention was to screen for all patients requiring invasive or noninvasive ventilation or receiving supplemental oxygen $\geq 40\%$, in hospitals with resources to treat patients with I + MV ≥ 24 h. The population studied was exclusively ICU patients, and as a result patients treated in general wards could potentially be missed. However, none of the participating countries have a tradition for respiratory therapy outside the ICU other than giving supplementary oxygen using oxy-

gen masks, and patients with signs of progressing respiratory distress are habitually transferred to the ICU. Hence, we believe that it is unlikely that any patients with ARF or ALI/ARDS would be found outside the studied patient group.

Incidence and Mortality of ARF

We have determined the incidence of ARF (defined as I + MV ≥ 24 h) to 77.6 per 100,000/yr. Only hospitals with resources to treat patients with ARF have participated in the study, and this together with the high rate of participation (88% of all) makes the error in the estimated ARF incidence small.

Lewandowski and colleagues (2) prospectively determined the incidence of ARF in Berlin, Germany between October 1st and November 30th, 1991. All patients ≥ 14 yr were included during the study period and they reported an incidence of 88.6 per 100,000/yr in a population of 3.44 million. However, to our knowledge they did not adjust the population for persons < 14 yr. We used the same definition of ARF, roughly the same study period and adjusted for persons < 15 yr. Our incidence of 77.6 per 100,000/yr appears lower even after consideration of the age difference in the studied populations as well as the lack of adjustment in the incidence calculation. Several reasons may influence these figures, such as differences in socioeconomic factors, degree of urbanization, patient smoking history, and ICU admission policies together with ICU capacity. In 1991–1992, Vasilyev and colleagues (3) conducted a prospective survey in 1,426 patients to determine the hospital survival rates after ARF. ARF was defined as MV ≥ 24 h with a $FI_{O_2} \geq 0.5$. The overall mortality rate was 44.4%, which compares with the 42.7% mortality in the study of Lewandowski and our mortality rate of 41.0%.

Definition, Incidence, and Mortality of ARDS

In the definition of ALI specified by the American-European Consensus Conference on ARDS (6), ALI is considered to be a syndrome of inflammation and increasing permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension. ARDS is defined as the more severe form of ALI.

Using the Consensus Conference definition, we found an overall ALI incidence of 17.9 per 100,000/yr and an overall ARDS incidence of 13.5 per 100,000/yr. There are several potential problems in this definition of ARDS apart from the difficulty in defining study and reference populations. These factors include definition of "acute onset" and timing of this evaluation, evaluation of the CXR, and evaluation of the cardiac function.

In the Consensus Conference report there is no strict definition of the term "acute onset" nor any recommendations concerning when to evaluate the degree of lung injury by means of $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio and CXR evaluation. We defined "acute onset" as an immediate need for oxygen therapy as described in the inclusion criteria starting at the time for ICU admission. We also felt that a 24-h observation period for this hypoxemia to develop and stabilize was important and that the hypoxemia could still be considered acute even after this period. We consequently calculated the $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio at the end of the 24-h period. It is possible that the condition of certain patients deteriorated further in the time period beyond the observation period in this study (i.e., development of ALI or ARDS later than 24 h of initiation of oxygen treatment) and that this deterioration passed unrecorded as a result of the study design. Progress of the respiratory failure within the first 24 to 72 h is reported from several investigators (2, 10). However, in 789 patients from Sweden and Iceland we continued to record ventilatory and arterial blood gas data through the first 6 d after inclusion criteria were met, as part of an additional study. At inclusion (0–24 h), 128 of these patients fulfilled criteria for ARDS. Within the interval of 24 to 72 h an additional 18 patients (2.3%) progressed further with deterioration in $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio meeting ARDS criteria. After 72 h only one additional patient with ARDS was identified.

At the other end of the spectrum, it is possible that certain patients during the first 24 h of treatment have had oxygen deficiencies of such severity that specific treatment modalities have been applied. These patients may well have improved their oxygenation index beyond the defined limit for ALI/ARDS at the time of evaluation. The Consensus Conference addressed this in relation to the effect of different levels of PEEP; however, other treatment modalities such as ECMO, INO, or PP may have a profound effect on the $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio. In our study, a total of 23 patients were treated with "advanced therapies" within the initial 24 h, ECMO ($n = 2$), INO ($n = 4$), and PP ($n = 17$). Of these patients, only nine had a $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio less than 200 mm Hg (INO $n = 4$ and PP $n = 5$) at study inclusion. Consequently, 14 patients did not fulfill ARDS criteria although it is likely that the principal reason for the use of the specific treatment was respiratory failure with a severe oxygenation deficiency.

The mode of ventilation is purposely not defined in the Consensus Conference report. In this study we have chosen only to evaluate patients who were intubated or given supplemental oxygen by a full-face oxygen mask. In this way, patients given oxygen by other systems (e.g., nasal catheters) with a calculated high inspired oxygen content could fulfill all ALI/ARDS criteria but be excluded from the evaluation ow-

ing to the study design. However, all cases of intubation were recorded and we believe that very few cases of true ALI/ARDS patients would ensue without intubation at a given time during the course of the respiratory failure.

In the diagnosis of ALI/ARDS both evaluation of a CXR and left atrial function may have an influence on the incidence figures. In 96% ($n = 1,448$) of all patients a CXR was available for evaluation. The possibility of progress from unilateral to bilateral infiltrates on the CXR after the evaluation should be kept in mind, as this would pass unrecorded because of the study design. The method of assessment of left atrial function (presence or absence of left pulmonary hypertension) may also be more or less accurate. The Consensus Conference has stated that this assessment may be performed clinically, by echocardiography, or by wedge pressure. In this study, a majority of the patients were assessed using clinical judgment, and this may introduce an error because we believe that the two latter methods are the most efficient to evaluate left atrial function.

It may also be pointed out that 39 patients fulfilling ARDS criteria in this study were nonintubated and given oxygen with CPAP or by full-face oxygen mask. An exact determination of Fi_{O_2} in this setting is not possible and a false $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio could ensue that would influence the diagnosis of ALI/ARDS.

Several attempts have been made to determine the true incidence and mortality of ARDS (2, 8, 11, 12). The more recent reported incidences have varied between 1.5 and 8.3 per 100,000/yr and are much lower than early estimates from the United States of 60 cases per 100,000/yr (13). Differences in the definitions of ARDS and the type and strength of study design may contribute to this variation (1, 14). We have used the recommended definition from the American-European Consensus conference on ARDS (6) to define ARDS. Our ARDS incidence of 13.4 per 100,000/yr may seem higher than the previously reported incidences. Villar and Slutsky determined the incidence of ARDS in 1989 in the Canary Islands as 1.5 patients per 100,000/yr using an oxygenation criteria of $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio of ≤ 110 mm Hg (11). In 1995, Thomsen and Morris (8) estimated an ARDS incidence of 4.8 to 8.3 patients per 100,000/yr in the state of Utah. Their definition of ARDS is similar to the Consensus Conference apart from the oxygenation criteria of arterial oxygen pressure/alveolar oxygen pressure ($\text{Pa}_{\text{O}_2}/\text{P}_{\text{A}_{\text{O}_2}} \leq 0.2$). However, they state in their discussion that this oxygenation index roughly corresponds to a $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio of ≤ 110 mm Hg and thus their incidence of 4.8 to 8.3 patients per 100,000/yr is higher than that reported from the Canary Islands. We believe that one possible reason for our higher incidence of ARDS is an effect of a wider oxygenation criterion ($\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio ≤ 200 mm Hg) as defined in the Consensus Conference definition. If we had used a $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio of ≤ 110 mm Hg in our study, the incidence would be 3.7 per 100,000/yr which is similar to that found by Thomsen in Utah. The study of Lewandowski (2) also prospectively studied the incidence of ARDS. ARDS was in this study defined as a LIS > 2.5 and the estimated incidence 3.0 per 100,000/yr. To compare our incidence with this report we also used the composite four-point scoring system proposed by Murray and colleagues (7) and calculated an incidence of 7.2 per 100,000/yr. This higher incidence may in part be explained by an underestimation of the incidence in Berlin owing to the lack of correction for the population < 14 yr.

Contrasting statements have been made on the mortality rates after ARDS. One report of a constant mortality in the 50% range (4) disagrees with other data that suggest a declining fatality rate (5). The overall mortality in this study was 41.2%. What is interesting is the lack of difference in the mor-

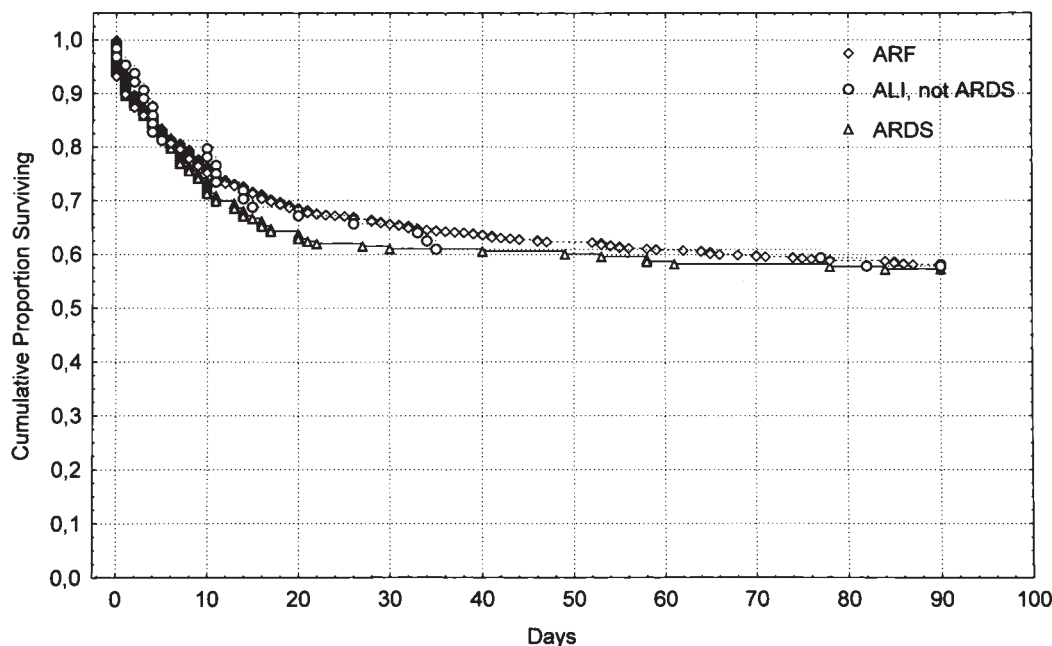


Figure 7. Cumulative proportion of surviving patients with ARF (not including ALI/ARDS), ALI (not including ARDS), and ARDS. Open diamonds: ARF, $n = 987$; open circles: ALI not ARDS, $n = 66$; open triangles: ARDS.

tality between ARDS and non-ARDS. The largest difference in mortality was seen 21 d after inclusion ($p = 0.049$), as illustrated in Figure 7. This finding may in part be due to an inhomogeneity of participating centers where a difference may well have been seen if the study only would have included centers with similar specialties and similar therapeutic traditions. However, we have refrained from focusing on smaller subgroups of ICUs because the complicated pattern of patient referrals in relation to diagnosis and resource allocation makes it almost impossible to view such subgroups of ICUs as independent from each other. There is a risk of potential erroneous conclusions drawn from such a subdivision.

How the severity of the respiratory failure at inclusion may influence the outcome is controversial. It is of interest to note that mortality in ARF was approximately 40% regardless of whether ARDS was present or not. This clearly brings into focus that factors other than pulmonary may be of much greater importance in determining the fate of an acute illness in the majority of ICU patients with ARF. Factors that independently were associated with mortality in the multivariate analysis were age, APS score, immunosuppression, more than two quadrants with infiltrates on a frontal CXR, and a nonpulmonary cause of the respiratory failure. That the extent of the respiratory failure as manifested by a P/F ratio > 200 mm Hg was not independently associated to mortality agrees with other reports that suggest that the long-term outcome after respiratory failure may be more related to other factors than the actual severity of the respiratory failure at inclusion (15).

In the subset of patients fulfilling criteria for ARDS, the multivariate analysis revealed an independent association for age and chronic liver disease. That age is a predictor of outcome in ARDS has been previously shown (16–18), and chronic liver disease has been shown to be associated with mortality in patients with ALI (10). In the ARDS subset, APS points were not significantly correlated with outcome, a finding previously described in patients with ALI from a medical ICU by Zilberberg and Epstein (17). In our patients with ARDS a P/F ratio

> 100 mm Hg was independently associated with survival. This finding indicates that at least in ARDS patients, the degree of respiratory failure may be indicative of a poor prognosis, and that a P/F ratio < 100 mm Hg may call for more aggressive therapies to improve oxygenation. It is interesting to speculate to what extent the general disease process and cause of death might be similar or different in patients with ARF with or without ALI/ARDS. Possibly, iatrogenic factors associated with mechanical ventilation and an artificial airway independently contribute to a poor prognosis with higher age and APS points. All these points should be clarified through further studies (15, 18, 19).

As to our secondary objective to examine the extent of congruency between respiratory insufficiency evaluated by the LIS and the definition given by the Consensus Conference, it seems fair to conclude that these definitions may not be used interchangeably as an indicator of lung dysfunction because they outline two groups of patients that only marginally overlap.

In summary, in this prospective population-based cohort study, we have determined the incidence and mortality of ARF and ARDS in Sweden, Denmark, and Iceland. Correction was made for unidentified patients from nonparticipating ICUs in Sweden and Denmark. No correction for in- or out-migration from the study area was made. The incidence of ARF was 77.6 per 100,000/yr with a subsequent 90-d mortality of 41.0% and the incidence of ARDS was 13.5 per 100,000/yr with a mortality of 41.2%. The ARF incidence and mortality correspond to previous reports. The incidence of ARDS is higher, mostly due to a novel definition, and with a lower mortality rate than previously reported.

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- Hospital ICU, *Mattias Szummer*; Kristianstad Central Hospital ICU, *Tomas Nolin*; Kristinehamn Hospital ICU, *Margareta Löwenborg*; Kungälv Hospital ICU, *Leif Backman*; Lidköping Hospital ICU, *Robert Nyström*; Lindesbergs Hospital ICU, *Luis Fernandez*; Linköping University Hospital ICU, *Kerstin Metcalf*; Ljungby Hospital ICU, *Peter Linné*; Luleå Hospital ICU, *Krister Ruuth*; Lund University Hospital ICU, *Anders Larsson*; Lund University Hospital, Thoracic ICU, *Lars Algotsson*; Lund University Hospital, Inf. 80, *Erling Myhre*; Lycksele Hospital ICU, *Bo Reinert*; Malmö University Hospital Inf., *Torbjörn Prellner*; Malmö University Hospital, Thoracic ICU, *Bertil Rosberg*; Malmö University Hospital, ICU, *Hans Koopmann*; Mora Hospital ICU, *Göran Blohm*; Motala Hospital ICU, *Anita Mohall*; Mölndals Hospital ICU, *Liselotte Iregård*; Norrköping, Vrinnevi Hospital ICU, *Sten Walther*; Norrtälje Hospital ICU, *Johan Sandberg*; Nyköpings Hospital ICU, *Ulf Riese*; Oskarshamn Hospital ICU, *Greger Fransson*; Piteå Hospital ICU, *Ulf Carlsson*; Skellefteå Hospital ICU, *Jan Remmets*; Skövde Hospital ICU, *Keld Brodersen*; Sollefteå Hospital ICU, *Göran Karlström*; Stockholm, Ersta Hospital ICU, *Annika Lindh*; Stockholm, Karolinska Hospital Burn ICU, *Carl-Johan Wallin*; Stockholm, Karolinska Hospital ICU, *Claes-Roland Martling*; Stockholm, Karolinska Hospital Thoracic ICU, *Elisabet Anjou-Lindskog*; Stockholm, Karolinska Hospital Neurosurgical ICU, *Sixten Bredbacka*; Stockholm, St. Göran Hospital ICU, *Anna Roland*; Stockholm, South Hospital, ICU, *Jan Häggqvist*; Stockholm, South Hospital, Medical ICU, *Ulf Ludwigs*; Sundsvall County Hospital ICU, *Sten Borgström*; Säffle Hospital ICU, *Lars Grapensson*; Södertälje Hospital ICU, *Håkon Ones*; Torsby Hospital ICU, *Torbjörn Karlsson*; Trelleborg Hospital ICU, *Mats Helder*; Trollhättan, Norra Älvsborg County Hospital ICU, *Örjan Lennander*; Uddevalla Hospital ICU, *Tommy Borg*; Umeå, The University Hospital of Northern Sweden ICU, *Anders Rydval*; Umeå, The University Hospital of Northern Sweden Thoracic ICU, *Erik Sandström*; Uppsala University Hospital ICU 70G, *Hans Stjernström*; Uppsala University Hospital Burn ICU, *Torbjörn Karlsson*; Uppsala University Hospital Neurosurgical ICU, *Johan Valtysson*; Varberg Hospital ICU, *Lilian Martinson*; Visby Hospital ICU, *Sven-Erik Bohrr*; Vänamo Hospital ICU, *Svend Höjsgaard*; Västerbik Hospital ICU, *Björn Guding*; Västerås Central Hospital ICU, *Stefan Ström*; Växjö Central Hospital ICU, *Håkan Edfeldt*; Ystad Hospital ICU, *Leif Perhag*; Örnköldsviks Hospital ICU, *Anders Mörtberg*; Östersunds Hospital ICU, *Caroline Starlander*; Örebro Medical Center Hospital ICU, *Anders Nydahl*.

Denmark

Aalborg Hospital ICU, *Marianne Toftegaard*, *Odd Ravlo*; Aalborg Hospital Neurosurgical ICU, *Finn Vestergaard*, *Lisa Seest Nielsen*; Aalborg Hospital South ICU, *Thorben Schultz-Lebahn*, *Ruth Hagerup*; Aarhus Hospital ICU, *Kim Schønnemann*, *Ole Viborg Jensen*; Aarhus KH Hospital ICU, *Christian Muff Hansen*; Amager Hospital ICU, *Finn Janstrup*; Bispebjerg Hospital ICU, *Jens Brushøj*, *Bente Dyrland Petersen*; Esbjerg Hospital ICU, *Bo Dilling*, *Axel Lahoz*; Farsø Hospital ICU, *Søren Rossing Nielsen*; Fredericia Hospital ICU, *Per Christensen*, *Per Smith Nielsen*; Fredriksberg Hospital ICU, *Anne Munksgaard*; Gentofte Hospital ICU, *Karen-Lise Welling*, *Ivar H. Gøthgen*; Glostrup Hospital ICU, *Helle Thy Østergaard*, *Elisabet Bryld*; Grenå Hospital ICU, *Peter Tredal*, *Peter Anders Christensen*; Haderslev Hospital ICU, *Johanne Markus*; Helsingør Hospital ICU, *Jan Nørtved*; Herlev Hospital ICU, *Kristian Antonsen*; Herning Hospital ICU, *Lars Blom*, *Michael Lindhart Rasmussen*; Hillerød Hospital ICU, *Søren Elkjær*, *Vagn Bach*; Hjørring Hospital ICU, *Ivan Nielsen*, *Niels-Ole Klausen*; Hobro Hospital ICU, *Birger Borell Rasmussen*, *Per Markers*; Holbæk Hospital ICU, *Erland Pedersen*, *Margit Brenøe*; Holstebro Hospital ICU, *Kurt Ebbensgaard*, *Lars Chemnitz Frey*; Hvidovre Hospital ICU, *Jan Emborg*, *Lene Larsen*; Kalundborg Hospital ICU, *Lars Bitsch-Larsen*; Kolding Hospital ICU, *Jette Iversen*, *Bent Uhrbrand*; København, Rigshospitalet Infectious Medicine, *Jesper Qvist*, *Lise Jørgensen*; København, Rigshospitalet Neurosurgical ICU, *Hans Jørgen Fredriksen*, *Susanne Mogensen*; København, Rigshospitalet Thoracic ICU, *Niels Erik Ove Andersen*, *Frede Sztuk*; Køge Hospital ICU, *Susanne Jørgensen*, *Marianne Waarkjær*; Middelfart Hospital ICU, *Ole Bo Olsen*, *Per Thordal Andersen*; Næstved Hospital ICU, *Anni Skoven*, *Bjarne Fogh*; Nyborg Hospital ICU, *Anne Marie Ulrik*; Nykøbing-Falster Hospital ICU, *Ole Mathiesen*, *Janus Glovinsky*; Odsher Hospital ICU, *Narain Rajani*; Odense

APPENDIX: THE ARF STUDY GROUP

Sweden

Alingsås Hospital ICU, *Ulf Garvang*; Bodens Hospital ICU, *Ivar Wizelius*; Bollnäs Hospital ICU, *Bo Magnusson*; Borås Hospital ICU, *Claes Håkan Björklund*; Danderyd Hospital ICU, *Carl-Johan Wickerts*; Eksjö, Höglands Hospital ICU, *Jesper Raaby*; Enköping Hospital ICU, *Jan Olsson*; Eskilstuna, Mälars Hospital ICU, *Peter Spetz*; Falu Hospital ICU, *Ingemar Ahlgren*; Gällivare Hospital ICU, *Dan Berndtsson*; Gävle County Hospital ICU, *John Mälstam*; Göteborg, Sahlgrenska University Hospital ICU, *Christian Rylander*; Göteborg, Sahlgrenska University Hospital Östra, Inf. 2, *Lars Hagberg*; Göteborg, Sahlgrenska University Hospital Östra ICU, *Björn Isacson*, *Svante Arvidsson*; Halmstad County Hospital ICU, *Bengt Brodin*; Helsingborgs Hospital ICU, *Karin Olofsson*; Stockholm, Huddinge University Hospital ICU, *Susanne Almqvist*; Hudiksvalls Hospital ICU, *Kim Nissen*; Jönköping, Ryhov County Hospital ICU, *Peter Nordlund*; Kalmar County Hospital, *Lars Larsson*; Karlskoga Hospital ICU, *Kerstin Thor*; Karlskrona Central Hospital ICU, *Christer Nilsson*; Karlstad Central Hospital ICU, *Lars-Åke Johansson*; Katrineholm, Kullbergska Hospital ICU, *Ingrid Rosén-Flink*; Kiruna

Hospital ICU, *Dorte Jungersen, Marlene Pall*; Odense Hospital Thoracic ICU, *Henrik Berg, Christine Bagger*; Randers Hospital ICU, *Niels Vestergaard*; Roskilde Hospital ICU, *Klaus Thornberg, Niels Erik Drenck*; Rønne Hospital ICU, *Jan Holsterbroe, Bo Hansen*; Silkeborg Hospital ICU, *Anne Vester, Lars Kjærsgaard*; Skive Hospital ICU, *Torben Palm, Gitte Islev*; Skjeby Hospital ICU, *Morten Noreng, Charles Pedersen*; Slagelse Hospital ICU, *Henrik Guldager, Claus Nilsson*; Svendborg Hospital ICU, *Kurt Jacobsen, Jan Kristensen*; Sønderborg Hospital ICU, *Carsten Engel*; Vejle Hospital ICU, *Jens Nørreslet, Bo Krogh*; Viborg Hospital ICU, *Jens Jørn Jensen, Anette Schultz*.

Iceland

Landspítalinn National University Hospital ICU, *Adalbjörn Thorsteins-*

son, Ivar Gunnarsson; Reykjavik Hospital, *Kristinn Sigvaldsson, Pall Helgason*; Central Hospital Akureyri, *Girish Hirlekar*.

Norway

Aker Hospital, *Jan Ole Kullerud*; Buskerud Central Hospital, *Roar Gravningsbråten, K. Brakke*; Elverum Hospital, *Dr. Kosiniski*; Hamar Hospital, *B. Johnstad*; Hammerfest Hospital, *Bo Lundström, Torben Wisborg*; Haugesund Hospital, *S. Gramstad, C. McTiernan*; Hauke-land Hospital, *Sidsel Aarda*; Nordland Central Hospital, *Knut Ryb- wik, Erik Waage Nielsen*; Ritø Hospital, *M. Osnes*; Baerum Hospital, *Dr. Rørvik, Dr. Nordentoft*; Vestfold Central Hospital, *Niels Hansen*.