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The impact of respiratory variables on mortality in non-ARDS and ARDS patients requiring mechanical ventilation

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Abstract *Objectives*: Primarily, to determine if respiratory variables, assessed on a daily basis on days 1–6 after ICU admission, were associated with mortality in non-ARDS and ARDS patients with respiratory failure requiring mechanical ventilation. Secondarily, to determine non-respiratory factors associated with mortality in ARDS and non-ARDS patients.
Design: Prospective multicentre clinical study.
Setting: Seventy-eight intensive care units in Sweden and Iceland.
Patients: Five hundred twenty non-ARDS and 95 ARDS patients.
Measurements and results: Potentially prognostic factors present at inclusion were tested against 90-day mortality using a Cox regression model. Respiratory variables (PaO_2/FIO_2, PEEP, mean airway pressure (MAP) and base excess (BE)) were tested against mortality using the model.
Primary aim: in non-ARDS a low PaO_2/FIO_2 on day 1, RR (risk ratio) = 1.17, CI (95% confidence interval) (1.00; 1.36), day 4, 1.24 (1.02; 1.50), day 5, 1.25 (1.02; 1.53) and a low MAP at baseline, 1.18 (1.00; 1.39), day 2, 1.24 (1.02; 1.52), day 3, 1.33 (1.06; 1.67), day 6, 2.38 (1.11; 5.73) were significantly associated with 90-day death.
Secondary aim: in non-ARDS a low age, RR = 0.77 (0.67; 0.89), female gender, 0.85 (0.74; 0.98), and low APS (acute physiologic score), 0.85 (0.73; 0.99), were associated with survival; chronic disease, 1.31 (1.12; 1.52), and non-pulmonary origin to the respiratory failure, 1.27 (1.10; 1.47), with death. In ARDS low age, RR = 0.65 CI (0.46; 0.91), and low APS, 0.65 (0.46; 0.90), were associated with survival.
Conclusions: No independent significant association was seen between 90-day mortality and degree of hypoxaemia, PEEP, MAP or BE for the first full week of ICU care in either ARDS or non-ARDS. In a sub-group of non-ARDS a lower PaO_2/FIO_2 and MAP tended to influence mortality where a significant association was seen for 3 of 7 study days. Age, gender, APS, presence of a chronic disease and a pulmonary/non-pulmonary reason for the respiratory failure were associated with mortality in non-ARDS, while only age and APS showed a similar association in ARDS.

Key words Acute respiratory distress syndrome · Acute lung injury · Mortality · Risk factors · Multivariate analysis · Prospective studies · Respiratory insufficiency · Positive-pressure respiration

Introduction

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) both define a syndrome of inflammation and increased permeability in the lung [1]. Both are clinically characterised by acute onset of arterial hypoxaemia, reduced respiratory system compliance and diffuse bilateral infiltrates on a chest radiograph. The reported mortality exceeds 40 % [2]. Patients defined as suffering from acute respiratory failure (ARF), of which ALI/ARDS represent a subset with more compromised oxygenation, have a similar reported mortality close to 40 % [3, 4]. In ARF, no variables reflecting the degree of respiratory failure at the time of diagnosis of ARF have been able to predict mortality [5]. However in ARDS, factors associated with mortality are aetiology of the respiratory failure, co-morbid conditions and the development of multiple organ failure [6, 7].

An early improvement in PaO_2/FIO_2 has also been suggested to define an ARDS population with a better chance of survival [8], but questions have recently been raised about whether mortality due to ARDS is related to the severity of the respiratory failure at all [9]. Convincing evidence linking degrees of oxygenation to subsequent mortality is absent in these patient groups. However, several therapies, such as inhaled nitric oxide [10] and prone positioning [11], have been suggested to improve oxygenation leading to enhanced survival, when intubation and mechanical ventilation (I + MV) with increasing fractions of inspired oxygen (FIO_2) alone have been considered inadequate. ARDS is the most studied sub-group of patients with ARF. On the other hand, they only represent a minority of all ARF patients. Factors associated with mortality in non-ARDS patients are less studied, and have so far been inconclusive. In addition, no studies have evaluated the independent contribution of oxygenation to mortality for the initial acute phase of an ARF.

The aim of this study was to determine if daily assessment of easily accessible respiratory variables, including oxygenation measured as PaO_2/FIO_2, during the first week of ICU care could predict mortality in non-ARDS and ARDS patients with respiratory failure requiring mechanical ventilation. To assess respiratory variables in this manner mimics actual clinical practice, where daily decisions are made to change respiratory treatment based on such information. To test this hypothesis, we included patients with ARF from a defined geographical area in a prospective non-randomised fashion. This resulted in a heterogeneous ICU population with varying degrees of respiratory failure. To compensate for the heterogeneity, we analysed the chosen respiratory variables independently in a regression model. In addition, to adjust this model fully for other factors associated with mortality, a secondary aim was to determine non-respiratory factors associated with mortality in these patients.

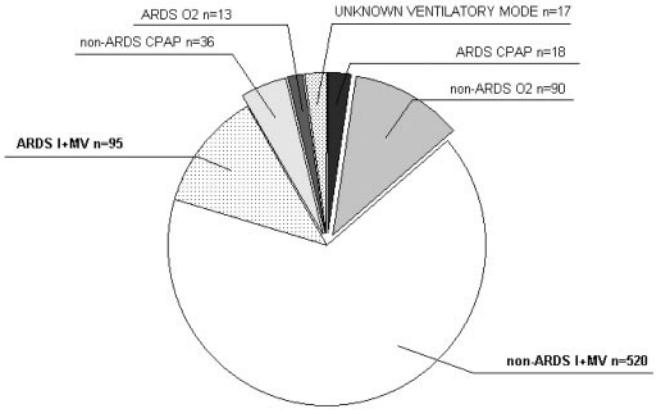

Fig. 1 Distribution of the total patient population (n = 789) of the original study covering Sweden and Iceland, with respect to fulfilment of ARDS criteria and applied ventilatory strategy for the first 24 h after ICU admission. Patients analysed in the present paper are those that were intubated and mechanically ventilated (n = 615), and are marked with bold text (*ARDS* acute respiratory distress syndrome, *O_2* oxygen treatment at inclusion with an oxygen delivery mask, *CPAP* treatment at inclusion with continuous positive airway pressure or bi-level positive airway pressure, *I + MV* treatment at inclusion with intubation and mechanical ventilation)

Material and methods

This investigation is a continuation of a previously reported prospective study [12] on the incidence and mortality of ARF and ARDS in Sweden, Denmark and Iceland. The inclusion criteria in the original study were designed to enable enrolment of both patients with ARF, defined as intubation and mechanical ventilation (I + MV) for 24 h or more regardless of FIO_2, and patients fulfilling the ARDS definition suggested by the American-European consensus conference on ARDS [1]. In this paper we report patients included in adult ICUs (n = 78) in Sweden and Iceland with resources to treat patients with I + MV for 24 h or more. For a detailed description of the original study procedure please see Luhr et al. [12].

Study population

From the original study population (n = 789) enrolled in Sweden and Iceland we followed those patients who were intubated and mechanically ventilated (n = 615). (Fig. 1).

Definition of acute lung injury and acute respiratory distress syndrome

To define ALI and ARDS we used the definition proposed by the American-European Consensus conference on ARDS [1]. The definition is based on the following criteria: (1) acute onset, (2) PaO_2/FIO_2 of 300 mmHg or less for ALI and PaO_2/FIO_2 of

200 mmHg or less for ARDS, (3) bilateral infiltrates seen on a frontal chest radiograph and (4) pulmonary artery wedge pressure of 18 mmHg or less or no clinical evidence of left atrial hypertension.

Ethics committee approval

Local ethics committee approval was sought and granted for all participating ICUs and the need for informed patient consent was waived by the regional ethics committees in the respective countries.

Data collection

For the patient population studied ($n = 615$) we prospectively registered respiratory variables and corresponding arterial blood-gas values at baseline (admission to the ICU) and then for the first 6 consecutive days of ICU care after study inclusion criteria were met.

Data were recorded when the patient fulfilled the inclusion criteria. This included demographic data and an assessment of the presence or absence of left atrial hypertension (pulmonary artery wedge pressure ≤ 18 mmHg or no clinical evidence of left atrial hypertension). An APACHE II score [13] was calculated for the 24 h prior to inclusion which corresponded to the first 24 h of ICU care in all patients. A chest radiograph was analysed for infiltrates. Arterial blood-gas data together with a simultaneous reading of ventilatory settings was recorded and a lung injury score (LIS) [14] was calculated. Each morning for 6 consecutive days after inclusion we recorded arterial blood-gas values together with respiratory variables assessed from ventilator measurements. The mode of ventilatory support, including alterations made following previous registrations due to improvement or deterioration in oxygenation, was noted. At the end of the study period the ICU investigator determined the cause or causes of the ARF from a previously used inventory [3] of known predisposing causes of ARDS. For the multivariate analysis, a pulmonary or non-pulmonary classification of causes was retrospectively assigned to each patient by the main investigator after reviewing all individual patient data. Pulmonary origin was defined as a disease process confined to the lung with the visceral pleura as the outer perimeter. Mortality 90 days after inclusion in the study was determined from the files of National Registration.

The local ICU investigator or the physician in charge of the patient recorded all data on case record forms (CRF). After the study period the forms were collected centrally in each country and manually entered into a computerised database (Microsoft Access 2.0) for subsequent analysis.

Statistical analysis

Mortality was evaluated 90 days after inclusion in the study. Survivors and non-survivors in the non-ARDS and ARDS groups were compared in a univariate analysis through Mann-Whitney U-test for continuous, and Pearson's chi-square test for dichotomous, variables.

Our primary goal was to ascertain if respiratory variables assessed daily were independently associated with mortality. In order to do this we used a Cox proportional hazard model. The proportional hazard assumption was made for the selected grouping variables based on visual inspection of the logarithms of the integrated cumulative hazards. In the Cox regression model we included baseline factors univariately shown to be associated with mortality, such as age, acute physiological score (APS) and chronic disease as defined in the APACHE II score. In addition, we included factors that could have a potential impact on mortality such as gender, left atrial hypertension, bilateral pulmonary infiltrates and pulmonary origin of the respiratory failure. In the construction of the model we also tested if sub-groups of non-ARDS patients arbitrarily dichotomised into age over 65 years, APS higher than 15 and LIS of 2.0 or more behaved differently from the group as a whole.

The final Cox regression model was used to assess independently the chosen respiratory variables over the first 6 days of ICU care. The respiratory variables tested consisted of PaO_2/FIO_2, positive end-expiratory pressure (PEEP), mean airway pressure (MAP) and base excess (BE). As we tested each respiratory variable separately, the other variables were left out of the model to avoid the problem that the chosen variables would interact due to co-linearity. To balance for the different patient populations among the study days (due to patients recovering or dying during the study period) all continuous variables were dichotomised into binary variables indicating less or greater than sample median for use in the Cox regression analyses. A further effect of this dichotomisation was that the results could be expressed as risk ratios (RR) with 95 % confidence intervals (CI).

Using the Cox regression model described, we tested the possible independent impact of the chosen respiratory variables on the risk intensity for the patient sub-group still alive on each separate day of the first week. Separate testing for each day was performed because the variables could have different importance on different days. We did not correct for multiplicity (Bonferroni correction) due to the repeated measurements since the respiratory variables were likely to be correlated and such a correction would result in overcompensation for the possible influence of chance. Since no overall significance level could be set, the exact p values of the analyses have to be interpreted with caution.

In choosing the respiratory variables for the analysis we disregarded FIO_2, minute ventilation, RR and $PaCO_2$ since they are directly influenced by the ventilatory strategy used. This relationship is not as clear for PaO_2/FIO_2, BE and standard bicarbonate (StBic), all significantly related to mortality in the univariate analysis. Because of the relationship between BE and StBic we analysed only the former. Even though directly related to the ventilatory strategy, we also wanted to assess the independent contribution of PEEP, since it has a profound effect on oxygenation. We also included MAP, since different levels may play a role in the development of ventilator-induced lung damage. For the statistical analyses we used only available data, assuming a random distribution of missing data among the patients, so no correction due to these missing values was considered necessary.

The results of the descriptive statistics are expressed as mean ± S.D. and results from the Cox regression as risk ratio (RR) with a 95 % CI. For all analyses a difference was considered significant if p was less than 0.05. The statistical software STATISTICA (1996; StatSoft, Tulsa, Okla.) and JMP 3.2 (1997; SAS Institute, Cary, N.C.) were used for all statistical calculations.

Results

Of the 615 ICU patients included, intubated and mechanically ventilated for ARF, 95 met criteria for ARDS and 520 were defined as non-ARDS patients.

Table 1 Patient characteristics and respiratory variables at baseline in non-ARDS and ARDS patients comparing survivors and non-survivors (*APS* acute physiological score, *FIO_2* fraction of inspired oxygen, *PIP* peak inspratory pressure, *MAP* mean airway pressure, *PEEP* positive endexpiratory pressure, *TV* tidal volume, *BE* base excess, *StBic* standard bicarbonate)

		Non-ARDS patients (n = 520)				ARDS patients (n = 95)			
		Survivors (n = 305) Mean ± SD		Non-survivors (n = 215) Mean ± SD	p-value	Survivors (n = 53) Mean ± SD		Non-survivors (n = 42) Mean ± SD	p-value
Mean survival time, days (significance testing Kaplan-Meier with log-rank test)		N/A		18 ± 21		N/A		14 ± 19	0.497
Age, yr		59 ± 18		68 ± 14	< 0.001	57 ± 17		68 ± 15	< 0.001
Sex M/F		168/137		137/78	0.049	28/25		27/15	0.261
APS		10 ± 6		13 ± 6	< 0.001	11 ± 6		15 ± 7	0.009
Chronic disease points		0.8 ± 1.7		1.4 ± 2.2	< 0.001	1.0 ± 2.0		0.9 ± 1.9	0.791
Lung Injury Score		1.3 ± 0.7		1.3 ± 0.7	0.832	2.3 ± 0.5		2.5 ± 0.5	0.133
Total APACHE II score		17 ± 7		23 ± 8	< 0.001	18 ± 8		22 ± 9	0.018
Presence of left atrial hypertension Y/N	(n =)	79/224		79/135	0.008	0/53		0/42	NA
Pulmonary/non-pulmonary/unknown origin (= missing data) for the respiratory failure	(n =)	139/147/19		79/125/11	0.030	35/13/5		31/8/3	0.476
Ventilatory settings	N/% tot n		N/% tot n			N/% tot n	N/% tot n		
FIO_2	304/99	0.45 ± 0.15	213/99	0.50 ± 0.19	0.006	53/100	0.58 ± 0.15	42/100	0.64 ± 0.19	0.239
Minute ventilation (L/min)	296/97	8.9 ± 2.2	211/98	9.4 ± 2.3	0.008	51/96	9.9 ± 2.2	39/93	9.7 ± 2.6	0.359
PIP (cm H_2O)	301/99	26 ± 7	205/95	26 ± 7	0.740	53/100	29 ± 6	41/98	29 ± 8	0.807
MAP (cm H_2O)	244/80	8 ± 5	162/75	7 ± 6	0.141	44/83	11 ± 7	33/79	12 ± 6	0.449
PEEP (cm H_2O)	305/100	5 ± 3	215/100	4 ± 3	< 0.001	53/100	7 ± 3	42/100	7 ± 3	0.379
I : E ratio	260/85	0.35 ± 0.07	184/86	0.36 ± 0.11	0.911	45/85	0.40 ± 0.11	35/83	0.37 ± 0.09	0.461
TV (mL)	292/96	604 ± 158	209/97	596 ± 170	0.304	51/96	593 ± 147	39/93	594 ± 157	0.772
TV/body weight (mL/kg)	258/85	8 ± 2	158/73	8 ± 2	0.937	49/92	7 ± 2	33/79	8 ± 3	0.112
Arterial blood-gas analysis										
PaO_2 (kPa)	302/99	12.6 ± 4.2	211/98	12.3 ± 4.4	0.305	53/100	9.8 ± 1.7	42/100	9.6 ± 1.8	0.479
$PaCO_2$ (kPa)	302/99	5.3 ± 1.0	210/98	5.2 ± 1.3	0.066	53/100	5.7 ± 1.3	42/100	5.6 ± 0.8	0.931
PaO_2 (mm Hg)/FiO_2	301/99	232 ± 109	211/98	209 ± 99	0.025	53/100	135 ± 34	42/100	124 ± 43	0.219
BE	291/95	3 ± 5	206/96	1 ± 5	0.007	49/92	3 ± 5	41/98	2 ± 4	0.448
StBic (mmol/L)	272/89	27 ± 4	173/80	26 ± 4	0.041	49/92	27 ± 4	34/81	26 ± 4	0.268
pH	302/99	7.44 ± 0.07	211/98	7.43 ± 0.09	0.424	53/100	7.42 ± 0.07	42/100	7.41 ± 0.08	0.842

Abbreviations: APS = Acute physiologic score; FIO_2 = fraction of inspired oxygen; PIP = Peak inspiratory pressure; MAP = Mean airway pressure; PEEP/CPAP = Positive end-expiratory pressure/continuous positive airway pressure; BE = Base excess; StBic = Standard bicarbonate

Univariate analysis of baseline factors

Mortality and age

Ninety-day mortality for the 520 non-ARDS patients was 41.3 % compared to 44.2 % in the ARDS group. In both non-ARDS and ARDS patients, the mean age for survivors was significantly lower than for non-survivors (Table 1). A difference in gender could only be shown for non-ARDS patients, where more males than females died. For non-ARDS patients arbitrarily stratified for age 65 years or younger (n = 247) and older than 65 years (n = 273), the impact on mortality of APS was non-significant in the group of 65-year-olds and younger. For patients over 65 years a strong association was seen with an RR of 0.74 (CI: 0.61–0.90) (p = 0.003) for an APS less than 11 (sample median).

Severity of disease

In non-ARDS patients the APACHE II score was significantly lower among survivors than non-survivors. This was due to significant differences in APS and age points together with a difference in chronic health evaluation points. Significantly more patients had left atrial hypertension among the non-survivors. When we arbitrarily stratified for APS of 15 or less (n = 404) and more than 15 (n = 116), no significant impact of respiratory variables were found in the former group. For the latter, the associations of respiratory variables were similar to the total non-ARDS group except for PaO_2/FIO_2, that showed a stronger association with mortality days 2, 3, 4 and 5.

In ARDS patients, a similar significant difference in age and APACHE II score was seen between survivors and non-survivors (Table 1). The reason for this was a

Table 2 Cox regression analysis of baseline factors in non-ARDS patients (*APS* acute physiological score)

Term	Risk ratio	95 % Confidence interval	p-value
Non-ARDS patients			
Age (lower than median/higher than median)	0.77	0.67–0.89	< 0.001
Sex (F/M)	0.85	0.74–0.98	0.023
Left atrial hypertension (No/Yes)	0.92	0.79–1.07	0.268
Unilateral/Bilateral infiltrates	0.99	0.81–1.24	0.931
APS (Lower than median/higher than median)	0.85	0.73–0.99	0.036
Presence of chronic disease in APACHE II (Yes/No)	1.31	1.12–1.52	0.001
Non-pulmonary/Pulmonary origin	1.27	1.10–1.47	0.001
ARDS patients			
Age (lower than median/higher than median)	0.65	0.46–0.91	0.011
Sex (F/M)	0.96	0.68–1.33	0.788
Left atrial hypertension (No/Yes)	N/A	N/A	N/A
Unilateral/Bilateral infiltrates	0.87	0.60–1.24	0.458
APS (lower than median/higher than median)	0.65	0.46–0.90	0.010
Presence of chronic disease in APACHE II (Yes/No)	0.93	0.59–1.41	0.746
Non-pulmonary/Pulmonary origin	0.75	0.48–1.10	0.144

Definition of abbreviations: APS = Acute Physiologic Score

significant difference in APS and age points. Of the non-ARDS patients (n = 520), 41 had compromised oxygenation and bilateral pulmonary infiltrates consistent with ARDS but did not fulfil the criteria due to left atrial hypertension.

Predisposing cause for the acute respiratory failure

In non-ARDS patients, a pulmonary origin was present in 41 %, a non-pulmonary in 53 % and an unknown cause (= missing data) in 6 %, of the patients. For ARDS patients the corresponding figures were 69 %, 23 % and 8 %, respectively. A pulmonary origin was associated with increased survival only in non-ARDS patients (Table 1). Cardiogenic pulmonary oedema was reported as contributing to the respiratory failure in 8 % and sepsis was present in 15 % of these patients (intra-abdominal sepsis 8 %, sepsis of unknown origin 5 % and uro-sepsis in 2 % of all patients).

Lung injury score

No difference in LIS at baseline between survivors and non-survivors could be seen in the whole material (Table 1). Furthermore, arbitrary stratification with respect to LIS of 2.0 or more (n = 106) and LIS below 2.0 (n = 414) could not show any different impact of baseline variables, with the single exception that a low APS was associated with survival in the group with LIS of 2.0 or more. The RR in this subgroup was estimated to be 0.63 (CI: 0.45–0.87) (p = 0.005).

Multivariate analysis of baseline factors

When we tested each chosen baseline factor independently, with simultaneous inclusion of the other factors in the Cox regression model, an association with survival was shown for low age, female gender, lower APS, lack of chronic disease and a pulmonary origin for the respiratory failure in the non-ARDS group (Table 2). In the ARDS group, this was only shown for age and APS.

Univariate analysis of respiratory variables

In the univariate analysis of non-ARDS patients FIO_2, MV, PEEP, PaO_2/FIO_2, BE and StBic were significantly different in survivors compared with non-survivors (Table 1). For ARDS patients, no such difference could be noted.

Multivariate analysis of respiratory variables

In the Cox regression analysis of the independent contribution of respiratory variables in non-ARDS patients (Table 3), a tendency could be seen whereby a lower PaO_2/FIO_2 than median (Table 4) for each separate study day and a lower MAP than median were associated with an increased mortality. A significant association between PaO_2/FIO_2 and mortality could be shown for three of seven days, on days 1, 4 and 5. A similar association could be seen for MAP for three of the study days, at baseline, days 2, 3 and 6. The significance on day 6 must be interpreted with caution however, since measurements of MAP only were available in 19 % of the patients (Table 4). At baseline, a low PEEP was associ-

Table 3 Cox regression analysis of respiratory variables in non-ARDS patients with adjustment for baseline factors described in Table 2. Each variable is tested individually with the baseline factors in the model and the risk ratio is expressed as risk below/risk above median value for each day (*RR* risk ratio, *95 % CI 95 %* confidence interval, *BE* base excess, *MAP* mean airway pressure, *PEEP* positive end-expiratory pressure)

Study day	PaO_2/FiO_2			BE			MAP			PEEP		
	RR	95 % CI	p =	RR	95 % CI	p =	RR	95 % CI	p =	RR	95 % CI	p =
Non-ARDS patients												
0	1.06	0.91–1.22	0.459	1.06	0.92–1.22	0.424	1.18	1.00–1.39	0.048	1.18	1.02–1.38	0.029
1	1.17	1.00–1.36	0.048	1.01	0.87–1.17	0.942	1.10	0.94–1.31	0.240	1.03	0.89–1.20	0.699
2	1.09	0.92–1.28	0.315	1.03	0.88–1.21	0.707	1.24	1.02–1.52	0.029	1.10	0.94–1.29	0.256
3	1.18	0.99–1.41	0.068	0.99	0.83–1.17	0.874	1.33	1.06–1.67	0.013	1.02	0.86–1.21	0.838
4	1.24	1.02–1.50	0.027	1.08	0.90–1.31	0.398	0.89	0.72–1.11	0.296	0.95	0.79–1.14	0.565
5	1.25	1.02–1.53	0.034	1.00	0.81–1.23	0.992	1.11	0.85–1.46	0.445	0.98	0.82–1.18	0.857
6	1.01	1.81–1.28	0.904	1.00	0.80–1.25	0.990	2.38	1.11–5.73	0.024	1.00	0.84–1.20	0.963
ARDS patients												
0	1.06	0.65–1.98	0.819	1.10	0.78–1.56	0.581	0.97	0.62–1.47	0.877	0.78	0.54–1.12	0.182
1	0.89	0.61–1.35	0.587	1.12	0.79–1.61	0.533	0.99	0.66–1.46	0.978	1.05	0.74–1.46	0.777
2	1.03	0.68–1.67	0.880	0.94	0.65–1.39	0.753	1.05	0.67–1.59	0.840	1.04	0.71–1.50	0.822
3	1.40	0.90–2.30	0.138	1.03	0.66–1.60	0.904	1.12	0.65–1.95	0.676	1.31	0.89–1.94	0.172
4	1.28	0.79–2.16	0.323	0.79	0.48–1.26	0.316	1.31	0.76–2.26	0.329	1.08	0.69–1.64	0.736
5	1.39	0.85–2.38	0.197	0.82	0.48–1.40	0.452	1.00	0.50–1.94	0.988	1.12	0.72–1.73	0.600
6	1.54	0.91–2.81	0.111	0.46	0.25–0.81	0.007	Sample too small			1.03	0.66–1.54	0.899

Definition of abbreviations: RR = Risk ratio; 95 % CI = 95 % confidence interval; BE = base excess; MAP = Mean airway pressure; PEEP = positive end-expiratory pressure

Table 4 Non-ARDS patients (number and % of sub-groups survivors and non-survivors), with median values used to dichotomise the variables in the Cox regression analysis. Data are given for 6 consecutive days for both PaO_2/FIO_2 and MAP with the group divided into survivors and non-survivors (*MAP* mean airway pressure (cmH_2O))

Non-ARDS patients												
Study day	Survivors						Non-survivors					
	PaO_2/FiO_2			MAP			PaO_2/FiO_2			MAP		
	n/% total n	median	range	n/% total n	median	range	n/% total n	median	range	n/% total n	median	range
0	301/99	209	53–669	243/80	8	3–25	211/98	197	58–598	162/75	7	3–43
1	274/92	223	42–837	205/69	9	3–25	179/87	181	49–582	144/70	8	3–23
2	227/91	212	61–650	166/66	3	4–24	148/88	197	43–543	106/63	3	3–19
3	200/93	202	78–664	129/60	3	3–24	124/88	181	50–818	83/59	3	3–22
4	174/94	212	93–533	116/62	9	3–26	107/90	180	50–825	85/71	9	3–29
5	151/90	214	80–513	74/44	12	5–27	93/87	187	52–564	57/53	11	3–27
6	116/86	213	85–553	25/19	10	5–21	76/88	200	64–645	11/13	8	3–12

Definition of abbreviations: PaO_2/FiO_2 (PaO_2 in mm Hg); MAP = Mean airway pressure (cm H_2O)

ated with mortality but no such association was seen for the following 6 days. BE was not significantly associated with mortality on any day. In comparison, only BE on day 6 was significantly associated with mortality in the ARDS group.

To evaluate if a co-linearity could be seen between the chosen respiratory variables, we included these simultaneously in the model and this had the effect that the influence of PaO_2/FIO_2 seemed weaker, apparently due to a negative co-linearity with MAP and PEEP. This weaker association of PaO_2/FIO_2 was equal in both non-ARDS and ARDS patients. To test the influence on mortality of an invariably increasing oxygenation over the 6 days, we also evaluated patients whose PaO_2/FIO_2 was steadily increasing over the daily observations. We isolated all patients with a PaO_2/FIO_2 that continuously improved or remained unchanged from the previous day (Table 5) but could not find any significant association with mortality. Similarly, no significant association was seen when we analysed patients with a deteriorating PaO_2/FIO_2 over the days.

Table 5 Median and range of PaO_2/FIO_2 as well as number of patients fulfilling ARDS criteria and displaying a continuously improving or stable PaO_2/FIO_2 over the study period. Note rapidly changing population

ARDS patients			
Study day	PaO_2/FiO_2		
	Median	range	n =
0	184	53–669	440
1	235	70–838	349
2	225	90–400	51
3	252	106–393	26
4	298	107–425	15
5	318	124–450	6
6	130	N/A	1

Definition of abbreviations: PaO_2/FiO_2 (PaO_2 in mm Hg)

Discussion

This study reports results from an analysis of 520 non-ARDS and 95 ARDS patients with ARF requiring intubation and mechanical ventilation in Sweden and Iceland. We succeeded in including close to 90 % of all such patients in the chosen geographical area [12]. The most important findings in the present follow-up study were the lack of association between the degree of hypoxaemia, measured as PaO_2/FIO_2, during the first week of ICU care and subsequent 90-day mortality. In addition, no association could be found for other clinically easily accessible respiratory variables, such as PEEP, MAP and BE, and mortality. In the sub-group of non-ARDS patients, a tendency was seen whereby a lower PaO_2/FIO_2 and MAP than the sample median (Table 4) could have an influence on mortality, where a significant association between these variables and mortality could be shown for three of the seven days studied. For ARDS patients no such association could be shown. Baseline factors independently contributing to mortality in non-ARDS were age, gender, APS, presence of a chronic disease and a pulmonary/non-pulmonary reason for the respiratory failure, whereas in ARDS only age and APS showed a similar association.

Our study is limited by the fact that we only followed respiratory variables, and registered them only once a day. However, all registrations were made at approximately the same time of day and the analysed variables are usually relatively stable for each 24-h period. Another limitation is that other important factors influencing mortality, such as the development of multiple organ system failure, were not controlled for. The heterogeneity of the population studied is also a drawback, since different predisposing factors may individually influence the prognosis. However, the strict use of a Cox regression model for all analyses should compensate for this variability to some extent. Our retrospective classification of causes for respiratory failure into pulmonary or non-pulmonary origin [Gattinioni (1998) No.197] may also introduce a possible bias. We therefore included this classification in the Cox regression model to minimise the bias when we independently assessed the impact from other variables. We have refrained from a further subdivision of the causes of respiratory failure to avoid loss of statistical power. It remains possible that respiratory variables may be predictive of mortality in a homogenous population with identical cause of respiratory failure.

The analysis of respiratory variables from day to day may introduce a multiple testing problem. However, in this context a formal correction due to multiplicity based on the repeated measurements does not seem reasonable, since the variables among the days seem likely to be correlated. Since no overall significance level can be set, the exact p values of these analyses have to be interpreted with caution.

We reached our primary aim, which was to determine to what extent daily assessments of easily accessible respiratory variables could predict mortality in non-ARDS and ARDS patients. Clinicians are faced daily with the problem of assessing an individual patient's prognosis based on, among other things, factors such as gas exchange and easily accessible respiratory measurements. We conclude that PaO_2/FIO_2 alone does not seem to have a great impact on mortality in ARF, even if a tendency towards such an association could be seen for three of the seven days studied in the non-ARDS sub-group. Furthermore, no association was found between oxygenation and mortality in ARDS patients. This contrasts with the fact that several recent therapies suggested for ARDS are specifically aimed at improving poor oxygenation [10, 11] with the aim to enhance survival. Our present observation is also in disagreement with results from Bone et al., who have suggested that a continuous improvement of oxygenation during the first week of ICU care would select an ARDS population with an increased survival [8]. That the favourable evolution of PaO_2/FIO_2 seems predictive in such an univariate analysis can be explained as a result of erroneously applied statistical methods combined with a lack of correction for a changing population over the observation period.

We used the median value of PaO_2/FIO_2 to create a dichotomous variable that made it possible to compare survivors with non-survivors in spite of a changing population among the days studied. This comparison was also made with adjustment for the prognostic variables at baseline in the Cox regression model. The limited or absent influence of oxygenation parameters on mortality in ARDS has recently been under discussion [9]. Knaus and co-workers [15], have shown that APACHE III, ICU admission diagnosis and treatment location before ICU provided greater accuracy in predicting mor-

tality than PaO_2/FIO_2 on ICU admission in ARDS patients.

However, patients simply fulfilling ARDS criteria have a wide variation in PaO_2/FIO_2 and we are aware that extreme hypoxaemia still remains as the main criterion for extracorporeal support of gas exchange. It is possible that patients with extreme hypoxaemia have a dramatically increased risk of death and that a significant association between PaO_2/FIO_2 and mortality exists in this sub-group of ARDS. In our material no patients were treated with extracorporeal support and only eight patients had a PaO_2 (mmHg)/FIO_2 of 60 or less at inclusion. Still, oxygenation alone does not seem to be associated with mortality for a majority of patients simply fulfilling recommended ARDS criteria. However, it must be remembered that at any time the presence or absence of such an association may only be valid for the analysed sample. It is important to point out that all conclusions drawn refer to comparisons of relatively large sub-groups of patients with respiratory failure, and that these conclusions cannot be extrapolated to forecast mortality for individual patients.

Of the other tested respiratory variables, no single variable was convincingly associated with mortality in non-ARDS or ARDS, studied alone or during the course of the 7 study days. However, in non-ARDS patients low MAP could be shown to correlate significantly with an increased mortality when measured at baseline, days 2, 3 and 6. We have no convincing biological explanation for this finding. MAP is correlated with PEEP, but PEEP alone was only univariately associated with mortality at baseline, whereas MAP continued to have an influence during several days of observation, also after adjustment of other associated factors in the regression model. It may be noted that this finding was present only in non-ARDS patients and that the mean MAP was quite low in both survivors (8 ± 5 cmH_2O) and non-survivors (7 ± 6 cmH_2O). All these patients lack the diffuse inflammation and low compliance seen in ARDS, where protective ventilation with limited tidal volumes and low distending pressures have been advocated to avoid ventilator-induced lung damage [16, 17]. The association shown between a lower MAP and increased mortality in non-ARDS patients could indicate that there might be a beneficial effect of applying a low PEEP in this patient group to prevent atelectasis formation.

As to our secondary aim, to determine non-respiratory factors associated with mortality in non-ARDS patients, we found several such factors. Age, APS and presence of chronic disease were associated with mortality in non-ARDS, while the initial severity of oxygenation defect was not. This is in agreement with findings by Jiménez and co-workers [5]. They found that the major condition influencing ICU mortality in patients with ARF was the severity of acute illness at admission and that the best predictor for survival was the number of associated complications on admission, simplified acute physiology score (SAPS) and age.

That age alone is a strong and significant predictor of outcome is in agreement with previous reports both in mechanically ventilated patients [15] and in patients with ALI/ARDS [6, 18]. In our patients, the acute physiological component illustrated by APS was independently predictive in both non-ARDS and ARDS patients. This is in contrast with the study by Zilberberg and co-workers [6] on patients with ALI, where they could show that the predictive value of APACHE II was due to the contribution of age and co-morbidity rather than APS. One of the reasons for this finding may be that they studied medical ICU patients, who may have a larger prevalence of co-morbidities than our mixed ICU population. Others have also shown the independently predictive contribution of severity of disease scoring in both non-ARDS [5] and ARDS patients [15].

The fact that a co-morbid condition, defined as the presence of a chronic disease in the APACHE II score, was predictive in non-ARDS but not in ARDS patients may be due to the exclusion of patients with left atrial hypertension in the latter group. Still, left atrial hypertension was not independently associated with mortality in non-ARDS in spite of a larger prevalence among the non-survivors.

Our finding that LIS at the time of diagnosis of ARF and ARDS does not correlate with mortality has been shown previously for the first 24 h of ICU care [6] and for days 1, 2 and 3 following criteria for ALI [7].

In summary, no independent significant association can be seen between 90-day mortality and the degree of hypoxaemia, measured as PaO_2/FIO_2, or other easily accessible respiratory variables such as PEEP, MAP and BE. This was true for the whole first week of ICU care in both non-ARDS and ARDS patients. We note that in the sub-group of non-ARDS patients, a lower PaO_2/FIO_2 and MAP tended to influence mortality. A borderline significant association between these variables and mortality was shown for three of the seven study days. For non-ARDS patients: age, gender, APS, presence of a chronic disease and a pulmonary/non-pulmonary reason for the respiratory failure showed an independent association with mortality. In contrast, only age and APS were associated with mortality in ARDS patients and no association could be established between respiratory variables and mortality. Finally, we conclude that the degree of lung injury, measured as lung injury score, did not predict mortality in any of the groups.

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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, Mälar 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: Mattias SzummerKristianstad 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 Helfer; Trollhättan, Norra Älvsborg County Hospital ICU: Örjan Lennander; Uddevalla Hospital ICU: Tommy Borg; Umeå, The University Hospital of Northern Sweden ICU: Anders Rydvall; 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 Bohrn; Värnamo Hospital ICU: Svend Höjsgaard; Västerviks Hospital ICU: Björn Guding; Västerås Central Hospital ICU: Stefan Ström; Växjö Central Hospital ICU: Håkan Edfeldt; Ystad Hospital ICU: Leif Perhag; Örnsköldsviks Hospital ICU: Anders Mörtberg; Östersunds Hospital ICU: Caroline Starlander; Örebro Medical Center Hospital ICU: Anders Nydahl.

Iceland

Landspitalinn National University Hospital ICU: Adalbjørn Thorsteinsson, Ivar Gunnarsson; Reykavik Hospital: Kristinn Sigvaldsson, Pall Helgason; Central Hospital Akureyri: Girish Hirlekar.

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