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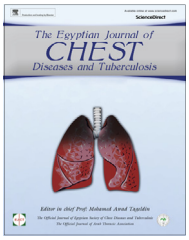

ORIGINAL ARTICLE

After implementation of a lung protective ventilation strategy, what are the outcome improvement predictors in acute respiratory distress syndrome?

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KEYWORDS

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Limits plateau pressure (Pplat);
Predictors

Abstract *Aim of the study:* To identify outcome improvement factors in ARDS patients managed with lung protective ventilation and defined according to the Berlin diagnostic criteria.

Patients and methods: A retrospective observational study was conducted in a total of 41 ARDS patients who were diagnosed according to the Berlin ARDS criteria. Demographic, clinical, laboratory, and radiological criteria were assessed for all patients, and sputum, blood, and urine samples were obtained on the first day of hospitalization and on the day of ventilator-associated pneumonia diagnosis. In addition, fluid balance was assessed by the end of the first week of ventilation. Significant factors associated with survival improvement and predictors of mortality were identified using the bivariate analysis. ROC curves were created to evaluate the accuracy of some of the factors affecting survival.

Results: In this study 25 variables were significantly correlated with mortality. The non-surviving patients had tachypnea and tachycardia; lower diastolic blood pressure, PaO_2/FiO_2, PO_2, O_2sat, and HCO_3 values; and higher FiO_2 and PCO_2 values. Additionally, they had lower serum Na and higher K, pH, and creatinine levels. The level of CRP and GCS score were significantly lower in the non-surviving patients. However, the average fluid balance in the non-surviving patients was positive. Additionally, 4 non-surviving patients (33.3%) developed hospital-acquired pneumonia. A

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good general condition, indicated by a GCS score was the most accurate improvement prediction factor, then proper oxygenation. In contrast, a delay in ICU admission, increase in serum creatinine level, and a positive fluid balance were accurate predictive factors of mortality.

Conclusions: Early diagnosis and ICU admission, a PaO_2/FiO_2 ratio maintained above 90, a GCS score above 9, a negative fluid balance, a serum creatinine level less than 1.5 mg/dl, and the prevention of HAP were factors associated with an improved outcome in ARDS.

Introduction

Worldwide, acute respiratory distress syndrome (ARDS) is among the major causes of morbidity and mortality in intensive care units (ICUs). The mortality rates in various studies vary from 30% to 70%, even with optimal conventional therapies [1,2]. Despite advances in our understanding of the pathophysiology and treatment of ARDS, mortality remains high; approximately 30–60% of patients die before hospital discharge [3–5]. Lung protective ventilation, a strategy that aims to achieve lower tidal volumes (Vt) and limits plateau pressures (Pplat) to less than 30 cm H_2O, was the only clinical intervention that demonstrated a mortality benefit in large randomized trials [6].

Recently, the American–European conference and workshop revisited the definitions of acute lung injury and ARDS and specifically re-evaluated the American–European consensus conference definition from 1994. The result of this workshop has been referred to as the Berlin definition of ARDS. The authors recommended that patients be categorized into three different classifications according to their PaO_2/FiO_2 ratio: (A) mild ARDS, PaO_2/FiO_2 <300 but >200 mmHg; (B) moderate ARDS, PaO_2/FiO_2 <200 but >100 mmHg; and (C) severe ARDS, PaO_2/FiO_2 <100 mmHg. As expected, mortality progressively declined in each of these groups. Using a receiver operating curve, this revised definition yielded a small but significant improvement in the area under the curve from 0.53, derived from the American–European Consensus Conference (AECC) definition, to 0.57, although the absolute difference is small [7].

Although ARDS is well studied worldwide, no local data are available to document the factors associated with mortality in ARDS and the outcome differences in patients with pulmonary and extra-pulmonary ARDS. Early identification of these factors will aid in the assessment of prognosis, improve treatment, and facilitate timely management. Furthermore, to the best of our knowledge, no published studies on mortality predictors have been conducted in Saudi Arabia since the implementation of a lung protective ventilation strategy. Thus, we conducted a retrospective study of these variables to identify the early predictors of mortality in ARDS after the adoption of a lung protective ventilation strategy and the use of the new diagnostic criteria implemented based on the Berlin definition of ARDS. We hypothesized that this ventilation strategy would attenuate the predictive value of previously identified pulmonary-specific measures.

Therefore, the aim of this study was to identify the factors that affect survival and to detect the predictors of mortality in ARDS patients managed with lung protective ventilation.

Subjects and methods

Location

The study was conducted in the Adult Intensive Care Unit at the Saudi German Hospital Al-Madinah, KSA.

Patients

A review of 41 medical records and physiological data was completed for adult patients admitted to the Adult Intensive Care Unit at the Saudi German Hospital Al-Madinah, KSA, between 2012 and 2014. The patients met the diagnostic criteria for ARDS according to the Berlin Definition 2012. These criteria were as follows: (i) respiratory symptoms must have begun within one week of a known clinical insult, or the patient must have new or worsening symptoms during the past week; (ii) bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or computed tomography (CT) scan, and these opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules; and (iii) the patient's respiratory failure must not be fully explained by cardiac failure or fluid overload (an objective assessment, e.g., echocardiography, to exclude hydrostatic pulmonary edema is required if no risk factors for ARDS are present); and (iv) moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to the fraction of inspired oxygen (PaO_2/FiO_2). The severity of the hypoxemia defines the severity of the ARDS:

- Mild ARDS – a PaO_2/FiO_2 of >200 mmHg, but $\leqslant 300$ mmHg, with ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) $\geqslant 5$ cm H_2O.
- Moderate ARDS – a PaO_2/FiO_2 of >100 mmHg, but $\leqslant 200$ mmHg, with ventilator settings that include PEEP $\geqslant 5$ cm H_2O.
- Severe ARDS – a PaO_2/FiO_2 of $\leqslant 100$ mmHg with ventilator settings that include PEEP $\geqslant 5$ cm H_2O [7,8].

All patients had pulmonary ARDS. The primary causes include the following: pneumonia, aspiration pneumonia, inhalation injury, and lung contusions.

All patients with a history or clinical evidence of congestive cardiac failure; patients with bronchogenic carcinoma, pulmonary metastasis, or any neoplasm at ICU admission; or patients who died within 24 h of ARDS diagnosis were excluded from the study.

Study design

This was a hospital record-based retrospective study of patients with ARDS admitted to the Adult Intensive Care Unit at the Saudi German Hospital Al-Madinah during the study period.

Study tools

Data from the medical records and physiological data obtained on the first day of admission and throughout the mechanical ventilation period, consisting of lung protective ventilation strategy implementation as recommended by the ARDS network, were collected from patients' files.

These data include the following:

1. Demographic data, including age, gender, body mass index (BMI), and smoking status;
2. Clinical data, including onset of illness; duration before ICU admission; duration in ICU; clinical data relevant to the chest, heart, and other body systems; and Glasgow Coma Scale (GCS) score;
3. Gas exchange indicators, including FiO_2, pH, PCO_2, PO_2, O_2sat, and HCO_3;
4. PaO_2/FiO_2 ratio;
5. Laboratory assessments, including complete blood count (CBC), blood gases, renal and liver function tests, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP);
6. Independent radiologist scoring of the chest X-ray appearance;
7. Sputum, blood, and urine samples obtained for sepsis work up on the first day of hospitalization and on the day of ventilator-associated pneumonia (VAP) diagnosis;
8. Hemodynamic and fluid balance data; and
9. Echocardiography assessments data.

This retrospective study was considered by the National Research Ethics Service as a 'service evaluation'. Therefore, it did not require Research Ethics Committee review [9].

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 19 (SPSS Inc., Chicago, IL, USA). The ARDS surviving and non-surviving groups were compared with respect to demographic criteria, clinical data, gas exchange indicators, laboratory assessment data, radiological data, and other possible factors affecting survival using the chi-square test for qualitative variables and Student's *t*-test for quantitative variables. Receiver operating characteristic (ROC) curves were created to evaluate the accuracy of some of the factors affecting survival.

Results

A total of 41 moderate to severe ARDS patients diagnosed according to the new classification and the Berlin definition were admitted to the ICU and managed with lung protective ventilation. The overall mortality rate was 29.27%. Compared with patients who survived, the non-surviving patients were older ($p < 0.001$), included more smokers ($p < 0.001$), had more prolonged durations of illness before ICU admission and more prolonged ICU admission stay ($p < 0.001$), and had higher frequencies of co-morbidities with DM ($p < 0.001$), hypertension ($p < 0.001$), and cardiac problems (Table 1).

On admission to the ICU, the non-surviving patients had a higher RR ($p < 0.05$) and HR ($p < 0.05$) and a lower DBP ($p < 0.001$) compared with the patients who survived. Additionally, compared with the patients who survived, the non-surviving patients had lower PaO_2/FiO_2, PO_2, O_2sat, and HCO_3 values ($p < 0.001$ each) and higher FiO_2 and PCO_2 values ($p < 0.05$). Additionally, they had lower Na levels ($p < 0.001$) and higher K levels ($p < 0.05$), pH values ($p < 0.05$), and creatinine levels ($p < 0.001$) compared with the surviving patients. CRP and GCS were significantly lower in the non-surviving patients ($p < 0.001$). However, the average weekly fluid balance in the non-surviving patients was positive and significantly higher than that in the surviving patients, who had negative fluid balance ($p < 0.001$). Additionally, 4 non-surviving patients (33.3%) developed positive blood Culture/sensitivity (C/S) and hospital-acquired pneumonia (HAP), whereas none of the surviving patients developed HAP. Other respiratory, hemodynamic, laboratory, and radiological parameters were not significantly different between the two groups (Table 2).

The serum creatinine level showed the highest accuracy in predicting non-survival (95.8%), with a sensitivity and specificity of 100% and 93.1%, respectively, at a cutoff point of 1.15 mg%, followed by fluid balance/week (90.7% accuracy, 91.70% sensitivity, and 93.10% specificity at a cutoff point of 2694.63 ml) and duration of illness before ICU admission (89.4% accuracy, 100% sensitivity, and 82.8% specificity at a cutoff point of 6.5 days). In contrast, GCS showed the highest accuracy in predicting survival (97.6%), with a sensitivity and specificity of 93.7% and 100%, respectively, at a cutoff point of 9, followed by the PaO_2/FiO_2 ratio (85.3% accuracy, 93.1% sensitivity, and 83.3% specificity at a cutoff level of 90.08; Table 3 and Figs. 1 and 2).

Discussion

In this study, we sought to determine the factors that improve outcomes in the treatment of ARDS in the new era of lung protective ventilation after application of the two main important factors that improve survival: low tidal volume and plateau pressure. After application of the Berlin definition of ARDS, we sought to determine the factors associated with mortality on the first day of admission and during the course of treatment.

In our study of 41 patients, the mortality rate was approximately 29%. Over the past two decades, there have been studies from the world's best medical centers claiming that mortality has decreased by up to 30% [10,11], which may be a result of improvement in the specific management of patients with ARDS as well as in the general management of ICU patients. However, in this same era of lung protective ventilator strategy implementation, other studies [12,1] still report mortality rates of 58%.

Other studies over the past 20 years have reported that mortality from ALI/ARDS has decreased [13,14], and the only

Table 1 Clinical characteristics of patients on the first day of ARDS.

	Total (n = 41)	Survivors (n = 29)	Non survivors (n = 12)	p value
Age	45.01 ± 17.14	35.90 ± 9.19	67.33 ± 9.54	< 0.001**
Gender (male %)	33 (80.50%)	21 (72.40%)	12 (100.00%)	> 0.05
BMI	32.36 ± 5.48	32.16 ± 3.46	32.83 ± 8.84	> 0.05
Smoking (smokers %)	9 (22.00%)	2 (6.90%)	7 (58.3%)	< 0.001**
Duration of illness before ICU admission (days)	6.87 ± 3.95	5.41 ± 3.35	10.41 ± 2.97	< 0.001**
Duration of ICU stay (days)	27.61 ± 9.26	25.55 ± 5.552	32.58 ± 13.98	< 0.05*
Co-morbidities				
DM	11 (26.8%)	2 (6.9%)	9 (75.0%)	< 0.001**
Hypertension	8 (19.5%)	0 (0.0%)	8 (66.7%)	< 0.001**
Cardiac problems	3 (7.3%)	0 (0.0%)	3 (25.0%)	< 0.05*
Liver cirrhosis	1 (2.4%)	0 (0.0%)	1 (8.3%)	–
Chronic renal impairment	1(2.4%)	0 (0.0%)	1 (8.3%)	–

* Significant.
** Highly significant.

Table 2 Clinical characteristics of patients on the first day of ARDS.

	Total (n = 41)	Survivors (n = 29)	Non survivors (n = 12)	p value
Vital signs				
RR	32.76 ± 4.06	31.62 ± 3.65	35.50 ± 3.80	< 0.05*
HR	103.22 ± 14.40	100.21 ± 15.86	110.50 ± 5.65	< 0.05*
SBP	122.85 ± 19.02	125.07 ± 21.33	117.50 ± 10.68	> 0.05
DBP	75.44 ± 13.31	79.69 ± 11.58	65.17 ± 11.82	< 0.001**
Gas exchange indicators				
PaO_2/FiO_2	110.04 ± 32.33	121.62 ± 25.69	82.04 ± 30.20	< 0.001*
FiO_2	0.64 ± 0.17	0.58 ± 0.08	0.79 ± 0.22	< 0.05*
PH	7.41 ± 0.08	7.43 ± 0.08	7.35 ± 0.05	< 0.001**
PCO_2	38.13 ± 5.92	37.15 ± 5.41	40.52 ± 6.65	> 0.05*
PO_2	65.77 ± 9.25	68.54 ± 9.55	59.08 ± 3.14	< 0.001**
O_2sat	91.34 ± 4.18	93.36 ± 2.80	86.47 ± 2.60	< 0.001**
HCO_3	24.95 ± 5.01	26.63 ± 5.02	20.90 ± 1.27	< 0.001**
Laboratory findings				
Na	137.90 ± 4.97	139.52 ± 4.49	134.00 ± 3.88	< 0.001**
K	4.45 ± 0.87	4.20 ± 0.87	5.05 ± 0.50	< 0.05*
Ca	8.40 ± 0.94	8.47 ± 1.09	8.21 ± 0.41	> 0.05
Ph	2.93 ± 0.73	2.68 ± 0.40	3.55 ± 0.98	< 0.05*
Mg	2.98 ± 6.89	3.49 ± 8.18	1.76 ± 0.29	> 0.05
SGOT	67.05 ± 49.72	61.00 ± 13.38	81.67 ± 90.58	> 0.05
SGPT	40.73 ± 22.92	37.00 ± 10.33	49.75 ± 38.91	> 0.05
Albumin	3.41 ± 0.78	3.47 ± 0.90	3.27 ± 0.40	> 0.05
Serum creatinine	1.13 ± 0.55	0.93 ± 0.40	1.59 ± 0.61	< 0.001**
WBC	16.22 ± 6.18	15.90 ± 6.41	16.99 ± 5.77	> 0.05
RBC	4.74 ± 0.97	4.63 ± 0.69	5.02 ± 1.45	> 0.05
HB	12.87 ± 1.34	13.05 ± 1.13	12.45 ± 1.73	> 0.05
HCT	38.49 ± 4.72	39.383.42	36.33 ± 6.65	> 0.05
Platelets	409.95 ± 193.56	427.97 ± 179.15	366.42 ± 227.21	> 0.05
INR	1.69 ± 0.79	1.52 ± 0.57	2.08 ± 1.11	> 0.05
PTT	28.40 ± 6.52	27.07 ± 4.57	31.60 ± 9.24	< 0.05*
CRP	221.15 ± 93.32	252.55 ± 75.05	145.25 ± 91.90	< 0.001**
ESR	78.37 ± 28.40	73.00 ± 31.75	91.33 ± 10.32	> 0.05
CVP	11.98 ± 5.52	11.62 ± 3.80	12.83 ± 8.54	> 0.05
Fluid balance/week	524.60 ± 5624.77	2178.25 ± 3345.04	7056.50 ± 4556.48	< 0.001**
GCS	10.07 ± 4.40	12.45 ± 2.50	4.33 ± 1.92	< 0.001**
Chest X-ray (no of quarter opacities)	3.51 ± 0.78	3.41.82	3.75.62	> 0.05
CT Rt. lung (lobes affected)	6.29 ± 1.17	6.34 ± 1.11	6.17 ± 1.34	> 0.05
CT Lt. lung (lobes affected)	5.32 ± 1.59	5.07 ± 1.60	5.92 ± 1.44	> 0.05
CT total lobes affected	11.61 ± 2.02	11.41 ± 1.92	12.08 ± 2.27	> 0.05
Abnormal ECHO no (%)	14 (34.10%)	10 (34.5%)	4 (33.3%)	> 0.05
Positive blood C/S HAP no (%)	4 (9.8%)	0 (0.0%)	4 (33.3%)	< 0.05*

* Significant.
** Highly significant.

Table 3 Validation of some selected parameters in the prediction of survival among the studied ARDS patients.

	Cutoff point	Area under the curve (95% CI)	Sensitivity (%)	Specificity (%)
Predictors of non-survival				
Fluid balance/week	2694.63	0.907 (0.831–0.982)	91.70	93.10
Duration of illness before ICU admission (days)	6.5	0.894 (0.823–0.964)	100.00	82.80
Serum creatinine (mg %)	1.15	0.958 (0.912–1.000)	100.00	93.10
Predictors of survival				
GCS total	9	0.976 (0.948–1.000)	93.7	100.00
PaO_2/FiO_2	90.08	0.853 (0.739–0.968)	93.10	83.30

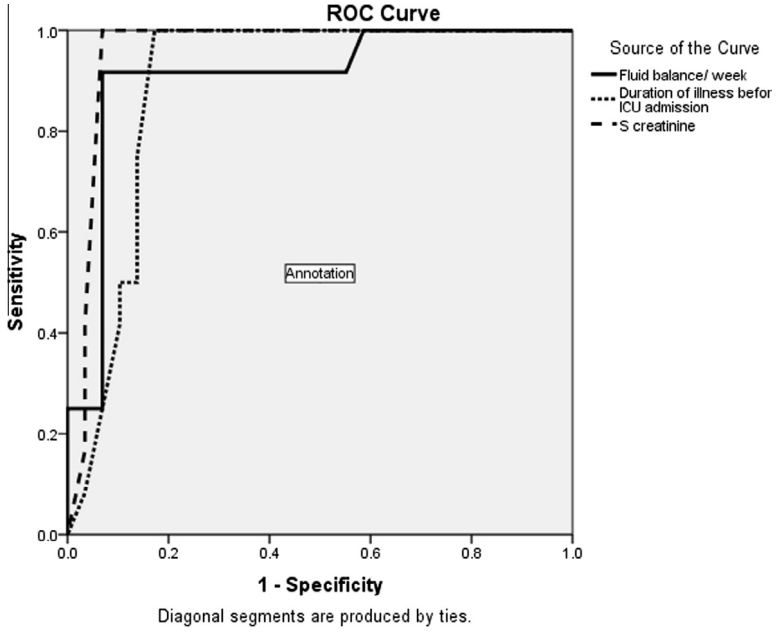

Fig. 1 ROC curve shows the accuracy of GCS and PaO_2 in the prediction of survival of the studied ARDS patients.

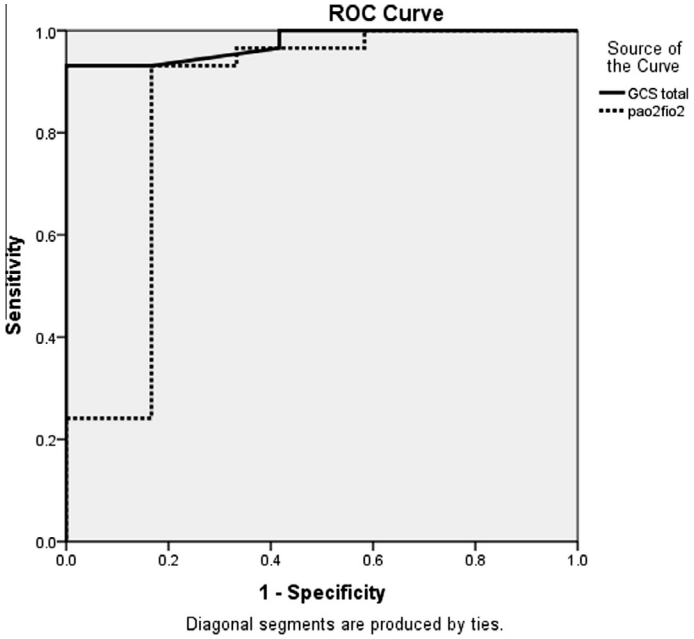

Fig. 2 ROC curve shows the accuracy of fluid balance per week, duration of illness before ICU admission, and serum creatinine level in the prediction of non-survival of the studied ARDS patients.

therapy shown to have a mortality benefit is lung protective ventilation [6]. Similarly, observational studies of ALI/ARDS performed at the University of California San Francisco Hospital System over the past 15 years have also shown a decline in mortality. In the early 1990s, Doyle et al. [4] reported a hospital mortality rate of 58% for patients with ALI/ARDS, whereas by the late 1990s, Nuckton et al. [5] found that the mortality rate of patients with ARDS alone was 42%. In the current study of patients with ALI/ARDS, the mortality rate was 41%. In another observational study where the ARDS Net protocol was more strictly adhered to, as evidenced by an average Vt of 6.2 ml/kg of the predicted body weight (PBW) that was maintained over the first week of ALI/ARDS, the hospital mortality rate was 32% despite the presence of some of the same comorbid conditions as those found in the present study [15].

This finding suggests the possibility that relatively higher mortality rate, despite the intention to use lung protective ventilation, may be a result of delayed recognition of ARDS or less rigorous adherence to the ARDS Net goal of a Vt of 6 ml/kg PBW. This suggestion is strongly supported by the finding of our study that delayed ICU admission was a significant factor in the non-surviving patients.

Recently, a New Berlin definition of ARDS [8] has been proposed, and it is endorsed by the European Society of Intensive Care Medicine, the American Thoracic Society (ATS), and the Society of Critical Care Medicine (SCCM). According to this new definition, three ARDS categories were developed on the basis of hypoxemia with a PEEP setting of 5+: mild (PaO_2/FiO_2 $\leqslant$300 mmHg but $>$200 mmHg), moderate (PaO_2/FiO_2 $\leqslant$200 mmHg but $>$100 mmHg), and severe (PaO_2/FiO_2 $\leqslant$100 mmHg). These groups, according to the consensus panel, were associated with increased mortality (27%, 32%, and 45%, respectively). In the present study, only moderate and severe ARDS patients were included; therefore, the mortality rate of less than 30% is more improved than the stated range in the Berlin definition of ARDS. As we recruited patients on the basis of the new definition, the sample size was small; because of the small sample size, only univariate analysis was possible, and we cannot calculate the independent risk factor of mortality using a multivariate analysis. However, we used receiver operating characteristic (ROC) curves to evaluate the accuracy of some of the factors affecting survival.

In recent years, there has been an increasing interest worldwide to determine the individual predictors of mortality in ARDS. Moreover, we found 25 significant predictors of mortality that can help improve prognosis evaluation within the first 24 h of admission.

We found that approximately 25 predictors of mortality were significantly different in the non-surviving patients based on the patient demographic data and the clinical and laboratory data; the non-surviving patients were older, were more likely to be smokers, had more prolonged durations of illness before ICU admission and more prolonged ICU admissions; and had higher frequencies of co-morbidities with DM, hypertension, and cardiac problems.

Important and simple predictors were suggested by this study. On admission to the ICU, the non-surviving patients' vital signs revealed tachypnea, tachycardia, and lower DBP compared with the patients who survived.

Additionally, based on the arterial blood gases, the non-surviving patients had lower PaO_2/FiO_2, PO_2, O_2sat, and HCO_3 values and higher PCO_2 values; therefore, they required a higher FiO_2. These results are consistent with an observational study of 3670 patients with ARDS which found that patients with mild (PaO_2/FiO_2 $>$200 but $\leqslant$300 mmHg), moderate (PaO_2/FiO_2 $>$100 but $\leqslant$200 mmHg), or severe (A PaO_2/FiO_2 of $\leqslant$100 mmHg) ARDS had increased mortality rates with increased disease severity [7].

Similarly, there is a general agreement that improvement of oxygenation during the early ICU course is correlated with survival [16].

Additionally, the non-surviving patients had lower Na levels, higher K levels, and higher acidotic pH and creatinine levels compared with the surviving patients. CRP and GCS were significantly lower in the non-surviving patients.

Additionally and importantly, the average weekly fluid balance in the non-surviving patients was positive and significantly higher than that in the patients who survived, who had a negative fluid balance. This finding and, therefore, the proposed therapeutic approach is supported and is consistent with a report by Sakr et al. in 2005 which showed that a positive fluid balance may be associated with higher mortality; in addition, the ARDSNet trial reported that a negative fluid balance on the day 4 was associated with decreased mortality compared with a positive fluid balance [17].

The additional therapeutic approach that has improved clinical outcomes in ARDS is the use of a conservative fluid strategy once shock has been resolved. Based on experimental studies, a reduction in the lung vascular hydrostatic pressure decreases the pulmonary edema in the setting of increased lung vascular permeability [18]. The NHLBI ARDS Network trial of 1000 patients reported that a conservative fluid strategy significantly reduced the average duration of mechanical ventilation by 2.5 days [17].

Finally, 4 non-surviving patients (33.3%) developed positive blood C/S HAP, whereas none of the surviving patients did. Other respiratory, hemodynamic, laboratory and radiological parameters were not significantly different between the two groups.

Conclusions

The ARDS mortality rate was improved after the implementation of the lung protective ventilation strategy. Early diagnosis and ICU admission, a PaO_2/FiO_2 ratio above 90, a GCS above 9, a negative fluid balance, and a serum creatinine level less than 1.5 mg/dl, in addition to the prevention of HAP, were outcome-improving factors in ARDS.

Conflict of interest

We have no conflict of interest and no financial support.

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