Original Article

Aetiology and Predictors of Outcome in Patients Presenting with Acute Respiratory Failure Requiring Mechanical Ventilation in a Medical Intensive Care Unit

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Abstract

Background. Sparse published data are available regarding the aetiology, course, complications and outcome in patients presenting with acute respiratory failure requiring mechanical ventilation from India.

Methods. Retrospective study of 116 patients with acute respiratory failure requiring mechanical ventilatory support (AcRF-MV) in the medical intensive care unit (ICU) at our tertiary care teaching hospital in South India.

Results. Patients with AcRF-MV (mean age 44.5±19.5 years; 52.6% females) constituted 23.9% of the 486 patients admitted to the medical ICU during the study period of 18 months. Aetiological causes included sepsis syndrome (46.6%), acute deliberate self-poisoning (22.4%), acute exacerbation of chronic obstructive pulmonary disease (15.5%), snake bite and tuberculosis (5.2% each), severe complicated malaria (3.4%), among others. The median (interquartile range [IQR]) duration (days) of mean hospital stay and medical ICU stay were 10 (4-13.8) and 7 (4-11), respectively. Median (IQR) duration of mechanical ventilator support was 5 (3-8) days. Complications observed during medical ICU stay were ventilator-associated pneumonia (13.8%), bed sore (7.8%), pneumothorax (2.6%); 12.1% patients required tracheostomy. Fifty-eight (50%) patients died. On multivariable analysis using binary logistic regression (forward conditional method) shock at initial presentation (odds ratio [OR] = 3, 95% confidence intervals [CI] 1.638-5.493, $p<0.001$) emerged as independent predictor of death.

Conclusions. Acute respiratory failure requiring mechanical ventilatory support is an important cause of admission to medical ICU and is associated with high mortality. Intense search for and monitoring of predictor variables can help clinicians in reducing the mortality. **[Indian J Chest Dis Allied Sci 2019;61;7-11]**

Key words: Acute respiratory failure, Aetiology, Outcome, Mechanical ventilation.

Introduction

Critical care medicine is an emerging speciality in India and during the last decade increasing number of medical intensive care units (ICUs) are becoming available in India.[1] Acute respiratory failure requiring mechanical ventilatory support (AcRF-MV) is a common cause of admission and mortality in the medical ICU. Despite significant advances in ventilatory support, the mortality in patients with AcRF-MV is still high. Knowledge about the demography, aetiology, course, outcome and other aspects of the patients with AcRF-MV is very important from the clinical perspective.

World over, most of the published data available regarding the aetiology and predictor variables of clinical outcome in patients with AcRF-MV are from studies that were carried out in developed countries[2,3] and little has been published on this topic from developing countries, like India.[4] This prompted us to undertake the present study. We had attempted to study the aetiology, course, complications, outcome, clinical and laboratory predictors of death in patients with AcRF-MV in medical ICU.

Material and Methods

We retrospectively studied 116 consecutive patients aged ≥18 years with AcRF-MV admitted to medical ICU at our tertiary care teaching hospital in South India during the period January 2013 to June 2014. The study was approved

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by the Institutional Research Approval Committee and the Ethics Committee. Patients under 18 years of age and those intubated during cardiopulmonary resuscitation (CPR) were excluded.

The details of the demographic, clinical and laboratory data of these patients during their medical ICU stay were recorded. Clinical data included the details of the duration of in-hospital stay, duration of medical ICU stay, duration of stay on MV support; clinical diagnosis, complications and treatment; serial recordings of the sensorium, body temperature, pulse rate, blood pressure, respiratory rate and the ventilator settings; and acute physiology and chronic health evaluation II (APACHE II) score[5] at admission. Laboratory data included complete haemogram, serum biochemistry, urinalysis, serial arterial blood gas (ABG) analysis, blood, urine and endotracheal aspirate culture and sensitivity reports, chest radiograph, 12-lead electrocardiogram (ECG) other special investigations done as per the needs of the individual patient. The outcome was recorded as dead or alive. All the patients were managed as per the treatment protocols of the institute.

AcRF-MV was defined as arterial oxygen tension (PaO_2) <60 mmHg on supplemental oxygen; and or arterial carbon dioxide tension ($PaCO_2$) ≥50 mmHg with a pH <7.25. Indications for instituting mechanical ventilatory support were PaO_2 <60 mmHg on supplemental oxygen, $PaCO_2$ ≥50 mmHg with a pH <7.25, tachypnoea (respiratory rate >35 per minute), apnoea/bradypnoea, severely depressed mental status (Glasgow coma scale <8), and refractory peripheral circulatory shock.

All patients received mechanical ventilation using Neumovent Graphnet (TECME; Argentina) ventilator. Assist control with pressure-limited ventilation was used as the initial mode of ventilation. Pressure support ventilation (PSV) was used if the patient's effort was good, ventilatory needs were moderate to low and patient was comfortable with PSV trial.[6]

If no infiltrates were evident on the chest radiograph, fraction of inspired oxygen (FIO_2) of 0.4 was initiated and titrated to ensure an arterial oxygen saturation measured by pulse oximetry (SpO_2) of 90% or more. If infiltrates were evident on the chest radiograph, FIO_2 of 0.8-1 was initiated and titrated accordingly to ensure a SpO_2 of 90% or more. Positive end-expiratory pressure (PEEP) was started at 5cm water (H_2O) and increased according to PaO_2, and FIO_2 with a goal of achieving a SpO_2 >90% and FIO_2 ≤0.6. Tidal volume was started at 8mL/kg and decreased to 6mL/kg over a few hours if acute respiratory distress syndrome (ARDS) was present. Respiratory rate was set at 10-20 breaths/min and adjusted for pH with a goal of achieving a pH >7.3 with maximal rate of 35.

Acute respiratory distress syndrome was diagnosed as per the New Berlin criteria.[7] Patients with ARDS were treated using the protocol followed by the ARDS Network[8] low-tidal volume ventilation strategy using ideal body weight to calculate tidal volumes. However, if plateau pressures (Pplat) exceeded 30cm H_2O or if the pH decreased to <7.3, the tidal volume was increased or the PEEP was decreased, as applicable.[9] Sepsis and related syndromes were diagnosed as per the Surviving Sepsis Campaign guidelines.[10] Ventilator-associated pneumonia (VAP) was defined as pneumonia developing in patients receiving MV support for at least 48 hours.[11]

Standard guidelines[6] were followed for the provision of nutrition, prophylaxis for deep vein thrombosis and stress ulcer prophylaxis, sedation, use of muscle relaxants, spontaneous breathing and awakening trials and extubation. Specific therapy for the underlying conditions that resulted in AcRF-MV was instituted.

Statistical Analysis

Univariate analysis was carried out to compare the demographic, clinical, and laboratory variables between alive and dead patients using unpaired t-test and Mann-Whitney U-test for continuous variables and Chi-square test for categorical variables. Continuous variables found to be significant ($p<0.3$) on univariate analysis were categorised into binary variables and were included in multi-variable model as predictor variables (covariates). Multi-variable analysis was carried out using step-wise binary logistic regression (forward-conditional method) to identify the *predictors of death* in patients with AcRF-MV. The statistical software IBM SPSS Statistics (Version 20; IBM Corp, Somers, USA); Stata/IC 12 for Windows (StataCorp LP, Texas, USA); and MedCalc Version 11.3.0 for Windows 2000/XP/Vista/7 (MedCalc Software bvba, Belgium) were used for statistical analysis.

Results

During the study period, 116 (23.9%) of the 486 patients admitted to the medical ICU had AcRF-MV. Their mean age was 44.5±19.5 years; there were 61 females. The aetiological causes of AcRF-MV are shown in figures 1 and 2. Sepsis (46.6%), acute deliberate self-poisoning with a suicidal intent (22.4%) and acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) (15.5%) constituted the most common aetiological causes for AcRF-MV. Other important treatable causes of AcRF-MV included snake bite and tuberculosis (TB) (n=6 each); severe complicated falciparum malaria (n=4).

The most common cause of sepsis (n=54) (Figure 2) was bacterial sepsis (46.3%), emerging causes, like scrub typhus (16.7%), leptospirosis (14.8%) were also frequently encountered. The in-hospital course of these patients is shown in table 1. Complications observed during medical ICU stay were VAP (13.8%), bed sore (7.8%), pneumothorax (2.6%); 12.1% patients required tracheostomy. Overall, 58 (50%) of the patients died.

Univariate analysis comparing continuous and categorical variables is shown in tables 2A and 2B. On univariate analysis, older age ($p=0.037$); and a higher mean APACHE II score ($p<0.001$) were identified as predictors

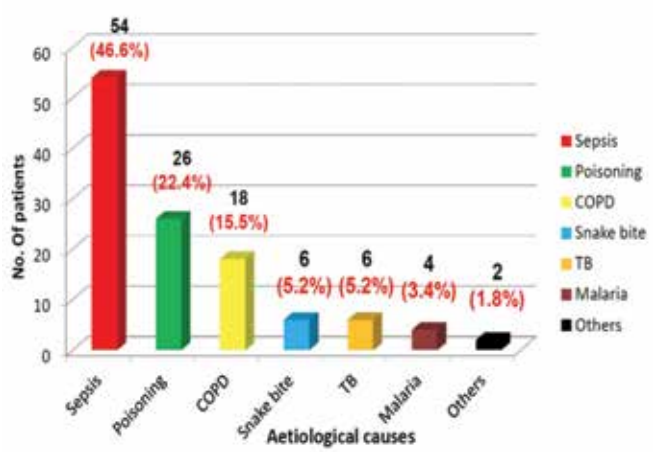

Figure 1. Aetiological causes of AcRF-MV requiring admission to MICU

Definition of abbreviations: AcRF-MV=Acute respiratory failure requiring mechanical ventilatory support, MICU=Medical intensive care unit, COPD=Chronic obstructive pulmonary disease, TB=Tuberculosis

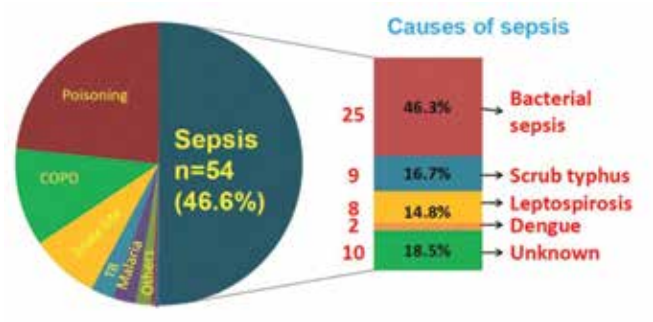

Figure 2. Aetiological causes of sepsis

Definition of abbreviations: COPD=Chronic obstructive pulmonary disease, TB=Tuberculosis

Table 1. In-hospital course

Variable	Median (IQR) (Days)
Duration of in-hospital stay	10 (4-13.8)
Duration ICU stay	7 (4-11)
Duration of mechanical ventilation	5 (3-8)

Definition of abbreviations: IQR=Interquartile range, ICU=Intensive care unit

Table 2A. Univariate analysis: comparison of continuous variables between alive and dead patients

Variable	Alive (n=58)	Dead (n=58)	p-value
Age (years)	40.7±19.3	48.2±19.1	0.037
APACHE II score	11.9±5.9	18.9±6.8	<0.001

* Data are presented as mean±SD

Definition of abbreviations: APACHE II score=Acute physiology and chronic health evaluation score

of death (Table 2A). Among categorical variables, presence of fever (p=0.002); sepsis (p=0.001); shock (p<0.001) and acute kidney injury (p<0.001) were identified as predictors of death on univariate analysis. However, only presence of

Table 2B. Univariate analysis: comparison of categorical variables between between alive and dead patients

Variable	Alive (n=58)	Dead (n=58)	$\chi 2$	p value
Gender				
Male	30	25	0.864	0.353
Female	28	33		
Diabetes mellitus				
Present = 22	8	14	2.019	0.155
Absent = 94	50	44		
Hypertension				
Present = 26	10	16	2.660	0.264
Absent =90	48	42		
Dyspnoea				
Present = 85	39	46	2.152	0.142
Absent = 31	19	12		
Fever				
Present = 76	30	46	9.768	0.002
Absent = 40	28	12		
Altered sensorium				
Present = 51	23	28	0.875	0.350
Absent = 65	35	30		
Seizures				
Present = 15	7	8	0.058	0.810
Absent = 101	51	50		
Sepsis				
Present = 54	18	36	11.226	0.001
Absent = 62	40	22		
Shock				
Present = 60	16	44	27.067	<0.001
Absent = 56	42	14		
ARDS				
Present = 26	12	14	0.198	0.656
Absent = 90	46	44		
AKI				
Present = 43	12	31	13.341	<0.001
Absent = 73	46	27		
Thrombocytopenia				
Present = 41	15	26	5.897	0.052
Absent = 75	43	32		

Definition of abbreviations: ARDS=Acute respiratory distress syndrome, AKI=Acute kidney injury

shock at the time of initial presentation was identified to be independent predictor of death on multi-variable analysis (OR 3; 95% CI 1.638-5.493; p<0.001).

Discussion

Present study was conducted in a medical ICU of a tertiary care teaching hospital in south India. In the present study, surgical patients who, as a sub-group, are considered to be less likely to die[12] have been excluded. Therefore, the present study is unique as it reflects the actual scenario in medical ICUs in south India. AcRF-MV due to specific conditions, such as, ARDS, COPD has been frequently studied,[4,13] but AcRF-MV in heterogeneous, unselected medical ICU patients in the field situation in India has not been widely reported, as in the present study. The present

study is the first from south India that had used critical illness scoring system (APACHE II) to assess the predictor variables of death for patients with AcRF-MV and to assess the risk of death in patients with AcRF-MV.[4]

A study from Chandigarh[4] had assessed the aetiology and outcome of acute lung injury (ALI)/ARDS admitted to a respiratory ICU. The demographic characteristics of the patients were similar in the present study and the study from Chandigarh.[4] While the Chandigarh study[4] included only patients with ALI/ARDs in that, the present study included all patients with AcRF-MV including ARDS. We had observed that the leading causes of AcRF-MV support is sepsis syndrome (46%), acute deliberate self-poisoning with a suicidal intent, AE-COPD, snake bite, emerging infections, like TB, malaria, among others. Earlier published studies from India have shown that TB[14], malaria[15] are important treatable causes of AcRF-MV and early confirmation of the diagnosis and the initiation of specific treatment can be life-saving. The observations from the present study support this view. Our observations suggest that in patients presenting with AcRF-MV, other emerging infections like leptospirosis[16], and scrub typhus[17] should be specifically searched for so that appropriate treatment can be initiated early. Acute deliberate self-poisoning, with a suicidal intent using organophosphate compounds (OPC) constitute a common cause of AcRF-MV in South Andhra Pradesh where our institute is located.[18] It can occur early or late in the course of the disease and clinicians treating patients with OPC should have a high index of clinical suspicion and carefully monitor the patients for complications.[19,20]

Compared with a multi-centre, multi-national study[21], in our study, the median (IQR) duration of MV in days (5[3-10] *versus* 5 [3-8]) and ICU stay in days (IQR) (7[4-14] *versus* 7[4-11]) were similar.

Many studies,[12,22-25] had reported the effect of age on mortality in AcRF-MV patients. Some studies[12,22-24] found age as an independent predictor of death, while another[25] did not. In the present study, on univariate analysis, non-survivors were significantly older than survivors (40.7±19.3 *versus* 48.2±19.1; p=0.037). In studies published on AcRF-MV males outnumbered females, in some studies[12,22,26] and in another[23] females outnumbered males; in our study, women outnumbered men. Though one study[23] reported that female gender was a predictor of poor outcome, this was not observed in another large study;[25] gender did not emerge as a predictor of poor outcome in our study. The differences observed between the previous studies[23,25] and the present study in terms of gender could have been due to the disparities in the process of care or gender-based treatment bias.

In the present study, a significantly higher mortality was observed in patients with sepsis with AcRF-MV compared with those without sepsis (66.7% *versus* 35.5%; p=0.001), similar findings were observed in other large studies.[12,25] Further, presence of shock at the time of initial presentation emerged as an independent predictor of death in our study, as reported in other studies.[12,23,25] Our observations suggest that patients with AcRF-MV, presenting with shock should be carefully monitored and aggressively treated so as to minimise the mortality.

Presence of ARDS emerged as an independent predictor of mortality in patients with AcRF-MV in several studies.[12,23,24] In our study, we did not find ARDS as a predictor variable for mortality. The reasons for this could be less number of ARDS patients (n=26), strict adherence to ARDS network protocol[8] for ventilatory management, and causes of ARDS with specific treatment like leptospirosis, scrub typhus and malaria, compared to other studies.[12,23] We found significant higher mean APACHE II score in non-survivors compared to survivors (18.9±6.8 *versus* 11.9±5.9; p<0.001). Similar observations were found in other studies.[4,12,23,27]

The mortality rate observed in our study was marginally higher (50%) in contrast with the large multi-centre studies[12,21,28] published form the western world, in which mortality rate ranged from 35%-40%. The higher mortality in our study compared to one large multi-centre study[12] where a mortality of 40% was reported can be explained as follows. In the present study, a substantially large number of patients with sepsis and related syndromes (48%), conditions that are associated with a high mortality[25] were included compared to the other study[12] where sepsis constituted only 9% of the patients. In another study[23] in patients with AcRF-MV from the USA, a mortality rate of 23% was reported. In other studies,[22,23] there were more post-operative patients (45%), and among them the mortality was only 1%, which had influenced the low mortality observed in that study. Moreover, post-operative state requiring AcRF-MV is independently associated with a better survival.[12] The mortality rate observed in the present study (50%) was similar to the observations reported in a study from Chandigrah[4] and less than the figure reported in the study (56.2%) from New Delhi[27] which included only ARDS patients.

Conclusions

Acute respiratory failure requiring mechanical ventilatory support is an important cause of admission to medical ICU and is associated with high mortality. Intense search for and monitoring of predictor variables can help clinicians in reducing mortality. However, the results of the present study should be interpreted cautiously because of the small sample size, single center and retrospective study. India is a large country with wide regional variations in the aetiological causes and threshold for admission of AcRF-MV in medical ICU. Since the aetiological cause also influences the outcome, there is a need for generating similar data from other parts of the country.

References

1. Prayag S. ICUs worldwide: critical care in India. *Crit Care* 2002;6:479–80.

2. Irish Critical Care Trials Group. Acute lung injury and the acute respiratory distress syndrome in Ireland: a prospective audit of epidemiology and management. *Crit Care* 2008;12:R30.
3. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, *et al*; ALIVE Study Group. Epidemiology and outcome of acute lung injury in European intensive care units: results from the ALIVE study. *Intensive Care Med* 2004;30:51–61.
4. Agarwal R, Aggarwal AN, Gupta D, Behera D, Jindal SK. Etiology and outcomes of pulmonary and extrapulmonary acute lung injury/ARDS in a respiratory ICU in North India. *Chest* 2006;130:724–9.
5. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
6. Esan A, Hess DR, Raoof S, George L, Sessler CN. Severe hypoxemic respiratory failure. Part 1: Ventilatory strategies. *Chest* 2010;137:1203–16.
7. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, *et al* for ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–33.
8. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–8.
9. Kallet RH, Liu K, Tang J. Management of acidosis during lung-protective ventilation in acute respiratory distress syndrome. *Respir Care Clin North Am* 2003;9:437–56.
10. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al*. Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165–228.
11. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2002;165:867–903.
12. Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, *et al*. Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002;287:345–55.
13. Mohan A, Premanand R, Reddy LN, Rao MH, Sharma SK, Kamity R, *et al*. Clinical presentation and predictors of outcome in patients with severe acute exacerbation of chronic obstructive pulmonary disease requiring admission to intensive care unit. *BMC Pulm Med* 2006;6:27.
14. Sharma SK, Mohan A, Banga A, Saha PK, Guntupalli KK. Predictors of development and outcome in patients with acute respiratory distress syndrome due to tuberculosis. *Int J Tuberc Lung Dis* 2006;10:429–35.
15. Mohan A, Sharma SK, Bollineni S. Acute lung injury and acute respiratory distress syndrome in malaria. *J Vector Borne Dis* 2008;45:175–93.
16. Bollineni S, Mohan A, Sharma KK, Gururajakumar A. Pulmonary manifestations in acute leptospirosis. *Am J Respir Crit Care Med* 2007;175:A218.
17. Goswami D, Hing A, Das A, Lyngdoh M. Scrub typhus complicated by acute respiratory distress syndrome and acute liver failure: a case report from Northeast India. *Int J Infect Dis* 2013;17:e644–5.
18. Mohan A, Srinivas B, Kiran DHN, Rao MH, Sharma SK. Critical care management of organophosphorus pesticide poisoning. *Am J Respir Crit Care Med* 2004;169:A629.
19. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. *Lancet* 2008;371:597–607.
20. Hulse EJ, Davies JO, Simpson AJ, Sciuto AM, Eddleston M. Respiratory complications of organophosphorus nerve agent and insecticide poisoning: implications for respiratory and critical care. *Am J Respir Crit Care Med* 2014;190:1342–54.
21. Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Peñuelas O, Abraira V, *et al*. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:220–30.
22. Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. *Chest* 2000;118:1100–5.
23. Kollef MH, O'Brien JD, Silver P. The impact of gender on outcome from mechanical ventilation. *Chest* 1997;111:434–41.
24. Azevedo LC, Park M, Salluh JI, Rea-Neto A, Souza-Dantas VC, Varaschin P, *et al*; ERICC (Epidemiology of Respiratory Insufficiency in Critical Care) Investigators. Clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: a multicenter, prospective, cohort study. *Crit Care* 2013;17:R63.
25. Epstein SK, Vuong V. Lack of influence of gender on outcomes of mechanically ventilated medical ICU patients. *Chest* 1999;116:732–9.
26. Metnitz PG, Metnitz B, Moreno RP, Bauer P, Del Sorbo L, Hoermann C, *et al*. SAPS 3 Investigators. Epidemiology of mechanical ventilation: analysis of the SAPS 3 database. *Intensive Care Med* 2009;35:816–25.
27. Sharma SK, Gupta A, Biswas A, Sharma A, Malhotra A, Prasad KT, *et al*, Aetiology, outcomes & predictors of mortality in acute respiratory distress syndrome from a tertiary care centre in north India. *Indian J Med Res* 2016;143:782–92.
28. Esteban A, Ferguson ND, Meade MO, Frutos-Vivar F, Apezteguia C, Brochard L, *et al* for VENTILA Group. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008;177:170–7.