J R Coll Physicians Edinb 2020; 50: 12–8 | doi: 10.4997/JRCPE.2020.105 ORIGINAL RESEARCH PAPER

Aetiology and short-term outcome of acute respiratory distress syndrome: a real-world experience from a medical intensive care unit in southern India

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Abstract

Background Acute respiratory distress syndrome (ARDS) is a highly fatal syndrome especially in resource constrained settings. In this study we prospectively studied the aetiology of ARDS and its short-term outcome.

Methods Consecutive adults with suspected ARDS were screened. ARDS was diagnosed by the Berlin criteria. Aetiology was determined clinically, and by imaging and microbiological investigations. Patients presenting with fever, prominent cough and expectoration had a throat swab tested for influenza H1N1 virus. Outcome was discharge from hospital or death.

Results A total of 42 patients, mean age 42.6 years, were studied. All received mechanical ventilation. Thirteen (31%) had pulmonary ARDS: H1N1 virus infection (n = 5), pneumonia (n = 7) and tuberculosis (n = 1). Twenty nine (69%) had extrapulmonary ARDS: sepsis (n = 16) and scrub typhus (n = 8). Thirty three (79%) died, of the nine survivors scrub typhus was diagnosed in seven patients.

Conclusion The aetiology of ARDS in tropical medical setting is infection related. ARDS due to scrub typhus appeared to be mild with good outcome.

Keywords: acute lung injury, ARDS, scrub typhus, tropical infections

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Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening disorder of the lungs seen in critically ill patients. It is characterised by refractory hypoxaemia, high permeability pulmonary oedema and stiff lungs. Without mechanical ventilation, most patients die early. A pooled analysis of 18,900 patients of observational studies and randomised controlled trials from 1984 to 2006 found that mortality due to ARDS was 44%.[1] There was no decrease in mortality between 1994 and 2006. It is estimated that there are 190,600 cases of ARDS per year in the US, causing substantial impact on the healthcare system.[2]

To date, the only best available effective treatment for ARDS is mechanical ventilation with low tidal volumes (TVs) as a lung protective strategy along with good supportive care.[3] In India we do not have reliable estimates on the occurrence of ARDS. Observational studies from India show that mortality associated with ARDS ranges from 36% to 60%.[4–7] The burden of ARDS on our intensive care units (ICUs) continues to be under appreciated. ARDS is under recognised even in ICUs from high-income countries.[8] In our region there exists a lacunae in knowledge on the frequency of occurrence and outcome. Moreover, the aetiology of ARDS might be different compared to other regions of the world. Hence, we set out to address the aetiology and outcome of this still highly fatal syndrome.

Methods

A prospective observational study was carried out in the medical ICU of a tertiary level hospital in Puducherry, India. The study period was from September 2014 to May 2016. Informed consent before enrolling in to the study was obtained from all study participants or from the next of kin if the patient was unable to give consent because of severe illness. The study protocol was approved by the institute ethics subcommittee on 25 October 2014, JIP/IEC/SC/2014/9/659.

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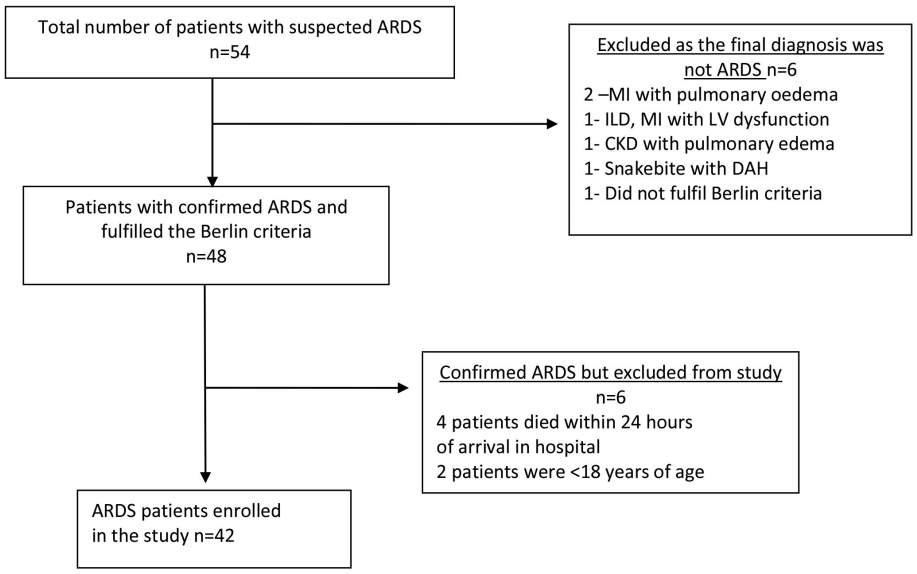

Figure 1 Flowchart of study participant recruitment. ARDS: acute respiratory distress syndrome; CKD: chronic kidney disease; DAH: diffuse alveolar haemorrhage; ILD: interstitial lung disease; LV: left ventricular; MI: myocardial infarction

Consecutive patients aged ≥18 years admitted to the medicine emergency team and medical ICU with suspected ARDS because of respiratory symptoms, hypoxaemia and plain radiograph findings suspicious for ARDS were screened. To diagnose ARDS the patient must fulfil the Berlin criteria.[9] Patients with heart failure, chronic kidney disease (CKD) with volume overload state and chronic obstructive pulmonary disease were excluded. Heart failure was excluded on the basis of transthoracic echocardiographic findings of left ventricular dysfunction and/or high central venous pressure (CVP). Pulmonary oedema due to volume overload as in CKD was ruled out by presence of high CVP and improvement with dialysis. Other conditions that had a similar presentation to ARDS, such as diffuse alveolar haemorrhage, were excluded. Patients with confirmed ARDS who died within 24 hours of admission were excluded from analysis.

Assessments

Following diagnosis, patient's demographic characteristics and duration of illness was noted. The aetiology of ARDS was determined on the basis of presenting symptoms, physical examination, plain chest radiograph and appropriate microbiological investigations. Patients who presented with fever, prominent cough and expectoration had a throat swab taken, and tested by real-time polymerase chain reaction (PCR) for influenza A H1N1 virus. The work up for patients who had a clinical syndrome of acute febrile illness either with or without renal dysfunction, transaminitis and thrombocytopenia typically included the Weil–Felix test and/or IgM serology for scrub typhus. Other tests included blood cultures, dengue serology, serology for leptospirosis and rapid diagnostic test for malaria. The work up was individualised based on each patient's clinical presentation. When any patient was suspected to have sepsis, blood cultures were sent.

All patients who were in the emergency department were eventually transferred to the medical ICU. Baseline partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio was recorded. Acute physiology and chronic health evaluation II (APACHE II) score was calculated within 24 hours of arrival in hospital.[10] Baseline platelet count, urea, serum creatinine and serum albumin were recorded. New organ failure was recorded using the sequential organ failure assessment (SOFA) score at admission and daily.[11]

For patients who were mechanically ventilated the daily average plateau pressure, TV and positive end-expiratory pressure (PEEP) were recorded in the initial 48 hours. Predicted body weight (PBW) was calculated using the formulae: for males PBW (kg) = 50 + 2.3 [height (inches) – 60]; for females: PBW (kg) = 45.5 + 2.3 [height (inches) – 60]. Ventilator settings used were as per recommendations by the ARDS Network. The TV given was 6 ml/kg body weight. Fluid management, nutrition, vasopressor agents, antibiotic use, decision on renal replacement therapy and adjustment of ventilator settings, such as TV and plateau pressure, were determined for each patient individually. During the course of illness whether the patient developed hypotension, required vasopressors, developed sepsis or ventilator-associated pneumonia (VAP), required dialysis and reached the maximum stage of acute kidney injury (AKI) was recorded. Patients were followed up daily and final outcome was either at discharge from hospital (survivor) or death (nonsurvivor). The aetiology of ARDS was classified as pulmonary or extrapulmonary based on whether the insult to the lung was direct or indirect.

Definitions

The severity of ARDS was defined by the oxygenation criteria:[9] mild ARDS, 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg with PEEP or CPAP ≥5 cm H_2O; moderate ARDS, 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg with PEEP or CPAP ≥5 cm H_2O; severe ARDS, PaO_2 FiO_2 <100 mmHg with PEEP ≥5 cm H_2O.

Hypotension was defined as systolic blood pressure (BP) <90 mmHg or requirement of vasopressors to maintain a mean arterial pressure (MAP) of 65 mmHg. Encephalopathy was defined as any decline in mental status or Glasgow coma scale <11. If a patient was sedated, the mental status was assessed after withholding sedation. Thrombocytopenia was defined as platelet count <100,000/mm^3. Hepatic involvement

Table 1 Baseline clinical characteristics and complications during the course of hospital stay

Clinical characteristic	ARDS patients n = 42
Duration of illness in days, mean ± SD	8.57 ± 3.19
Hypotension, n (%)	7 (16.7)
Initial SBP mmHg, mean ± SD	99.52 ± 16.73
Initial DBP mmHg, mean ± SD	70 ± 7.711
Initial GCS, mean ± SD	11.62 ± 3.349
Predicted body weight kg, mean ± SD	50.5 ± 11.10
PaO_2/FiO_2 ratio, median (IQR)	102 (77–177)
CVP cm H_2O, mean ± SD	5.95 ± 1.884
Number of patients with ARDS at admission, n (%)	22 (52)
Number of patients who developed ARDS during hospital stay, n (%)	20 (48)
APACHE II score, median (IQR)	12 (8–18)
SOFA score, median (IQR)	7 (4.75–10)
Complications during hospital stay	
Vasopressor use, n (%)	35 (83.3)
Noradrenaline mcg/min, mean ± SD	33.67 ± 7.18
Vasopressin units/hour, mean ± SD	1.9 ± 0.663
Dopamine, mean ± SD	nil
Acute kidney injury, n (%)	31 (73.8)
Hepatic involvement, n (%)	25 (59.5)
Thrombocytopenia (platelet <100,000/mm^3), n (%)	29 (69)
Encephalopathy, n (%)	34 (81)
VAP, n (%)	18 (42.9)

APACHE II: acute physiology and chronic health evaluation 2; ARDS: acute respiratory distress syndrome; CVP: central venous pressure; DBP: diastolic blood pressure; FiO_2: fraction of inspired oxygen; GCS: Glasgow coma scale; IQR: interquartile range; PaO_2: partial pressure of oxygen; SBP: systolic blood pressure; SD: standard deviation; SOFA: sequential organ failure assessment; VAP: ventilator associated pneumonia

was defined as any rise in serum transaminases (aspartate transaminase or alanine transaminase) or serum bilirubin. Infections (specific acute and healthcare associated) were defined by the Centers for Disease Control/National Health Surveillance Network surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care.[12] Sepsis was defined by the 2001 Society for Critical Care Medicine/European Society for Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society International Sepsis Definitions Conference definition, which is the presence of systemic inflammatory response syndrome when an infectious aetiology is proven or strongly suspected.[13] AKI was defined by the Kidney Disease: Improving Global Outcomes criteria.[14]

Statistical analysis

All categorical data were expressed as frequencies and percentages. Continuous data, such as age, duration of illness, number of days in hospital, number of days on ventilator, BP, length of ICU stay, APACHE II score, MAP, SOFA score, TV, PEEP and plateau pressure, were expressed as mean ± standard deviation, or median with range. Comparison of aetiological factors between survivor and nonsurvivor were carried out using independent student t-test or Mann Whitney U test based on normality of data. All statistical analyses were carried out at 5% level of significance and p-value <0.05 considered as significant. Statistical analysis was carried out using SPSS version 17 (IBM Corp, USA).

Results

Fifty four patients with suspected ARDS were admitted to the medical ICU during the study period. After applying the inclusion and exclusion criteria there were 42 patients with confirmed ARDS (Figure 1). Their mean age was 42.6 ± 15.3 years, 21 (50%) were men. The mean duration of current illness was 8.57 ± 3.19 days.

Of 42 patients, 22 (52%) had ARDS at admission while 20 (48%) developed ARDS during hospital stay. At the time of ARDS diagnosis, the median PaO_2/FiO_2 ratio was 102 (range: 77–177). CVP was measured to rule out cardiogenic pulmonary oedema. The mean CVP recorded was 5.95 ± 1.884 cm H_2O. Thirteen (30%) had APACHE II scores ≤8, 21 (50%) had APACHE II scores between 9 and 18, and in eight (19%) APACHE II scores were ≥19. The baseline characteristics are given in Table 1.

Severity of ARDS and ventilatory parameters

Fifteen (36%) patients had severe ARDS, 14 (33%) had moderate ARDS and the remaining 13 (31%) had mild ARDS. All the 42 patients required mechanical ventilation. The mean TV as per PBW was 261.05 ± 53.85 ml, mean PEEP was 9.93 ± 1.43 cm and duration of ventilation was 6.55 ± 4.9 days.

Course during hospital stay

Table 1 shows that 35 out of 42 (83%) patients had hypotension and required vasopressors (noradrenaline and/or vasopressin) during their hospital stay. Dopamine was not used in any of the patients. Among those who developed AKI, eight (19%) required renal replacement therapy (haemodialysis). The course of 18 (43%) was further complicated by development of VAP. The risk of VAP was calculated as 65.4 per 1,000 ventilator days.

Pulmonary ARDS

A total of 13 out of 42 (31%) patients had pulmonary ARDS. Pulmonary ARDS was due to influenza A H1N1 virus infection in five patients, community-acquired pneumonia in six patients, one patient was a case of hospital-acquired pneumonia and one was miliary tuberculosis (Figure 2).

All the patients diagnosed with influenza A H1N1 presented with acute respiratory symptoms, throat swabs tested positive for H1N1 by real-time PCR. Among the six patients with community-acquired pneumonia, four patients had negative sputum cultures and in two patients the sputum grew nonfermenting Gram-negative bacilli.

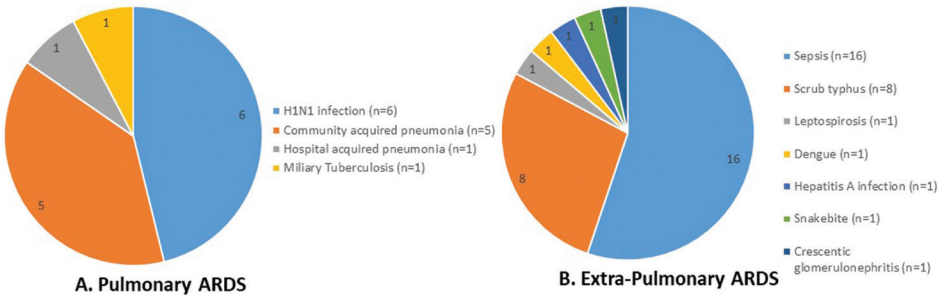

Figure 2 Aetiology of acute respiratory distress syndrome (ARDS) in the pulmonary and extrapulmonary groups

The patient with hospital-acquired pneumonia had been admitted elsewhere and presented to our hospital with ARDS. This patient's blood culture was positive for *Klebsiella* species.

Extrapulmonary ARDS

A total of 29 patients (69%) had extrapulmonary ARDS. The most common extrapulmonary aetiology encountered was sepsis (n = 16), followed by patients with scrub typhus (n = 8). Scrub typhus was diagnosed in the presence of compatible clinical features; six had positive Weil–Felix test (OXK titres of ≥1 : 320) and two patients were positive by PCR. Eschar was noted in five out of eight patients. The other extrapulmonary causes are depicted in Figure 2.

Among the patients with sepsis, there were two patients with Gram-negative sepsis, urosepsis was identified in one patient, while the remaining 12 patients had syndrome of sepsis but there were no organisms isolated in culture. One patient had active systemic lupus erythematosus who soon developed cytopenia following cyclophosphamide pulse infusion; she further developed sepsis, ARDS and refractory hypotension.

Outcome

Thirty three (79%) patients died, only nine (21%) survived and were discharged from hospital. All patients (13 out of 13) in the pulmonary ARDS group died, in the extrapulmonary ARDS group 20 out of 29 (69%) died. All nine survivors had extrapulmonary ARDS (scrub typhus n = 7, acute hepatitis A with liver failure n = 1 and sepsis n = 1). The terminal event among those who died was multiorgan dysfunction syndrome and refractory hypotension. The median duration of hospital stay was 6 days [interquartile range (IQR): 3.75–10 days], median duration of stay in the ICU was 4.5 days (IQR: 3–7.5 days). The median days on ventilator was 5 days (IQR: 3–7 days).

The mean systolic blood pressure, diastolic blood pressure, MAP and mean PaO_2/FiO_2 ratio were significantly lower in nonsurvivors than in survivors. Both APACHE II and SOFA scores were significantly higher (i.e. worse) in nonsurvivors (Table 2). The occurrence of AKI, VAP, thrombocytopenia, requirement for vasopressors and severe ARDS was significantly higher among nonsurvivors (Tables 3 and 4).

Discussion

In this study the majority of ARDS was extrapulmonary (69%), and the most common conditions encountered were sepsis and scrub typhus. In general extrapulmonary causes of ARDS predominate in most medical ICUs. For example, a study from Mumbai, India, found that 75% of their ARDS

Table 2 Comparison of clinical features between ARDS survivors and nonsurvivors

Clinical characteristic	Survivors n = 9 (%)	Nonsurvivors n = 33 (%)	p-value
Age in years, mean ± SD	46.36 ± 15.17	30.44 ± 7.36	0.004
GCS median (IQR)	15 (15–15)	11 (8–13)	<0.001
Hypotension at arrival, n (%)	0	7 (21.2)	0.310
SBP, mean ± SD	108.89 ± 16.15	96.67 ± 15.70	0.052
DBP, mean ± SD	74.44 ± 8.81	68.62 ± 6.93	0.046
MAP, mean ± SD	67.44 ± 6.5 0	61.83 ± 5.77	0.018
PaO_2/FiO_2, mean ± SD	228.33 ± 40.01	100.18 ± 39.15	<0.001
APACHE II score, median (IQR)	6 (3.5–6)	14 (11.5–19)	<0.001
SOFA, median (IQR)	2 (2–4)	8 (6–10)	<0.001
Maximum SOFA, median (IQR)	2 (2–4.5)	8 (6–10.5)	<0.001
Plateau pressure cm H_2O, mean ± SD	29.33 ± 2.00	31.45 ± 3.00	0.053
PEEP cm, mean ± SD	8.78 ± 1.39	10.24 ± 1.30	0.005

AKI: acute kidney injury; APACHE II: acute physiology and chronic health evaluation; DBP: diastolic blood pressure; FiO_2: fraction of inspired oxygen; GCS: Glasgow coma scale; IQR, interquartile range; MAP: mean arterial pressure; PaO_2: partial pressure of oxygen; PEEP: positive end expiratory pressure; SBP: systolic blood pressure; SD, standard deviation; SOFA: sequential organ failure assessment; VAP: ventilator-associated pneumonia

Complication	Survivors n = 9, frequency (%)	Nonsurvivors n = 33, frequency (%)	Odds ratio (95% CI)	p-value
AKI	2 (22)	29 (87)	25.4 (3.8–167.5)	<0.001
Dialysis	0 (0)	8 (24)	1.36 (1.11–1.66)	0.16
Thrombocytopenia	3 (33)	26 (89)	7.4 (1.47–37.45)	0.016
VAP	1 (11)	17 (51)	8.5 (0.95–75.8)	0.030
Vasopressors	2 (28)	33 (100)		<0.001

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; CI: confidence interval; VAP: ventilator-associated pneumonia

Table 3 Comparison of the complications that occurred during hospital stay between ARDS survivors and nonsurvivors

patients were extrapulmonary and 66% of cases of total acute lung injury/ARDS were tropical infectious diseases.[6,15] A retrospective analysis from another mixed medical–surgical ICU also found that 70% were extrapulmonary ARDS.[4] However, a large retrospective series from a respiratory ICU (India) showed that pulmonary ARDS is more common than extrapulmonary ARDS.[5] Similarly, a prospective study involving 64 patients from a medical ICU in northern India also found that pneumonia constituted 68% of ARDS cases.[16] In the pulmonary ARDS group all our patients had pulmonary infection as has also been observed by others.[5,6,17,18]

Scrub typhus is an emerging and easily treatable cause of ARDS. In our study nine patients had scrub typhus (all mild ARDS) of whom one died. Recently, ARDS is a well-recognised complication of scrub typhus, in some series occurring in up to 8% of scrub typhus patients.[19] Another series from a referral centre suggests that ARDS is quite common and was observed in 43% cases of scrub typhus.[20] However, the series did not describe how ARDS was diagnosed. As seen in our study and others, lung injury in scrub typhus appears to be mild, and survival is much better than in pneumonia or sepsis.

We had six patients with PCR-confirmed influenza A H1N1 infection. All had severe ARDS and died owing to refractory hypotension and multiorgan failure. Kumar et al.[21] described 32 patients with influenza H1N1 admitted to the ICU. The majority of their patients were young, 24 out of 32 patients (75%) had ARDS; 20 patients with ARDS died. Hence it may be deduced that H1N1 pneumonia with ARDS has high mortality.

Overall the patients in our series were young with a mean age of 42 years, a pattern that has previously been reported from tropical countries. In contrast, patients from advanced nations are often older with mean age of 62 years.[2,5,6,15] It is projected that male predominance and young age in tropical countries is because of outdoor jobs and occupational exposure of working men to vectors of tropical illnesses.[6,15] Mortality analysis studies have shown that male gender is associated with higher mortality than female gender.[22]

Survival in ARDS is determined by the severity of lung injury, multiorgan dysfunction, presence of comorbid conditions and the quality of supportive care. In our study the baseline PaO_2/FiO_2 was significantly lower among nonsurvivors, though older studies have shown no association of baseline PaO_2/FiO_2 with mortality.[6,23,24] For example, the study by Zilberberg et al.[23] found similar mortality in patients with baseline PaO_2/FiO_2 <200 and those with PaO_2/FiO_2 between 201 and 300. However, recent reports indicate otherwise.[2,25] A study of 196 ARDS cases in 14 centres all across Ireland found that low PaO_2/FiO_2 ratio at baseline was associated with mortality.[25] In an Indian study of 46 ARDS patients classified according to the American European consensus definition,[7,26] all the four patients categorised as severe ARDS by Berlin classification died. In our study also all with severe ARDS died.

The mortality due to ARDS continues to remain high, although mortality clearly depends on the country, type of ICU, aetiology, definition of ARDS, etc. Mortality of ARDS in the western population from 1967 to 1994 was an average of 50%.[27] In 1998 a US centre recorded 65% mortality of ARDS patients,[28] another observational study by Bauer and colleagues[29] recorded mortality of 80%, Lu and colleagues from Shanghai reported 68% in-hospital mortality,[30] another Chinese group reported 55% mortality,[31] while from Belgium the mortality was 46%.[32] In India the mortality of ARDS patients still ranges from 48% to 60%.

We recorded an unusually high mortality of 78%, and we had not expected this high mortality figure. At the time the study was conducted Puducherry was experiencing a seasonal rise in H1N1 cases, and it is known that H1N1 and ARDS carries high mortality. Some patients were ventilated outside the ICU because of a limited number of beds in ICU and transferred later on to ICU. The difference between initial and maximum

Severity of ARDS	Survivors, frequency (%)	Nonsurvivors, frequency (%)	p-value
Mild ARDS	7 (77)	6 (18)	<0.001
Moderate ARDS	2 (22)	12 (36)	
Severe ARDS	0	15 (45)	

Table 4 Comparison of the severity of acute respiratory distress syndrome (ARDS) between ARDS survivors and nonsurvivors

SOFA score was nearly the same, which means that most of our patients had severe underlying organ dysfunction at admission. The Irish study also found higher (worse) SOFA scores in nonsurvivors.[25] The study by Sharma et al.[16] from India also found that high simplified acute physiology score (SAPS) was an independent predictor of death. In our study, nonsurvivors were haemodynamically unstable, and had higher prevalence of AKI. Both ARDS and AKI in ICUs are syndromes associated with high mortality.[33] A recent large observational study (in French ICUs) including >1,800 patients with ARDS showed that AKI occurred in 44% of ARDS patients.[34] As expected hospital mortality was greater in patients with ARDS plus AKI than with ARDS alone.

Another reason for excess mortality was the occurrence of VAP, which occurred in 18 (43%) patients, the tracheal aspirates from these patients showed highly resistant organisms. VAP in ARDS patients is usually late onset and caused by highly antibiotic-resistant microorganisms.[35] The excess mortality was partly contributed by nonadherence to mechanical ventilation strategies. Advances in ventilatory management of ARDS have translated into practice; however, a large gap exists between recommendations and application of evidence in day-to-day practice as was documented in a recent survey of ARDS epidemiology from across the world.[36]

The strengths of this study are its prospective design and recruitment of all consecutive cases. The limitations of our study are its short duration and observational nature. Moreover, the independent predictors for mortality have not been assessed on a logistic regression model because of extremely small sample size.

In conclusion, the aetiology of ARDS in our hospital is predominantly infection related. Scrub typhus is a re-emerging tropical infection that can cause ARDS. Correct identification and early diagnosis of scrub typhus is important as it responds very well to doxycycline. In our experience ARDS due to scrub typhus appeared to be mild and has good outcomes compared to other causes. Moreover, we need to ensure adherence to recommended mechanical ventilation strategies, sepsis management and prevention of hospital-acquired infection, and early referral to ICU for patients with hypoxaemia suspected of ARDS.

References

1 Phua J, Badia JR, Adhikari NKJ et al. Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med* 2009; 179: 220–7.
2 Rubenfeld GD, Caldwell E, Peabody E et al. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 20; 353: 1685–93.
3 The 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.
4 Vigg A, Mantri S, Vigg A et al. Clinical profile of ARDS. *J Assoc Physicians India* 2003; 51: 855–8.
5 Agarwal R, Aggarwal AN, Gupta D et al. Etiology and outcomes of pulmonary and extrapulmonary acute lung injury/ARDS in a respiratory ICU in North India. *Chest* 2006; 130: 724–9.
6 Bhadade RR, de Souza RA, Harde MJ et al. Clinical characteristics and outcomes of patients with acute lung injury and ARDS. *J Postgrad Med* 2011; 57: 286–90.
7 George T, Viswanathan S, Karnam AH et al. Etiology and outcomes of ARDS in a rural-urban fringe hospital of South India. *Crit Care Res Pract* 2014; 2014: 1815–93.
8 Ferguson ND, Frutos-Vivar F, Esteban A et al. Acute respiratory distress syndrome: under recognition by clinicians and diagnostic accuracy of three clinical definitions. *Crit Care Med* 2005, 33: 2228–34.
9 ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012; 307: 2526–33.
10 Knaus WA, Draper EA, Wagner DP et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985, 13: 818–29.
11 Vincent JL, Moreno R, Takala J et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22: 707–10.
12 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; 36: 309–32.
13 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20: 864–74.
14 Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. *Kidney Int Suppl* 2012; 2: 1–138.
15 Bhadade R, de'Souza R, Harde M et al. Mortality predictors of ARDS in medical intensive care unit of a tertiary care centre in a tropical country. *J Assoc Physicians India* 2015; 63: 16–22.
16 Sharma SK, Gupta A, Biswas A 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.
17 Baumann WR, Jung RC, Koss M et al. Incidence and mortality of adult respiratory distress syndrome: a prospective analysis from a large metropolitan hospital. *Crit Care Med* 1986; 14: 1–4.

18 Luhr OR, Antonsen K, Karlsson M et al. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group. *J Respir Crit Care Med* 1999; 159: 1849–61.
19 Vivekanandan M, Mani A, Priya YS et al. Outbreak of scrub typhus in Pondicherry. *J Assoc Physicians India* 2010; 58: 24–8.
20 Varghese GM, Janardhanan J, Trowbridge P et al. Scrub typhus in South India: clinical and laboratory manifestations, genetic variability, and outcome. *Int J Infect Dis* 2013; 17: e981–7.
21 Kumar TC, Shivakumar NS, Deepak TS et al. H1N1-infected patients in ICU and their clinical outcome. *N Am J Med Sci* 2012; 4: 394–8.
22 Moss M, Mannino DM. Race and gender differences in acute respiratory distress syndrome deaths in the United States: an analysis of multiple-cause mortality data (1979–1996). *Crit Care Med* 2002; 30: 1679–85.
23 Zilberberg MD, Epstein SK. Acute lung injury in the medical ICU: Comorbid conditions, age, etiology, and hospital outcome. *Am J Respir Crit Care Med* 1998; 157: 1159–64.
24 Doyle RL, Szaflarski N, Modin GW et al. Identification of patients with acute lung injury. Predictors of mortality. *Am J Respir Crit Care Med* 1995; 152: 1818–24.
25 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.
26 Bernard GR, Artigas A, Brigham KL et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818–24.
27 Krafft P, Fridrich P, Pernerstorfer T et al. The acute respiratory distress syndrome: definitions, severity and clinical outcome. An analysis of 101 clinical investigations. *Intensive Care Med* 1996; 22: 519–29
28 Monchi M, Bellenfant F, Cariou A et al. Early predictive factors of survival in the acute respiratory distress syndrome: a multivariate analysis. *Am J Respir Crit Care Med* 1998; 158: 1076–81.
29 Bauer TT, Valencia M, Badia JR et al. Respiratory microbiology patterns within the first 24 h of ARDS diagnosis: influence on outcome. *Chest* 2005; 128: 273–9.
30 Lu Y, Song Z, Zhou X et al. A 12-month clinical survey of incidence and outcome of acute respiratory distress syndrome in Shanghai intensive care units. *Intensive Care Med* 2004; 30: 2197–203.
31 Li JB, Zhang L, Zhu KM et al. Retrospective analysis on acute respiratory distress syndrome in ICU. *Chin J Traumatol* 2007; 10: 200–5.
32 Pierrakos C, Vincent JL. The changing pattern of acute respiratory distress syndrome over time: a comparison of two periods. *Eur Respir J* 2012; 40: 589–95.
33 Kraman S, Khan F, Patel S et al. Renal failure in the respiratory intensive care unit. *Crit Care Med* 1979; 7: 263–6.
34 Darmon M, Clec'h C, Adrie C et al. Acute respiratory distress syndrome and risk of AKI among critically ill patients. *Clin J Am Soc Nephrol* 2014; 9: 1347–53.
35 Wunderink RG, Waterer GW. Pneumonia complicating the acute respiratory distress syndrome. *Semin Respir Crit Care Med* 2002; 23: 443–8.
36 Bellani G, Laffey JG, Pham T et al; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315: 788–800.