SRYAHWA PUBLICATIONS

Archives of Emergency Medicine and Intensive Care
ISSN: 2638-5007 | Volume 6, Issue 1, 2025
https://doi.org/10.22259/2638-5007.0601001

RESEARCH ARTICLE

Evaluation of Acute Respiratory Distress Syndrome in Participants Enrolled in the Protocolized Care for Early Septic Shock (ProCESS) Trial

Krishan K. Sharma, MD[1], Thiago M. Oliveira, MD[2], Chuan-Chin Huang, ScD[3], Seth J. Berkowitz, MD[4], Maria A. Duran-Mendicuti, MD[5], Efren J. Flores, MD[6], Rebecca M. Baron, MD[7], Paul B. Dieffenbach, MD[7], Donald M. Yealy, MD[8], Michael R. Filbin, MD[9], Peter C. Hou, MD[2]

[1]Division of Cardiology, Department of Medicine, Mount Sinai Hospital, Newy York City, NY
[2]Division of Emergency Critical Care Medicine, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA
[3]Division of Global Health Equity, Department of Medicine, Brigham and Women's Hospital, Boston, MA
[4]Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA
[5]Department of Radiology, Brigham and Women's Hospital, Boston, MA
[6]Department of Radiology, Massachusetts General Hospital, Boston, MA
[7]Division of Pulmonary Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA
[8]Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA
[9]Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA

Received: 16 February 2025 Accepted: 03 March 2025 Published: 14 March 2025
Corresponding Author: Peter C. Hou, MD, Division of Emergency Critical Care Medicine, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA, USA.

Abstract

Background: Sepsis is the most common etiology of acute respiratory distress syndrome (ARDS), and the latter, if severe, has mortality rate averaging 45%. The frequency of early septic shock-associated ARDS and the subsequent short-term mortality is poorly described.

Methods: We conducted an ancillary study of the Protocolized Care for Early Septic Shock (ProCESS) trial to determine the incidence of ARDS and to describe baseline characteristics and clinical outcomes for these participants with early septic shock presenting to the emergency departments of two ProCESS study sites. We applied the Berlin Criteria for ARDS, and for participants with PaO2/FiO2 (P/F) ≤ 300, with chest radiographs independently reviewed by two radiologists to determine consistency with criteria. Discordance between the radiologists was adjudicatedby a panel of pulmonary intensivists.

Results: Of 179 participants, 47 received invasive mechanical ventilation with P/F ≤ 300. After radiographic determination, ARDS incidence was 12.3% (22/179). Of the participants who developed ARDS, the median and mean P/F ratios were 122.1 and 122.9 mmHg, respectively. ARDS case severity frequencies were "mild" (5%, P/F 201-300) "moderate" (55%, P/F 100 - 200), or "severe" (41%, P/F <100), with corresponding mortality rates of 0%, 33%, 78%, respectively. After multivariable adjustment, ARDS development was associated with a 3.7-fold higher 60-day in-hospital mortality rate (95% confidence intervals [CIs]: 1.16-5.71), 4.86-fold longer ICU length-of-stay (LOS) (95% CI: 1.69- 8.04), and 4.86-fold longer hospital LOS (95% CI: 1.69-8.04).

Conclusion: ARDS incidence in ED participants presenting with early septic shock is high. Compared to early septic shock participants without ARDS, participants with early septic shock who developed ARDS have a significantly higher mortality rate and both ICU and hospital LOS. Further investigations are needed to verify if our findings remain true.

Citation: Krishan K. Sharma, Thiago M. Oliveira, Chuan-Chin Huang, *et.al* Evaluation of Acute Respiratory Distress Syndrome in Participants Enrolled in the Protocolized Care for Early Septic Shock (ProCESS) Trial. Archives of Emergency Medicine and Intensive Care 2025; 6(1): 01-06.

1. Background

Sepsis develops in up to 3 million adults in the U.S. annually and causes significant morbidity and mortality.[1] Acute respiratory distress syndrome (ARDS) is a devastating complication of sepsis and septic shock.[2] For ARDS, the in-hospital mortality rate estimate is 38% with 190,600 cases and 3.6 million hospital days in the U.S. annually. [2] Despite sepsis and septic shock being the most common etiology of ARDS, little is known regarding the incidence of early septic shock associated ARDS. Although there are important challenges in the design and reporting of clinical trials regarding sepsis and septic shock, reporting of ARDS development from sepsis trials is an important outcome because it contributes to short-term mortality and long-term resource utilization.[2-3]

The grading of evidence and recommendation of fluid treatment protocols for sepsis and septic shock have recently been updated.[5] The Protocolized Care for Early Septic Shock (ProCESS) trial was a multicenter, randomized controlled trial that evaluated the efficacy of early goal-directed therapy (EGDT) in the treatment of early septic shock for patients presenting in the ED.[6] The ProCESS trial found that protocol-based treatment, such as EGDT, did not improve outcomes compared to other early care approaches. Early sepsis care involves varying amounts of fluid resuscitation that is often associated with a positive fluid balance. ARDS, characterized by inflammatory pulmonary edema, is associated with increased mortality in patients with positive fluid balance.[7] Little is known regarding the incidence of ARDS with the use of protocolized care for early septic shock.[8-9]

Our objective was to determine the incidence of ARDS in patients with early septic shock presenting to the ED and to describe the clinical characteristics and outcomes of this ARDS population.

2. Methods

2.1 Study Setting and Selection of Participants

Our study participants included all subjects who participated in the ProCESS trial from two sites, Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH), who presented to the ED with suspected sepsis. Participants were at least 18 years of age, met at least two criteria for the systemic inflammatory response syndrome, and had refractory hypotension *or* a serum lactate level of 4 mmol/L or higher. The specific inclusion and exclusion criteria are in the original ProCESS trial publication. (clinicaltrials.gov NCT00793442)[6]

2.2 Definition of ARDS

Applying the Berlin Criteria for ARDS,[10] we identified participants from two sites of the ProCESS trial on mechanical ventilation with a PaO2/FiO2 (P/F) ratio ≤ 300. For all participants who met these physiologic parameters, we obtained the participants' chest radiographs within 24 hours of the corresponding arterial blood gas with a P/F ratio ≤ 300. All chest radiographs were uploaded onto a secure and HIPAA-compliant electronic data collection web platform. Two board-certified radiologists independently reviewed all chest radiographs and determined if each radiograph supported a diagnosis of ARDS. In situations of discordance between the radiologists, the determination of ARDS was adjudicated by a panel of pulmonary critical care physicians.

2.2.1 Descriptive Analyses

We performed a descriptive analysis between ARDS cases and non-ARDS cases for all collected baseline and outcome variables, including the means, standard deviations, absolute counts, and proportions when applicable.

2.2.2 Regression Analyses

We evaluated associations between ARDS and 60-days hospital mortality using a modified Poisson regression, and between ARDS and LOS data using a linear regression. We first performed univariate analyses, followed by a multivariate adjustment for potential confounders collected at admission or pre-randomization (APACHE II score, treatment arm in the ProCESS trial, source of sepsis diagnosis, bacterial culture results, corticosteroid use, vasopressor use, antibiotic use, mechanical ventilation use, blood transfusion, intravenous fluid per body weight, history of congestive heart failure, history of hepatic cirrhosis, history of chronic respiratory disease, and history of renal impairment). All potential confounders were entered into a backwards stepwise algorithm, and variables with a p-value less than 0.2 were retained in the multivariate model. In the sensitivity analyses, we used 90-days hospital mortality as the outcome to evaluate whether ARDS predicted long-term, in-hospital mortality. We used complete data analyses in all multivariate adjustment models and conducted all statistical analyses in R version 4.1.1 (https://www.r-project.org).

3. Results

3.1 Study Cohort and Incidence of ARDS

Of the 1341 total participants in the original ProCESS trial, 179 participants received care at BWH and MGH. From these 179 participants, we identified 47 participants who received invasive mechanical ventilation and had P/F ≤ 300. Upon radiographic determination, the incidence of ARDS was 12.3% (22/179). Of the participants who developed ARDS, the median and mean P/F ratios were 122.1 and 122.9 mmHg, respectively. We categorized 5% of ARDS cases as "mild" (P/F 201-300), 55% as "moderate" (P/F 100 – 200), and 41% as severe (P/F <100). Treatment arm was not associated with the development of ARDS. The incidence of ARDS for patients randomized to EGDT, protocolized-standard care, and usual care were 45.5% (10/22), 27.3% (6/22), and 27.3% (6/22), respectively.

Out of 434 radiographs, we found moderate levels of raw (0.735) and chance-corrected (κ = 0.315, 95%CI 0.223 to 0.408) agreement between both radiologists. We observed varying levels of raw (0.697, 0.426) and chance-corrected (κ = 0.365, 0.118) agreement between the adjudicating panel of intensivists with both radiologists, respectively. Following adjudication, 22 subjects were identified as having ARDS.

3.2 Association Between ARDS and Hospital Mortality

The 60-day mortality rates for those with mild, moderate, and severe ARDS were 0%, 33.3%, 77.8%, respectively. Notably, 90-day mortality was 2.3-fold higher compared to participants with versus without ARDS (66.7% vs. 28.8%, $p < 0.01$).

In our univariate analyses, ARDS was associated with increased 60-days hospital mortality. After multivariate adjustment, patients with ARDS had 2.57-fold risk of inpatient death within 60 days of admission compared to those without ARDS (95% confidence intervals [CIs]: 1.16-5.71). In a sensitivity analysis using 90-days hospital mortality as out outcome of interest, ARDS was no longer associated with increased in-hospital mortality (Risk Ratio (RR):1.66 [95% CIs=0.84-3.30]).

3.3 Association Between ARDS and Length of Hospital Stay (LOS)

In our univariate analyses, ARDS was associated with increased ICU-LOS and hospital-LOS. After adjustment for potential confounders, patients with ARDS had 4.86 more ICU-LOS days and 4.76 more hospital-LOS days than patients without ARDS.

4. Discussion

Early identification of patients with sepsis and septic shock who are at risk for the development of ARDS is critical given that limited therapies improve mortality for septic-shock associated ARDS aside from lung protective ventilation.[3] Recent studies on sepsis and septic shock do not explicitly state the incidence of ARDS in this patient population. [4] We performed a subanalysis to determine the incidence of ARDS, and its possible risk factors, using data from the ProCESS trial. Previous literature suggests the incidence of ARDS in ED patients with septic shock to be near 6%.[8] Our results indicate a higher incidence of 12.3%. Consistent with previous studies, our data supports that illness severity and pulmonary sources of infection are risk factors for the development of ARDS.[8] Otherwise, we did not identify any other baseline factors associated with development of ARDS, though this may be due to a limited sample size.

Our participants with ARDS had higher mortality rates and increased resource utilization, including longer intensive care unit and hospital lengths of stay. Given the devastating outcomes and high resource utilization in this population, research priorities should include early identification of and preventative measures for sepsis-associated ARDS.

4.1 Limitations

This was a retrospective study and utilized a limited sample size of participants from two study sites. Our study cannot detect lower frequency relationships or associations in participants with sepsis-associated ARDS. An additional limitation includes possible ARDS misclassification given this retrospective design and our dependence on available radiographs and our radiologists' interpretation. To minimize this bias, we based our determination of ARDS on established criteria and utilized two independent radiologists to review each chest radiograph and an adjudication panel of pulmonary intensivists when there was discordance in interpretation between the radiologists.

5. Conclusions

The incidence of ARDS in patients with early septic shock is high and is associated with a high mortality rate and increased resource utilization.

Table 1. *Baseline characteristics of participant sample, comparing ARDS and non-ARDS cohorts. Plus–minus values are means ±SD.*

Table S1. Baseline characterisitics			
	Total (N = 179)	ARDS (N=22)	Non-ARDS (N=157)
Age - yr	61.7 ± 15.0	60.6 ± 12.5	61.9 ± 15.3
Male sex - no. (%)	86 (48.0)	12 (54.5)	74 (47.1)
Ethnicity			
Hispanic	21 (11.7)	1 (4.5)	20 (12.7)
Non-hispanic	158 (88.3)	21 (95.5)	137 (87.3)
Race			
White	148 (82.7)	19 (86.4)	129 (82.2)
Black	19 (10.6)	1 (4.5)	18 (11.5)
Asian	7 (3.9)	2 (9.1)	5 (3.2)
Other	7 (3.9)	0 (0)	5 (3.2)
Comorbidities			
Hypertension	106 (59.2)	15 (68.2)	91 (58.0)
Diabetes melltius	52 (29.1)	7 (31.8)	45 (28.7)
Chronic respiratory disease	41 (22.9)	3 (13.6)	38 (24.2)
Cancer	58 (32.4)	9 (40.9)	49 (31.2)
Renal impairment	25 (14.0)	4 (18.2)	21 (13.4)
Congestive heart failure	30 (16.8)	6 (27.3)	24 (15.3)
Prior myocardial infarction	20 (11.2)	0 (0)	20 (12.7)
Cerebral vascular disease	11 (6.1)	0 (0)	11 (7.0)
Peripheral vascular disease	16 (8.9)	2 (9.1)	14 (8.9)
Chronic dementia	6 (3.4)	0 (0)	6 (3.8)
Hepatic cirrhosis	10 (5.6)	4 (18.2)	6 (3.8)
Peptic ulcer disease	10 (5.6)	1 (4.5)	9 (5.7)
AIDS or related syndromes	2 (1.1)	0 (0)	2 (1.3)
Residence before admission — no. (%)			
Nursing home	23 (12.8)	0 (0)	23 (14.6)
Other	156 (87.2)	22 (100)	134 (85.4)
Source ofsepsis — no. (%)			
Pneumonia	61 (34.1)	12 (54.5)	49 (31.2)
Urinary tract infection	35 (19.6)	3 (13.6)	32 (20.4)
Intraabdominal infection	28 (15.6)	2 (9.1)	26 (16.6)
Infection of unknown source	15 (8.4)	1 (4.5)	14 (8.9)
Skin or soft-tissue infection	11 (6.1)	1 (4.5)	10 (6.4)
Catheter-related infection	9 (5.0)	1 (4.5)	8 (5.1)
Central nervoussystem infection	2 (1.1)	0 (0)	2 (1.3)
Endocarditis	4 (2.2)	1 (4.5)	3 (1.9)
Endocarditis	12 (6.7)	1 (4.5)	11 (7)
Determined after review not to have infection	2 (1.1)	0 (0)	2 (1.3)
Positive blood culture — no. (%)	45 (25.1)	7 (31.8)	38 (24.2)
Charlson comorbidity score	3.0 ± 2.7	3.8 ± 3.4	2.9 ± 2.6
APACHE II score	19.1± 6.3	22.7± 7.0	18.5± 6.0
Entry criterion for ProCESS trial— no. (%)			
Refractory hypotension	147 (82.1)	19 (86.4)	128 (81.5)
Hyperlactatemia	62 (34.6)	10 (45.5)	52 (33.1)
Physiological variables			
Systolic blood pressure (mm Hg)	98.3 ± 21.0	100.5 + 20.3	98.0 + 21.2
Serum lactate (mmol/liter)	3.7 ± 2.6	4.6 ± 2.6	3.6 ± 2.6

Table 2. *Outcome data of participant sample, comparing ARDS and non-ARDS cohorts. Plus–minus values are means ±SD.*

Table S2: Outcomes			
	Total (N = 179)	**ARDS (N=22)**	**Non-ARDS (N=157)**
Treatment arm			
Protocol-based EGDT	58 (32.4)	10 (45.5)	48 (30.6)
Protocol-based standard therapy	61 (34.1)	6 (27.3)	55 (35.0)
Usual care	60 (33.5)	6 (27.3)	54 (34.4)
Death — no./total no. (%)			
In-hospital death by 60 days	32 (17.9)	11 (50)	21 (13.4)
Death by 90 days	54/164 (32.9)	12.0/18 (66.7)	42/146 (28.8)
New organ failure in the first week — no./total no. (%)			
Cardiovascular	136 (78.0)	22 (100)	114 (72.6)
Respiratory	55/178 (30.9)	21/21 (100)	34/157 (21.7)
Renal	2/162 (1.2)	1/18 (5.6)	1/144 (0.7)
Use of hospital resources			
Admission to intensive care unit — no. (%)	164 (91.6)	22 (100)	142 (90.4)
Stay in intensive care unit among admitted patients — days	4.8 ± 7.8	9.9 ± 12.5	4.1 ± 6.6
Stay in hospital — days	10.2 ± 9.9	14.3 ± 15.6	9.6 ± 8.7
Discharge status at 60 days — no. (%)			
Not discharged	2(1.1)	1 (4.5)	1
Discharged to a long-term acute care facility	19 (10.6)	1(4.5)	18
Discharge to another acute care hospital	1(0.56)	1(4.5)	0
Discharged to nursing home	27 (15.1)	1(4.5)	26
Discharged home	91 (50.8)	5 (22.7)	86
Other or unknown	7(3.9)	2(9.1)	5
Corticosteroid adminsitration, prerandomization	30 (16.8)	6 (27.3)	24 (15.3)
Corticosteroid adminsitration, randomization to 6 hours	16 (8.9)	3 (13.6)	13 (8.3)
Antibiotic adminsitration, prerandomization	149(83.2)	19 (86.4)	130 (82.8)
Antibiotic adminsitration, randomization to 6 hours	176 (98.3)	22 (100)	154 (98.1)
Mechnical ventilation, pre-randomization	19(10.6)	4 (18.2)	15 (9.6)
Mechnical ventilation, randomization to 6 hours	37 (20.7)	13 (59.1)	24 (15.3)
Mechnical ventilation, randomization to 72 hours	51 (28.5)	20 (90.9)	31 (19.7)
Blood transfusion, prerandomization	2 (1.1)	0 (0)	2 (1.3)
Blood transfusion, randomization to 72 hours	46 (25.7)	8 (36.4)	38 (24.2)
Vasopressor use, pre-randomization	52 (29.1)	9 (40.9)	43 (27.4)
Vasopressor use, randomization to 6 hours	126 (70.4)	20 (90.9)	106 (67.5)
Vasopressor use, randomization to 72 hours	132 (73.7)	21 (95.5)	111 (70.7)
Dobutamine use, pre-randomization	0(0)	0(0)	0(0)
Dobutamine use, randomization to 6 hours	3 (1.7)	0 (0)	3(1.9)
Dobutamine use, randomization to 72 hours	4 (2.2)	0 (0)	4 (2.5)
Intravenous fluids, pre-randomization	2823.2 ± 1466.0	3752.3 ± 1831.0	2693.1 ± 1364.5
Intravenous fluids, prerandomization per body weight	40.4 ± 23.7	53.5 ± 28.6	38.5 ± 22.5
Intravenous fluids, randomization to 6 hours	2389.0 ± 1474.4	2366.6 ± 1651.7	2392.2 ± 1453.6
Intravenous fluids, randomization to 72 hours	6054.7 ± 4203.8	7322.4 ± 4303.8	5877.0 ± 4172.8

Table 3. *Association between ARDS and 60-days hospital mortality*

		Univariate (N=179)			**Multivariate (N=179)***	
	No. of 60-days hospital mortality (%)	Risk ratio (95% CI)	p-values		Risk ratio (95% CI)	p-values
No ARDS	11 (7%)	Ref	-		Ref	-
ARDS	11 (55%)	3.74 (1.8-7.75)	<0.001		2.57 (1.16-5.71)	0.02

**Adjusted for APACH II scores, source of sepsis diagnosis, vasopressor use, and intravenous fluid per body weight*

Table 4. *Association between ARDS and 90-days hospital mortality*

		Univariate (N=179)			Multivariate (N=179)*	
	No. of 90-days hospital mortality (%)	Odds ratio (95% CI)	p-values		Odds ratio (95% CI)	p-values
No ARDS	42 (27%)	Ref	-		Ref	-
ARDS	12 (55%)	2.04 (1.07 – 3.87)	0.0295		1.66 (0.84-3.30)	0.15

** Adjusted for APACH II scores, source of sepsis diagnosis, vasopressor use, and intravenous fluid per body weight*

Table 5. *Association between ARDS and ICU Length of Stay*

		Univariate (N=179)			Multivariate (N=179)*	
	ICU Length of Stay (mean, SD)	Mean Difference (95% CI)	p-values		Mean Difference (95% CI)	p-values
No ARDS	4.1 (6.6)	Ref	-		Ref	-
ARDS	9.9 (12.4)	5.81 (2.45 to 9.18)	<0.001		4.86 (1.69- 8.04)	0.0031

**Adjusted for APACH II scores, corticosteroid use, antibiotic use, mechanical ventilation use, and intravenous fluid per body weight.*

Table 6. *Association between ARDS and Hospital Length of Stay*

		Univariate (N=179)			Multivariate (N=179)*	
	Hospital Length of Stay (mean, SD)	Mean Difference (95% CI)	p-values		Mean Difference (95% CI)	p-values
No ARDS	9.6 (14.3)	Ref	-		Ref	-
ARDS	14.3 (12.5)	4.67 (0.31 -9.04)	0.037		4.76 (0.44 - 9.08)	0.032

**Adjusted for corticosteroid use, antibiotic use, mechanical ventilation use, and intravenous fluid per body weight.*

Meetings

Previously presented as an oral presentation and abstract at the American College of Emergency Physicians (ACEP) Annual Meeting 2017, Washington DC.

Financial Support

Awarded the Emergency Medicine Foundation (EMF) medical student research grant.

Word count: Abstract – 282; Manuscript – 1,315

Author contributions

PCH, MRF, and DMY conceived the study and designed the methods. KKS, MRF, and PCH collected the data, and KKS, CCH, and PCH performed the statistical analysis and interpretation of results. PCH and MRF acquired radiographic data and SB created the software platform for repository of radiographic data. MAD, EJF, RMB, and PBD were involved in radiographic interpretation. KKS, TMO, CCH, and PCH drafted the manuscript, and all authors contributed substantially to its revision.

7. References

1. Angus, D. C., & Van der Poll, T. (2013). Severe sepsis and septic shock. *N Engl J Med*, *369*, 840-851.
2. Blank, R., & Napolitano, L. M. (2011). Epidemiology of ARDS and ALI. *Critical care clinics*, *27*(3), 439-458.
3. Meduri, G. U., Marik, P. E., Chrousos, G. P., Pastores, S. M., Arlt, W., Beishuizen, A., ... & Annane, D. (2008). Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. *Intensive care medicine*, *34*(1), 61-69.
4. Eworuke, E., Major, J. M., & McClain, L. I. G. (2018). National incidence rates for acute respiratory distress syndrome (ARDS) and ARDS cause-specific factors in the United States (2006–2014). *Journal of critical care*, *47*, 192-197.
5. Nguyen, H. B., Jaehne, A. K., Jayaprakash, N., Semler, M. W., Hegab, S., Yataco, A. C., ... & Rivers, E. P. (2016). Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. *Critical Care*, *20*(1), 1-16.
6. ProCESS Investigators. (2014). A randomized trial of protocol-based care for early septic shock. *New England Journal of Medicine*, *370*(18), 1683-1693.
7. Sakr Y, Vincent JL, Reinhart K, et al. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. Chest. 2005;128(5):3098-3108. doi:10.1378/chest.128.5.3098
8. Mikkelsen ME, Shah CV, Meyer NJ, et al. The epidemiology of acute respiratory distress syndrome in patients presenting to the emergency department with severe sepsis. Shock. 2013;40(5):375-381. doi:10.1097/SHK.0b013e3182a64682
9. Murphy, C. V., Schramm, G. E., Doherty, J. A., Reichley, R. M., Gajic, O., Afessa, B., ... & Kollef, M. H. (2009). The importance of fluid management in acute lung injury secondary to septic shock. *Chest*, *136*(1), 102-109.
10. Force, A. D. T., Ranieri, V. M., Rubenfeld, G. D., Thompson, B., Ferguson, N., & Caldwell, E. (2012). Acute respiratory distress syndrome. *Jama*, *307*(23), 2526-2533.