6-1-2022

Oliguria on the Day of Intubation Is Associated With Mortality in Patients With Acute Respiratory Distress Syndrome

Raef A. Fadel

Ivanna O. Murskyj

Elian D. Abou Asala

Nour Nasiri

Ayman Alsaadi

See next page for additional authors

Authors

Raef A. Fadel, Ivanna O. Murskyj, Elian D. Abou Asala, Nour Nasiri, Ayman Alsaadi, Ashley Scott, and Daniel R. Ouellette

ORIGINAL CLINICAL REPORT

OPEN

Oliguria on the Day of Intubation Is Associated With Mortality in Patients With Acute Respiratory Distress Syndrome

Raef A. Fadel, DO[1]
Ivanna Murskyj, MD[1]
Elian Abou Asala, MD[1]
Nour Nasiri, MD[1]
Ayman Alsaadi, MD[1]
Ashley Scott, MD[2]
Daniel Ouellette, MD[3]

OBJECTIVES: To investigate the relationship between oliguric acute kidney injury (AKI) and mortality in patients with acute respiratory distress syndrome (ARDS).

DESIGN: Retrospective cohort study.

SETTING: This investigation took place at a single-center, tertiary referral multidisciplinary comprehensive healthcare hospital in metropolitan Detroit, Michigan.

PATIENTS: Adult patients 18 years old or older hospitalized in the ICU and diagnosed with ARDS on mechanical ventilation.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Three hundred eight patients were included in the final analysis. Risk factors associated with mortality included advanced age ($p < 0.001$), increased body mass index ($p = 0.008$), and a history of chronic kidney disease ($p = 0.023$). Presence of AKI by day 1 of intubation, with elevated creatinine ($p = 0.003$) and oliguria ($p < 0.001$), was significantly associated with mortality. On multivariate analysis, advanced age (relative risk [RR], 1.02), urine output on the day of intubation (RR, 0.388), bicarbonate level (RR, 0.948), and Sequential Organ Failure Assessment severity score (RR, 1.09) were independently associated with mortality. A receiver operating characteristic curve identified a threshold urine output on the day of intubation of 0.7 mL/kg/hr (area under the curve, 0.75; $p < 0.001$) as most closely associated with inpatient mortality (i.e., urine output < 0.7 mL/kg/hr is associated with mortality).

CONCLUSIONS: For patients with ARDS, oliguria on the day of intubation was independently associated with increased mortality. Urine output of less than 0.7 mL/kg/hr predicted 80% of inpatient deaths. These findings herald an augmented understanding of the role of urine output in medical decision-making and prognostication.

KEY WORDS: acute kidney injury; artificial ventilation; intensive care units; renal failure; respiratory distress syndrome; urine

Critically ill patients often experience complex end-organ dysfunction that contributes to a high mortality rate (1, 2). Acute kidney injury (AKI) is a frequent complication due to a variety of insults that impact renal function, including decreased renal perfusion in a shock state, medication insults (e.g., nephrotoxic antimicrobials and vasoactive agents), and possibly contrast (3). Such impact is further magnified in the presence of underlying chronic kidney disease (CKD) (4). Many studies have demonstrated an association between AKI and poor outcomes in patients with acute respiratory distress syndrome (ARDS) (3, 5), compounded by comorbid conditions (6).

In patients who develop AKI in the context of ARDS, it remains unclear whether it is the metabolic effects of renal disease or the respiratory failure itself that increases the mortality in this population. One investigation of patients

DOI: 10.1097/CCE.0000000000000717

previously enrolled in the ARDS Network (ARDSNet) trial identified a correlation between low urine output and increased mortality in hospitalized patients with ARDS (7). Additionally, factors such as age, high clinical severity scores, and acidosis were associated with the development of AKI in a cohort of patients with ARDS (8).

The aim of this study was to investigate the relationship between oliguric AKI and mortality in patients with ARDS. We hypothesized that oliguric AKI is an independent risk factor for all-cause mortality in this population.

MATERIALS AND METHODS

Study Design and Population

We performed a retrospective review of patients admitted to a single-center healthcare system in metropolitan Detroit, Michigan (Henry Ford Health System), between December 2012 and February 2018.

Hospital charts were screened for patients 18 years old or older, admitted to the ICU, and carrying a diagnosis of ARDS or acute respiratory distress. Patients were included if they met the Berlin criteria for moderate or severe ARDS, with a Pao_2/Fio_2 ratio (P/F) of less than 200 (9).

Patients were excluded if externally transferred to or from Henry Ford Health System, if they did not have consistent measurements of intake or output in the electronic health record (EHR), if ventilator mechanics were not documented by respiratory therapy, or if they required dialysis prior to onset of ARDS.

The study and waiver of informed consent were approved by the Henry Ford Health System Institutional Review Board (Number 14963).

Data Collection, Study Definitions, and Calculations

All data were gathered through chart review and manual abstraction of the EHR, selected based on the above inclusion criteria. Baseline demographics, underlying comorbidities, clinical severity scores, and outcomes were evaluated by the research team and adjudicated by the study investigators. Body mass index (BMI) was auto-calculated and abstracted from the EHR. Mechanical ventilation data were obtained from respiratory therapy flowsheets in the EHR for the first 7 days of mechanical ventilation; days were defined by intubation day, with day 1 representing the first day of intubation. Intake and output (I/O) data were ascertained from nursing documentation, with data screening per exclusion criteria above.

ARDS was defined by the 2012 Berlin definition (9). Sequential Organ Failure Assessment (SOFA) scores were calculated for the entire population.

AKI was defined by the Kidney Disease Improving Global Outcomes 2012 guidelines, primarily based on a reduction in urine output, calculated, and recorded as milliliters of urine per body weight in kilograms per hour (mL/kg/hr) (10). In our study, urine output was determined on the day of intubation. All but seven patients in the study also met criteria for AKI by creatinine level elevation, but this qualification was not formally used.

Static compliance was calculated from abstracted tidal volume, positive end-expiratory pressure (PEEP), and plateau pressures according to the formula: static compliance = tidal volume/(plateau pressure–PEEP). Driving pressure was calculated from abstracted plateau pressures and PEEP according to the formula: driving pressure = plateau pressure–PEEP. Vasopressor and paralytic use were defined as any use during the first 7 days of mechanical ventilation, not including induction for intubation.

Ventilator-free days (VFDs) was defined as the number of days alive and free of mechanical ventilation within 28 days after the initial intubation of the hospital stay of interest. Total ventilator days was defined as total days on mechanical ventilation since primary intubation. New renal replacement therapy (RRT) was defined by the need for emergent RRT in the ICU with no prior history of dialysis need. ICU and total length of stay were defined as time to discharge (alive or deceased) during the index hospitalization.

Outcomes

The primary outcome was inpatient mortality. Secondary outcomes included VFD, ICU length of stay, and total hospital length of stay.

Statistical Analysis

Considering the primary dichotomous endpoint of inpatient mortality, we predicted a baseline all-cause mortality of 30% in patients with ARDS without AKI

and 50% in patients with ARDS and AKI (8). With this, we projected 182 total patients included in the analysis would achieve 80% power, assuming a two-sided α less than 0.05 to be statistically significant and reported odds ratio with 95% CIs.

Continuous variables were described as medians (with interquartile ranges) and categorical variables as frequency rates and percentages. The Mann-Whitney *U* test or *t* test were used for continuous variables, whereas chi-square or Fisher exact tests were used for categorical variables. A univariate analysis was performed to determine the association of underlying risk factors with inpatient mortality.

Multiple logistic regression was performed with in-hospital mortality as the dependent variable. Risk factors were chosen for the model if they were significantly associated with the dependent variable by univariate analysis and if data were available for the risk factor in at least 80% of the subjects. Of the risk factors significantly associated with in-hospital mortality in the univariate analysis (**Table 1**; and **Supplemental Digital Content 1**, http://links.lww.com/CCX/B11), creatinine on day 1 of intubation was excluded from the multivariate analysis due to collinearity with urine output and less significant association. The remaining risk factors were included in a multivariate model. Complete data were available for a total of 306 of 308 subjects who were included in the analysis. For the multivariate analysis, risk factors were considered to be significantly associated with in-hospital mortality for *p* values of less than 0.05. The odds ratio and CI were reported for each risk factor.

A receiver operating characteristic (ROC) curve was then used to model the performance of urine output in predicting inpatient mortality, with determination of a threshold value for application in clinical practice with calculation of area under the curve (AUC) reported with 95% CIs, assuming a significance level of 0.05. Statistical analyses were performed using SPSS 27 (IBM, Armonk, NY).

RESULTS

A total of 1,195 patients were initially screened for enrollment. Four hundred sixty-four patients (40%) met inclusion criteria based on age and presence of ARDS. Of this group, 166 patients were excluded, with 298 patients included in the final analysis (**Fig. 1**).

Of the included patients, the majority were hospitalized for bacterial pneumonia (176 patients, 57%). Approximately 169 (57%) were male, 161 (54%) Caucasian, and 109 (37%) Black. Baseline demographics associated with mortality included advanced age (52 ± 17 yr in alive vs 60 ± 17 in deceased; $p < 0.001$), increased BMI (30 ± 9 vs 32 ± 11 kg/m^2; $p = 0.008$), and a history of CKD (33 vs 42 patients; $p = 0.023$). Additionally, higher SOFA scores at admission to the ICU were associated with increased mortality (10 ± 3 vs 12 ± 4; $p < 0.001$). Presence of AKI by day 1 of intubation was significantly associated with mortality, as highlighted by elevated creatinine (1.56 ± 1.40 vs 1.93 ± 1.51 mg/dL; $p = 0.003$) and decreased urine output (1.05 ± 0.87 vs 0.48 ± 0.52 mL/kg/hr; $p < 0.001$). Additionally, bicarbonate levels were significantly lower in deceased patients as compared with alive (20.51 ± 5.16 vs 22.5 ± 5.71 mEq/L; $p = 0.001$). $Paco_2$, net I/O, and P/F on day 1 of intubation did not statistically significantly differ between alive and

TABLE 1.
Multivariate Analysis of Risk Factors Associated With Dependent Variable of Inpatient Mortality

Risk Factors	Relative Risk (95% CI)	*p*
Age	1.020 (1.03–1.04)	**0.019**
Body mass index	1.021 (0.992–1.05)	0.161
Chronic kidney disease	1.114 (0.612–2.03)	0.724
Urine output on day 1 of MV	0.388 (0.230–0.654)	**< 0.001**
Bicarbonate on day 1 of MV	0.948 (0.901–0.997)	**0.039**
Sequential Organ Failure Assessment on admit to ICU	1.089 (1.01–1.18)	**0.035**

MV = mechanical ventilation.
Significant $p < 0.05$ are bolded.

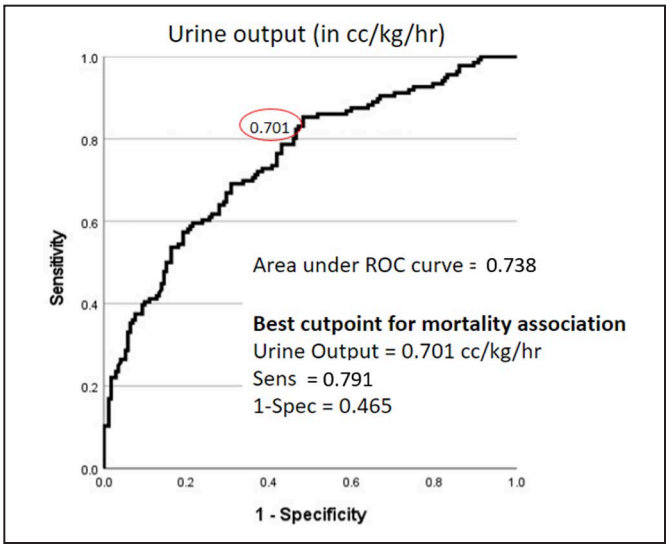

Figure 1. Receiver operating characteristic (ROC) curve of urine output (in mL/kg/hr) as a risk factor for inpatient mortality.

deceased cohorts. Supplemental Digital Content 1 (http://links.lww.com/CCX/B11) highlights these findings, including baseline demographics and risk factors. Supplemental Digital Content 1 (http://links.lww.com/CCX/B11) highlights the etiologies of ARDS in included patients.

On multivariate analysis to assess risk factors independently associated with mortality, advanced age (relative risk [RR], 1.02; 95% CI, 1.03–1.04; $p = 0.019$), urine output on day 1 of intubation (RR, 0.388; 95% CI, 0.230–0.654; $p < 0.001$), bicarbonate level on day 1 of intubation (RR, 0.948; 95% CI, 0.901–0.997; $p = 0.039$), and SOFA scores at admission to ICU (RR, 1.089; 95% CI, 1.01–1.18; $p = 0.035$) were independently associated with mortality (i.e., advanced age and higher SOFA score are associated with increased mortality, and elevated urine output and bicarbonate appear to be protective). Table 1 demonstrates results of the multivariate analysis.

Of the 464 patients meeting inclusion criteria, 10 patients had end-stage renal disease and required dialysis prior to the illness that led to the development of ARDS. Of these 10 patients, three survived and seven died. Six of the 10 renal failure patients had non-negligible urine output on the day of intubation. The three survivors had urine outputs of 0.185, 0.506, and 1.187 mL/kg/hr on the day of intubation. The threshold urine output most significantly associated with increased mortality as identified by an ROC curve upon excluding these 10 patients from the analysis was less than 0.7 mL/kg/hr (AUC, 0.738; 95% CI, 0.68–0.795; $p < 0.001$), correlating with a sensitivity of 79.1% and specificity of 53.8%. These findings are highlighted in **Figure 2**.

A total of 180 patients (60%) fell below the identified threshold, termed low (< 0.7 mL/kg/hr) urine output. When patients were recategorized according to this designation, age ($p < 0.001$), creatinine ($p < 0.001$), BMI ($p < 0.001$), history of CKD ($p < 0.001$), and SOFA score at admission to the ICU ($p < 0.001$) were significantly different between both high and low urine output groups, in addition to P/F ratio on day 1 (172 ± 124 vs 144 ± 113; $p = 0.015$), plateau pressure on day 3 (23 ± 7.0 vs 26 ± 7.0 cm H_2O; $p < 0.001$), PEEP on day 3 (9.6 ± 4.5 vs 11 ± 5.2 cm H_2O; $p < 0.001$), and net I/O on day 3 (2.1 ± 5.6 vs 3.4 ± 5.1 L; $p = 0.042$). Baseline characteristics of low and high urine output cohorts can be found in **Table 2**.

In assessing outcomes associated with urine output on day of intubation above or below the specified threshold of 0.7 mL/kg/hr, patients below the threshold experienced fewer VFD (6.77 ± 10 vs 13.4 ± 11; $p < 0.001$) and increased need for emergent new RRT initiation (30% vs 13%; $p = 0.003$). There was no significant difference in the use of vasopressor support or paralytics between the two groups. Outcome results are highlighted in **Table 3**.

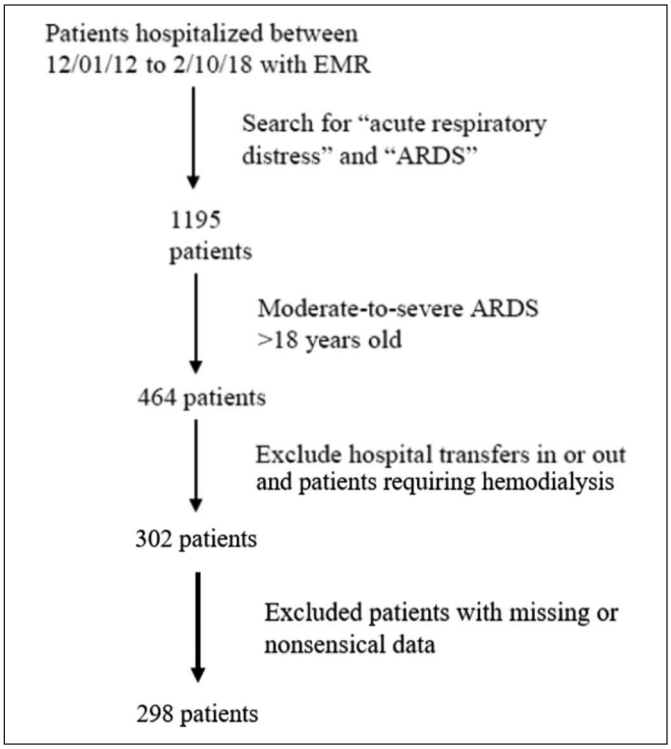

Figure 2. Patient inclusion and exclusion diagram. ARDS = acute respiratory distress syndrome, EMR = electronic medical record.

TABLE 2.

Baseline Characteristics and Risk Factors Associated With Mortality in Patients Categorized by Low (< 0.7 cc/kg/hr) and High (> 0.7 cc/kg/hr) Urine Output

Baseline Characteristics	High, *n* = 118	Low, *n* = 180	*p*
Demographics			
Age, mean (SD)	48.1 ± 15.1	60.4 ± 16.7	**< 0.001**
Male, *n* (%)	67 (57)	102 (57)	0.787
White, *n* (%)	57 (48)	104 (58)	0.332
Black, *n* (%)	44 (37)	65 (57)	0.716
Body mass index, mean (SD)	26.6 ± 6.59	33.3 ± 10.4	**< 0.001**
Comorbidities, *n* (%)			
Chronic obstructive pulmonary disease	67 (56)	102 (57)	0.787
Asthma	14 (12)	21 (12)	0.894
Obstructive sleep apnea	8 (7)	27 (15)	**0.038**
On home oxygen	10 (8)	26 (15)	0.144
Diabetes mellitus	37 (31)	68 (38)	0.337
Hypertension	60 (50)	126 (70)	**0.003**
Chronic kidney disease	16 (13)	59 (33)	**< 0.001**
Coronary artery disease	13 (11)	33 (19)	0.107
Congestive heart failure	10 (8)	38 (22)	**0.005**
Tobacco use	76 (63)	95 (54)	**0.031**
Prior venous thromboembolism	23 (19)	41 (24)	0.579
Severity of illness			
sCr on admit to ICU–mg/dL, mean (SD)	1.43 ± 1.39	2.00 ± 1.44	**0.010**
sCr on day 1 of MV–mg/dL, mean (SD)	1.44 ± 1.45	1.90 ± 1.44	**< 0.001**
Bicarbonate on day 1 of MV–mEq/L, mean (SD)	22.0 ± 5.54	21.0 ± 5.56	0.129
pH on day 1 of MV, mean (SD)	7.32 ± 0.121	7.0 ± 0.127	**0.009**
Acute respiratory distress syndrome severity, *n* (%)			
Moderate	68 (57)	72 (40)	**0.002**
Severe	40 (42)	113 (63)	**0.0015**
P_{CO_2} on day 1 of MV, mean (SD)			
Net I/O on day 1 of MV–L	2.26 ± 4.98	2.84 ± 4.01	0.266
Net I/O on day 3 of MV–L	2.07 ± 5.64	3.41 ± 5.14	**0.042**
P/F on day 1 of MV	171 ± 124	145 ± 113	**0.015**
P/F on day 3 of MV	180 ± 116	165 ± 92	0.263
Sequential Organ Failure Assessment on admit to ICU	9.74 ± 3.00	11.5 ± 3.60	**< 0.001**

I/O = intake and output, MV = mechanical ventilation, P/F = ratio of Pa_{O_2}/Fi_{O_2}, sCr = serum creatinine.
Significant $p < 0.05$ are bolded.

DISCUSSION

This was a retrospective, single-center study aiming to investigate the relationship between development of oliguric AKI, as measured by low urine output and creatinine elevation, and mortality in patients hospitalized with all-cause ARDS. We hypothesized that oliguric AKI is an independent risk factor for all-cause mortality in this population. This hypothesis was developed through careful examination of an ARDSNet

TABLE 3.
Outcomes in Patients Categorized by Low (< 0.7 cc/kg/hr) and High (> 0.7 cc/kg/hr) Urine Output

Outcome	High, *n* = 118	Low, *n* = 180	*p*
Inpatient death, *n* (%)	27 (23)	109 (61)	**< 0.001**
Ventilator-free day–d, mean (SD)	13 ± 11	7 ± 10	**< 0.001**
ICU LOS–d, mean (SD)	20 ± 17	15 ± 13	**0.030**
Hospital LOS–d, mean (SD)	26 ± 21	19 ± 14	**< 0.001**
New renal replacement therapy initiation, *n* (%)	16 (13)	52 (30)	**0.003**
Vasopressor required, *n* (%)	34 (28)	72 (40)	0.073
Paralytics required, *n* (%)	25 (21)	50 (29)	0.263

LOS = length of stay.
Significant $p < 0.05$ are bolded.

secondary analysis that identified a mortality benefit with increased urine output at the time of ARDS development (7). We also attempted to investigate underlying risk factors for mortality in patients with AKI prior to the onset of ARDS, as previously detailed in a retrospective review (8).

Our results confirm the hypothesis that development of oliguric AKI on the day of intubation is independently associated with inpatient mortality, with a urine output cutoff of less than 0.7 mL/kg/hr (termed "low urine output") serving as the single strongest factor associated with mortality, associated with roughly 80% of inpatient death in this cohort of patients with ARDS that predominantly occurred secondary to bacterial pneumonia, sepsis, and postoperative complications. Shen et al (7) previously described the impact of urine output on survival in the ARDS population, using a novel calculation of urine output/fluid intake ratio to yield a cutoff of 0.5, with urine output below this significantly associated with mortality. However, their study population included significantly fewer Black patients (17.7% vs 35%), with no discussion regarding underlying history of CKD. The association between baseline renal impairment and mortality, predominantly in the ICU setting, is well documented (3, 4, 6, 11, 12). Additionally, patients with a net positive fluid balance may experience compounded negative effects, including increased morbidity and mortality (11–14). Therefore, to truly demonstrate an association between urine output and mortality, a heterogeneous sample of patients with and without underlying CKD is pivotal, especially considering such patients with baseline renal impairment are at increased risk of AKI, which may lead to clinicians overestimating fluid need. In our study, not only was urine output on the day of intubation associated with mortality at a RR of 0.388 (0.230–0.654), the cutoff urine output of 0.7 mL/kg/hr predicted roughly 80% of patient deaths in our cohort.

We further demonstrate several risk factors associated with mortality, including advanced age, elevated BMI, history of CKD, degree of acidosis (indicated by pH and bicarbonate levels) at the time of intubation, and SOFA score at admission to the ICU. However, the risk factor most significantly associated with mortality in this population was reduction in day 1 urine output (< 0.7 mL/kg/hr cutoff). In contrast, P/F was not a significant risk factor associated with mortality, primarily due to the design of this cohort review. We selected patients based on their P/F at the time of ARDS onset, so all patients included were already predetermined to have moderate-to-severe gas exchange abnormalities.

This association between oliguria on the day of intubation and mortality has significant clinical implications, providing a useful and easy-to-measure risk factor for mortality on the first day of intubation in patients with moderate-severe ARDS, with increased practical application as compared with prior urine output measures (7). Knowing the relationship between such a ubiquitous variable as urine output on the day of intubation and mortality in ARDS can help clinicians, even in resource-poor settings, to inform discussions with patients and families about whether mechanical ventilation should be pursued.

Understanding how urine output is associated with mortality and the factors associated with low urine output, as demonstrated here, can aid providers in further risk stratifying patients with ARDS. Both ARDS and mechanical ventilation itself are well-recognized risk factors for development of AKI (15), in addition to acidosis, which leads to development and worsening of AKI (16). But presence of renal injury prior to onset of ARDS is a clinically significant mortality risk factor, a hypothesis further supported by this study. The interplay of acidosis, progressive worsening of renal function, severity of ARDS, and mortality further supports the idea that ARDS is a multiple organ disease, and an inflammatory pathway may explain mortality in these patients beyond respiratory failure itself (1–3, 11, 12, 15). In particular, our study recognized acidosis as a risk factor for mortality in ARDS, similar to prior investigations (7, 8).

Our study has several advantages. First, as stated earlier, we include a large percentage of Black patients with a high baseline prevalence of CKD. Additionally, our large cohort of heterogeneous ARDS triggers increases the applicability of the study. Last, the hand abstracted nature of the data minimizes the risk of clinically irrelevant or nonsensical values.

We do acknowledge several components that limit the generalizability of our study. First, the retrospective nature of our review is, as all retrospective studies are, prone to selection and detection bias, misclassification bias, and variability in both patient inclusion and medical care. Additionally, patients were single-center, possibly lending performance bias. I/O data in hospitalized patients is dependent on healthcare providers input into the EHR and prone to documentation error. Last, data on the use of diuretics was not collected due to the significant variation in practice patterns regarding routine use of diuretics in patients with AKI in the setting of ARDS. At our institution, use of diuretics is not commonplace and so the utility of such data was in question. The question regarding use of diuretic therapy in patients with AKI in the setting of ARDS would best be answered in future investigations.

CONCLUSIONS

In this retrospective cohort review of patients admitted to the ICU with all-cause ARDS, oliguria on the day of intubation was independently associated with increased mortality. A cutoff of urine output less than 0.7 mL/kg/hr predicted 80% of inpatient deaths. Such findings further advance the understanding of ARDS as a systemic multiple organ disease, with extrapulmonary organ failure contributing to the burden of morbidity and mortality. Additionally, our findings can be used to inform prognostication discussions with patients and their families before intubation, empowering those we care for to make goals of care decisions that are congruent with their values and anticipated outcomes.

ACKNOWLEDGMENTS

We would like to thank the medical assistants, nurses, respiratory therapists, physicians, and ancillary staff of the ICU of Henry Ford Hospital for their assistance in patient care. We would also like to thank Dr. Eric Scher, MD, as well as Dr. John D Buckley, MD, for their continued support of clinical and educational initiatives through the Department of Internal Medicine and Division of Pulmonary & Critical Care Medicine.

1 Department of Internal Medicine, Henry Ford Hospital, Detroit, MI.

2 Department of Pulmonary and Critical Care Medicine, University of Arizona, Tucson, AZ.

3 Department of Pulmonary and Critical Care Medicine, Henry Ford Hospital, Detroit, MI.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Dr. Ouellette receives grant support for research from a Patient Centered Outcome Research Institute grant (U.S. Federal Government) for research concerning oral agents to prevent chronic obstructive pulmonary disease (COPD) exacerbations; he also receives grant support from Sanofi Pharmaceutical for research involving a novel biologic agent to treat patients with COPD and eosinophilia. All funds go to the institution, and this investigator does not receive salary support from this project. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: imursky1@hfhs.org

REFERENCES

1. Wang CY, Calfee CS, Paul DW, et al: One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. *Intensive Care Med* 2014; 40:388–396
2. 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

3. Liu KD, Glidden DV, Eisner MD, et al; National Heart, Lung, and Blood Institute ARDS Network Clinical Trials Group: Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. *Crit Care Med* 2007; 35:2755–2761
4. Bagshaw SM: Short- and long-term survival after acute kidney injury. *Nephrol Dial Transplant* 2008; 23:2126–2128
5. Ranieri VM, Giunta F, Suter PM, et al: Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. *JAMA* 2000; 284:43–44
6. Bagshaw SM, Laupland KB, Doig CJ, et al: Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: A population-based study. *Crit Care* 2005; 9:R700–R709
7. Shen Y, Cai G, Chen S, et al: Fluid intake-related association between urine output and mortality in acute respiratory distress syndrome. *Respir Res* 2020; 21:24
8. Panitchote A, Mehkri O, Hastings A, et al: Factors associated with acute kidney injury in acute respiratory distress syndrome. *Ann Intensive Care* 2019; 9:74
9. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533
10. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2:1–138
11. McNicholas BA, Rezoagli E, Pham T, et al; ESICM Trials Group and the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) Investigators: Impact of early acute kidney injury on management and outcome in patients with acute respiratory distress syndrome: A secondary analysis of a multicenter observational study. *Crit Care Med* 2019; 47:1216–1225
12. Roch A, Guervilly C, Papazian L: Fluid management in acute lung injury and ARDS. *Ann Intensive Care* 2011; 1:16
13. Jia X, Malhotra A, Saeed M, et al: Risk factors for ARDS in patients receiving mechanical ventilation for > 48h. *Chest* 2008; 133:853–861
14. van Mourik N, Metske HA, Hofstra JJ, et al: Cumulative fluid balance predicts mortality and increases time on mechanical ventilation in ARDS patients: An observational cohort study. *PLoS One* 2019; 14:e0224563
15. Visconti L, Santoro D, Cernaro V, et al: Kidney-lung connections in acute and chronic diseases: Current perspectives. *J Nephrol* 2016; 29:341–348
16. Hu J, Wang Y, Geng X, et al: Metabolic acidosis as a risk factor for the development of acute kidney injury and hospital mortality. *Exp Ther Med* 2017; 13:2362–2374