Relation of Ischemic Heart Disease to Outcomes in Patients With Acute Respiratory Distress Syndrome

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Patients with ischemic heart disease (IHD) are often excluded from acute respiratory distress syndrome (ARDS) clinical trials. As a result, little is known about the impact of IHD in this population. We sought to assess the association between IHD and clinical outcomes in patients with ARDS. Participants from 4 ARDS randomized controlled trials with shared study criteria, definitions, and end points were included. Using multivariable logistic regression, we assessed for the association between IHD and a primary outcome of 60-day mortality. Secondary outcomes included 90-day mortality, 28-day ventilator-free days, and 28-day organ failure. Among 1,909 patients, 102 had a history of IHD (5.4%). Patients with IHD were more likely to be older and male ($p < 0.05$). Noncardiac co-morbidities, severity of illness, and other markers of ARDS severity were not statistically different (all, $p > 0.05$). Patients with IHD had a higher 60-day (39.2% vs 23.3%, $p < 0.001$) and 90-day (40.2% vs 24.0%, $p < 0.001$) mortality, and experienced more frequent renal (45.1% vs 32.0%, $p = 0.006$) and hepatic (35.3% vs 25.2%, $p = 0.023$) failure. After multivariable adjustment, 60-day (odds ratio [OR] 1.76; 95% confidence interval [CI]: 1.07 to 2.89, $p = 0.025$) and 90-day (OR 1.74; 95% CI: 1.06 to 2.85, $p = 0.028$) mortality remained higher. IHD was associated with 10% fewer ventilator-free days (incidence rate ratio 0.90; 95% CI: 0.85 to 0.96, $p = 0.001$). In conclusion, co-morbid IHD was associated with higher mortality and fewer ventilator-free days in patients with ARDS. Future studies are needed to identify predictors of mortality and improve treatment paradigms in this critically ill subgroup of patients. **(Am J Cardiol 2022;176:24−29)**

Introduction

Respiratory failure occurs in over 1/3 of admissions to the modern cardiac intensive care unit (CICU) and is associated with substantial morbidity and mortality.[1−5] Acute respiratory distress syndrome (ARDS) represents a particularly severe form of respiratory failure[6] and can complicate common CICU diagnoses, such as cardiogenic shock and cardiac arrest.[7,8] Additionally, due to troponin elevations and the presence of ventricular dysfunction,[9] cardiologist are often asked to consult patients with ARDS. Unfortunately, patients with cardiovascular disease are often excluded or poorly represented in ARDS clinical trials,[10] leaving little guidance for cardiac intensivists and cardiac consultants caring for these patients. Given these gaps in knowledge and the unique effects of positive pressure ventilation on these patients,[11] there is a critical need to better define clinical outcomes to improve treatment paradigms in patients with cardiovascular disease and ARDS. Therefore, we examined the association between ischemic heart disease (IHD) and 60-day mortality in a multicenter, pooled analysis of randomized controlled trials of patients with ARDS.

Methods

We included patient-level data from 4 National Heart, Lung and Blood (NHLBI)-sponsored ARDS Network clinical trials—ALTA, EDEN, OMEGA, and SAILS.[12−15] These trials were included because of their availability from NHLBI's Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), inclusion of variables specific to cardiovascular disease, and shared outcomes. Inclusion criteria among all 4 trials had the same definition of ARDS, including bilateral pulmonary infiltrates, partial pressure of oxygen (P_AO_2) to fraction of inspired oxygen (F_IO_2) <300 mm Hg, and without evidence of left atrial hypertension. SAILS randomized patients to rosuvastatin or placebo.[12] The ALTA trial randomized patients to albuterol or placebo every 4 hours for up to 10 days.[13] EDEN randomized patients to trophic or full enteral feeding.[14] The first 272 patients in EDEN were simultaneously included in the OMEGA trial and randomized to enteral supplementation of n-3 fatty acids, gamma-linolenic acid, and antioxidants compared with an isocaloric control.[15] Notable exclusion criteria included a history of myocardial infarction within 30 days in ALTA and 6 months in SAILS as well as New York Heart Association class 4 heart failure in all of the trials. Because all data was

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See page 28 for disclosure information.

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deidentified, this study was deemed exempt from the Yale University Institutional Review Board.

Demographics variables upon admission included age, gender, race and ethnicity, use of vasoactive medications within 24 hours of randomization, severity of illness represented by the baseline APACHE (Acute Physiologic Assessment and Chronic Health Evaluation) 3 score, alcohol use, and smoking history. Available co-morbidities included a history of previous myocardial infarction, hypertension, heart failure, peripheral vascular disease, stroke, diabetes, chronic dialysis, chronic pulmonary disease, malignancy, immune suppression within the past 6 months, hepatic disease (cirrhosis or hepatic failure), dementia, AIDS, and peptic ulcer disease. Baseline vital signs included systolic and diastolic blood pressure, mean arterial pressure, heart rate, weight, height, body mass index, temperature, arterial saturation, Glasgow coma scale, and central venous pressure. Initial ventilator settings and measures included respiratory rate, FiO_2, PaO_2/FiO_2 (P/F) ratio, tidal volume, positive end-expiratory pressure (PEEP), plateau pressure, peak inspiratory pressure, and mean airway pressure.

Our exposure of interest was co-morbid IHD, defined as a previous history of myocardial infarction. The primary outcome for this study was 60-day mortality. Secondary outcomes included 90-day mortality, 28-day ventilator-free days, and organ failure at 28 days, which included cardiovascular, renal, coagulation, hepatic, and combined organ failure. All 4 trials included the same variable and outcome definitions.[16] Cardiovascular failure was defined as a systolic blood pressure ≤90 mm Hg or requirement of a vasopressor. Renal failure was defined as a creatinine ≥2 mg/dL. Hepatic failure was defined as a serum bilirubin ≥2 mg/dL. Coagulation abnormality was defined as a platelet count ≤80,000/ml. Ventilator-free days were defined as the number of days alive without ventilatory support up to Day 28.

Continuous variables were described as means and standard deviation and categorical variables were described as frequencies and percentage. The *t* test was used to compare continuous variables and chi-square test for categoric variables across categories of patients with and without IHD. Using multivariable logistic regression, we assessed the association between IHD and 60-day mortality. We included, as covariates, purposefully selected variables known to be associated with mortality in patients with ARDS, including age, APACHE 3, P/F ratio, mean airway pressure, malignancy, chronic lung disease, hepatic failure, and heart failure.[10,17–20] Secondary outcomes, including 90-day mortality and 28-day organ failure, were assessed using multivariable logistic regression with the same covariates as the primary outcome. Kaplan-Meier survival curves were constructed for patients with and without IHD and compared using log-rank tests. To assess for differences in 28-day ventilator-free days, we used adjusted Poisson regression, which was exponentiated into incidence rate ratios for interpretation.

Additionally, we performed sensitivity analyses to confirm our findings in specific populations. Given that age is an important risk factor for mortality in patients with ARDS, and patients with cardiovascular disease are more likely to be older, we compared outcomes for only patients ≥50 years of age (representing 87% of patients with IHD), excluding age as a covariate. Second, we assessed for the association between 60-day mortality and IHD in patients with moderate to severe ARDS (P/F ratio ≤200 mm Hg), excluding P/F ratio as a covariate. Third, we assessed for the association between 60-day mortality and IHD in patients with an infectious etiology as the inciting event of their ARDS. Fourth, we assessed for the association between heart failure and 60-day mortality. Finally, we also tested for an interaction between IHD and treatment allocation (placebo vs intervention) with 60-day mortality. All analyses were performed on STATA 16.0 (Stata Corp, College Station, Texas) with statistical significance considered at a 2-tailed $p < 0.05$.

Results

Among 1,909 patients with ARDS, 5.4% (n = 102) had a history of IHD and 6.2% (n = 119) had heart failure. Baseline demographics and characteristics stratified by presence of IHD are shown in Table 1. Patients with IHD were substantially older and more commonly men (both, $p < 0.01$). Patients with and without IHD were similar with respect to race, body mass index, and smoking history (all, $p > 0.05$). Markers of acuity, including initial APACHE 3 score and P/F ratio, were not significantly different between patients with and without IHD (both, $p > 0.05$). Patients with a history of IHD were more likely to have common cardiovascular co-morbidities, including diabetes, heart failure, peripheral vascular disease, and stroke (all, $p < 0.05$). However, the proportion of patients with noncardiac co-morbidities, including chronic dialysis, hepatic disease, chronic lung disease, and malignancy was not significantly different between those with and without IHD (all, $p > 0.05$).

Patients with IHD had lower initial heart rates and diastolic blood pressures than those without IHD (both, $p < 0.05$), whereas other vital sign measurements did not significantly differ between the 2 groups. Initial ventilator settings and measures were similar between groups with the exception of a lower initial PEEP and mean airway pressure in those with IHD (both, $p < 0.05$, Table 2). Baseline creatinine, P_AO_2, partial pressure of carbon dioxide (P_ACO_2), and pH were not different between groups (all, $p > 0.05$). The remainder of laboratory values were not different between groups and are shown in Supplementary Table 1.

In unadjusted analyses, 60-day mortality was 39.2% and 23.4% in patients with and without a history of IHD, respectively ($p < 0.001$) (Table 3). At 90 days, mortality in those with IHD remained significantly higher (log rank, $p < 0.001$) (Figure 1). Patients with a history of IHD were more likely to have renal (45.1% vs 32.0%, $p = 0.006$) and hepatic failure (35.3% vs 25.2%, $p = 0.023$) by 28 days. Cardiovascular failure, coagulation abnormality, and total organ failure by 28 days were not different between groups (all, $p > 0.05$). At 28 days, patients with IHD had fewer ventilator-free days than patients without IHD (12.8 vs 15.1 days, $p = 0.036$).

After multivariable adjustment, both the 60-day (odds ratio [OR] 1.76; 95% confidence interval [CI]: 1.07 to 2.89, p=0.025) and 90-day (OR 1.74; 95% CI: 1.06 to 2.85, p=0.028) mortality remained higher in patients with IHD

Table 1
Baseline recipient characteristics stratified by ischemic heart disease

Variable	Ischemic Heart Disease		p Value
	No (n=1,807)	Yes (n=102)	
Age (years)	52.1 (16.0)	66.7 (13.7)	<0.001
Men	899 (49.8%)	67 (65.7%)	0.002
Black	286 (15.6%)	10 (9.8%)	0.10
White	1,386 (76.7%)	88 (86.3%)	0.03
Body mass index (kg/m^2)	30.2 (8.8)	29.5 (7.2)	0.48
Smoker*	941 (57.6%)	61 (66.3%)	0.10
Intravenous vasopressor or inotrope at baseline†	924 (51.2%)	62 (60.8%)	0.06
Diabetes mellitus	443 (24.5%)	43 (42.2%)	<0.001
Chronic dialysis	51 (2.8%)	4 (3.9%)	0.52
Malignancy	131 (7.2%)	7 (6.9%)	0.88
Hepatic disease	98 (5.4%)	3 (2.9%)	0.28
Heart failure	89 (4.9%)	30 (29.4%)	<0.001
Peripheral vascular disease	71 (3.9%)	14 (13.7%)	<0.001
Stroke	49 (2.7%)	9 (8.8%)	<0.001
Dementia	55 (3.0%)	8 (7.8%)	0.008
Chronic pulmonary disease	240 (13.3%)	20 (19.6%)	0.07
Peptic ulcer disease	94 (5.2%)	9 (8.8%)	0.12
Primary lung injury			0.14
Aspiration	168 (9.3%)	17 (16.7%)	
Multiple transfusions	24 (1.3%)	1 (1.0%)	
Pneumonia	1,149 (63.9%)	58 (56.9%)	
Sepsis	319 (17.7%)	19 (18.6%)	
Trauma	59 (3.3%)	5 (4.9%)	
Other	79 (4.4%)	2 (2.0%)	
APACHE III	92.0±27.9	95.6±24.6	0.20
Heart rate (beats/min)	96.1±19.6	87.9±18.6	<0.001
Systolic blood pressure (mm Hg)	112.9±19.8	110.5±18.6	0.23
Diastolic blood pressure (mm Hg)	60.3±12.6	57.5±11.7	0.03
Mean arterial pressure (mm Hg)	76.9±13.8	74.3±12.3	0.06
Oxygen saturation (%)	95.8±3.5	96.4±3.2	0.09
Temperature (°C)	37.3±0.9	37.2±0.9	0.09
Central venous pressure (mm Hg)	11.7±5.0	11.2±4.9	0.35
Creatinine, mg/dl	1.64±1.5	1.7±1.2	0.55
PaO_2, mm Hg	93.2±37.4	90.7±34.4	0.52
$PaCO_2$, mm Hg	39.8±9.8	39.2±10.1	0.57
pH	7.36±0.09	7.36±0.07	0.43

APACHE III = Acute Physiologic Assessment and Chronic Health Evaluation.

* Ever smoker with greater than 100 cigarettes in lifetime.

† Within 24 hours preceding randomization.

Data are presented as mean (standard deviation) for continuous measures, and n (%) for categorical variables.

(Figure 2). Differences in total organ failure and organ failure stratified by organ system were no longer statistically significant (all, p >0.05). Co-morbid IHD was associated with an adjusted 10% (incidence rate ratio 0.90; 95% CI: 0.85 to 0.96, p = 0.001) fewer ventilator-free days by Day 28.

In a sensitivity analysis restricting patients to those ≥50 years of age, co-morbid IHD was associated with a higher 60-day mortality, which persisted after multivariable adjustment (OR 2.52; 95% CI: 1.50 to 4.25, p <0.001). Patients with moderate to severe ARDS (P/F ratio ≤200 mm Hg) and a history of IHD had a higher unadjusted (OR 2.12; 95% CI: 1.29 to 3.48, p = 0.003) but not adjusted (OR 1.63; 95% CI: 0.90 to 2.94, p = 0.11) 60-day mortality. For patients with an infectious inciting event for ARDS, co-morbid IHD was similarly associated with a higher unadjusted (44.2% vs 24.4%, p <0.001) and adjusted mortality (OR 2.13; 95% CI: 1.21 to 3.76, p = 0.009) than patients without IHD. Fourth, compared with patients with a history of heart failure, adjusted 60-day mortality was not statistically different for patients without heart failure (OR 1.24; 95% CI: 0.77 to 1.98, p = 0.38). Finally, there was no interaction between IHD and treatment allocation (patients randomized to treatment compared with placebo, interaction p = 0.37).

Table 2
Ventilator measures stratified by ischemic heart disease

Variable	Ischemic Heart Disease		p Value
	No (n=1,807)	Yes (n=102)	
F_IO_2	0.63±0.21	0.60±0.19	0.20
Respiratory rate (breaths/min)	25.4±7.2	24.0±7.0	0.06
Tidal volume/IBW (ml/kg)	6.8±1.4	6.7±1.1	0.59
Minute ventilation (L/min)	11.0±3.4	10.6±3.3	0.20
P/F ratio (mm Hg)	171.4±83.6	170.2±76.3	0.88
PEEP (cmH_2O)	9.4±4.0	8.4±3.2	0.01
Plateau pressure (cmH_2O)	23.7±6.1	22.7±5.2	0.15
Peak inspiratory pressure (cmH_2O)	28.2±8.8	27.4±8.4	0.38
Mean airway pressure (cmH_2O)	15.2±5.0	14.1±4.5	0.03

IBW = Ideal body weight; PEEP=Positive end-expiratory pressure; FiO2=Inspired fraction of oxygen.

Data are presented as mean (standard deviation) for continuous measures.

Discussion

In this pooled analysis from randomized controlled trials of patients with ARDS, we found that a history of IHD was associated with a higher 60- and 90-day mortality, which persisted after multivariable adjustment. Not unexpectedly, patients with IHD were more likely to be older and have other cardiovascular co-morbidities. However, known risk factors for poor outcomes in ARDS, including malignancy, chronic lung disease, and hepatic disease as well as markers

Table 3
Unadjusted clinical outcomes stratified by ischemic heart disease

Variable	Ischemic Heart Disease		p Value
	No (n=1,807)	Yes (n=102)	
60-d mortality	420 (23.3%)	40 (39.2%)	<0.001
90-d mortality	433 (24.0%)	41 (40.2%)	<0.001
Organ failure by day 28	807 (44.7%)	53 (52.0%)	0.15
Cardiovascular failure	534 (29.6%)	37 (36.3%)	0.15
Renal failure	578 (32.0%)	46 (45.1%)	0.006
Coagulation abnormality	438 (24.2%)	33 (32.4%)	0.06
Hepatic failure	455 (25.2%)	36 (35.3%)	0.02
Ventilator-free days by Day 28	15.1 (10.7)	12.8 (11.8)	0.04

Data are presented as mean (standard deviation) for continuous measures, and n (%) for categorical measures.

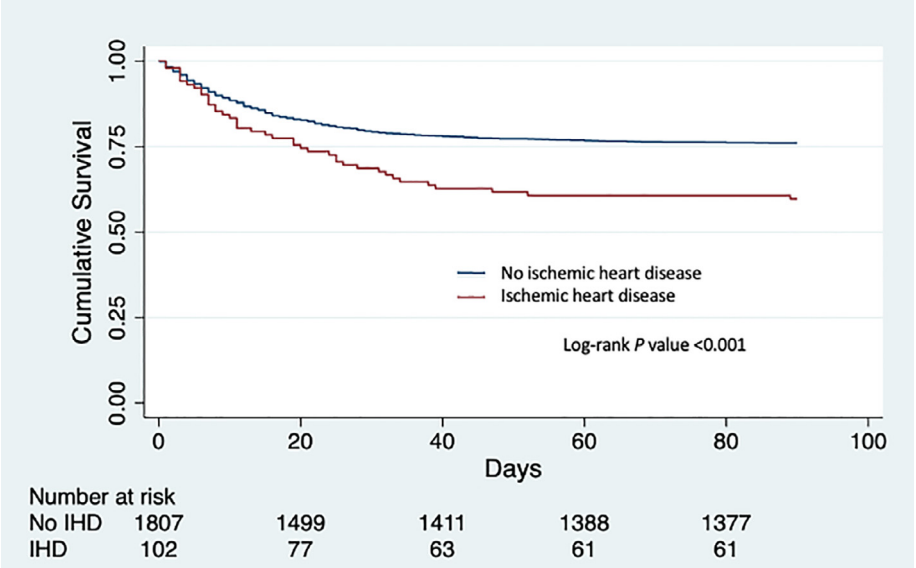

Figure 1. Kaplan-Meier survival curves stratified by ischemic heart disease. IHD = ischemic heart disease.

of acuity, such as severity of illness and P/F ratio, were not statistically different between groups. We also found that patients with IHD had a greater proportion of renal and hepatic failure and fewer ventilator-free days than those without IHD at 28 days. In summary, patients with IHD represent a particularly high-risk subgroup of patients with ARDS, which require dedicated study to determine optimal management.

To the best of our knowledge, this is the first study to assess the association between IHD or a history of coronary artery disease in patients with ARDS (outside of COVID-19). In contrast, several studies have investigated the impact of heart failure in patients with ARDS. In an analysis including approximately 5,000 patients with ARDS and 19 ICUs, Azoulay et al[10] found that chronic heart failure (etiology and ejection fraction not specified) was the second most common co-morbidity. Furthermore, patients with a history of heart failure had a significantly higher adjusted 28-day mortality.[10] In a study of nearly 30,000 patients with ARDS from 50 countries, concomitant heart failure was a primary reason for lack of clinician awareness of ARDS, leading to delays in evidence-based treatment.[6] After pooling ARDS Network clinical trials, we found the prevalence of heart failure was 6.2% (n = 119) and was not associated with an increased mortality after multivariable adjustment. These differences likely reflect the inclusion criteria of our clinical trial population and the likely exclusion of more severe heart failure.

Mechanistically, there are several potential reasons why a history of IHD may be associated with poorer outcomes

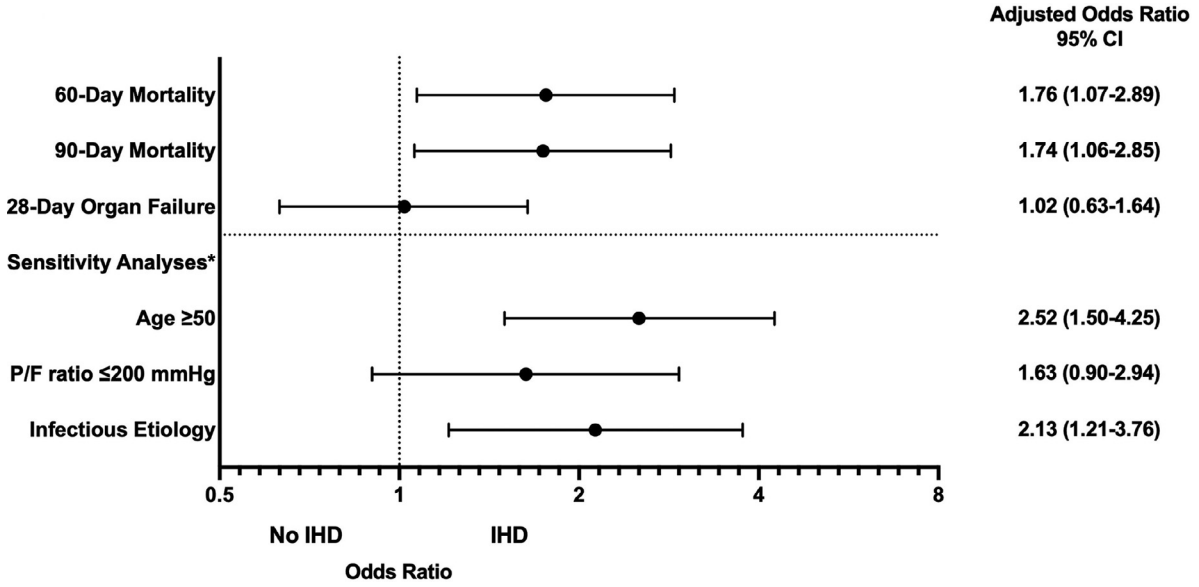

Figure 2. Forest plot of clinical outcomes stratified by ischemic heart disease *60-day mortality evaluated for each sensitivity analysis

in patients with ARDS. First, it is very possible that co-morbid IHD simply represents a higher-risk older cohort of patients with critical illness. Previous studies assessing myocardial injury in patients with ARDS have found that the association between myocardial injury and mortality disappears when adjusted for illness severity, suggesting a relation between myocardial injury and overall critical illness as opposed to being an independent predictor of outcomes.[9] In comparison, progression of troponin elevations from the first to third days was independently associated with mortality.[21] Although neither of these studies assessed the impact of co-morbid cardiovascular disease, it is clear that myocardial injury is common in patients with ARDS, at least progression of this injury may be prognostic, and this relation is likely more pronounced in patients with IHD.

Another potential etiology for worse outcomes may be that IHD can predispose patients to right ventricular dysfunction,[22] which is an important predictor of increased mortality in patients with ARDS.[23] Patients with IHD and right ventricular dysfunction may be a particularly good targets for further investigations, including inotropic support, unloading strategies (either pharmacologically or with extracorporeal membrane oxygenation), and echocardiography-guided management.[21] Third, in addition to many of the inciting causes (e.g., sepsis) as well as ventilator-induced lung injury,[24] ARDS itself is associated with systemic inflammation, circulating cytokines, and endothelial injury,[25−27] potentially predisposing at-risk patients, such as those with IHD, to develop myocardial injury and possibly infarction. Finally, weaning from mechanical ventilation can cause myocardial ischemia in patients with coronary artery disease.[28−30] Given the lack of patients with cardiovascular disease in ARDS clinical trials,[10] it is possible that patients with cardiovascular disease may be a unique subgroup requiring specialized management.

In addition to being retrospective in nature, our findings should be assessed in light of several limitations. First, although our study is unique in assessing the impact of IHD on patients with ARDS, the included clinical trials lack several cardiovascular-specific variables. For example, the trials did not collect important details, such as extent of coronary disease, coronary anatomy, and/or previous coronary interventions. Biomarkers of myocardial injury, such as troponins, were not available. Similarly, details for patients with heart failure, such as etiology and ejection fraction, were not collected. Second, important cardiovascular events of interest, such as ventricular failure or incident myocardial infarction were not available. Third, patients with a myocardial infarction within 30 days in ALTA and 6 months in SAILS were excluded, limiting the ability to assess our findings in patients with acute myocardial infarction. Finally, the cohorts with and without IHD had significant differences, such as age. However, our results persisted after including age as a covariate in our multivariable model, as well as in our sensitivity including only patients ≥50 years of age (representing approximately 87% of patients with IHD).

In conclusion, we found that a history of IHD in patients with ARDS was an independent predictor of increased mortality and fewer ventilator-free days. Our results persisted after multivariable adjustment and when confined to only patients ≥50 years of age. These findings highlight the need for further study to investigate whether IHD simply represents a predictor of increased mortality or if these patients represent a unique subgroup of ARDS requiring specific treatment paradigms. Finally, given the underrepresentation of patients with cardiovascular disease in ARDS clinical trials, it is imperative that future trials include more patients with cardiovascular disease to improve generalizability to an increasingly prevalent disease and aging population.

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Disclosures

The authors have no conflict of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.04.034.

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