Title

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Trends in Cholesterol and Lipoproteins are Associated with ARDS Incidence and Death Among Sepsis Patients

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Abstract

Objective: Compare changes in cholesterol and lipoprotein levels occurring in septic patients with and without acute respiratory distress syndrome (ARDS) and by survivorship.

Methods: We reanalyzed data from prospective sepsis studies. Cholesterol and lipoprotein levels were analyzed using univariate testing to detect changes between septic patients with or without ARDS, and amongst ARDS survivors compared to non-survivors at enrollment (first 24 hours of sepsis) and 48–72 hours later.

Results: 214 patients with sepsis were included of whom 48 had ARDS and 166 did not have ARDS. Cholesterol and lipoproteins among septic ARDS versus non-ARDS showed similar enrollment levels. However, 48–72 hours after enrollment, change in median total cholesterol (48/72 hr – enrollment) was significantly different between septic ARDS (−4, IQR −23.5, 6.5, N=35) and non-ARDS (0, −10.0, 17.5, p =0.04; N=106). When compared by ARDS survivorship, ARDS non-survivors (N=14) had lower median total cholesterol levels (75.5, IQR 68.4, 93.5) compared to ARDS survivors (113.0, IQR 84.0, 126.8, p = 0.022), and lower median enrollment LDL-C levels (27, IQR 19.5–34.5) compared to ARDS survivors (43, IQR 27–67, p = 0.013; N=33). Apolipoprotein A-I (apoA-I) levels were also significantly lower in ARDS non-survivors (N=14) (87.6, IAR 76.45–103.64) compared to ARDS survivors (130.0, IQR 73.25–165.47, p=0.047; N=33). At 48–72 hours, for ARDS non-survivors, median levels of HDL-C (9.0, IQR 4.3, 18.0; N=10), LDL-C (17.0, IQR 5.0, 29.0; N = 9), and total cholesterol (59.0, 45.3, 81.5; N = 10) were significantly lower compared to ARDS survivors' (N=25) levels of HDL-C (20.0, IQR 12.0–39.0, p =0.014), LDL-C (42.0, IQR 27.0–58.0, p = 0.019), and total cholesterol (105.0, IQR 91.0, 115.0, p = 0.003)..

Conclusions: Change in total cholesterol was different in septic ARDS vs non-ARDS. Total cholesterol, LDL-C and apoA-I levels were lower in ARDS non-survivors compared to survivors.

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Future studies of dysregulated cholesterol metabolism in septic ARDS patients are needed to understand biology and links to potential therapies.

Keywords

Acute respiratory distress syndrome; sepsis; cholesterol; lipoproteins

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening condition consisting of widespread inflammation, apoptosis, and necrosis of the pulmonary interstitium, alveoli, and microvasculature leading to cell injury, noncardiogenic pulmonary edema, decreased respiratory compliance, and hypoxemia.[1] It occurs frequently in critically ill patients, affecting 200,000 patients yearly in the United States with approximately 40% mortality.[2,3] Nearly 10% of all ICU admissions and approximately 25% of patients on mechanical ventilation experience ARDS,[2] a substantial proportion of which occurs shortly after ICU admission, with a median onset of 1–2 days in at-risk patients.[4–7]

Sepsis due to pneumonia (59%) and non-pulmonary infections (16%) is the most common cause of ARDS.[2] Sepsis is a dysregulated response to infection that leads to organ dysfunction, with an annual U.S. case incidence of 1.7 million, and is the costliest reason for hospital admission worldwide.[8–11] During sepsis, lipoproteins play a critical role.[12] Cholesterol has several important functions in sepsis including maintaining cell membrane integrity, cell membrane signaling, immunity, and vitamin D metabolism.[13] High density lipoprotein (HDL) and low density lipoprotein (LDL) have a variety of protective effects during sepsis, including their shared ability to transport bacterial endotoxins to the liver for elimination from the body.[12,14–20] HDL can prevent inflammatory cell migration and reduces monocyte CD11b expression inhibiting neutrophil migration and cytokine release, thereby limiting harmful inflammatory sequelae of sepsis.[21–23] It also prevents endothelial dysfunction by promoting proliferation of endothelial cells and preventing cell death and suppresses inflammatory mediators.[24–27] However, though levels have not been clearly defined, HDL-C and LDL-C drop to critically low levels in sepsis and are predictive of organ failure and death.[28,29] Further, HDL can become pro-inflammatory and dysfunctional (Dys-HDL), which correlates with organ failure severity.[29]Cholesterol and lipoproteins may also influence clinical management in septic ARDS (ARDS due to sepsis). Recent literature demonstrated that patients with low cholesterol and septic ARDS treated with rosuvastatin had a higher mortality, while patients with low cholesterol treated with simvastatin were more likely to survive.[30]

Lung function is critically dependent on cholesterol and lipoproteins.[31] Type 2 pneumocytes produce pulmonary surfactant and also contribute to systemic phospholipid and cholesterol homeostasis by expressing ATP binding cassette transporter A1 (ABCA1),[31–33] which transfers phospholipids and cholesterol to apolipoprotein A-I (apoA-I, HDL's major lipoprotein).[34–36] Type 2 pneumocytes play a major role in systemic phospholipid and cholesterol homeostasis.[37,38]

To better understand the changes in cholesterol and lipoprotein metabolism that occur over time we compared enrollment and delayed (48–72 hr.) levels in septic patients with or without ARDS, and among septic ARDS survivors vs. non-survivors. Our objective was to

gain a better understanding of the cholesterol and lipid metabolism during septic ARDS and its associations with survival. We also sought to investigate associations between HDL's known antioxidant proteins (apoA-I & PON-1) with survival. We hypothesized that septic ARDS patients would have lower HDL-C, LDL-C, apoA-I, and PON-1 levels compared to sepsis patients without ARDS, and that ARDS non-survivors would have lower levels than survivors.

Methods

Design

We analyzed clinical data and cholesterol levels from prospective studies of sepsis patients enrolled from 2016 to 2022 from the emergency department (ED) at UF Health Jacksonville. Studies were approved by the University of Florida Institutional Review Board (IRB-01, approved through 01/06/2023) and registered with clinicaltrials.gov (NCT02934997; NCT04576819; NCT03405870). STROBE guidelines for observational studies were followed.[39]

Patient Selection and Enrollment

Patients were enrolled from the UF Health Jacksonville Emergency Department as in prior studies.[40] Patients were prospectively identified and approached for enrollment within 24 hours of sepsis recognition, seven days per week between the hours of 8 am and 10 pm. Patients from three observational studies and one ongoing clinical trial were included.[40,41] Inclusion criteria for observational studies were: (1) age greater than 18, (2) meeting Sepsis-3 criteria for sepsis or septic shock.[3] For the observational studies, exclusion criteria included: (1) significant traumatic brain injury, (2) refractory shock, (3) alternative or confounding diagnosis causing shock, (4) uncontrollable source of sepsis, (5) advanced directives limiting resuscitative efforts, (6) Child-Pugh Class B or C liver disease, (7) HIV/AIDS causing severe immunocompromise or AIDS with a CD4 count less than 200, (8) organ transplant recipient on immunosuppressive agents, (9) known pregnancy, (10) inability to obtain informed consent, (11) familial/genetic disorders of lipid metabolism, (12) received CPR, and (13) actively seizing. For the sepsis readmission observational study, those patients with a recent prior admission for sepsis or for whom follow-up was deemed difficult were excluded. Those patients in the LIPIDS clinical trials had somewhat stricter criteria, of note for inclusion criteria: (1) SOFA score greater than or equal to 4 and (2) total cholesterol less than or equal to 100 mg/dL or HDL+LDL less than or equal to 70 mg/dL; and of note had these additional exclusion criteria: (1) total bilirubin greater than 2 mg/dL, (2) serum albumin less than 1.5 mg/dL, (3) severe hyperlipidemia or primary blood coagulation disorder, (4) acute pancreatitis with hyperlipidemia or acute thromboembolic disease, (5) receiving IV lipid formulations, and (6) actively on or anticipating imminent need for ECMO.

Data Collection

Prospectively collected data included demographics, place of residence, source of infection, and comorbidities. Clinical and laboratory data were entered into a Research Electronic Data Capture (REDCap) database by trained research coordinators. Clinical variables

included triage and enrollment vital signs, SOFA score, timing of antibiotics, volume of intravenous fluids, vasopressor use and duration, and mechanical ventilation use and duration. In-hospital mortality, hospital length of stay (LOS), and ICU LOS were also documented.

Clinical Outcomes and Adjudication

The primary outcome was in-hospital mortality. Septic patients were grouped according to ARDS status. Berlin criteria were used to diagnose ARDS, which was required to be present within the first 24 hours of enrollment.[42] Group adjudication by at least two clinician investigators was performed for the sepsis and ARDS diagnoses, and *a priori* selected primary outcomes, primary and secondary sources of infection, culture positivity, and hospital disposition during sepsis adjudication meetings.[43] Discrepancies were resolved by the inclusion of a third clinician investigator. The social security death index was used to determine mortality for patients lost to follow up.

Blood Sampling

Blood was drawn at the time of enrollment and within 24 hours of sepsis recognition and prior to any clinical trial drug administration. Clinical laboratory testing included cholesterol levels, and sequential organ failure assessment (SOFA) score laboratory measures including platelets, creatinine, and total bilirubin levels. Serum total cholesterol, HDL-C, and triglyceride levels were directly measured from serum samples. LDL-C was calculated using the Friedewald formula.[34] PON-1 activity was measured and reported as in prior studies.[28] Quantikine™ ELISA kits (R&D Systems, Inc, Minneapolis, MN) were used to measure plasma apoA-I levels.

Data Analysis

Univariate Comparisons—Presenting vital signs, demographic information, clinical features, and cholesterol levels at enrollment and 48–72 hours after triage were analyzed for the cohort as well as across ARDS severity groups. Within the ARDS cohort, cholesterol levels by in-hospital mortality were also analyzed. We calculated medians and interquartile ranges for continuous variables and counts and proportions for categorical variables. For statistical comparisons of cholesterol levels among outcomes, we first ran the Shapiro-Wilkes test of normality for each variable. None were found to be normally distributed; therefore, we used the non-parametric Wilcoxon Rank Sum test to test for statistical differences between the ARDS and non-ARDS populations (Supplemental Table 3) as well as the mortality outcomes within the ARDS group (Table 2). In Supplemental Table 1 we display medians and interquartile ranges for the cholesterol levels across the ARDS severity types. Analysis and calculations were completed in R (version 4.1.2; Vienna, Austria) using statistical tests from the Stats package.

Results

The analysis includes 214 patients with sepsis, of whom 48 had septic ARDS. In general, demographic features were similar among septic ARDS versus non-ARDS patients. The median age for ARDS and non-ARDS septic patients was similar, ranging from 61–63

years of age. There was a near equal distribution of male to female patients, and Black to White patients, except for the most severe ARDS group who had a larger proportion of White patients. There was a slightly higher proportion of shock patients in the ARDS group than in the non-ARDS group. Septic ARDS patients had higher respiratory SOFA scores and a higher incidence of pneumonia than non-ARDS patients. Septic ARDS patients also had higher rates of mechanical ventilation (71%) compared to non-ARDS patients (21%), and ARDS non-survivors also had higher rates of mechanical ventilation (86%, N=12/14) compared to ARDS survivors (65%, N=22/34). In-hospital mortality was highest for severe ARDS patients (37%), compared to moderate (25%) and mild (22%) ARDS, and non-ARDS (7%). Demographics and clinical features are presented in Table 1.

Lipoprotein levels for septic patients with versus without ARDS were overall similar at enrollment within the first 24 hours (Supplemental Table 3). However, change in median total cholesterol (48/72 hr – enrollment) was significantly different between ARDS (−4, IQR −23.5, 6.5, N=35) and non-ARDS sepsis patients (0, −10.0, 17.5, p =0.04; N=106). At 48–72 hours after enrollment, only LDL-C levels were lower in ARDS patients (mild: 32.0, IQR 22.0–56.0; moderate: 52.0, IQR 20.8–58.0; severe: 29.0, IQR 12.0–40.5) compared to non-ARDS sepsis (48.0, IQR 28.0–58.0, p = 0.067). In a subset with available data on PON-1 (n=191) and apoA-1 (n=213) at enrollment, there were also no significant differences between ARDS and non-ARDS sepsis. For the subset of patients with ARDS only, cholesterol and lipoprotein levels were summarized by ARDS severity, and trends towards lower cholesterol and apoA-I levels in more severe ARDS patients (Supplemental Table 1).

When evaluating trends in enrollment levels of cholesterol and lipoproteins over time by ARDS survivorship, ARDS non-survivors (N=14) had significantly lower median total cholesterol levels (75.5, IQR 68.4, 93.5) compared to ARDS survivors (113.0, IQR 84.0, 126.8, p = 0.022). Similarly, enrollment LDL-C levels between ARDS non-survivors (27, IQR 19.5–34.5) and ARDS survivors (N=33) (43, IQR 27–62, p = 0.013) was also different. Median apoA-I levels were lower at enrollment in ARDS non-survivors (87.6, IQR 76.45 −103.64) compared to ARDS survivors (130, IQR 73.25–165.47, p = 0.047). At 48–72 hours, cholesterol levels were all significantly lower in non-survivors compared to ARDS survivors. For ARDS non-survivors, HDL-C (9.0, IQR 4.3–18), LDL-C (17, IQR 5–29), and total cholesterol (59, IQR 45.3–81.5) levels were all significantly lower compared to survivors' levels of HDL-C (20, IQR 12–39), LDL-C (42, IQR 27–58), and total cholesterol (105, IQR 91–115). Cholesterol levels by ARDS survivorship are presented in Table 2. Figure 1 displays trends in cholesterol levels over time in septic ARDS survivors vs. non-survivors. Finally, statin use was not found to be significantly different between the ARDS and non-ARDS cohorts (p = 0.387). However, there was a significant difference between ARDS patients (N =11/34, 32%) who survived compared to ARDS patients who died (N=11/14, 79%, p = 0.009). Pneumonia status with or without ARDS was also not found to be influential on cholesterol levels (Supplemental Table 2).

Discussion

In this study of 215 sepsis patients, including 48 with septic ARDS, we studied cholesterol and lipoprotein levels over time and compared values between sepsis with or without ARDS, and between septic ARDS survivors and non-survivors. We showed that in comparison to sepsis without ARDS, septic ARDS patients had similar initial cholesterol and lipoprotein levels. However, compared to sepsis without ARDS, septic ARDS patients demonstrated lower LDL-C levels 48–72 hours later. Among septic ARDS patients, non-survivors at enrollment had lower LDL-C and total cholesterol levels and lower apoA-I levels in the first 24 hours. Interestingly, 48–72 hours later, all cholesterol levels (HDL-C, LDL-C, total cholesterol) were significantly lower in non-survivors compared to survivors. Triglycerides were not significantly different across any of the comparisons.

This study is unique in that we compared cholesterol and lipoprotein levels in septic ARDS patients to the broader cohort of sepsis patients without ARDS. Overall, our finding that LDL-C was lower in septic ARDS patients compared to sepsis patients at 48–72 hours is a new finding that has not been previously reported in the literature. We also showed strong signals that LDL-C levels may represent an important pathobiological signal amongst septic ARDS as they were the most significantly different of all cholesterol and lipoprotein levels that we studied. Animal studies of septic ARDS have importantly shown that LDL may play a central role in pathobiology, in which LDL has been shown to become oxidized and turn to oxLDL, which binds LOX-1.[44] Within the lung, this leads to the expression of cellular adhesion molecules resulting in the increased attachment and migration of inflammatory cells and worsening pulmonary endothelial dysfunction due to increased production of vasoconstrictors, increased reactive oxygen species (ROS), and depletion of endothelial nitric oxide.[44] We have shown that pro-inflammatory and dysfunctional HDL (Dys-HDL) present in sepsis, leads to the generation of oxidized LDL, which may indicate a potential link between abnormally low HDL-C and LDL-C levels in septic ARDS non-survivors.[29,45]

Cholesterol metabolism in septic ARDS is less well studied than in sepsis. One study showed that ARDS patients had significant decreases in plasma cholesterol levels and discoidal HDL, which they interpreted as due to a reduction in plasma lecithin cholesterol acyltransferase (LCAT) activity.[46] Another study demonstrated that in a cohort of bacterial and viral sepsis ARDS patients, HDL-C levels were significantly lower in bacterial ARDS but not in viral ARDS patients, and inversely correlated with disease severity (APACHE II and SOFA score).[47] HDL-C level was also found to be an independent predictor of death in bacterial ARDS.[47] Yang et. al found significantly decreased levels of HDL-C, HDL-apolipoproteins, and paraoxonase-1 activity in septic ARDS patients without any significant HDL differences between mild, moderate, or severe ARDS patients.[48]

Clinicians and researchers have recently recognized that ARDS patients are quite heterogeneous. In one study of septic ARDS patients, Bos et al[38] studied leukocyte transcriptomics from 210 patients with the “reactive” phenotype of septic ARDS and noted upregulation of neutrophil activation genes compared to the “uninflamed” phenotype. These patients had significantly worse disease severity and organ failure. Within the “reactive” phenotype, several pathways involved in cholesterol metabolism were upregulated including

cholesterol biosynthesis suggesting that cholesterol metabolism may play an important role in this relatively inflammatory phenotype of ARDS and may help distinguish septic ARDS phenotypes.[49] In clinical trials, there has been interest in harnessing the anti-inflammatory effects of cholesterol lowering drugs (statins) to improve ARDS outcomes. Though statin ARDS trials were negative,[50,51] a post-hoc analysis showed that hyperinflammatory phenotype patients may have benefitted from statin therapy.[52]

Studying cholesterol and lipoprotein metabolism in septic ARDS may lead to new therapies via mimetic peptides, which mimic the function of certain lipoproteins. Sharifov and colleagues utilized a LPS-induced (lipopolysaccharide) rodent ARDS model and demonstrated decreased HDL, apoA-I, and reduced activity of paraoxonase-1 (PON1, an HDL-associated antioxidant protein). They administered an apoA-I mimetic peptide (L4-F), which mimics apoA-I's functions, and found that it significantly reduced mortality and lung and liver injury 1-hour post LPS administration.[53] ApoA-I mimetics show great potential as potential therapy in septic ARDS, however, the major challenge is selecting patients likely to respond. Immunomodulation by reducing omega-6 fatty acids and increasing omega-3 fatty acids may have benefit in ARDS improving physiologic and histologic parameters.[54–56] However, one major clinical trial showed no benefit to the administration of omega-3 fatty acids in ARDS patients.[54] One must consider seriously the possibility that the failure of prior clinical trials was due wholly or in-part to patient selection and heterogeneity.

Limitations

This study had several limitations. First, the sample of septic ARDS patients was rather small and unbalanced in comparison to the overall group of sepsis patients. However, despite the small sample size, we found several significant differences in cholesterol and lipoprotein levels amongst comparisons between sepsis patients with vs. without ARDS, and by ARDS survivorship. The small ARDS sample may have also limited our ability to detect differences in specific lipoproteins such as PON-1. In future studies, we will include a larger cohort of ARDS patients to allow for more definitive conclusions.

Conclusion

In this study of septic ARDS patients, we showed that LDL-C levels were significantly lower at 48–72 hours in septic patients with ARDS vs. those without ARDS. Total cholesterol, LDL-C, and apoA-I levels were also significantly lower in ARDS non-survivors at enrollment compared to survivors. All cholesterol levels were significantly lower in ARDS non-survivors compared to survivors 48–72 hours later.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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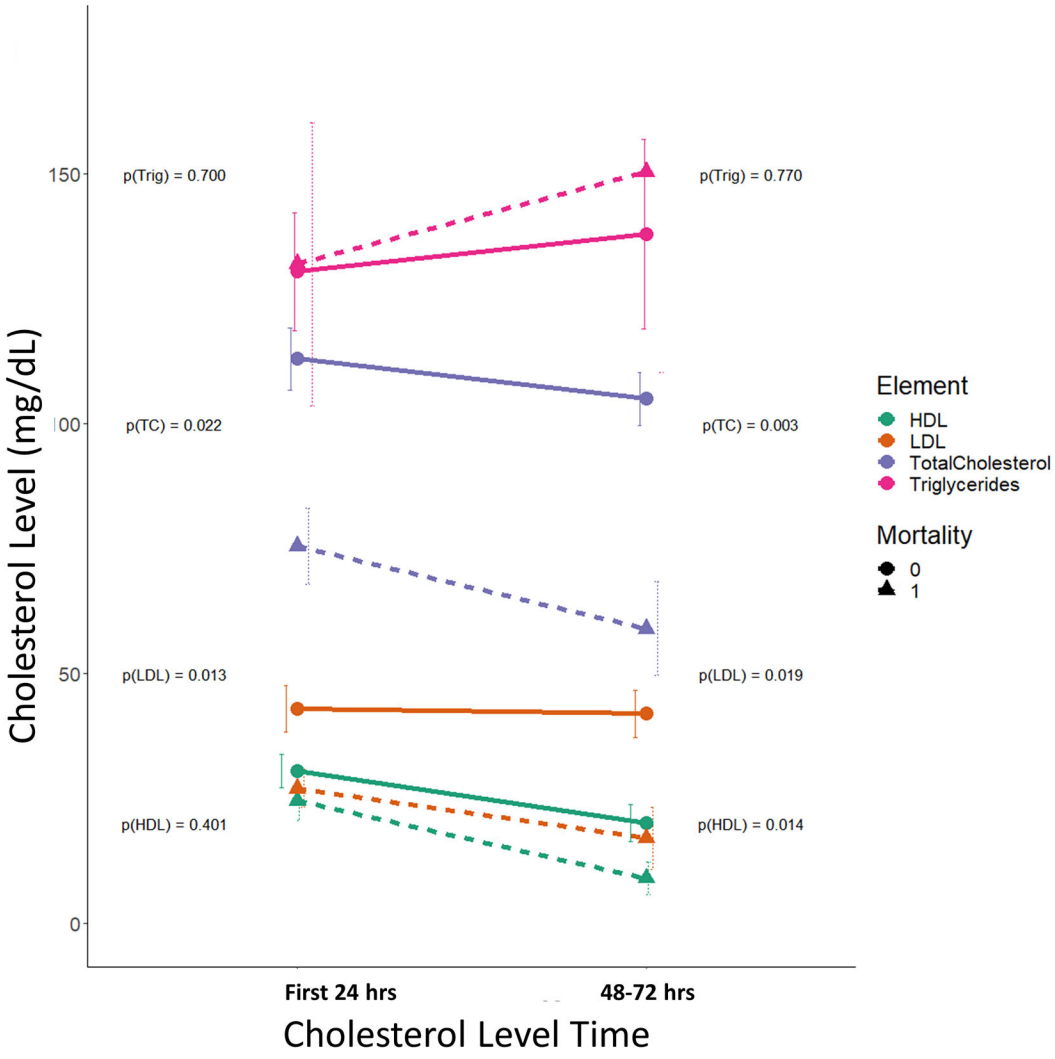

Figure 1. Cholesterol levels by ARDS mortality.

Cholesterol levels of high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), total cholesterol and triglycerides at enrollment (first 24 hours) and 48–72 hours later comparing sepsis ARDS survivors to non-survivors. P-values are for comparisons in cholesterol levels by time point. Enrollment total cholesterol and LDL-C levels were lower in ARDS non-survivors compared to survivors. At 48–72 hours, total cholesterol, LDL-C, and HDL-C levels were different lower in ARDS non-survivors vs. survivors.

Table 1.
Descriptive statistics by Sepsis and ARDS status.

Descriptive statistics of demographics, disease severity, emergency department (ED) disposition, and infectious source of sepsis patients with and without ARDS included in the analysis.

Variable		Total Cohort (n = 214)	Sepsis without ARDS (n = 166)	Sepsis with ARDS			
				All (n = 48)	Mild (n = 9)	Moderate (n = 20)	Severe (n = 19)
Age (median [IQR])		62.0 [56.0, 70.0]	62.0 [54.3, 70.0]	61.5 [56.8, 72.0]	61.0 [59.0, 66.0]	63.0 [56.8, 75.3]	61.0 [56.0, 72.0]
Gender – Male (n, %)		114 (53%)	89 (54%)	25 (52%)	5 (56%)	11 (55%)	9 (47%)
Race (n, %)	Black	107 (50%)	88 (53%)	19 (40%)	4 (44%)	11 (55%)	4 (21%)
	White	101 (47%)	72 (43%)	29 (60%)	5 (56%)	9 (45%)	15 (79%)
	Other	6 (3%)	6 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Septic Shock (n, %)		110 (51%)	81 (49%)	29 (60%)	6 (67%)	10 (50%)	13 (68%)
SOFA Score (median [IQR])		6.0 [4.0, 9.0]	5.5 [4.0, 9.0]	9.0 [6.8, 11.3]	7.0 [5.0, 9.0]	9.0 [6.0, 13.0]	10.0 [7.5, 11.0]
Respiratory SOFA Score (median [IQR])		1.0 [0.0, 3.0]	0.0 [0.0, 1.0]	3.0 [2.0, 3.3]	2.0 [2.0, 2.0]	3.0 [3.0, 3.0]	4.0 [3.0, 4.0]
Pneumonia (n, %)		72 (34%)	37 (22%)	35 (73%)	8 (89%)	13 (65%)	14 (74%)
Mechanical Ventilation (n, %)		69 (32%)	35 (21%)	34 (71%)	5 (56%)	16 (80%)	13 (68%)
Statin Use (n, %)		81 (38%)	59 (36%)	22 (46%)	2 (22%)	12 (60%)	8 (42%)
In Hospital Death (n, %)		25 (12%)	11 (7%)	14 (29%)	2 (22%)	5 (25%)	7 (37%)
ED Disposition (n, %)	Floor	41 (19%)	35 (21%)	6 (13%)	2 (22%)	1 (5%)	3 (16%)
	ICU	125 (58%)	91 (55%)	34 (71%)	6 (67%)	15 (75%)	13 (68%)
	OR	2 (1%)	1 (1%)	1 (2%)	0 (0%)	0 (0%)	1 (5%)
	Not Available	46 (21%)	39 (23%)	7 (15%)	1 (11%)	4 (20%)	2 (11%)
Infection Source	Urinary Tract	75 (35%)	67 (40%)	8 (17%)	1 (11%)	5 (25%)	2 (11%)
	Pulmonary	62 (29%)	31 (19%)	31 (65%)	7 (78%)	11 (55%)	13 (68%)
	Skin/Soft Tissue	26 (12%)	23 (14%)	3 (6%)	0 (0%)	1 (5%)	2 (11%)
	Intra-Abdominal	20 (9%)	17 (10%)	3 (6%)	0 (0%)	3 (15%)	0 (0%)
	Blood without Another Source	7 (3%)	7 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Endocarditis	7 (3%)	7 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Other	6 (3%)	4 (2%)	2 (4%)	1 (11%)	0 (0%)	1 (5%)
	Osteomyelitis	5 (2%)	5 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Surgical	4 (2%)	3 (2%)	1 (2%)	0 (0%)	0 (0%)	1 (5%)
	Necrotizing Soft Tissue	2 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 2.

Cholesterol and Lipoprotein Levels at Enrollment and 48–72 hours for ARDS Survivors and Non-survivors.

Cholesterol and lipoprotein Levels at enrollment and 48–72 hours later according to ARDS survival for septic ARDS patients. HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; PON-1, paraoxonase-1.

Lipid Panel Component	Time Point	Total Cohort (n = 48)	Survived (n = 34)	Died (n = 14)	Survived vs Died P[a]
HDL (median [IQR])	Enrollment	30.0 [17.6, 38.2]	30.5 [17.9, 39.0]	24.5 [18.0, 35.8]	0.401
	48–72 Hrs *	18.0 [10.0, 35.5] (n = 35)	20.0 [12.0, 39.0] (n = 25)	9.0 [4.3, 18.0] (n = 10)	**0.014**
	Change *	−5.0 [−9.0, −0.5] (n = 35)	−5.0 [−9.0, −1.0] (n = 25)	−3.5 [−18.5, −0.3] (n = 10)	1.0
LDL (median [IQR])	Enrollment	37.0 [24.5, 58.4] (n = 47)	43.0 [27.0, 67.0] (n = 33)	27.0 [19.5, 34.5] (n = 14)	**0.013**
	48–72 Hrs *	33.0 [17.0, 55.5] (n = 34)	42.0 [27.0, 58.0] (n = 25)	17.0 [5.0, 29.0] (n = 9)	**0.019**
	Change *	−2.0 [−14.0, 5.0] (n = 33)	−1.5 [−12.5, 5.3] (n = 24)	−3.0 [−18.0, −1.0] (n = 9)	0.466
Triglycerides (median [IQR])	Enrollment	130.5 [78.8, 154.0]	130.5 [82.1, 162.2]	132.0 [76.8, 143.8]	0.700
	48–72 Hrs *	144.0 [93.0, 211.5] (n = 35)	138.0 [92.0, 205.0] (n = 25)	150.5 [110.0, 252.0] (n = 10)	0.770
	Change *	15.0 [−33.5, 46.5] (n = 35)	18.0 [−37.0, 47.0] (n = 25)	12.5 [−31.3, 23.3] (n = 10)	0.971
Total Cholesterol (median [IQR])	Enrollment	92.5 [76.3, 122.3]	113.0 [84.0, 126.8]	75.5 [68.4, 93.5]	**0.022**
	48–72 Hrs *	96.0 [61.5, 112.0] (n = 35)	105.0 [91.0, 115.0] (n = 25)	59.0 [45.3, 81.5] (n = 10)	**0.003**
	Change *	−4.0 [−23.5, 6.5] (n = 35)	2.0 [−16.0, 8.0] (n = 25)	−15.5 [−24.3, −3.0] (n = 10)	0.130
ApoA-I (mg/dL)	Enrollment	94.14 [74.56, 151.42] (n = 47)	130.0 [73.25, 165.47] (n = 33)	87.6 [76.45, 103.64] (n = 14)	**0.047**
PON-1	Enrollment	82.5 [50.5, 116.6] (n = 43)	88.1 [49.2, 111.0] (n = 30)	74.1 [53.2, 123.4] (n = 13)	0.990

* Does not include clinical trial patients that received drug from the LIPIDS-P Trial.