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HDL Cholesterol Efflux is Impaired in Older Patients with Early Sepsis: A Subanalysis of a Prospective Pilot Study

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Abstract

Background—Proper functioning of high density lipoprotein (HDL) is necessary for protection against sepsis. However, previous work has demonstrated that HDL becomes oxidized and dysfunctional (Dys-HDL) during sepsis. Older (age > 65 years) patients are at particularly high risk of sepsis and poor outcomes from sepsis.

Study Objective—To compare functional properties of HDL (cholesterol efflux capacity and paraoxonase enzyme 1 (PON-1) activity) and Dys-HDL between older (age > 65 years) sepsis patients and older healthy volunteers.

Methods—This was a subanalysis of a prospective study in which patients with sepsis were prospectively enrolled from the emergency department within the first 24 hours. Serum and plasma samples were drawn from septic patients and age and sex-matched control subjects. Percent cholesterol efflux, HDL inflammatory index, and PON1 activity were measured. Data were analyzed using Students T- or Wilcoxon rank sum test.

Results—Ten sepsis and ten healthy controls were analyzed. Mean age of sepsis patients (80 ± 2 years (SD)) and control subjects (77 ± 2 years) was similar (p = 0.31). Mean systolic blood pressures were significantly different in sepsis patients (113 ± 8 mm Hg) compared to controls (133 ± 6 mm Hg) (p = 0.049). Median SOFA scores for sepsis patients were 5.5 (IQR 4–9). Mean percent cholesterol efflux was significantly reduced in sepsis (24.1 ± 1.2%) compared to controls (31.5 ± 1.0%) (p < 0.001). HDL inflammatory index was also significantly elevated in septic patients (1.63, IQR 1.3–2.34) compared with controls (0.62, IQR 0.56–0.67 (p < 0.001). However, PON1 activity was not significantly different between septic patients (70.3 ± 16.3 nmol/min/ml) and control subjects (88.8 ± 18.3 nmol/min/ml).

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Study Site: All patients were enrolled at UF Health Jacksonville, 655 West 8th Street, Jacksonville, FL 32209

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Conclusions—Cholesterol efflux capacity appears to be significantly impaired in sepsis patients who also exhibited a higher index of Dys-HDL. The findings suggest that HDL function may be impaired in older individuals with sepsis.

Keywords

sepsis; septic shock; organ dysfunction; HDL

Introduction

Sepsis involves dysregulated innate and adaptive immunity which results in inflammation and immunosuppression, and involves protein catabolic processes as well.[1–4] This combination of aberrancies in immune function are the result of cellular signaling processes triggered by pathogens (pathogen-associated molecular patterns) or tissue damage (damage-associated molecular patterns) that propagate the immunologic features of the disease, and contribute to the clinical phenotype of prolonged organ dysfunction and indolent death.[2]

Though many pathways are involved in the pathogenesis of sepsis, there is evidence that lipoproteins play an important role. Previous research has shown that high density lipoprotein (HDL-C) and low density lipoprotein cholesterol (LDL-C) are necessary for several key protective functions during sepsis, including bacterial toxin clearance, the prevention of excessive inflammatory cell migration, endothelial protection, and steroid synthesis.[5–9] The mechanisms for two of these defensive features of cholesterol are based on a process called reverse cholesterol transport, whereby HDL gathers cholesterol (including bound bacterial toxins) from peripheral tissues and delivers it to the liver for elimination from the body or to the adrenal glands for hormone and steroid synthesis. However, in the setting of inflammatory conditions such as sepsis, circulating lipids can become oxidized.[10] In general, oxidation of circulating lipoproteins results in the loss of their protective functions and contributes to ongoing inflammation, and can occur with both chronic or acute inflammatory diseases, such as sepsis.[11–16] One of the main anti-oxidant enzymes of HDL is paraoxonase-1 (PON-1), an HDL-associated esterase that protects lipoproteins, most likely by hydrolyzing lipid peroxides including oxidized cholesteryl esters and phospholipids.[17] When deficient in PON-1, mice exhibit an inability for HDL to protect LDL from oxidation.[18] Our group has recently demonstrated that oxidized and pro-inflammatory dysfunctional HDL (Dys-HDL) is present in patients with sepsis, and that the persistent presence of Dys-HDL is associated with poor clinical outcomes.[14]

The purpose of this study was to measure HDL function (cholesterol efflux and PON-1 activity) and Dys-HDL in older patients with sepsis in comparison to older healthy subjects. Older patients (age > 65) were used for this analysis because they are at increased risk of sepsis as well as poor outcomes after sepsis.[19,20] Cholesterol efflux is a measure of reverse cholesterol transport and PON-1 was included as previous studies of patients with sepsis have shown a direct relationship between HDL's antioxidant status and PON-1 activity.[21] We hypothesized that HDL from older septic patients would exhibit impaired cholesterol efflux, increased Dys-HDL, and reduced PON-1 activity in comparison to healthy control subjects.

Methods

Study Setting, Design and Patient Selection

This was a subgroup analysis of a larger study which prospectively enrolled adult patients (age ≥ 18 years) presenting to the University of Florida (UF) Health Jacksonville emergency department (ED) with sepsis or septic shock within 24 hours of presentation. The UF Health Jacksonville ED is a high acuity, academic, urban ED which treats approximately 95,000 patients per year. The research protocol was approved by the UF College of Medicine, Jacksonville Institutional Review Board (IRB).

Study inclusion criteria were: 1) infection with > 1 SIRS criteria, 2) serum lactate > 2 mmol/L, 3) sequential Sepsis-related Organ Failure Assessment (SOFA) score ≥ 4, and 4) primary diagnosis of sepsis on admission. Exclusion criteria were: 1) pregnancy, 2) lack of valid consent, 3) familial or genetic disorders of lipid metabolism, 4) active seizure, 5) cardiopulmonary resuscitation prior to enrollment. Informed consent was obtained from the patient or their legal representative per IRB requirements. For this sub-study, five male and five female older patients (age ≥ 65 years) were selected for testing as lipid profiles are known to very based on gender.

Samples were obtained from five age and sex matched male and female healthy older adult subjects for this comparative analysis. Control subject samples were obtained from another study evaluating indices of skeletal muscle mass and function in older, healthy adults. Participants in the study were community-dwelling men and women over the age of 70 years who were free of chronic comorbid conditions.[22]

Measurements and Interventions

Sepsis study patient data were prospectively collected and included demographic data and comorbidities, physiologic and treatment variables including lactate levels, SOFA scores upon enrollment and at 48 hours, triage and enrollment vital signs, timing of antibiotics, volume of intravenous fluids, medications, and critical care interventions. Additional collected data included familial disorders of lipid metabolism, statin use, admission disposition, hospital length of stay (LOS), and ICU LOS. At 48 hours, repeat clinical assessments were performed and data collected including vital signs, Glasgow Coma Scale scores, SOFA scores, and critical care interventions. Chart reviews after enrollment were performed to confirm sepsis diagnosis, culture results, ICU and hospital LOS, and outcomes.

Blood sampling for septic patients occurred at baseline and 48 hours after enrollment and included total cholesterol levels, HDL-C, LDL-C, triglycerides, laboratory tests for SOFA score calculation, PON-1 activity, cholesterol efflux and Dys-HDL testing. At both time points, serum and plasma samples were obtained and frozen at −80°C until further testing. The study protocol required blood to be drawn within four hours of planned collection times.

For healthy older control patients, blood samples were obtained prospectively and data on demographics, comorbidities, functional status, and vital signs were also collected as cited in previous work.[22]

Cholesterol efflux Assay—The cholesterol efflux assay assesses the ability of an individual's HDL to transport cholesterol out of macrophages and bind it for transport. This process is a key first step in reverse cholesterol transport and cholesterol homeostasis. To measure this, mouse macrophage RAW264.7 cells were cultured on 24-well tissue culture plates and grown in DMEM media with 10% FBS overnight. The cells were washed and loaded with ^{3}H-cholesterol (0.33 μCi/ml) and acetylated LDL (50 μg/ml) in DMEM media supplemented with 50 mM glucose, 2 mM glutamine and 0.2% fatty acid free bovine serum albumin overnight to allow cell cholesterol pools to equilibrate. Cells were washed twice and incubated overnight with DGGB (DMEM (Dulbeco's Minimal Essential Medium) with glucose, glutamine, and BSA (bovine serum albumin)) + 0.1 mM Br-cAMP (Sigma-Aldrich (St. Louis, MO). Cholesterol efflux from macrophages by HDL was determined by incubating the test HDL at 25 μg/ml, (isolated from plasma by dextran bead method), in DGGB with labelled cells for 4 h at 37°C.[10] Radioactivity in the supernatants and total cell extracts were measured and expressed as the percentage of total radioactive counts removed from the cells by HDL during the efflux period.[23]

Dysfunctional HDL testing—Dys-HDL was quantitated using a cell-free assay (CFA) and expressed as HDL Inflammatory Index (HII) as in previous studies.[14] Briefly, the cell free assay for Dys-HDL requires HDL isolation from blood samples using dextran sulphate precipitation and LDL prepared from a normal donor. After incubating experimental (patient HDL plus control LDL) and control subject samples (control LDL only) with dichlorofluorescein, the ability of sample HDL to protect LDL from oxidation was quantitated by the decline in fluorescence and expressed as a ratio of the fluorescence released, the HII. Values for intra-assay and inter-assay variability are 5.3 ± 1.7% and 7.1 ± 3.2%, respectively.[10]

Determination of Paraoxonase 1 Activity Assay—Paraoxonase 1 (PON-1) activity was quantified using paraoxon as the substrate and measuring the increase in absorbance at 405 nm due to the formation of 4-*p*-nitrophenol over a period of 12 minutes (at 20-second intervals). Paraoxon was purchased from Sigma-Aldrich (St. Louis, MO) and was further purified using chloroform extraction. One unit of PON-1 activity was defined as the formation of 1 nmole of 4-*p*-nitrophenol per minute per milliliter of sample used. Enzyme activity was measured with 40-fold–diluted plasma (final concentration) in a reaction mixture containing 4 mM paraoxon working solution, 500 mM glycine/10 mM $CaCl_2$ buffer at pH 10.5, and 155 mM NaCl/3 m*M* NaN_3 buffer at pH 8.2.[24]

Outcomes, Data Analysis, and Sample Size Justification

Descriptive statistics including means with standard deviations (SDs) and medians with interquartile ranges were reported for demographic characteristics, vital signs, and laboratory test results. For the comparison of cholesterol efflux and PON-1 assay data, Students t test was used as these data are normally distributed. Wilcoxon rank sum test was used for the comparison of HII data between groups as these data do not follow a normal distribution.

Since cholesterol efflux was the main outcome of interest it was used for the basis of the sample size calculation. Assuming a normal distribution of cholesterol efflux percentage based on previous work, and with an approximate standard deviation of 5, we calculated that a sample size of ten sepsis patients and ten control patients would be sufficient to detect a difference in cholesterol efflux of 7% with a power of 0.84 at a significance level of 0.05.

Results

Data from ten older sepsis patients and ten older healthy subjects were analyzed. Each group consisted of five males and five females. Mean age in years for sepsis patients was 77 ± 2 and mean age for control patients was 80 ± 2. Mean initial systolic blood pressures for patients with sepsis (113 ± 25 mm Hg) was lower than for control (133 ± 18 mm Hg) patients ($p = 0.049$). Mean arterial pressures showed a similar trend for sepsis patients (102 ± 18 mm Hg) compared with controls (114 ± 22 mm Hg) patients ($p = 0.17$) but did not reach statistical significance.

In the sepsis cohort, six patients had diabetes mellitus, one patient had end stage renal disease, two had cancer, and three were nursing home residents. Five of the patients were taking statins at the time of enrollment. The most common type of infection was urinary tract (six patients), followed by pneumonia (three patients), and one patient had endocarditis. Mean initial lactate values were 4.3 mmol/L and median initial SOFA scores were 5.5 (IQR 4–9). In general patients were critically ill, with 20% (2/10) initially receiving vasopressors, 20% (2/10) on mechanical ventilation, and 80% (8/10) initially admitted to the ICU. Discharge disposition included 40% (4/10) discharged to home or to a rehab facility, and 60% (6/10) discharged to hospice, a nursing home, or a long-term acute care facility. No patients died in-hospital, but there was a 10% (1/10) 28 day mortality. Sepsis patient characteristics can be found in Table 1.

For the primary outcome of interest, mean percent cholesterol efflux was significantly reduced in sepsis patients (24.1 ± 1.2%) compared to control subjects (31.5 ± 1.0%) ($p < 0.001$) (Figure 1). HDL inflammatory index was also significantly elevated in septic patients (1.63, IQR 1.3–2.34) compared with control subjects (0.62, IQR 0.56–0.67, $p < 0.001$) indicating an increased presence of Dys-HDL. For all patients, there was a significant inverse correlation between cholesterol efflux and HII ($\rho = -0.698$, $p < 0.001$) (Figure 2). Furthermore, there were no control patients with HII > 1, indicating that none of them had Dys-HDL present. In contrast, 90% (9/10) of septic patients had HII > 1, indicating that almost all of the septic patients had Dys-HDL present (Figure 3). PON-1 activity was not significantly different between septic patients (70.3 ± 16. nmol/min/ml plasma) and control subjects (88.8 ± 18.3 nmol/min/ml plasma) ($p = 0.46$) (Figure 4).

Discussion

In this study, we have demonstrated that blood HDL from older septic patients exhibits impaired cholesterol efflux and dysfunctional characteristics in comparison to healthy older subjects. PON-1 activity, however, was not significantly different between the two groups.

These data imply, that HDL from acutely septic patients is both pro-inflammatory and dysfunctional.

To our knowledge, this is the first study to clearly demonstrate that specific functions performed by HDL are impaired in a critically ill, older population of acutely septic patients. On the whole, this study supports our hypothesis that HDL becomes dysfunctional during sepsis, and that this dysfunction may lead not only to the inability of HDL to protect against sepsis, but also the propagation of inflammation and oxidative stress that may contribute to organ failure.

HDL may be vitally important in defense against sepsis. More specifically, cholesterol efflux is an important physiologic process which, when HDL functions properly, should be protective against sepsis. Its major contribution to the prevention of atherosclerosis by preventing a build-up of foam cells from peripheral macrophages has been well studied, largely due to drug development and the desire for preventive treatments for myocardial infarctions and stroke.[25–27] However, with regards to clinical and translational sepsis research, it has been largely ignored despite previous work demonstrating the central role of HDL in bacterial toxin clearance and steroid synthesis in response to stress.[5,6,8,9,28,29] There may be one exception, however, a multi-center, double-blinded phase II clinical trial of a phospholipid emulsion (GR270773, NCT00089986) studied in patients with gram-negative severe sepsis in 2009.[30] Though this study found no differences in mortality between placebo, low-dose, and high-dose experimental drug groups, a secondary analysis in patients with a serum albumin ≥ 1.5 g/dL, and either a cholesterol ≥ 1mM or HDL ≥ 0.5 mM demonstrated reduced mortality in these subgroups by 6.6% ($p < 0.025$) and 10.8% ($p < 0.005$), respectively.[31] This post-hoc analysis also interestingly demonstrated a strong negative interaction between the study drug and intravenous corticosteroids, thought to be due to the ability of bile acids to slow clearance of the drug and raise corticosteroid concentrations. Overall, however, this study may be an unappreciated proof of concept study for lipid-based therapies for sepsis and demonstrates specifically, that in a septic patients with adequate liver function and a sufficient quantity of circulating HDL and total cholesterol, augmenting the process of reverse cholesterol transport may improve outcomes.

Our study also demonstrated that nearly all of our septic older patients possessed Dys-HDL, in comparison to none of the healthy older controls. Healthy older individuals do not appear to have any intrinsic dysfunction of their HDL or any defect in their cholesterol efflux. These findings in general are in good consensus with our previous work which demonstrated that Dys-HDL is not only present in most septic patients, but that persistent elevation of Dys-HDL is significantly associated with poor outcomes from sepsis.[14] In addition, this knowledge emphasizes that HDL function may be more important than quantity. Cardiovascular studies have demonstrated that elevating HDL levels in patients does not protect against adverse cardiovascular events.[32] In a related manner, elevation of HDL levels in septic patients is unlikely to be beneficial as the structure of HDL is likely to become altered from the acute inflammatory state.[33] For this reason, future research must focus on providing drug therapies which augment the process of reverse cholesterol transport while providing an HDL mimetic or similar drug which can facilitate this process.[34]

This study has several limitations. Sample size is small, and large scale implications should be withheld until larger more robust work can be done to validate these results. The subjects in control group were healthier overall than the septic patients and lacked chronic comorbidities, which may have also contributed to control subjects having better overall HDL function compared with septic patients. Also, PON-1 activity may have differed between groups; however, given the small sample size, and the fact that the sample size calculation was based on cholesterol efflux, we may have failed to demonstrate a difference. PON-1 activity also may vary based on gene polymorphisms which we did not measure in this study due to the small sample size.[24]

Conclusion

In conclusion, data from this small study demonstrate that HDL from older septic patients appears to exhibit impaired cholesterol efflux capacity and is more highly oxidized relative to healthy older subjects. This study did not demonstrate a difference in PON-1 activity between groups. Future studies should evaluate HDL function in larger cohorts with sepsis and with varying outcomes to make additional conclusions about HDL function in sepsis.

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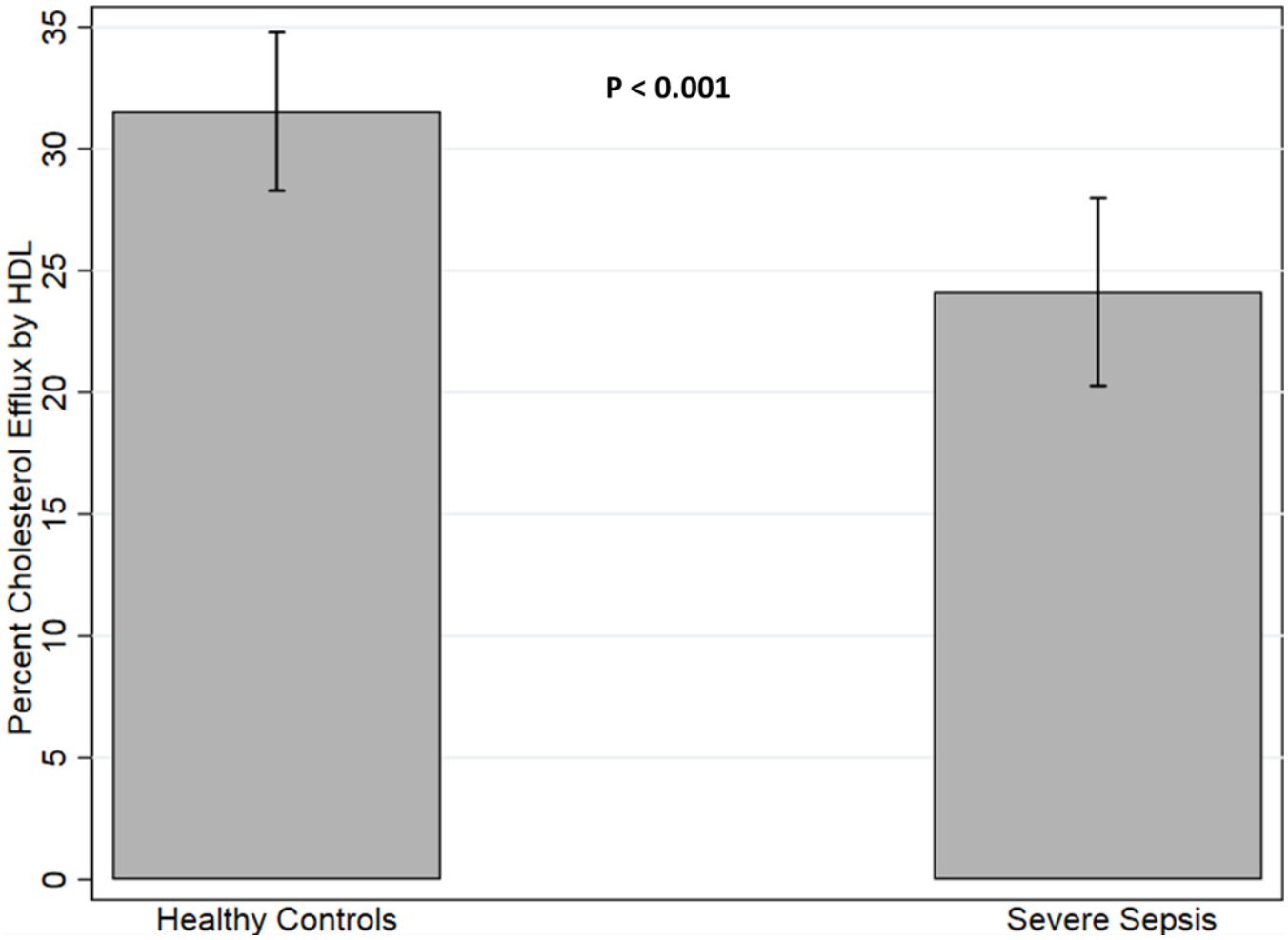
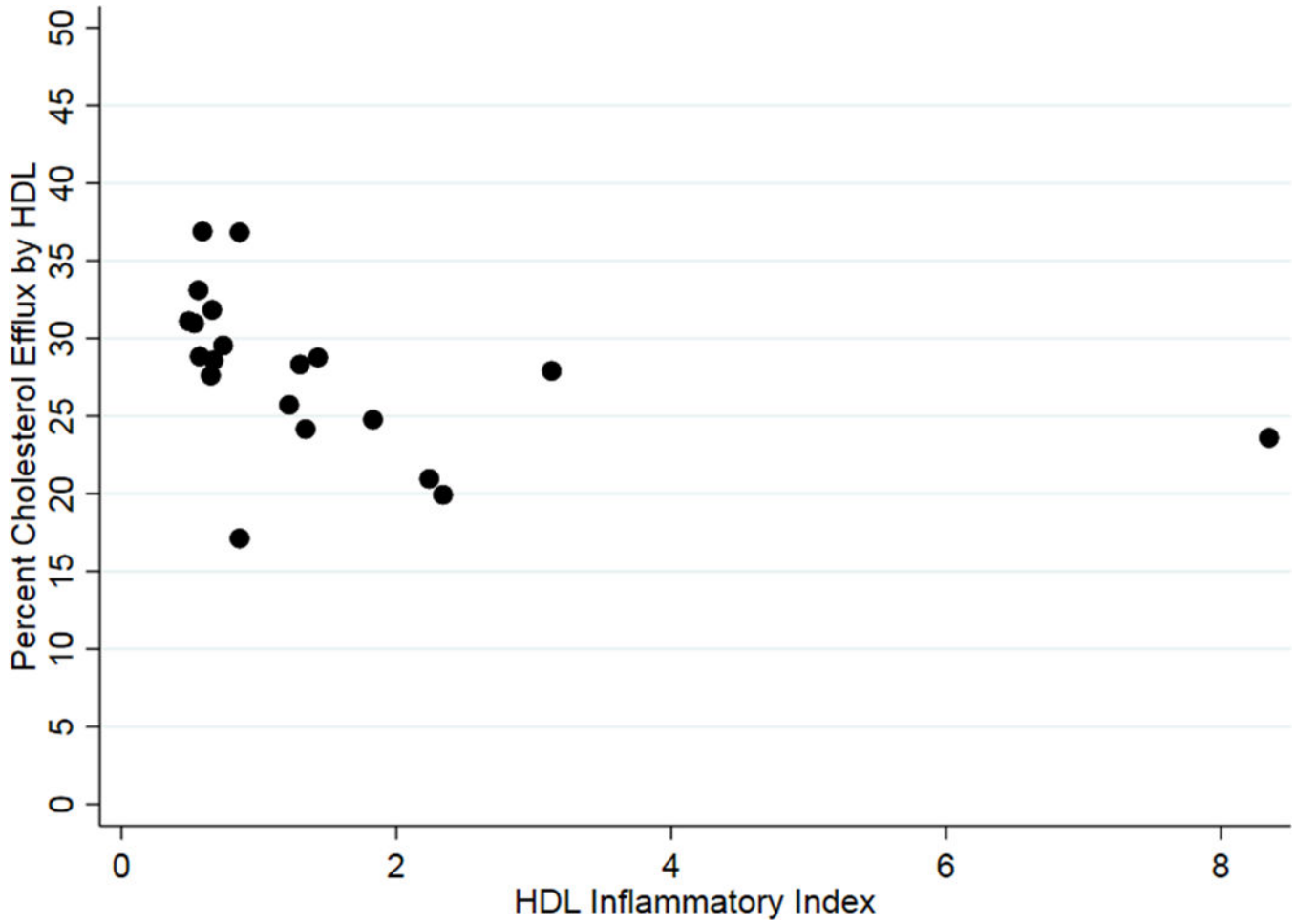


Figure 1.



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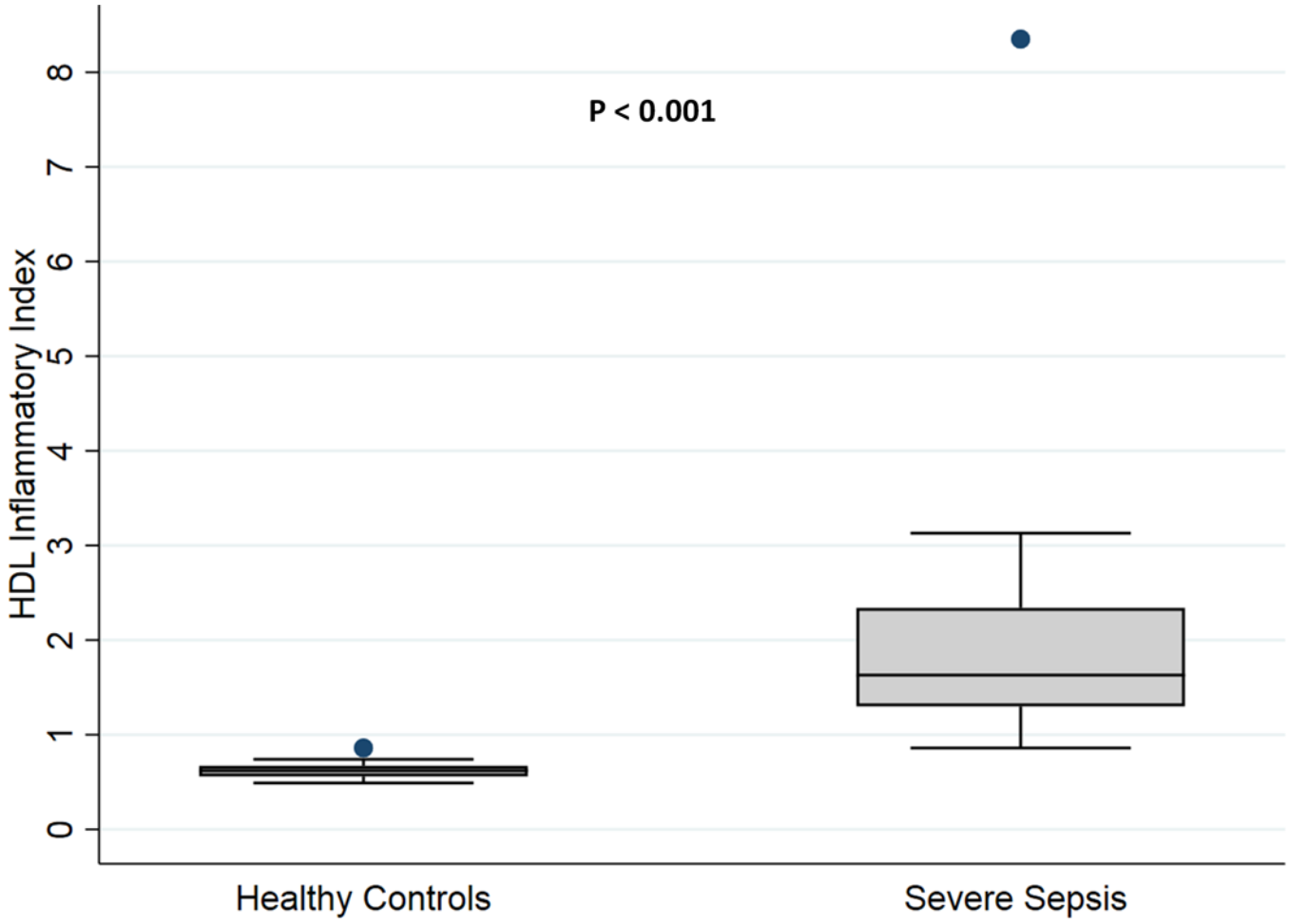

Figure 3.

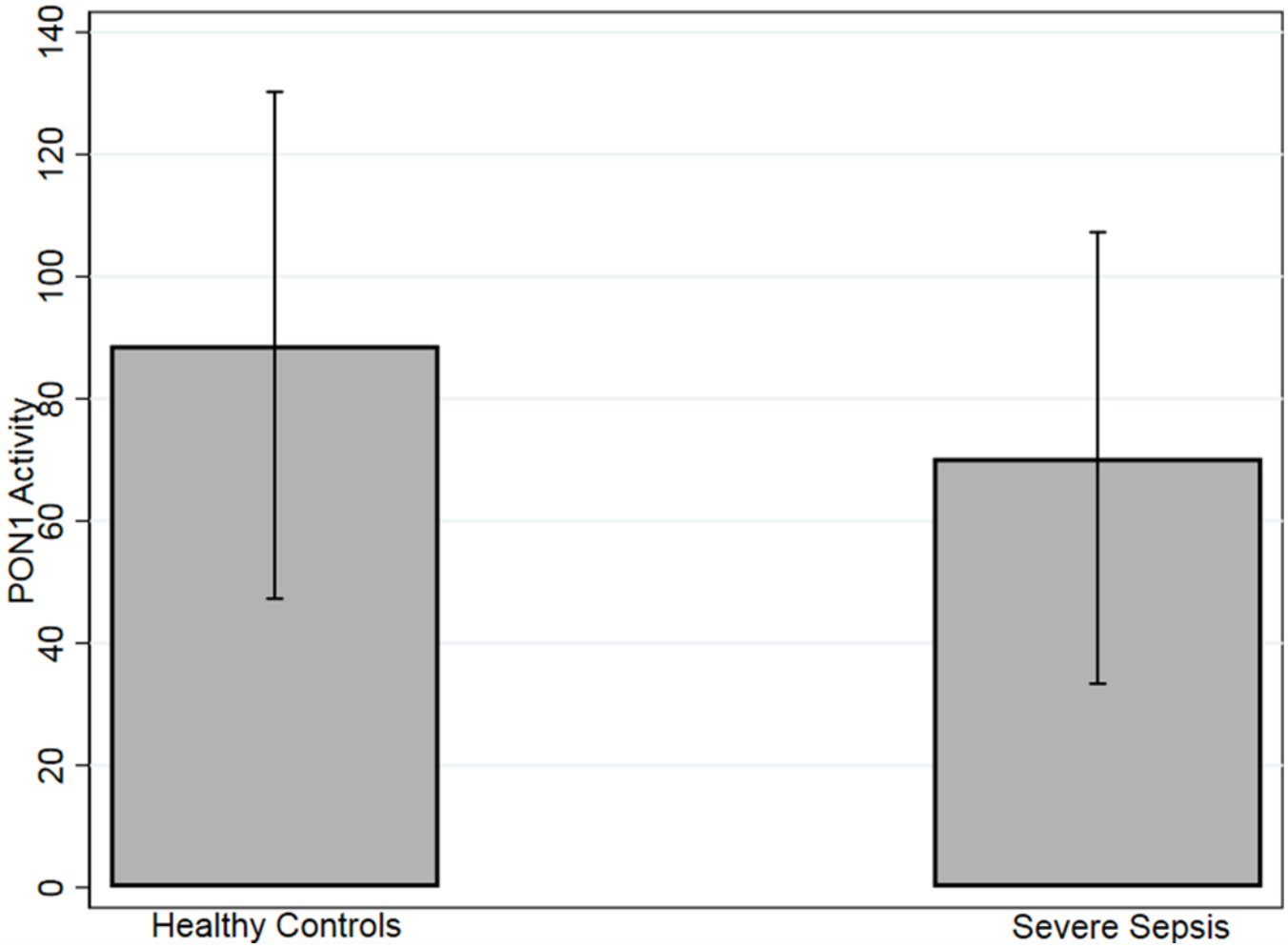

Figure 4.

Table 1

Clinical features, early management, outcomes and disposition of study patients with severe sepsis.

Features of Sepsis Patients, N = 10	
Source of Sepsis, % (N)	
Pulmonary	30% (3)
Urinary tract	60% (6)
Endocarditis	10% (1)
Early Clinical Features	
Enrollment systolic blood pressure, mm Hg, mean (SD)	113 (8)
Initial mean arterial pressure, mm Hg, mean (SD)	102 (6)
Initial heart rate, beats/min, mean (SD)	95 (20)
Initial temperature, °F, mean (SD)	100.1 (2.3)
Initial oxygen saturation, mm Hg, median (IQR)	97 (96–100)
Initial respiratory rate, breaths/min, median (IQR)	20 (18–26)
Initial lactate, mmol/L, mean (SD)	4.3 (1.4)
Repeat lactate, mmol/L, mean (SD)	3.9 (1.9)
Initial SOFA score, median (IQR)	5.5 (4–9)
Early Sepsis Management	
Intravenous fluids in the first 6 hours, mL, median (IQR)	3125 (2000–4000)
Intravenous fluids in the first 24 hours, mL, median (IQR)	4625 (4000–6000)
Time to antibiotic administration, minutes, mean (SD)	77 (28)
Mechanical ventilation use on enrollment, % (N)	20 (2)
Vasopressor use on enrollment, % (N)	20 (2)
Duration of vasopressor use, hours, median (IQR)	35 (28)
Outcomes and Disposition	
Initial ICU admission, % (N)	80 (8)
ICU LOS, days, median (IQR)	4 (1–6)
Hospital LOS, days, median (IQR)	7 (5–9)
Disposition at discharge – Home or Rehab facility	40 (4)
Disposition at discharge – NH, hospice, LTAC	60 (6)
28-day mortality, % (N)	10 (1)

SD = standard deviation, IQR = interquartile range, ICU = intensive care unit, LOS = length of stay, NH = nursing home, LTAC = long-term acute care facility.