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Shock Phenotypes in Hemophagocytic Lymphohistiocytosis: Distinct Outcomes Associated with Septic and Cardiogenic Shock

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ABSTRACT

Background:

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperin lammatory syndrome frequently complicated by circulatory collapse and multiorgan failure. Although septic shock (SS) is a recognized predictor of poor outcomes in HLH, the clinical significance of cardiogenic shock (CS) in this population remains poorly defined.

Methods:

Using the National Inpatient Sample (NIS) database (2016–2020), we identi ied 2,506 adult hospitalizations with a diagnosis of HLH and strati ied patients into three cohorts: no shock (NS; n = 2,015), SS (n = 481), and CS (n = 10). Primary outcomes included in-hospital mortality, cardiac arrest, acute kidney injury (AKI), dialysis initiation, acute respiratory failure (ARF), and mechanical circulatory support (MCS) utilization. Secondary outcomes included length of stay (LOS) and total hospitalization charges. Multivariable logistic regression models were adjusted for demographics and baseline comorbidities.

Results:

Patients with CS had a signi icantly greater burden of cardiovascular comorbidity, including heart failure, coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease (all $p < 0.001$ vs. NS). In-hospital mortality was highest in the CS cohort (70.0%), followed by SS (56.7%) and NS (14.1%) ($p < 0.001$). Both shock phenotypes were associated with increased rates of cardiac arrest, AKI, dialysis initiation, and ARF compared with NS. MCS utilization was markedly higher in CS than in SS (20.0% vs. 1.7%, $p < 0.001$). After multivariable adjustment, SS independently predicted mortality (adjusted odds ratio [aOR] 8.25; 95% con idence interval [CI] 6.49–10.48), AKI (aOR 7.45; 95% CI 5.80–9.57), dialysisinitiation (aOR 5.29; 95% CI 4.03–6.94), ARF (aOR 5.87; 95% CI 4.70–7.34), and cardiac arrest (aOR 4.02; 95% CI 2.65–6.12) (all $p \leq 0.001$). CS independently predicted mortality (aOR 2.91;95% CI 1.25–6.81; $p = 0.014$), ARF (aOR 3.17; 95% CI 1.32–7.63; $p = 0.010$), and MCSutilization (aOR 22.58; 95% CI 2.78–183.60; $p = 0.004$).

Conclusion:

Shock complicating HLH is associated with substantially worse clinical outcomes. SS confers the greatest burden of multiorgan dysfunction, whereas CS, though rare, identifies a distinct high-risk cardiovascular phenotype characterized by extensive cardiac comorbidity, elevated mortality, and markedly greater need for advanced hemodynamic support.

Keywords: Hemophagocytic Lymphohistiocytosis; Cardiogenic Shock; Septic Shock; Mechanical Circulatory Support; Outcomes

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but frequently fatal hyperinflammatory syndrome characterized by uncontrolled immune activation, excessive cytokine release, and progressive multiorgan dysfunction [1–5,8]. The syndrome results from dysregulated activation of cytotoxic T lymphocytes, natural killer cells, and macrophages, producing a hypercytokinemia that drives immune-mediated injury across multiple organ systems [11,13]. HLH is most often triggered by infections, malignancies, autoimmune diseases, and immunosuppressive states [3,5,12]. Diagnostic criteria, originally established by the HLH-2004 guidelines, include fever, splenomegaly, cytopenias,

hypertriglyceridemia, hypofibrinogenemia, elevated ferritin, elevated soluble interleukin-2 receptor, and hemophagocytosis on tissue biopsy [8]; the HScore has since emerged as a validated probabilistic tool for adult populations [11]. Despite advances in diagnostic recognition and the development of HLH-directed therapies, mortality among critically ill patients remains exceptionally high, with systematic reviews reporting pooled ICU mortality rates of approximately 58% to 65% [1,2], and population-based studies demonstrating one-year survival rates of only 50–55% [10]. In the largest nationally representative analysis of adult HLH hospitalizations in the United States, Abdelhay et al. documented rising HLH-related admissions and persistently high in-hospital mortality, underscoring the ongoing burden of this disease [10]. The 2022 EULAR/ACR points to consider have further emphasized the critical importance of prompt syndrome recognition, systematic evaluation of underlying contributors, and early intervention targeting hyperinflammation to prevent organ failure and death [14].

Cardiovascular dysfunction is increasingly recognized as a major contributor to morbidity and mortality in HLH [5–7]. The cytokine storm that characterizes HLH can produce vasoplegia, capillary leak, myocardial depression, arrhythmias, stress cardiomyopathy, and circulatory collapse [5,6]. Similar mechanisms have been extensively characterized in sepsis, where TNF-α and IL-1β depress myocardial contractility [17], 40–50% of patients with prolonged septic shock develop myocardial dysfunction [18], and elevated IL-1, IL-6, and TNF-α are associated with impaired cardiomyocyte function [19]. Sepsis-induced cardiomyopathy encompasses left ventricular systolic, diastolic, and right ventricular dysfunction, all associated with increased mortality [16]. Because HLH shares these cytokine-mediated pathways, these mechanisms provide a biologically plausible explanation for cardiovascular compromise in HLH.

Septic shock (SS) is commonly encountered in HLH because infections represent one of the most frequent triggers and because the clinical presentation often overlaps substantially with severe sepsis [3,5,12]. However, cardiogenic shock (CS) may also develop secondary to inflammatory myocardial injury, stress-induced cardiomyopathy, myocarditis, acute heart failure, or exacerbation of pre-existing cardiovascular disease [5,6]. Distinguishing between these shock phenotypes is clinically essential because SS and CS differ fundamentally in pathophysiology,hemodynamic profile, and management strategy [20,21]. Mixed cardiogenic and distributive shock may also occur in HLH, further complicating diagnosis and management [20,21]. Failure to recognize CS in HLH may delay cardiology consultation, echocardiographic evaluation, consideration of invasive hemodynamic assessment, and timely consideration of mechanical circulatory support (MCS).

Despite growing recognition of cardiovascular involvement in HLH, the existing literature evaluating shock phenotypes in this population remains limited. Most studies have focused broadly on circulatory failure or on differentiating HLH from sepsis rather than characterizing distinct shock subtypes within HLH itself [1,2,5,9,15]. In one of the few studies specifically examining acute circulatory failure in HLH, Frapard et al. evaluated critically ill adults with HLH requiring vasopressor support and reported hospital mortality exceeding 50%; notably, all patients were empirically managed as SS, and no distinction between shock phenotypes was made [9]. Similarly, broader ICU-based studies by Knaak et al. and Haar et al. demonstrated remarkably high mortality rates among critically ill HLH patients but did not stratify outcomes by shock subtype [1,2]. A narrative review of 148 critically ill adult HLH patients by Montrucchio et al. confirmed an overall mortality of 47.5% and emphasized the importance of prompt clinical suspicion, yet shock phenotype classification was not addressed [15]. To date, no large nationally representative study has directly compared clinical outcomes between SS and CS among hospitalized HLH patients.

Accordingly, we used the National Inpatient Sample (NIS) database to compare outcomes, healthcare utilization, and complications among hospitalized HLH patients stratified by shock phenotype: no shock (NS), SS, and CS. We hypothesized that both shock phenotypes would be associated with substantially increased mortality and organ failure, while CS would identify a distinct high-risk cardiac subgroup with greater utilization of advanced hemodynamic therapies.

METHODS

Study Design and Data Source

We performed a retrospective cohort study using the NIS database from 2016 to 2020.The NIS, maintained by the Agency for Healthcare Research and Quality (AHRQ) as part of the Healthcare Cost and Utilization Project (HCUP), is the largest publicly available all-payer inpatient database in the United States. It contains hospitalization-level data including patient demographics, hospital characteristics, comorbidities, procedures performed during hospitalization, and inpatient outcomes. Each hospitalization is recorded as an individual entry; therefore, repeat admissions for the same patient may be captured as separate records. Because the NIS is a publicly available, deidentified database, this study was exempt from Institutional Review Board approval

Study Population and Definitions

Adult patients (aged ≥18 years) with a primary or secondary diagnosis of HLH were identi ied using International Classi ication of Diseases, Tenth Revision, Clinical Modi ication (ICD-10-CM) diagnosis codes. Patients younger than 18 years were excluded.

Hospitalizations were subsequently strati ied into three mutually exclusive cohorts based on the presence and type of shock: NS, SS, and CS. All diagnoses, comorbidities, procedures, and outcomes of interest were identi ied using validated ICD-10-CM diagnosis and procedure codes.

Baseline Characteristics and Comorbidities

Baseline patient characteristics collected included age, sex, race/ethnicity, hospitalization location, and discharge status. Comorbidities identi ied using ICD-10-CM codes included heart failure, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), obesity, atrial ibrillation or lutter, venous thromboembolism (VTE), stroke, chronic kidney disease (CKD; without dialysis), end-stage renal disease (ESRD), hyperthyroidism, hypothyroidism, and peripheral artery disease (PAD).

Outcomes

The primary outcomes of interest were in-hospital mortality, cardiac arrest, acute kidney injury (AKI), dialysis initiation, acute respiratory failure (ARF), and MCS utilization. Secondary outcomes included hospital length of stay (LOS) and total hospitalization charges.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (IBM Corp., Armonk, NY), with NIS sampling weights applied to generate nationally representative estimates. Continuous variables were expressed as means with standard deviations and compared using the independent-samples t-test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. Multivariable logistic regression analyses were performed to evaluate the independent associations between shock phenotype and clinical outcomes. Regression models were adjusted for age, sex, race/ethnicity, diabetes mellitus, hypertension, dyslipidemia, overweight body mass index, obesity, smoking history, CKD stages 3–5, ESRD, and CAD. Adjusted odds ratios (aORs) with corresponding 95% con idence intervals (CIs) were reported. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 2,506 adult hospitalizations with a diagnosis of HLH were identi ied in the NIS between 2016 and 2020. Patients were strati ied into three cohorts: NS (n = 2,015), CS (n = 10), and SS (n = 481). Baseline characteristics differed signi icantly across groups (Table 1). Patients with shock were older overall, with a mean age of 52.3 ± 14.5 years in the CS cohort and 51.8 ± 17.4 years in the SS cohort, compared with 49.1 ± 19.0 years in the NS cohort ($p = 0.017$). The CS cohort demonstrated a markedly greater burden of baseline cardiovascular and systemic comorbidities. Heart failure was present in 60.0% of CS patients compared with 10.2% in SS patients and 7.4% in NS patients ($p < 0.001$). CAD, CKD, and COPD were also significantly more prevalent among CS patients (all $p < 0.001$ vs. NS). Hypertension (70.0% in CS vs. 39.4% in NS vs. 38.5% in SS; $p = 0.129$) and diabetes mellitus (40.0% in CS vs. 19.8% in NS vs. 21.2% in SS; $p = 0.231$) were numerically more common in the CS cohort, although these differences did not reach statistical significance. No statistically significant differences in sex or race/ethnicity were observed across cohorts.

Clinical Outcomes

Shock was associated with markedly worse clinical outcomes compared with HLH patients without shock (Table 2). Unadjusted in-hospital mortality was substantially higher in both shock cohorts: 70.0% in CS patients and 56.7% in SS patients, compared with 14.1% in the NS cohort ($p < 0.001$). Cardiac arrest occurred more frequently among patients with shock, affecting 10.0% of CS patients and 10.4% of SS patients, compared with 2.7% in NS patients ($p < 0.001$). AKI was significantly more common in shock cohorts, occurring in 60.0% of CS patients and 79.6% of SS patients versus 35.2% in the NS cohort ($p < 0.001$). Dialysis initiation was also more frequent among CS (20.0%) and SS patients (34.7%) compared with NS patients (10.0%) ($p < 0.001$). ARF was observed in 80.0% of CS patients and 65.9% of SS patients, compared with 23.3% of NS patients ($p < 0.001$). MCS utilization was markedly higher among CS patients relative to SS patients (20.0% vs. 1.7%, $p < 0.001$), reflecting the increased burden of primary cardiovascular compromise within the CS cohort

Healthcare Utilization

Healthcare utilization differed substantially across groups. Patients with SS experienced the longest hospital LOS (24 days for SS vs. 19 days for CS vs. 13 days for NS; $p < 0.01$) and the greatest total hospitalization charges compared with CS and NS cohorts, suggesting a particularly high burden of prolonged multiorgan critical illness among patients with SS.

Multivariable Regression Analysis

After multivariable adjustment for demographics and baseline comorbidities (Table 3), SS remained strongly and independently associated with adverse outcomes relative to the NS cohort. SS was independently associated with significantly increased odds of in-hospital mortality (aOR 8.25; 95% CI 6.49–10.48; $p < 0.001$), AKI (aOR 7.45; 95% CI 5.80–9.57; $p < 0.001$), dialysis initiation (aOR 5.29; 95% CI 4.03–6.94; $p < 0.001$), ARF (aOR 5.87; 95% CI 4.70–7.34; $p < 0.001$), and cardiac arrest (aOR 4.02; 95% CI 2.65–6.12; $p < 0.001$).

CS was independently associated with increased in-hospital mortality (aOR 2.91; 95% CI 1.25–6.81; p = 0.014) and ARF (aOR 3.17; 95% CI 1.32–7.63; p = 0.010), although the magnitude of these associations was smaller than those observed for SS. Notably, CS was associated with markedly greater MCS utilization (aOR 22.58; 95% CI 2.78–183.60; p = 0.004) compared with SS (aOR 14.85; 95% CI 2.61–84.41; p = 0.002). Associations between CS and AKI, dialysis initiation, and cardiac arrest were no longer statistically significant following multivariable adjustment.

DISCUSSION

In this nationally representative analysis of hospitalized adults with HLH, we found that both septic shock (SS) and cardiogenic shock (CS) were associated with markedly increased mortality, organ failure, and healthcare utilization compared with HLH patients without shock. SS represented the predominant shock phenotype and conferred the greatest burden of multiorgan dysfunction and adjusted mortality risk. Although only ten patients met criteria for CS, this subgroup identified a distinct and particularly high-risk cardiovascular phenotype characterized by extensive baseline cardiac comorbidity, severe respiratory failure, markedly elevated mortality, and substantially greater utilization of mechanical circulatory support (MCS).

The existing literature evaluating shock phenotypes in HLH remains remarkably limited [1,2,5,9,15]. Hayden et al. highlighted the heterogeneity of HLH presentations in adults and the frequent overlap with sepsis syndromes but did not specifically address shock subtype classification [5]. Frapard et al. demonstrated high mortality among HLH patients with acute circulatory failure requiring vasopressor support, although all patients were empirically managed as SS without differentiation between shock phenotypes [9]. Likewise, Knaak et al. reported ICU mortality approaching 58% among critically ill HLH patients, while Haar et al. described similarly poor outcomes in a contemporary ICU cohort; however, neither study stratified outcomes according to shock subtype [1,2]. Montrucchio et al. reviewed 148 critically ill adults with HLH and identified viral infections and hematologic malignancies as predictors of mortality, yet shock phenotype was not evaluated [15]. To our knowledge, the present study is the first large nationally representative analysis directly comparing outcomes between SS and CS in hospitalized patients with HLH.Our findings further support the growing recognition that cardiovascular involvement contributes importantly to adverse outcomes in HLH [5,6,11]. HLH is characterized by uncontrolled macrophage and cytotoxic T-cell activation, resulting in excessive cytokine production and systemic inflammation capable of causing vasoplegia, myocardial depression, endothelial dysfunction, and multiorgan injury [3,8,11,13]. Similar mechanisms have been extensively characterized in sepsis. Kumar et al. demonstrated that TNF-α and IL-1β synergistically depress myocardial contractility [17], while Rudiger and Singer reported clinically significant myocardial dysfunction in 40–50% of patients with prolonged septic shock through cytokine-mediated impairment of β-adrenergic signaling, calcium handling, and mitochondrial function [18]. More recently, Frapard et al. confirmed that IL-1, IL-6, and TNF-α are strongly associated with impaired cardiomyocyte contractility and septic myocardial dysfunction [19]. Together with the broad spectrum of ventricular dysfunction described in sepsis-induced cardiomyopathy by Sato et al. [16], these data provide biologic plausibility for CS as a manifestation of HLH-associated cytokine storm. Prior reports describing HLH-associated myocarditis, stress cardiomyopathy, fulminant myocardial injury, and troponin elevation further support the concept that cardiovascular injury contributes substantially to adverse outcomes in this population [5–7]. Because HLH frequently presents with fever, shock, elevated inflammatory markers, and multiorgan dysfunction, it may initially be mistaken for severe sepsis, potentially delaying HLH-directed therapy [4,5,12]. Accordingly, current expert recommendations emphasize early recognition and prompt immunosuppressive treatment to interrupt the hyperinflammatory cascade [4,14].

The observed 70% mortality among patients with CS underscores the severity of cardiovascular involvement in HLH. Although the number of CS cases was small, these patients demonstrated a markedly greater burden of heart failure, coronary artery disease, chronic kidney disease, and COPD, suggesting that pre-existing cardiovascular disease may predispose patients to severe inflammatory myocardial dysfunction and circulatory collapse. While the small sample size precludes definitive conclusions, these findings are consistent with the growing recognition that cardiovascular injury represents an important manifestation of HLH and support the need for heightened clinical suspicion when patients develop hemodynamic instability [4–8,11].

One of the most notable findings of this study was the markedly increased utilization of MCS among patients with CS (aOR 22.58). This likely reflects profound hemodynamic instability requiring escalation to advanced therapies such as intra-aortic balloon pump, percutaneous ventricular assist devices, or venoarterial extracorporeal membrane oxygenation (VA-ECMO). However, this estimate should be interpreted cautiously given the very small number of MCS events and the resulting wide confidence intervals. The potential role of VA-ECMO in severe sepsis-induced cardiogenic shock is supported by Bréchot et al., who demonstrated improved 90-day survival among patients with sepsis-induced cardiogenic shock treated with VA-ECMO compared with matched controls (60% vs. 25%) [22]. Although these data were derived from septic rather than HLH populations, the shared pathophysiology of cytokine-mediated myocardial dysfunction suggests that similar rescue strategies may have a role in carefully selected patients with HLH-associated CS. Given the high mortality observed in our CS cohort, prompt recognition of myocardial dysfunction

should prompt cardiology consultation, echocardiographic evaluation, consideration of invasive hemodynamic assessment, and timely referral for advanced heart failure therapies when appropriate. As emphasized by Thiele and Hassager, differentiating cardiogenic from distributive shock, and recognizing mixed shock physiology, is essential because management strategies differ fundamentally [20].

In contrast, SS demonstrated the strongest independent associations with mortality, AKI, dialysis initiation, respiratory failure, and cardiac arrest after multivariable adjustment. These findings likely reflect the profound systemic inflammatory burden and multiorgan dysfunction characteristic of HLH-associated distributive shock. The prolonged hospital stays and higher hospitalization charges observed among patients with SS further underscore the substantial healthcare burden associated with septic complications, consistent with prior reports describing prolonged, resource-intensive ICU courses in critically ill HLH patients [1,2,9,10].

This study has several important limitations. First, its retrospective observational design precludes causal inference. Second, diagnoses were identified using administrative ICD-10-CM codes and are therefore subject to coding inaccuracies and potential misclassification bias, particularly regarding differentiation between SS and CS. Third, the NIS lacks detailed clinical information, including inflammatory biomarkers, echocardiographic findings, vasopressor requirements, invasive hemodynamic measurements, and medication data. Fourth, the small number of CS cases (n = 10) limits statistical power, contributes to wide confidence intervals, and may underestimate the true prevalence of HLH-associated cardiogenic shock. Finally, because the NIS captures hospitalization-level rather than patient-level data, longitudinal outcomes following discharge could not be assessed. Despite these limitations, the NIS provides a large, nationally representative cohort that enables evaluation of rare but clinically important complications across diverse hospital settings.

CONCLUSION

Shock complicating HLH is associated with profoundly worse clinical outcomes and increased healthcare utilization. SS remains the predominant and most resource-intensive shock phenotype, whereas CS represents a rare but particularly high-risk cardiovascular manifestation associated with substantial mortality and markedly increased need for MCS. These findings underscore the importance of early cardiovascular risk stratification, multidisciplinary management involving both hematology and cardiology services, and prompt recognition of myocardial dysfunction in HLH patients presenting with hemodynamic instability. Future prospective studies are needed to better define the mechanisms of cardiac injury in HLH, optimize hemodynamic assessment strategies, and evaluate the role of advanced cardiovascular support in this critically ill population.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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TABLES AND FIGURES

Table 1: Baseline Characteristics of HLH patients by Shock Type

Variable	No Shock (N=2,015)	Cardiogenic Shock (N=10)	Septic Shock (N=481)	Total (n)	p-value
Age (years), Mean± SD	49.08 ±18.99	52.30 ± 14.45	51.76 ± 17.41	2,506	0.017
Co-morbidities					
Congestive Heart Failure	149 (7.39%)	6 (60.00%)	49 (10.19%)	204	<0.001
Hypertension	793 (39.35%)	7 (70.00%)	185 (38.46%)	985	0.129
Diabetes Mellitus	399 (19.80%)	4 (40.00%)	102 (21.21%)	505	0.231
Hyperlipidemia	480 (23.82%)	3 (30.00%)	111 (23.08%)	594	0.844
Coronary Artery Disease (CAD)	244 (12.11%)	5 (50.00%)	84 (17.46%)	333	<0.001
Chronic Obstructive Pulmonary Disease (COPD)	119 (5.91%)	4 (40.00%)	39 (8.11%)	162	<0.001
Obesity	221 (10.97%)	1 (10.00%)	70 (14.55%)	292	0.087
Atrial Fibrillation/ Flutter	223 (11.07%)	2 (20.00%)	89 (18.50%)	314	<0.001
Venous Thromboembolism	131 (6.50%)	1 (10.00%)	43 (8.94%)	175	0.158

Stroke	74 (3.67%)	0 (0.00%)	40 (8.32%)	114	<0.001
Chronic Kidney Disease (CKD)	207 (10.27%)	5 (50.00%)	46 (9.56%)	258	<0.001
End-Stage Renal Disease (ESRD)	73 (3.62%)	0 (0.00%)	29 (6.03%)	102	0.045
Hyperthyroidism	7 (0.35%)	0 (0.00%)	5 (1.04%)	12	0.139
Hypothyroidism	175 (8.68%)	1 (10.00%)	41 (8.52%)	217	0.982
Peripheral Artery Disease (PAD)	6 (0.30%)	0 (0.00%)	0 (0.00%)	6	0.481
Sex					
Male	1,133 (56.23%)	5 (50.00%)	266 (55.30%)	1,404	0.868
Female	882 (43.77%)	5 (50.00%)	215 (44.70%)	1,102	
Race					
Caucasian	1,076 (55.12%)	7 (70.00%)	223 (48.58%)	1,306	0.208
African American	326 (16.70%)	2 (20.00%)	93 (20.26%)	421	
Hispanic	314 (16.09%)	0 (0.00%)	83 (18.08%)	397	
Asian/Paci ic Islander	134 (6.86%)	0 (0.00%)	33 (7.19%)	167	
Native/Other	21 (1.08%)	0 (0.00%)	2 (0.44%)	23	
Unknown	81 (4.15%)	1 (10.00%)	25 (5.45%)	107	
Hospital Census Division					
New England	168 (8.34%)	0 (0.00%)	23 (4.78%)	191	0.326
Middle Atlantic	277 (13.75%)	1 (10.00%)	68 (14.14%)	346	
East North Central	266 (13.20%)	2 (20.00%)	78 (16.22%)	346	
West North Central	152 (7.54%)	1 (10.00%)	34 (7.07%)	187	
South Atlantic	327 (16.23%)	4 (40.00%)	87 (18.09%)	418	
East South Central	105 (5.21%)	0 (0.00%)	26 (5.41%)	131	
West South Central	247 (12.26%)	0 (0.00%)	63 (13.10%)	310	
Mountain	141 (7.00%)	1 (10.00%)	28 (5.82%)	170	
Pacific	332 -16.48%	1 (10.00%)	74 (15.38%)	407	

Note: p-values for categorical variables by Pearson chi-square test. Age by one-way ANOVA (F=4.08, p=0.017). PAY1 not available in Stata output.

Table 2: Univariate Analysis of Outcomes

Variable	No Shock (N=2,015)	Cardiogenic Shock (N=10)	Septic Shock (N=481)	Total (n)	p-value
Medical Outcomes					
In-Hospital Death	283 (14.06%)	7 (70.00%)	272 (56.67%)	562	<0.001
Cardiac Arrest	54 (2.68%)	1 (10.00%)	50 (10.40%)	105	<0.001
Acute Decompensated HF	83 (4.12%)	1 (10.00%)	25 (5.20%)	109	0.395
Acute Kidney Injury (AKI)	709 (35.19%)	6 (60.00%)	383 (79.63%)	1,098	<0.001

Hemodialysis Initiation	201 (9.98%)	2 (20.00%)	167 (34.72%)	370	<0.001
Acute Respiratory Failure	469 (23.28%)	8 (80.00%)	317 (65.90%)	794	<0.001
Use of Mechanical Circulatory Support (MCS)	0 (0.00%)	2 (20.00%)	8 (1.66%)	10	<0.001
Length of Stay and Charges					
LOS (days), Mean ± SD	13.33 ± 14.96	18.90 ± 28.00	23.98 ± 27.72	2,506	<0.001
Total Charges ($), Mean ± SD	$202,057 ± $388,483	$317,628 ± $442,549	$506,473 ± $716,195	2,480	<0.001
Discharge Status					
Home	989 (49.13%)	1 (10.00%)	64 (13.33%)	1,054	<0.001
Short-term Hospital	160 (7.95%)	0 (0.00%)	27 (5.62%)	187	
Another Type of Facility	232 (11.53%)	1 (10.00%)	71 (14.79%)	304	
Home Health Care	331 (16.44%)	1 (10.00%)	42 (8.75%)	374	
AMA	18 (0.89%)	0 (0.00%)	3 (0.62%)	21	
Died in Hospital	283 (14.06%)	7 (70.00%)	272 (56.67%)	562	
Unknown/Missing	0 (0.00%)	0 (0.00%)	1 (0.21%)	1	

Note: p-values for categorical variables by Pearson chi-square test. LOS and Total Charges by one-way ANOVA (LOS: F=66.90, p<0.001; TOTCHG: F=80.90, p<0.001).

Table 3: Multivariable logistic regression with effects of Shock Types on HLH Outcomes

Outcome	**Shock Group**	**aOR**	**95% CI**	**p-value**
In-Hospital Death	Cardiogenic Shock	2.91	1.25 – 6.81	0.014
	Septic Shock	8.25	6.49 – 10.48	<0.001
Acute Kidney Injury (AKI)	Cardiogenic Shock	1.16	0.49 – 2.74	0.733
	Septic Shock	7.45	5.80 – 9.57	<0.001
Hemodialysis Initiation	Cardiogenic Shock	1.25	0.55 – 2.89	0.593
	Septic Shock	5.29	4.03 – 6.94	<0.001
Acute Respiratory Failure	Cardiogenic Shock	3.17	1.32 – 7.63	0.01
	Septic Shock	5.87	4.70 – 7.34	<0.001
Use of Mechanical Circulatory Support (MCS)	Cardiogenic Shock	22.58	2.78 – 183.60	0.004
	Septic Shock	14.85	2.61 – 84.41	0.002
Cardiac Arrest	Cardiogenic Shock	1.02	0.29 – 3.57	0.972
	Septic Shock	4.02	2.65 – 6.12	<0.001

Notes: MCS model — COPD, AFib/flutter, PAD, hypothyroidism omitted (predict failure perfectly). Cardiac arrest model — hyperthyroidism, PAD omitted. Death/ hemodialysis models — PAD omitted. ADHF logistic regression not included (no significant model in Stata output).