







ORIGINAL RESEARCH

Lactate Clearance as a Surrogate for Mortality in Cardiogenic Shock: Insights From the DOREMI Trial

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BACKGROUND: Recent studies have shown improved outcomes in cardiogenic shock through protocols directed toward early identification and initiation of mechanical circulatory support. However, objective therapeutic targets—based on clinical and/or laboratory data—to guide real-time clinical decision making are lacking. Lactate clearance has been suggested as a potential treatment target because of its independent association with mortality.

METHODS AND RESULTS: In a post hoc analysis of the DOREMI (Dobutamine Compared to Milrinone in the Treatment of Cardiogenic Shock) trial—a randomized, double-blind, controlled trial comparing milrinone to dobutamine in the treatment of cardiogenic shock—we used prospectively collected lactate data to evaluate lactate clearance as a surrogate marker for in-hospital mortality. In total, 82 (57.7%) patients survived to hospital discharge (survivors). In multivariate logistic regression analysis, complete lactate clearance, percentage lactate clearance, and percentage lactate clearance per hour were independently associated with survival beginning as early as 8 hours after enrollment. Complete lactate clearance was the strongest predictor of survival at all time points, with odds ratios ranging between 2.46 (95% CI, 1.09–5.55; $P=0.03$) at 8 hours to 5.44 (95% CI, 2.14–13.8; $P<0.01$) at 24 hours.

CONCLUSIONS: Complete lactate clearance is a strong and independent predictor of in-hospital survival in patients with cardiogenic shock. Together with previously published data, these results further support the validity of lactate clearance as an appropriate surrogate for mortality and as a potential therapeutic target in future cardiogenic shock trials.

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Key Words: cardiogenic shock ■ lactate clearance ■ mortality ■ surrogate end point

Cardiogenic shock (CS) management strategies have evolved considerably during the past 2 decades as temporary mechanical circulatory support devices have grown in both number and availability.^{1–4} However, this shift in clinical practice has yet to translate into improved patient outcomes, with clinical trials continuing to report mortality rates of 30% to 60%.^{5–8}

Although there are many reasons for the lack of progress in CS outcomes, among the most important has been the absence of clear criteria for diagnosing and risk-stratifying patients, leading to a wide variability in CS management.⁹ The recent Society for Coronary Angiography and Intervention (SCAI) CS classification system has addressed this deficiency in part by providing a framework that can be used to

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CLINICAL PERSPECTIVE

What Is New?

- This is an original study evaluating the association between lactate clearance and survival in patients with cardiogenic shock (CS).
- In a substudy of the DOREMI (Dobutamine Compared to Milrinone in the Treatment of Cardiogenic Shock) trial, lactate clearance was found to be an independent predictor of in-hospital survival in a cohort of patients with CS who were randomly assigned to treatment with dobutamine or milrinone.
- These results provide evidence in support of lactate clearance as a surrogate for mortality in CS.

What Are the Clinical Implications?

- In the setting of CS, elevated blood lactate levels are the result of severe hemometabolic disarray and a marker of poor prognosis.
- Lactate clearance may be an appropriate therapeutic target used to guide clinical decision making in patients with CS.
- Using lactate clearance as a surrogate outcome may improve the feasibility and execution of future clinical trials evaluating CS treatments.

Nonstandard Abbreviations and Acronyms

CLC	complete lactate clearance
CS	cardiogenic shock
DOREMI	Dobutamine Compared to Milrinone in the Treatment of Cardiogenic Shock
LC	lactate clearance
RRT	renal replacement therapy
SCAI	Society for Coronary Angiography and Intervention

risk-stratify patients according to their hemometabolic profile.¹⁰ Using baseline patient characteristics, this classification system has demonstrated a consistent association between increasing SCAI shock stage and mortality.^{3,11–14}

Among the clinical, hemodynamic, and biochemical parameters that have been incorporated into the SCAI classification, lactate is perhaps the most widely used for prognosticating outcomes in clinical practice. Certainly, there is ample evidence among large cohorts of critically ill patients demonstrating a direct correlation between baseline lactate levels and patient outcomes.

Lactate levels, however, are not static over time, and therefore it has been postulated that temporal lactate trends may increase diagnostic precision and provide a potential therapeutic target for guiding clinical decisions in real time. Zhang and colleagues provided evidence to support this assertion in a large cohort of patients admitted to the intensive care unit, where they demonstrated that the time to lactate normalization provided additional prognostic value beyond baseline lactate.¹⁵ Similarly, early lactate clearance (LC)—within 6 hours of emergency department presentation—has been shown to directly correlate with survival in patients with severe sepsis or septic shock.¹⁶ Although these data support the relationship between LC and survival among a heterogeneous population of critically ill patients, there is little data validating LC as a surrogate for survival in CS.^{17–21} As such, whether LC may be an appropriate treatment target in CS has not yet been established. In a substudy of the recently published DOREMI (Dobutamine Compared to Milrinone in the Treatment of Cardiogenic Shock) trial, we sought to confirm that LC is directly associated with survival in patients with CS and therefore may be a reasonable therapeutic target for clinicians and surrogate end points for researchers^{8,22} (Figure 1).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The presented study is a post hoc analysis of the DOREMI trial, an investigator-initiated, single-center, double-blind, randomized clinical trial comparing outcomes in patients with CS randomly assigned to treatment with dobutamine or milrinone.⁸ The study was approved by the Ottawa Health Science Network Research Ethics Board, and the study was conducted in accordance with the Helsinki Declaration. All patients or their substitute decision makers provided written informed consent before randomization. The full details of the DOREMI trial protocol and design have been previously published.²³ Briefly, adult patients who were admitted with SCAI stages B through E CS between September 1, 2017, and May 17, 2020, were eligible for inclusion.¹² We excluded patients who were pregnant, presented with an out-of-hospital cardiac arrest, had milrinone or dobutamine initiated before enrollment, or were participating in another interventional trial and those for whom written informed consent was not able to be obtained.

Participants were randomly assigned in a 1:1 ratio to milrinone or dobutamine. The randomization was

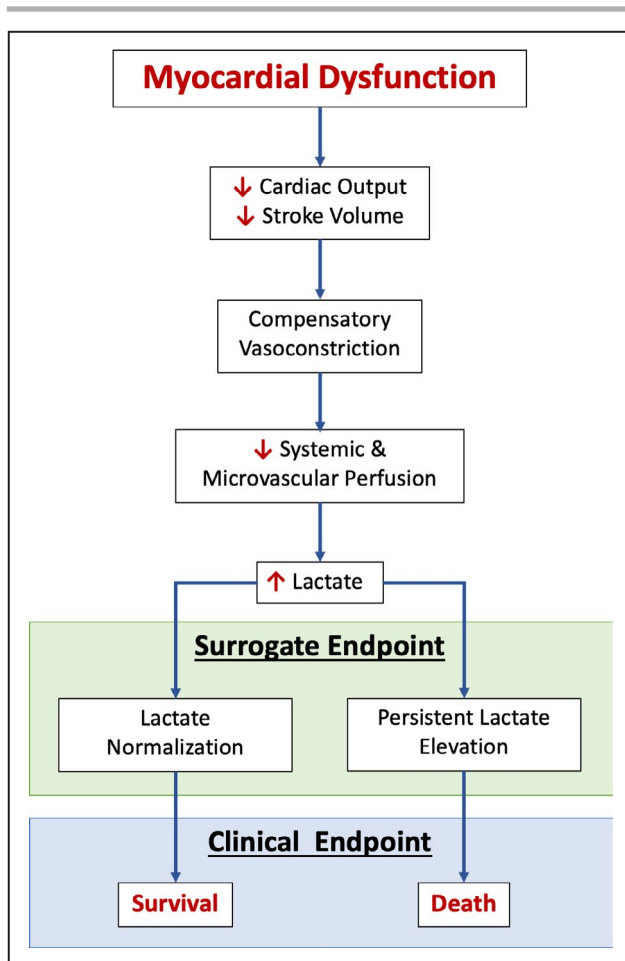


Figure 1. Representation of blood lactate as a surrogate end point in cardiogenic shock, demonstrating the relationship between myocardial dysfunction, lactate levels, and mortality.

performed using a computer-generated random sequence. Patients were allocated to treatment groups using sequential, serially numbered, opaque envelopes. Patients, treating physicians, and all other research personnel were blinded to the treatment allocation. Per protocol, once randomly assigned patients were initiated on intravenous dobutamine or milrinone. The inotrope dose was titrated using a standardized staging system, ranging from stages 1 to 5, which corresponded to 2.5, 5.0, 7.5, 10.0, and >10.0 $\mu\text{g}/\text{kg}$ per minute and 0.125, 0.250, 0.375, 0.500, and >0.500 $\mu\text{g}/\text{kg}$ per minute for dobutamine and milrinone, respectively.

Once treatment had been initiated, patients were reassessed by the treating team to determine if the inotrope dose should be maintained, increased, or decreased. Frequency and timing of patient reassessments were prespecified to occur at the following intervals after treatment initiation: 4, 8, 12, 18, 24, 36, 48, 60, and 72 hours then daily. At the time of

enrollment as well as at each reassessment, clinical, laboratory, and hemodynamic (when available) data were collected. Pulmonary artery catheters were placed per the primary team and were not required as part of the treatment protocol. All patients enrolled in the Capital DOREMI trial who had elevated blood lactate levels at baseline were included in this analysis, and all data included in the analysis were collected prospectively.

Study Outcomes

The primary goal of this analysis was to determine the utility of LC as a surrogate marker for in-hospital mortality in patients with CS. Lactate levels were measured at baseline and at each reassessment, as noted previously. Throughout the literature, LC has been defined in several different ways. In an attempt to identify the optimal surrogate marker, we performed all analyses using each of the following definitions, where L° is the baseline lactate level, L_t is the lactate level at time t , and Δt is the time difference between L° and L_t .

$$\% \text{Lactate Clearance (LC1)} = (L^{\circ} - L_t) \div L^{\circ} \times 100$$

$$\% \text{Lactate Clearance per hour (LC2)} = (L^{\circ} - L_t) \div (L^{\circ} \times \Delta t (L^{\circ}, L_t)) \times 100$$

LC1 is the percentage reduction in lactate from baseline to time t , and LC2 is the percentage reduction in lactate per hour from baseline to time t . Finally, patients were assessed at each time point for the presence or absence of complete LC (CLC), which was defined by a serum lactate level (<2.0 mmol/L).

Statistical Analysis

Patients were grouped into survivors and nonsurvivors based on in-hospital mortality. When normally distributed, continuous variables are summarized as mean \pm SD and otherwise expressed as median (interquartile range [IQR]). Categorical variables are summarized as number (percentage). All data were analyzed according to the intention-to-treat principle, which included all patients according to the group to which they were randomly assigned. The Pearson χ^2 test was used to compare discrete variables, and continuous variables were compared using either the Student t test or Mann-Whitney U test, as appropriate.

As the goal of our analysis was to evaluate LC, patients who had normal lactate levels (<2.0 mmol/L) at baseline were excluded. Absolute lactate levels were compared between groups at baseline and 4, 8, 12, 18, 24, and 36 hours. LC1 and LC2 were calculated for survivors and nonsurvivors at 4, 8, 12, 18, 24, and

36 hours, as was the frequency of CLC among survivors and nonsurvivors at each of these time points.

Univariate logistic regression analyses were conducted to assess the unadjusted relationship of survival with baseline demographic and clinical parameters as well as LC1, LC2, and CLC at 4, 8, 12, 18, 24, and 36 hours. Baseline and clinical parameters were chosen for univariate regression analysis based on known or presumptive association with survival in CS. Next, a multivariate logistic regression model was constructed to evaluate the adjusted relationship between LC and survival at each of the aforementioned time points. The multivariate model was constructed using a stepwise forward entry approach, whereby all variables with $P < 0.10$ in univariate analysis were assessed for inclusion. An entry level of $P < 0.05$ was used for inclusion in the final model. Next, LC1, LC2, and CLC were individually forced into the model, thereby creating an individual model for each definition of LC, and receiver operating characteristic curves were calculated for CLC at 8, 12, and 24 hours. Finally, survival curves were plotted for survivors and nonsurvivors according to CLC status at 12 and 24 hours using the Wilcoxon test. All reported P values are 2-sided, and a value < 0.05 was considered statistically significant. Analyses were conducted in R version 4.0.2 (R Core Team, Vienna, Austria).

RESULTS

In total, 192 patients were enrolled in the Capital DOREMI clinical trial, and 116 (60.4%) of them survived to hospital discharge. The median baseline lactate levels were 2.75 mmol/L (IQR, 1.78–4.15 mmol/L) and 3.00 mmol/L (IQR, 2.23–4.50 mmol/L) among survivors and nonsurvivors, respectively ($P = 0.386$). After the exclusion of patients who had normal baseline lactate ($N = 50$), 74% of the total cohort ($N = 142$) was included in the present analysis (Figure 2). Baseline characteristics and clinical outcomes between patients with normal compared with elevated baseline lactate are compared in Table S1. Of the patients who had a normal baseline lactate, 48% ($N = 24$) of them subsequently had a rise in lactate, and 25% of those patients ($N = 6$) died.

Of the 142 patients included in our analysis, 82 (57.7%) were discharged alive from the hospital (survivors). The overall mean \pm SD patient age was 70.1 ± 13.1 years; however, survivors were significantly younger than nonsurvivors (66.8 ± 13.0 years versus 74.5 ± 11.9 years; $P < 0.001$). Men comprised the majority of survivors (68.3%) and nonsurvivors (65.0%), but there was no significant difference in the proportion of men between groups ($P = 0.68$). Otherwise, the baseline demographics and medical histories were similar between survivors and nonsurvivors.

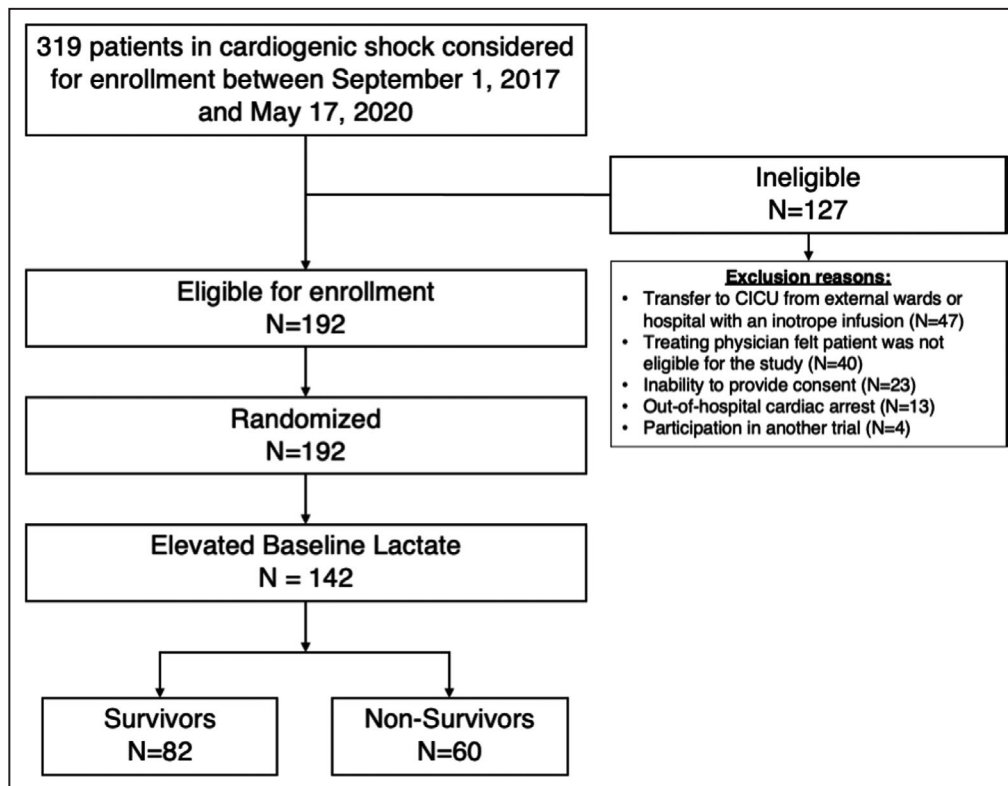


Figure 2. Patient flow.

CICU indicates cardiac intensive care unit.

With respect to baseline clinical characteristics, survivors had higher heart rates (97.5 ± 23.2 bpm versus 88.1 ± 20.3 bpm; $P=0.01$) and mean arterial blood pressures (80.5 ± 13.4 mm Hg versus 73.9 ± 13.3 mm Hg; $P=0.007$) than nonsurvivors. They were also less likely to require baseline intravenous vasopressors (35.4% versus 59.3%; $P=0.01$) and mechanical ventilation (9.8% versus 28.3%; $P=0.01$; Table 1). There was limited initiation or escalation of mechanical circulatory support in both survivors and nonsurvivors. Among patients who survived, 7 intra-aortic balloon pumps and 4 Impella devices were placed. In nonsurvivors, 8 intra-aortic balloon pumps were placed, and venoarterial extracorporeal membrane oxygenation was initiated in 1 patient.

Absolute blood lactate levels were similar between the survivors and nonsurvivors at baseline (survivors, 3.75 mmol/L [IQR, 2.63–5.40 mmol/L] versus nonsurvivors, 3.70 mmol/L [IQR, 2.68–5.98 mmol/L]; $P=0.58$) and at 4 hours (survivors, 2.50 mmol/L [IQR 1.80–3.33 mmol/L] versus nonsurvivors, 2.95 mmol/L [IQR, 2.10–4.97 mmol/L]; $P=0.08$); yet, as demonstrated in Figure 3 and Table S2, at all time points from 8 to 36 hours absolute blood lactate levels were significantly lower in survivors.

There was no difference between groups in the proportion of patients who had CLC within 4 hours (survivors, 30.5%, versus nonsurvivors, 20.0%; risk ratio, 0.80 [95% CI, 0.61–1.07]; $P=0.16$), but a significantly greater percentage of patients who survived had CLC at each time point thereafter (Figure 4A and Table S3). Similarly, LC1 and LC2 were significantly greater in survivors at 8, 12, 18, 24, and 36 hours (Table S4). Renal replacement therapy (RRT) was initiated in 20 (33.3%) survivors, and 7 (8.5%) nonsurvivors. Although RRT may partially clear serum lactate, there was no significant difference in the rate of CLC at 24 (RRT, 59.3%, versus no RRT, 75.7%; $P=0.09$) or 48 hours (RRT, 66.7%, versus no RRT, 81.7%; $P=0.08$) between patients who did and did not receive RRT.

Multivariate logistic regression modeling identified age, mean arterial blood pressure, and mechanical ventilation to be independent predictors of survival. LC was independently associated with survival at each time point from 8 to 36 hours, irrespective of the definition used. Among the definitions of LC evaluated, CLC was the strongest predictor of survival at all time points, with odds ratios ranging between 2.46 (95% CI, 1.09–5.55; $P=0.03$) at 8 hours to 5.44 (95% CI, 2.14–13.8; $P<0.01$) at 24 hours (Table 2 and Table S5).

As CLC was the most powerful surrogate marker, we plotted receiver operating characteristic curves for CLC at 8, 12, and 24 hours, which demonstrated a modest improvement in area under the curve during this time frame (Figure 5). Finally, survival curves were plotted for patients with and without CLC at 24 hours (Figure 4B).

DISCUSSION

In a cohort of patients with CS randomly assigned to treatment with dobutamine or milrinone, LC was an independent predictor of in-hospital survival. The independent association between survival and LC was observed at all time points evaluated between 8 and 36 hours, irrespective of how LC was defined. Moreover, these results remained consistent in both adjusted and unadjusted analyses. When compared to one another, CLC was the most powerful definition of LC with respect to predicting in-hospital survival.

Lactic acid is produced as a byproduct of anaerobic glycolysis, which functions to provide glucose in the setting of hypoxia.²⁴ Although a normal physiologic process, the delicate balance between lactate production and clearance becomes significantly impaired in the setting of CS. Decreased cardiac output resulting in tissue hypoperfusion, reduced oxygen use attributed to microcirculatory dysfunction, and the release of catecholamines and other inflammatory mediators all contribute to increased lactate production in CS.²⁴ Also, concomitant renal and hepatic injury serve to impair LC, thereby further raising serum lactate levels. The prognostic importance of this relationship between tissue hypoperfusion, elevated lactate levels, and mortality has been understood for decades.^{25–27}

Recently, investigators have determined that LC may be a more reliable surrogate marker than absolute lactate levels. Although the majority of evidence in support of this theory originates from non-CS populations (ie, sepsis, trauma), its mechanistic rationale applies equally to CS. However, the appropriateness of LC-guided resuscitation in CS is yet to be established. That said, observational data supporting LC as a surrogate for mortality in CS have steadily grown in recent years. In 1 study of 139 patients treated with extracorporeal membrane oxygenation for refractory CS, LC 24 hours after extracorporeal membrane oxygenation initiation was predictive of 30-day mortality.²⁸ Tongers and colleagues found that LC 12 hours after the initiation of combined therapy with Impella (Abiomed, Danvers, MA) and extracorporeal membrane oxygenation was independently associated with survival; Ataná et al demonstrated similar results among patients with ST-segment-elevation myocardial infarction.^{20,29} Finally, in a recent systematic review and meta-analysis evaluating the association between LC and survival in patients with CS, there was a significant difference in LC between survivors and nonsurvivors as early as 6 to 8 hours after diagnosis.³⁰ However, it is important to note that none of the studies included in this analysis implemented treatment protocols targeting LC. Therefore, the utility of LC as a target for resuscitation efforts remains to be directly studied.

Table 1. Baseline Demographic and Clinical Characteristics

Baseline characteristics	Total, N=142	Survivors, n=82	Nonsurvivors, n=60	P Value
Age, y	70.1±13.1	66.8±13.0	74.5±11.9	<0.001
Male sex	95 (66.9)	56 (68.3)	39 (65.0)	0.680
Body mass index, kg/m ²	27.4±5.73	27.2±5.6	27.7±6.2	0.593
Race and ethnicity				0.869
White patients	123 (86.6)	70 (85.4)	53 (88.3)	
Black patients	4 (2.8)	3 (3.7)	1 (1.7)	
Asian patients	7 (4.9)	5 (6.0)	2 (5.3)	
Middle Eastern patients	6 (4.2)	3 (3.7)	3 (5.0)	
Other races or ethnicities	2 (1.4)	1 (1.2)	1 (1.7)	
Medical history				
Diabetes	73 (51.4)	43 (52.4)	30 (50.0)	0.774
Previous myocardial infarction	48 (33.8)	29 (35.4)	19 (31.7)	0.645
Previous coronary bypass grafting	31 (21.8)	16 (19.5)	15 (25.0)	0.434
Previous stroke or TIA	22 (15.5)	13 (15.9)	9 (15.0)	0.890
Previous percutaneous coronary intervention	35 (24.6)	23 (28.0)	12 (20.0)	0.272
Atrial fibrillation	74 (52.1)	48 (58.5)	26 (43.3)	0.073
Chronic kidney disease	33 (23.2)	19 (23.2)	14 (23.3)	0.982
Chronic obstructive pulmonary disease	19 (13.4)	13 (15.9)	6 (10.0)	0.311
Chronic liver disease	8 (5.6)	5 (6.1)	3 (5.0)	0.779
Home medications before presentation				
Aspirin	86 (60.6)	48 (58.5)	38 (68.3)	0.563
P2Y12 inhibitor	64 (45.1)	34 (41.5)	30 (50.0)	0.313
Warfarin	19 (13.4)	11 (13.4)	8 (13.3)	0.989
Direct oral anticoagulant	36 (25.4)	23 (28.0)	13 (21.7)	0.388
β-blocker	69 (48.6)	41 (50.0)	28 (46.7)	0.695
Statin	90 (63.4)	54 (65.9)	36 (60.0)	0.474
ACEi, ARB, or ARNI	63 (44.4)	39 (47.6)	24 (40.0)	0.370
Mineralocorticoid receptor antagonist	20 (14.1)	12 (14.6)	8 (13.3)	0.826
Nitrates and/or hydralazine	17 (12.0)	10 (12.2)	7 (11.7)	0.924
Diuretic	109 (76.8)	64 (78.0)	45 (75.0)	0.671
Digoxin	10 (7.0)	6 (7.3)	4 (6.7)	0.881
Baseline clinical characteristics				
Etiology of left ventricular dysfunction	0.282			
Ischemic cardiomyopathy	94 (66.2)	57 (69.5)	37 (61.7)	
Nonischemic cardiomyopathy	48 (33.8)	25 (30.5)	23 (38.3)	
Heart rate, bpm	93.5±22.5	97.5±23.2	88.1±20.3	0.01
Mean arterial blood pressure, mm Hg	77.7±13.7	80.5±13.4	73.9±13.3	0.007
Cardiac index, L/min per m ²	1.54±0.39	1.59±0.43	1.52±0.39	0.769
Systemic vascular resistance, dynes×sec/cm ⁵	1914±634	1735±739	2025±582	0.724
SCAI shock class				
SCAI C	118 (83.1)	71 (86.6)	47 (78.3)	0.195
SCAI D	19 (13.4)	8 (9.8)	11 (18.3)	0.138
SCAI E	4 (2.8)	2 (2.4)	2 (3.3)	0.750
Invasive ventilation	25 (17.6)	8 (9.8)	17 (28.3)	0.004
Intravenous vasopressors	64 (45.4)	29 (35.4)	35 (59.3)	0.005

(Continued)

Table 1. Continued

Baseline characteristics	Total, N=142	Survivors, n=82	Nonsurvivors, n=60	P Value
Vasoactive–inotropic score*	15.3±47.7	9.0±16.0	24.2±71.1	0.006
Mechanical circulatory support				
Intra-aortic balloon pump	10 (7.0)	4 (4.9)	6 (10.0)	0.239
Pulmonary artery catheter	13 (9.2)	5 (6.1)	8 (13.3)	0.140
Hemoglobin, g/dL	122±24.1	124±25.0	119±22.6	0.118
Lactate, mmol/L	4.67±3.21	4.38±2.71	5.07±3.78	0.578
Aspartate transaminase, units/L	655±1113	722±1184	571±1020	0.535
Renal function				
Serum creatinine, mmol/L	192±136	173±96.5	218±173	0.069
Estimated GFR, [†] mL/min per 1.73 m ²	72.0±38.5	76.3±37.9	65.6±38.8	0.081

Data are presented as mean±SD or number (percentage). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; GFR, glomerular filtration rate; P2Y12 inhibitor indicates P2Y12 platelet receptor inhibitors; SCAI, Society for Cardiovascular Angiography and Interventions; and TIA, transient ischemic attack.

*Vasoactive–inotropic score=dopamine dose (mcg/kg per min)+dobutamine dose (mcg/kg per min)+(100×epinephrine dose [mcg/kg per min])+(10×milrinone dose [mcg/kg per min])+(10 000×vasopressin dose [units/kg per min])+(100×norepinephrine dose [mcg/kg per min]).

[†]Modification of Diet in Renal Disease equation.

To the best of our knowledge, a substudy of the IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) trial is the only prior evaluation of LC as a surrogate for mortality in a randomly assigned cohort of patients with CS.³¹ In this analysis of 671 patients, absolute lactate at 8 hours and LC2 were both independent predictors of mortality. Furthermore, the

authors determined that a minimum LC of 3.45% per hour in the first 8 hours was the optimal cutoff for predicting mortality. Our data fit with these conclusions, as the median LC in survivors and nonsurvivors at 8 hours was 5.55% and 3.06% per hour, respectively. Although not addressed in the IABP-SHOCK II substudy, there was no difference in LC between survivors

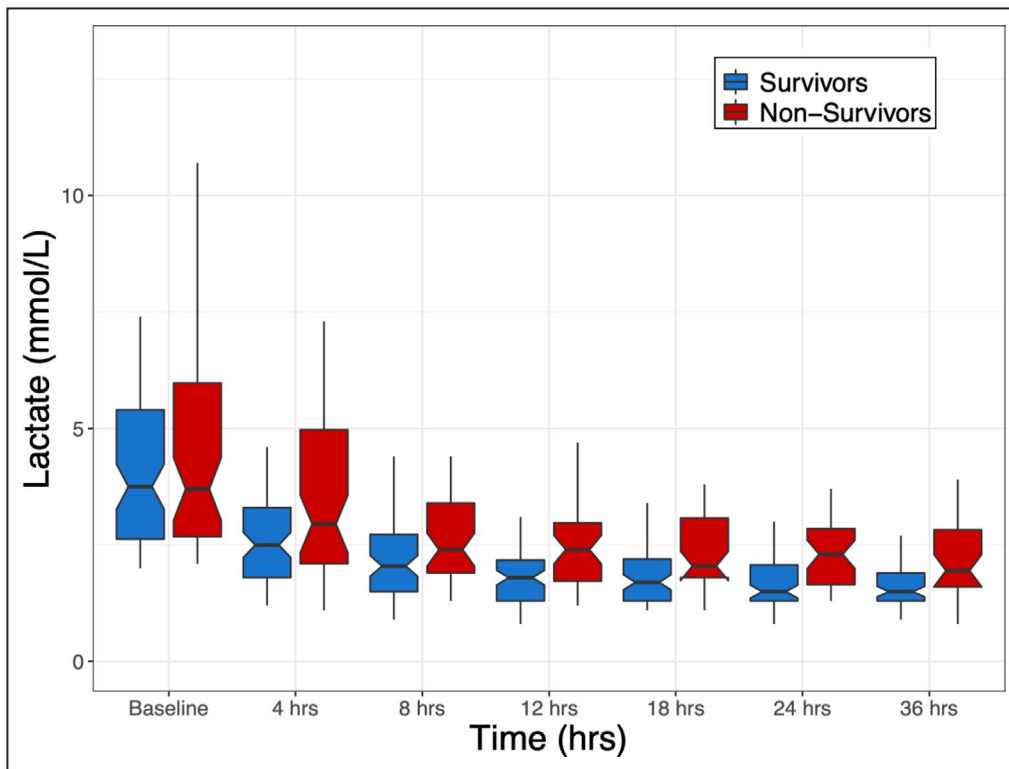


Figure 3. Box-and-whisker plots of absolute lactate levels over time, grouped by survivors and nonsurvivors.

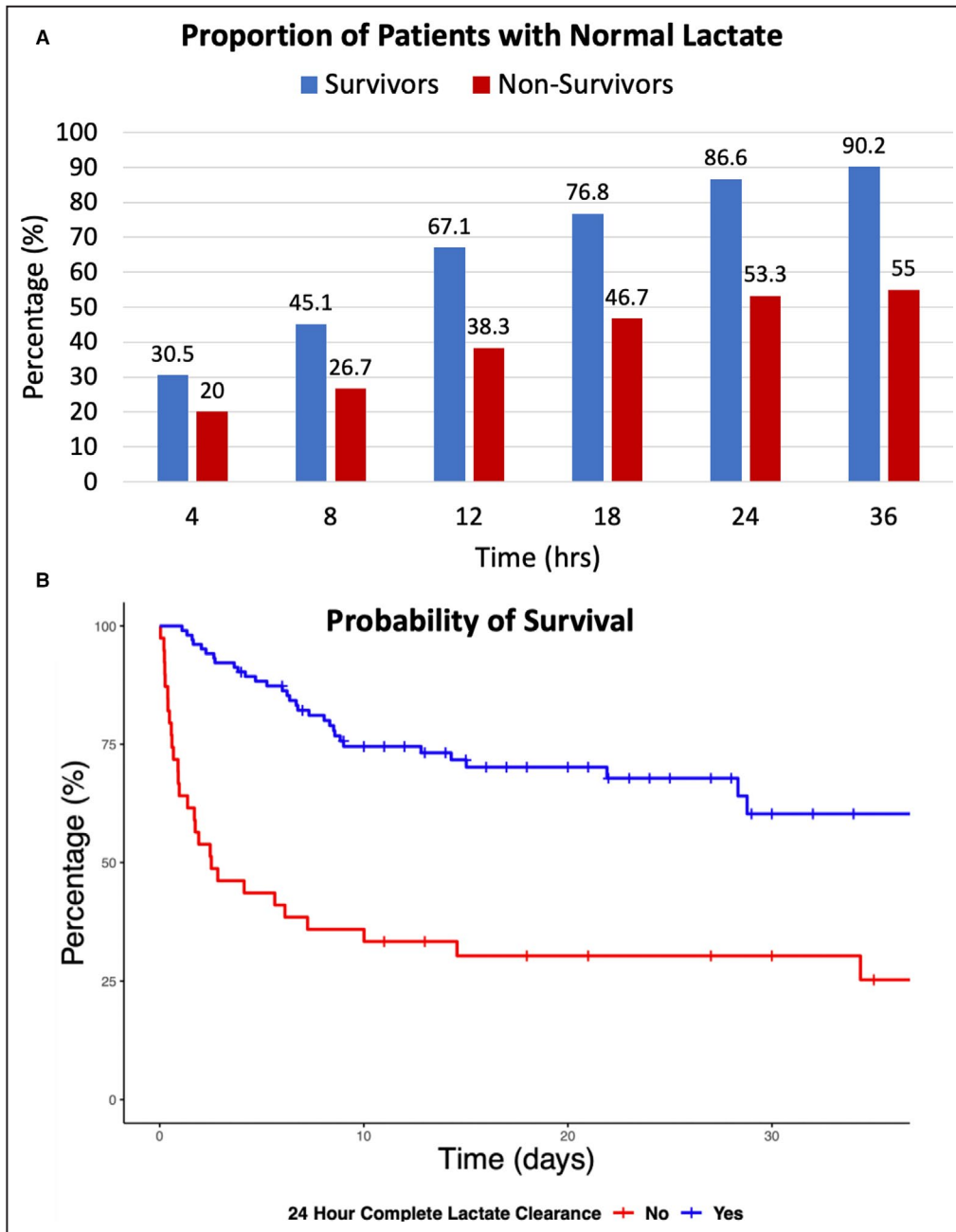


Figure 4. Association between survival and complete lactate clearance.
A, Proportion of survivors and nonsurvivors who achieved complete lactate clearance from 4 to 36 hours. **B,** Probability of survival for patients with and without complete lactate clearance at 24 hours.**B,** Probability of survival for patients with and without complete lactate clearance at 24 hours.

and non survivors in our analysis at 4 hours. While this suggests that failure to clear lactate within the first 4 hours of treatment is not necessarily detrimental to a patient’s overall prognosis, it should push clinicians to determine if adequate support is being provided or if escalation is required.

The IABP-SHOCK II analysis focused on evaluating LC within the first 8 hours, and the authors did not specifically evaluate the prognostic significance of

CLC, which was the strongest predictor of survival in our cohort. In fact, we found that only 45% of patients who survived had CLC at 8 hours, whereas this increased to 67.1% at 12 hours and 86.6% by 24 hours. Thus, although the probability of improved survival with CLC first becomes apparent at 8 hours, a significant portion of survivors will normalize their lactate between 8 and 24 hours. Interestingly, the absolute lactate data reported in the IABP-SHOCK II analysis

Table 2. Multivariate Logistic Regression for In-Hospital Mortality According to Lactate Clearance Definition

Variable	Odds ratio	95% CI	P value
6–8 h			
Age	0.95	0.92–0.98	<0.01
Baseline MAP	1.03	1.00–1.07	0.03
Mechanical ventilation	0.28	0.10–0.79	0.02
Complete lactate clearance	2.46	1.09–5.55	0.03
12 h			
Age	0.94	0.91–0.94	<0.01
Baseline MAP	1.04	1.00–1.07	0.03
Mechanical ventilation	0.31	0.11–0.89	0.03
Complete lactate clearance	3.98	1.76–8.99	<0.01
18 h			
Age	0.95	0.91–0.98	<0.01
Baseline MAP	1.03	1.00–1.07	0.04
Mechanical ventilation	0.29	0.10–0.84	0.02
Complete lactate clearance	3.68	1.62–8.38	<0.01
24 h			
Age	0.95	0.92–0.99	<0.01
Baseline MAP	1.03	0.99–1.07	0.05
Mechanical ventilation	0.25	0.08–0.74	0.01
Complete lactate clearance	5.44	2.14–13.8	<0.01

MAP indicates mean arterial blood pressure.

tell a similar story, with the median lactate level among survivors being in the normal range (<2 mmol/L) at 16 and 24 hours, and remaining >3 mmol/L in nonsurvivors.

This current study has several limitations. First, this is a post hoc analysis of a randomized trial. That said, all data analyzed were collected prospectively during

the conduct of the Capital DOREMI trial. Second, the overall trial sample size is quite small at 192 patients. In addition, a significant proportion of the enrolled patients had normal lactate levels at baseline. As the purpose of the present analysis was to evaluate LC as a surrogate for mortality, these patients were excluded from our analysis. The exclusion of these patients led to a reduction in our sample size by ~20%, in addition to limiting the generalizability of our results to patients with CS with elevated lactate levels at the time of presentation. As demonstrated in Table S1, nearly a quarter of the patients excluded from this analysis were SCAI stage B at the time of enrollment, whereas all included patients were SCAI stages C, D, or E. Consequently, many lower risk patients were excluded, which likely explains the numerically lower, although not statistically significant, reduction in mortality among those who were excluded. Nevertheless, patients with CS with a normal baseline lactate had an in-hospital mortality rate of >30%, signifying that although LC may be an important prognostic marker in CS, a normal baseline lactate by itself is not sufficient to determine prognosis in these patients.

As discussed previously, the relationship between LC and mortality as well as the biochemical rationale for this relationship is well established. The data presented here are consistent with previous randomized and observational literature demonstrating an independent association between LC and mortality in patients with CS. Together, these facts further support the establishment of LC as a valid surrogate end point in CS, which has the potential to significantly improve the feasibility of developing and successfully completing future CS trials.³²

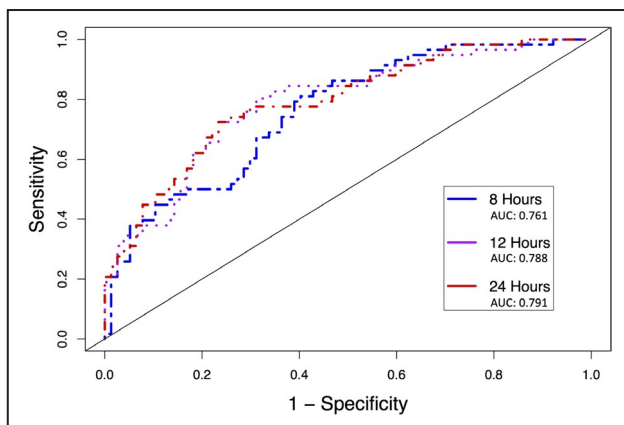


Figure 5. Receiver operator curves of multivariate logistic regression for association between complete lactate clearance and death at 8 hours, 12 hours, and 24 hours.

Receiver operator curves of multivariate logistic regression for association between complete lactate clearance and death at 8 hours (Blue), 12 hours (Purple), and 24 hours (Red). AUC – area under the curve.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S5

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SUPPLEMENTAL MATERIAL

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Table S1. Baseline Characteristics and Clinical Outcomes in patients with normal compared to elevated baseline lactate levels

Baseline Characteristics	Normal Lactate (N = 50)	Elevated Lactate (N = 142)	P Value
Age, mean (SD), yrs	71.0 (13.3)	70.3 (12.6)	0.57
Male, No. (%)	28 (56.0)	94 (66.2)	0.2
Body mass index, mean (SD), kg/m ²	27.1 (6.0)	27.5 (5.8)	0.82
Ethnicity			0.79
Caucasian	42 (84.0)	123 (86.6)	
Black	1 (2.0)	4 (2.8)	
Asian	4 (8.0)	7 (4.9)	
Middle Eastern	3 (6.0)	6 (4.2)	
Other	0 (0)	2 (1.4)	
Medical History, No. (%)			
Diabetes	28 (56.0)	74 (52.1)	0.64
Previous myocardial infarction	18 (36.0)	50 (35.2)	0.92
Previous Coronary bypass grafting	7 (14.0)	32 (22.5)	0.20
Previous stroke or TIA	5 (10.0)	23 (16.2)	0.29
Previous percutaneous coronary intervention	14 (28.0)	35 (24.6)	0.64
Atrial fibrillation	21 (42.0)	74 (52.1)	0.22
Chronic kidney disease	18 (36.0)	32 (22.5)	0.06
Chronic obstructive pulmonary disease	5 (5.0)	20 (14.1)	0.46
Chronic liver disease	5 (10.0)	8 (5.6)	0.29
Home medications prior to presentation, No. (%)			
ASA	41 (82.1)	86 (60.6)	0.006
P2Y12 Inhibitor	34 (68.0)	65 (45.8)	0.007
Warfarin	2 (4.0)	19 (13.4)	0.07
Direct oral anticoagulant	3 (6.0)	36 (25.4)	0.004
Beta blocker	24 (48.0)	69 (48.6)	0.94
Statin	34 (68.0)	92 (64.8)	0.68
ACEi, ARB, or ARNI	21 (42.0)	64 (45.1)	0.71
Mineralicoid receptor antagonist	9 (18.0)	20 (14.1)	0.51
Nitrates and/or hydralazine	9 (18.0)	17 (12.0)	0.29
Diuretic	41 (82.0)	110 (77.5)	0.5
Digoxin	5 (10.0)	9 (6.3)	0.40
Baseline Clinical Characteristics			
Heart rate (SD), bpm	83.4 (19.1)	93.5 (22.4)	0.008
Mean arterial blood pressure (SD), mmHg	72.5 (12.0)	77.9 (14.1)	0.02
Cardiac index (SD), L/min/m ²	1.77 (0.34)	1.54 (0.39)	0.23

Systemic vascular resistance (SD) dynes·sec·cm-5	1548 (436)	1913 (634)	0.19
Society for Cardiovascular Angiography & Interventions (SCAI) Shock Class			
SCAI B	11 (22.0)	0 (0)	< 0.001
SCAI C	35 (70.0)	120 (84.5)	0.03
SCAI D	4 (8.0)	18 (12.7)	0.37
SCAI E	0 (0)	4 (2.8)	0.23
Invasive ventilation, No. (%)	15 (30.0)	25 (17.6)	0.04
Intravenous vasopressors, No. (%)	28 (56.0)	64 (45.4)	0.20
Intra-aortic balloon pump, No. (%)	0 (0)	10 (7.0)	0.06
Pulmonary artery catheter, No. (%)	10 (20.0)	13 (9.2)	0.04
Hemoglobin, mean (SD), g/dL	10.9 (2.13)	12.1 (2.39)	0.002
Lactate, mean (SD), mmol/L	1.39 (0.32)	4.70 (3.24)	<0.001
Aspartate transaminase, mean (SD), units/L	311 (1050)	670 (1116)	<0.001
Renal Function, mean (SD)			
Serum creatinine, mmol/L	163.8 (98.3)	191.2 (136.4)	0.13
Estimated GFR [‡] , mL/min/1.73 m ²	66.2 (38.9)	72.4 (38.8)	0.15
Clinical Outcomes			
MACE, No. (%)	23 (46.0)	76 (53.5)	0.36
30-day survival, No. (%)	34 (68.0)	82 (57.7)	0.20
SD – standard deviation; TIA – transient ischemic attack; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin II receptor blocker; ARNI – angiotensin receptor-neprilysin inhibitor			
[‡] Modification of Diet in Renal Disease equation			

Table S2. Absolute lactate levels grouped by survivors and non-survivors

Absolute lactate, median (IQR), mmol/L	Survivors	Non-survivors	P Value
Baseline	3.75 (2.63-5.40)	3.70 (2.68-5.98)	0.578
4 hours	2.50 (1.80-3.30)	2.95 (2.10-4.97)	0.083
8 hours	2.05 (1.50-2.73)	2.40 (1.90-3.40)	0.024
12 hours	1.80 (1.30-2.18)	2.40 (1.72-2.98)	<0.001
18 hours	1.70 (1.30-2.20)	2.05 (1.80-3.08)	<0.001
24 hours	1.50 (1.30-2.08)	2.30 (1.65-2.85)	<0.001
36 hours	1.50 (1.30-1.90)	1.95 (1.60-2.82)	<0.001

IQR – interquartile range

Table S3. Complete lactate clearance grouped by survivors and non-survivors

Complete Lactate Clearance*, No. (%)	Total (N=142)	Survivors (N=60)	Non-survivors (N=82)	Relative Risk	P Value
4 hours	37 (28.2)	25 (30.5)	12 (20.0)	0.80 (0.61-1.07)	0.16
8 hours	16 (26.7)	37 (45.1)	16 (26.7)	0.72 (0.55-0.95)	0.03
12 hours	78 (54.9)	55 (67.1)	23 (38.3)	0.60 (0.43-0.83)	< 0.01
18 hours	91 (64.1)	63 (76.8)	28 (46.7)	0.54 (0.37-0.79)	< 0.01
24 hours	103 (72.5)	71 (86.6)	32 (53.3)	0.41 (0.24-0.69)	< 0.01
36 hours	107 (75.4)	74 (90.2)	33 (55.0)	0.33 (0.18-0.62)	< 0.01

*Complete lactate clearance – lactate < 2 mmol/L

Table S4. Lactate clearance grouped by survivors and non-survivors

Lactate Clearance 1, median (IQR), %	Survivors	Non-survivors	P Value
4 hours	33.3 (6.45-45.8)	20.9 (0.93-39.6)	0.075
8 hours	44.4 (13.4-59.4)	24.4 (8.11-45.2)	0.011
12 hours	56.9 (30.6-65.3)	26.0 (0.16-47.6)	<0.001
18 hours	52.0 (29.7-69.0)	28.8 (5.75-51.4)	0.002
24 hours	58.7 (39.3-70.3)	37.9 (8.28-56.2)	<0.001
36 hours	55.4 (43.1-71.8)	42.4 (8.59-54.4)	<0.001
Lactate Clearance 2, median (IQR), %			
4 hours	8.33 (1.61-11.5)	5.22 (0.23-9.90)	0.075
8 hours	5.55 (1.67-7.43)	3.06 (1.01-5.65)	0.011
12 hours	4.74 (2.55-5.44)	2.16 (0.01-3.97)	<0.001
18 hours	2.89 (1.65-3.83)	1.60 (0.32-2.86)	0.002
24 hours	2.45 (1.64-2.93)	1.58 (0.35-2.34)	<0.001
36 hours	1.54 (1.20-1.99)	1.18 (0.24-1.51)	<0.001
IQR – interquartile range			

Table S5. Multivariate logistic regression analysis assessing the relation between clinical variable and in-hospital survival

	6-8 Hours								
	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value
Age	0.94	0.91 – 0.98	<0.01	0.94	0.91 – 0.98	<0.01	0.95	0.92 – 0.98	<0.01
Baseline MAP	1.04	1.00 – 1.08	0.04	1.04	1.00 – 1.08	0.04	1.03	1.00 – 1.07	0.03
Mechanical Ventilation	0.18	0.06 – 0.50	<0.01	0.18	0.06 – 0.55	<0.01	0.28	0.10 – 0.79	0.02
Lactate Clearance 1	1.02	1.00 – 1.03	0.01						
Lactate Clearance 2				1.15	1.03 – 1.29	0.01			
Complete Lactate Clearance							2.46	1.09 – 5.55	0.03
	12 Hours								
	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value
Age	0.95	0.91 – 0.98	<0.01	0.95	0.91 – 0.98	<0.01	0.94	0.91 – 0.94	<0.01
Baseline MAP	1.05	1.01 – 1.09	<0.01	1.05	1.01 – 1.10	<0.01	1.04	1.00 – 1.07	0.03
Mechanical Ventilation	0.22	0.07 – 0.73	0.01	0.22	0.07 – 0.74	0.01	0.31	0.11 – 0.89	0.03
Lactate Clearance 1	1.02	1.01 – 1.04	<0.01						
Lactate Clearance 2				1.31	1.12 – 1.53	<0.01			
Complete Lactate Clearance							3.98	1.76 – 8.99	<0.01
	18 Hours								
	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value
Age	0.94	0.91 – 0.98	<0.01	0.94	0.91 – 0.98	<0.01	0.95	0.91 – 0.98	<0.01
Baseline MAP	1.04	1.00 – 1.08	0.05	1.04	1.00 – 1.08	0.05	1.03	1.00 – 1.07	0.04
Mechanical Ventilation	0.15	0.04 – 0.52	<0.01	0.15	0.04 – 0.52	<0.01	0.29	0.10 – 0.84	0.02
Lactate Clearance 1	1.02	1.01 – 1.03	<0.01						
Lactate Clearance 2				1.33	1.10 – 1.61	<0.01			
Complete Lactate Clearance							3.68	1.62 – 8.38	<0.01
	24 Hours								
	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value
Age	0.96	0.92 – 0.99	0.03	0.96	0.92 – 0.99	0.03	0.95	0.92 – 0.99	<0.01
Baseline MAP	1.02	0.98 – 1.06	0.35	1.02	0.98 – 1.06	0.35	1.03	0.99 – 1.07	0.05
Mechanical Ventilation	0.15	0.04 – 0.51	<0.01	0.15	0.04 – 0.51	<0.01	0.25	0.08 – 0.74	0.01
Lactate Clearance 1	1.03	1.01 – 1.05	<0.01						
Lactate Clearance 2				1.96	1.30 – 2.96	<0.01			

Complete Lactate Clearance							5.44	2.14 – 13.8	<0.01
MAP – mean arterial pressure									