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ORIGINAL RESEARCH

Association Between the Acidemia, Lactic Acidosis, and Shock Severity With Outcomes in Patients With Cardiogenic Shock

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BACKGROUND: Lactic acidosis is associated with mortality in patients with cardiogenic shock (CS). Elevated lactate levels and systemic acidemia (low blood pH) have both been proposed as drivers of death. We, therefore, analyzed the association of both high lactate concentrations and low blood pH with 30-day mortality in patients with CS.

METHODS AND RESULTS: This was a 2-center historical cohort study of unselected patients with CS with available data for admission lactate level or blood pH. CS severity was graded using the Society for Cardiovascular Angiography and Intervention (SCAI) shock classification. All-cause survival at 30 days was analyzed using Kaplan-Meier curves and Cox proportional-hazards analysis. There were 1814 patients with CS (mean age, 67.3 years; 68.5% men); 51.8% had myocardial infarction and 53.0% had cardiac arrest. The distribution of SCAI shock stages was B, 10.8%; C, 30.7%; D, 38.1%; and E, 18.7%. In both cohorts, higher lactate or lower pH predicted a higher risk of adjusted 30-day mortality. Patients with a lactate ≥5 mmol/L or pH <7.2 were at increased risk of adjusted 30-day mortality; patients with both lactate ≥5 mmol/L and pH <7.2 had the highest risk of adjusted 30-day mortality. Patients in SCAI shock stages C, D, and E had higher 30-day mortality in each SCAI shock stage if they had lactate ≥5 mmol/L or pH <7.2, particularly if they met both criteria.

CONCLUSIONS: Higher lactate and lower pH predict mortality in patients with cardiogenic shock beyond standard measures of shock severity. Severe lactic acidosis may serve as a risk modifier for the SCAI shock classification. Definitions of refractory or hemometabolic shock should include high lactate levels and low blood pH.

Key Words: acidemia ■ acidosis ■ cardiogenic shock ■ lactic acidosis ■ shock

Cardiogenic shock (CS) is associated with poor survival despite optimal contemporary therapy.[1–9] CS exists on a spectrum of severity, with a greater degree of hemodynamic compromise correlating to worse outcomes.[1,10] The degree of hemodynamic compromise during CS can be graded using the Society for Cardiovascular Angiography and Intervention (SCAI) shock classification. Shock severity defined by the SCAI shock classification is associated with mortality in patients with CS and unselected patients treated in cardiac intensive care units.[6–12] Despite the potential to improve hemodynamics, an array of increasingly sophisticated percutaneous mechanical circulatory support devices have failed to improve survival in randomized trials.[13–16] Selection of appropriate patients, that is, those in whom the restoration of cardiac output

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CLINICAL PERSPECTIVE

What Is New?

- This analysis demonstrates that an elevated lactate level (lactic acidosis) and a low blood pH (acidemia) are independently associated with higher 30-day mortality in patients with cardiogenic shock beyond the prognostic effects of shock severity itself, with lactic acidosis having the stronger association.
- Lactic acidosis and acidemia were associated with higher mortality across the spectrum of cardiogenic shock severity, as defined by the Society for Cardiovascular Angiography and Intervention shock classification, and patients with both severe lactic acidosis (lactate level ≥5 mmol/L) and severe acidemia (blood pH <7.2) had the highest mortality risk at each level of shock severity.

What Are the Clinical Implications?

- Patients with cardiogenic shock with severe lactic acidosis and acidemia should be recognized as a high-risk subgroup typically characterized by severe shock, multiorgan dysfunction and poor outcomes; the label "hemometabolic shock" has been proposed to classify these patients.
- Further research is needed to determine whether novel treatments or management strategies are needed for patients with cardiogenic shock with severe lactic acidosis and acidemia or hemometabolic shock, and it is necessary to evaluate whether therapies directed at acidemia itself could be beneficial.

Nonstandard Abbreviations and Acronyms

CA	cardiac arrest
CS	cardiogenic shock
MCR	Mayo Clinic Rochester
SCAI	Society for Cardiovascular Angiography and Intervention
UHZ	University Heart and Vascular Center Hamburg

will reverse CS, seems paramount to improve outcomes with mechanical circulatory support.[17]

Noncardiovascular factors influence both prognosis and response to treatment in patients with CS, affecting the observed efficacy of tested therapies independent of shock severity.[5,6,8] During CS, tissue hypoperfusion and organ failure lead to metabolic deficiencies and a treatment-resistant hemometabolic CS phenotype.[5,8,17–19] Simple blood biomarkers can capture this, as lactic acidosis (defined as an elevated blood lactate level) is a well-established predictor of mortality in patients with CS.[8,20–25] Likewise, systemic acidemia (defined as a low blood pH) predicts mortality in patients with CS and may quantify the severity of the hemometabolic disturbance.[8,26,27] To determine whether lactic acidosis (elevated lactate level) and systemic acidemia (low blood pH) reflect different aspects of hypoperfusion and metabolic compromise, or whether they are markers for similar biological processes, we analyzed associations between the severity of systemic acidemia and lactic acidosis on 30-day mortality in 2 cohorts of patients with CS from mixed etiologies stratified on the basis of the SCAI shock severity scheme.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. This study was approved by the institutional review board of each institution separately as minimal risk to subjects, under a waiver of informed consent. This is a retrospective subgroup analysis of our previously reported 2-center historical cohort study that included consecutive unique adult patients with an *International Classification of Diseases*, *Ninth Revision* or *Tenth Revision* (*ICD-9*; *ICD-10*) diagnosis code for CS from the Mayo Clinic Rochester cardiac intensive care unit (MCR, 2007–2015) and University Heart and Vascular Center Hamburg (UHZ, 2009–2019) who were classified as SCAI shock stage B or greater.[6] This analysis included only those patients with available data for lactate or pH and excluded patients without either of these measurements.

Briefly, clinical, laboratory, and outcome data were extracted from the medical record at each institution. Because of different data definitions used at each institution, analyses were performed in each cohort separately. The SCAI shock stage at the time of admission was assigned using previously validated algorithms that were distinct for each cohort, as described in prior publications.[5–7] Admission values of lactate and blood pH were recorded, with arterial values used preferentially and venous values substituted when arterial values were not available. Based on the cutoffs suggested by the SCAI shock classification statement, lactate was dichotomized as </≥5 mmol/L, and pH was dichotomized as </≥7.2; patients were subsequently separated into 4 groups based on these lactate and pH cutoffs.[10]

Statistical Analysis

The primary outcome was all-cause 30-day mortality/survival, determined using the Kaplan-Meier method.

Continuous variables are summarized as mean (SD), and groups were compared using Student *t* tests or ANOVA. Categorical variables are summarized as numbers (percentage), and groups were compared using chi-square tests. Unadjusted 30-day survival was compared between groups using Kaplan-Meier curves. Lactate and pH were first analyzed as continuous variables and subsequently as dichotomous variables grouped using accepted thresholds (pH <7.2, lactate ≥5 mmol/L).[10–12] Unadjusted Cox analysis was performed in subgroups of patients with CS stratified by SCAI shock stage (C, D, and E only). Subgroup analyses for patients with acute coronary syndrome (ACS) or cardiac arrest (CA) were performed using stratified multivariable Cox proportional hazards analysis after excluding these variables. Statistical analyses were performed using JMP 14.0 Pro (SAS Institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population Characteristics

This analysis included 802 patients from the MCR cohort and 1012 patients from the UHZ cohort (n=1814 total patients; Figure 1). The combined mean age was 67.3 (14.6), 68.5% were men. CS was attributable to ACS or myocardial infarction in 51.8%, and preceding CA was present in 53.0%. The combined mean lactate was 5.7 (5.0), with 37.8% having a lactate ≥5 mmol/L. The combined mean pH was 7.26 (0.17), with 26.8% having a pH <7.2. The overall distribution of SCAI shock stages was B, 10.8%; C, 30.7%; D, 38.1%; and E, 18.7%. There were significant differences between the MCR and UHZ cohorts, including the distribution of SCAI shock stages (Table 1). The UHZ cohort demonstrated higher overall severity of shock, more use of critical care therapies, and a greater degree of acidosis with higher lactate and lower blood pH.

Patients with available data for both lactate level and blood pH (n=1581) were separated into the following groups (Table 2): lactate <5 and pH ≥7.2, 53.6%; lactate <5 and pH <7.2, 5.6%; lactate ≥5 and pH ≥7.2, 17.6%; and lactate ≥5 and pH <7.2, 23.1%; the distribution of these groups differed between the 2 cohorts (*P*<0.001). Several clinical characteristics differed across these groups, particularly SCAI shock stages, the prevalence of CA, and the use of vasoactive drugs and mechanical ventilation. Patients with low pH and either low or high lactate had higher carbon dioxide levels and base deficit, without worse markers of kidney and liver injury. Patients with SCAI stage E accounted

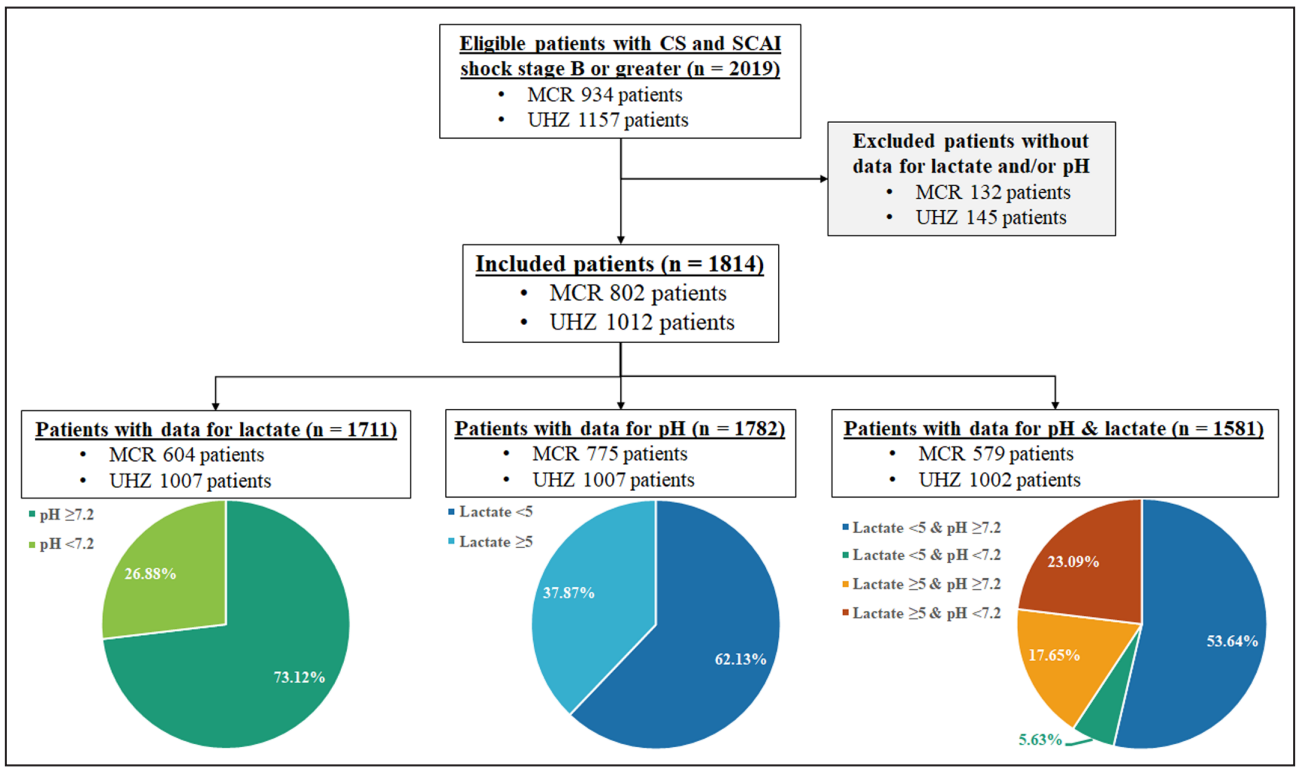

Figure 1. Flow diagram demonstrating study inclusion/exclusion criteria and prevalence of high lactate and low pH in the final study population.
CS indicates cardiogenic shock; MCR, Mayo Clinic Rochester; SCAI, Society for Cardiovascular Angiography and Intervention; and UHZ, University Heart and Vascular Center Hamburg.

Table 1. Clinical Characteristics and Outcomes of the Mayo Clinic Rochester and University Heart Center Hamburg Cardiogenic Shock Cohorts

	Mayo Clinic Rochester (n=802)	University Heart Center Hamburg (n=1012)	*P* value
Demographics and comorbidities			
Age, y	67.7 (14.0)	67.0 (15.1)	0.31
Male sex	516 (64.3)	726 (71.8)	<0.001
Number of comorbidities	1.2 (1.1)	1.3 (1.2)	0.99
Hypertension	274 (34.2)	484 (50.7)	<0.001
Diabetes	234 (29.3)	262 (27.4)	0.71
Chronic kidney disease	164 (20.5)	173 (18.2)	0.21
Prior myocardial infarction	159 (19.9)	236 (24.5)	0.02
Prior stroke	90 (11.3)	83 (8.6)	0.07
Characteristics of shock			
Acute coronary syndrome	464 (57.9)	475 (46.9)	<0.001
STEMI	311 (38.8)	337 (33.6)	0.02
Cardiac arrest*	341 (42.5)	621 (61.5)	<0.001
Treatments received			
Mechanical ventilator	383 (47.8)	722 (71.8)	<0.001
Vasoactive drugs	389 (48.5)	886 (90.3)	<0.001
Use of temporary MCS†	357 (44.5)	316 (31.3)	<0.001
PCI	258 (32.2)	372 (36.8)	0.04
Dialysis	137 (17.1)	332 (32.9)	<0.001
Admission data			
Systolic blood pressure, mm Hg	110.2 (28.5)	103.4 (35.5)	<0.001
Heart rate, BPM	93.3 (24.2)	89.0 (34.6)	0.003
BUN, mg/dL	31.8 (19.6)	…	…
Creatinine, mg/dL	1.6 (1.1)	2.0 (1.7)	<0.001
eGFR, mL/min	55.3 (28.1)	43.9 (23.4)	<0.001
Bicarbonate, mmol/L	20.7 (5.4)	19.8 (5.9)	<0.001
Chloride, mmol/L	102.9 (6.8)	…	…
Anion gap, mmol/L	14.5 (5.0)	…	…
Base deficit, mmol/L	5.3 (6.1)	7.3 (8.5)	<0.001
Arterial P_{CO_2}, mm Hg	41.7 (12.3)	48.8 (22.6)	<0.001
AST, IU/mL	464.2 (1406.5)	572.8 (1530.8)	0.15
ALT, IU/mL	292.6 (820.9)	349.7 (855.0)	0.19
Lactate, mmol/L	4.1 (3.7)	6.6 (5.4)	<0.001
Lactate ≥5 mmol/L	163 (27.0)	485 (48.2)	<0.001
pH, units	7.30 (0.12)	7.23 (0.20)	<0.001
pH <7.2	138 (17.8)	341 (33.9)	<0.001
Lactate and pH group			<0.001
<5 mmol/L and ≥7.2	370 (63.9)	478 (47.7)	
<5 mmol/L and <7.2	48 (8.3)	41 (4.1)	
≥5 mmol/L and ≥7.2	92 (15.9)	187 (18.7)	
≥5 mmol/L and <7.2	69 (11.9)	296 (29.5)	
SCAI shock stage			<0.001
B	156 (19.5)	40 (4.0)	
C	124 (15.5)	433 (42.8)	
D	439 (54.7)	282 (27.9)	
E	83 (10.3)	257 (25.4)	
Outcomes			
30-d survival	480 (59.9)	423 (41.8)	<0.001

Data are from time of admission. Data displayed as mean (SD) for continuous variables and number (percentage) for categorical variables. *P* value is for Student *t* test (continuous variables) or chi-square test (categorical variables). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BPM, beats per minute; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Cardiac arrest in the Mayo Clinic Rochester cohort was defined based on admission diagnosis, and in the University Heart Center Hamburg cohort it was defined as preceding cardiopulmonary resuscitation.

†Temporary MCS included intra-aortic balloon pump, Impella, and extracorporeal membrane oxygenator; the intra-aortic balloon pump was not used in the University Heart Center Hamburg cohort.

for 7.9% of patients with lactate <5 mmol/L and blood pH ≥7.2 and 48.2% of patients with lactate ≥5 mmol/L and blood pH <7.2 (Figure S1A); 55.0% of patients with SCAI stage E had lactate ≥5 mmol/L and blood pH <7.2 (Figure S1B).

Unadjusted 30-Day Mortality Analysis in the Overall Cohort

A total of 911 patients died within 30 days of admission, yielding a combined 30-day survival rate of 50.2%. The 30-day survival was higher in the MCR cohort (59.9% versus 41.8%; *P*<0.001; Table 1). When analyzed separately as continuous variables, a higher lactate level (Figure 2A) or a lower blood pH (Figure 2B) were associated with higher unadjusted 30-day mortality (both *P*<0.001; Table 3). The optimal cutoffs for lactate (2.8 mmol/L in MCR and 8.2 mmol/L in UHZ) and blood pH (7.32 in MCR and 7.20 in UHZ) differed substantially between cohorts. Either a lactate ≥5 mmol/L (Figure S2A and S2B) or a blood pH <7.2 (Figure S3A and S3B) was associated with higher unadjusted 30-day mortality in both cohorts on Kaplan-Meier analysis (both *P*<0.001). When patients were divided into groups based on a lactate cut-off of 5 and a blood pH cutoff of 7.2 (Table 2), a gradient of 30-day survival was observed in both cohorts on Kaplan-Meier analysis (Figure S4A and S4B). Patients with lactate <5 and blood pH ≥7.2 had the lowest mortality and patients with lactate ≥5

Table 2. Clinical Characteristics and Outcomes of the Combined Cohort According to Lactate and Blood pH Groups (Based on a Lactate Cutoff of 5 and a Blood pH Cutoff of 7.2)

	Lactate <5 and pH ≥7.2 (n=848)	Lactate <5 and pH <7.2 (n=89)	Lactate ≥5 and pH ≥7.2 (n=279)	Lactate ≥5 and pH <7.2 (n=365)
Demographics and comorbidities				
Age, y	67.5 (14.7)	67.0 (13.2)	67.6 (16.2)	66.4 (13.8)
Male sex	570 (67.2)	68 (76.4)	174 (62.4)	275 (75.3)
Number of comorbidities	1.3 (1.2)	1.2 (1.1)	1.2 (1.1)	1.1 (1.1)
Characteristics of shock				
Acute coronary syndrome	447 (52.7)	48 (53.9)	128 (45.9)	179 (49.0)
STEMI	334 (39.4)	32 (36.0)	89 (31.9)	151 (41.4)
Cardiac arrest*	332 (39.2)	60 (67.4)	158 (56.6)	323 (88.5)
Treatments received				
Mechanical ventilator	446 (52.6)	59 (66.3)	183 (65.6)	331 (90.7)
Vasoactive drugs	556 (65.6)	64 (71.9)	217 (77.8)	339 (92.9)
Use of temporary MCS†	340 (40.1)	30 (33.7)	104 (37.3)	114 (31.2)
PCI	309 (36.4)	29 (32.6)	90 (32.3)	128 (35.1)
Dialysis	217 (25.6)	31 (34.8)	86 (30.8)	107 (29.3)
Admission data				
Systolic blood pressure, mm Hg	110.2 (31.7)	105.9 (34.0)	103.7 (30.6)	98.7 (38.9)
Heart rate, BPM	92.6 (27.5)	90.5 (28.0)	91.4 (28.6)	83.2 (40.6)
BUN, mg/dL‡	33.2 (21.3)	32.1 (18.1)	30.2 (17.0)	28.2 (17.0)
Creatinine, mg/dL	1.8 (1.7)	2.2 (1.8)	1.9 (1.1)	2.0 (1.5)
eGFR, mL/min	50.7 (27.4)	45.5 (28.4)	44.1 (23.5)	42.6 (20.6)
Bicarbonate, mmol/L	22.6 (4.8)	18.8 (5.0)	19.0 (4.8)	14.9 (4.7)
Chloride, mmol/L‡	102.6 (7.1)	105.2 (6.5)	102.9 (7.0)	105.1 (6.0)
Anion gap, mmol/L‡	13.6 (3.9)	15.5 (4.4)	17.9 (5.6)	21.2 (6.9)
Base deficit, mmol/L	2.6 (5.6)	9.4 (4.7)	7.3 (5.3)	15.8 (5.6)
Arterial P_{CO_2}, mm Hg	40.8 (15.2)	57.8 (16.5)	37.5 (9.7)	61.9 (24.4)
AST, IU/mL	369.2 (1074.4)	390.0 (831.7)	989.3 (2474.9)	716.9 (1586.8)
ALT, IU/mL	230.7 (573.8)	220.4 (481.0)	569.0 (1273.5)	470.1 (1070.1)
SCAI shock stage				
B	94 (11.1)	5 (5.6)	0 (0)	0 (0)
C	265 (31.2)	30 (33.7)	112 (40.1)	107 (29.3)
D	412 (48.6)	44 (49.4)	100 (35.8)	82 (22.5)
E	67 (7.9)	10 (11.2)	67 (24.0)	176 (48.2)
Outcomes				
30-d survival	517 (61.0)	39 (43.8)	108 (38.7)	81 (22.2)

Data are from time of admission. Data displayed as mean (SD) for continuous variables and number (percentage) for categorical variables. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BPM, beats per minute; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Cardiac arrest in the Mayo Clinic Rochester cohort was defined based on admission diagnosis, and in the University Heart Center Hamburg cohort it was defined as preceding cardiopulmonary resuscitation.

†Temporary MCS included intra-aortic balloon pump, Impella, and extracorporeal membrane oxygenator; the intra-aortic balloon pump was not used in the University Heart Center Hamburg cohort.

‡Reported values are from Mayo Clinic only, as these data were not available in the University Heart Center Hamburg cohort.

and blood pH <7.2 had the highest mortality; the other groups had intermediate mortality. Patients in the highest-risk group (lactate ≥5 and blood pH <7.2) had markedly higher unadjusted 30-day mortality than patients in the lowest-risk group (lactate <5 and blood pH ≥7.2) in both cohorts (both $P<0.001$; Table 3).

Unadjusted 30-Day Mortality Analysis by SCAI Shock Stage

As the SCAI shock stage increased, lactate increased and blood pH decreased, with a higher prevalence of patients with lactate ≥5 mmol/L or blood pH <7.2

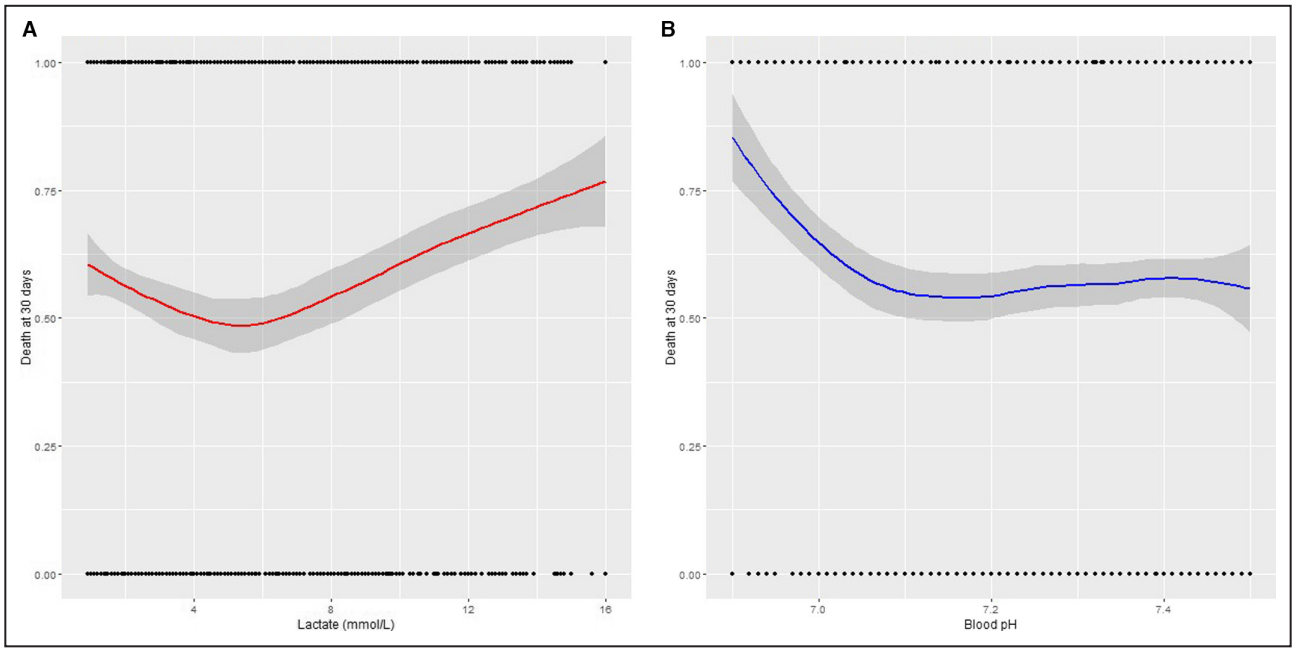

Figure 2. Locally estimated scatterplot smoothing (LOESS) curves demonstrating observed 30-day mortality in cardiogenic shock patients as a function of admission lactate level (A) or admission blood pH (B) in the combined cohort.

(data not shown); based on the definition of SCAI shock stage B, no patients with SCAI shock stage B had an elevated lactate level. Survival at 30 days progressively decreased with the rising SCAI shock stage, regardless of the lactate level (Figure 3A) or blood pH (Figure 3B). Patients with lactate ≥5 mmol/L had lower 30-day survival in each SCAI shock stage (all $P<0.05$; Figure 3A). Patients with blood pH <7.2 had lower 30-day survival in each SCAI shock stage except for SCAI shock stage B (all others $P<0.05$; Figure 3B). The gradient of 30-day survival across the SCAI shock stages was influenced by the presence of a lactate ≥5 mmol/L and/or blood pH <7.2, which were associated with lower 30-day survival (Figure 4). In each SCAI shock stage, patients with lactate ≥5 mmol/L and blood pH <7.2 had lower 30-day survival than patients with lactate <5 and blood pH ≥7.2 (all $P<0.01$, Figure 4).

Multivariable-Adjusted 30-Day Mortality Analysis

After multivariable adjustment, a higher lactate level or lower blood pH was associated with incrementally higher adjusted 30-day mortality when analyzed separately as continuous variables (both $P<0.001$; Table 3). Either a lactate ≥5 mmol/L or a blood pH <7.2 was associated with higher adjusted 30-day mortality in both cohorts (both $P<0.001$; Table 3). Patients with lactate ≥5 and blood pH <7.2 had ≈2-fold higher adjusted 30-day mortality than patients with lactate <5 and blood

Table 3. Hazard Ratio and 95% CI Values for 30-Day Mortality in Each Cohort Using Cox Proportional Hazard Analysis*

	Mayo Clinic Rochester cohort		University Heart Center Hamburg cohort	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Lactate (per 1 mmol/L higher)	1.13 (1.11–1.16)	1.09 (1.05–1.12)	1.10 (1.09–1.12)	1.07 (1.05–1.09)
Blood pH (per 0.1 unit higher)	0.66 (0.61–0.72)	0.77 (0.70–0.86)	0.78 (0.75–0.81)	0.87 (0.82–0.92)
Lactate ≥5 mmol/L	2.91 (2.27–3.73)	1.96 (1.48–2.59)	2.26 (1.91–2.66)	1.49 (1.22–1.82)
Blood pH <7.2	2.91 (2.28–3.71)	1.92 (1.47–2.49)	2.45 (2.08–2.89)	1.72 (1.39–2.12)
Lactate ≥5 mmol/L and blood pH <7.2 vs lactate <5 mmol/L and blood pH ≥7.2	4.48 (3.23–6.22)	2.73 (1.87–3.99)	3.04 (2.52–3.68)	1.94 (1.52–2.48)

*Before and after adjustment for age and sex; Society for Cardiovascular Angiography and Intervention shock stage; number of comorbidities (hypertension, diabetes, stroke, myocardial infarction, chronic kidney disease); admission diagnosis of acute coronary syndrome or myocardial infarction; preceding cardiac arrest; use of vasoactive drugs and mechanical ventilation on admission; inpatient use of percutaneous coronary intervention or temporary mechanical circulatory support; admission heart rate, systolic blood pressure, and estimated glomerular filtration rate.

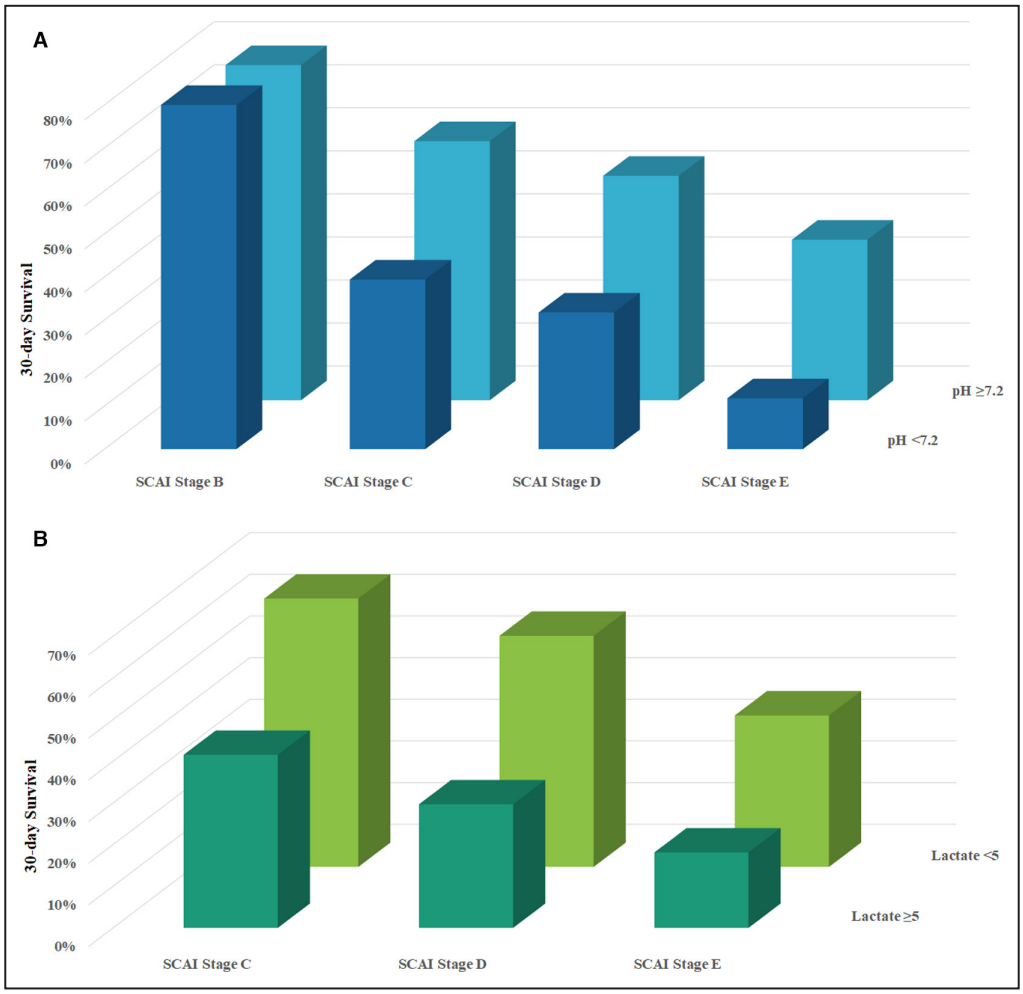

Figure 3. Observed 30-day survival in cardiogenic shock patients as a function of SCAI shock stage and admission lactate level (A) or admission blood pH (B). Note that no patients in SCAI shock stage B had an elevated lactate.
All *P*<0.05 between patients with lactate level <5 mmol/L and lactate level ≥5 mmol/L. All *P*<0.05 between patients with pH <7.2 and pH ≥7.2, except for SCAI shock stage B (*P*>0.1). Note that all patients with SCAI shock stage B had a lactate level <5 mmol/L and were excluded from this analysis. SCAI indicates Society for Cardiovascular Angiography and Intervention.

pH ≥7.2 in both cohorts (both *P*<0.001; Table 3). When both lactate and blood pH were entered into a multivariable Cox model together as continuous variables, only lactate remained significantly associated with 30-day mortality (*P*<0.01 in both cohorts). When lactate level ≥5 mmol/L and blood pH <7.2 were entered into a multivariable Cox model together as categorical variables, they were associated with higher 30-day mortality in the MCR cohort (both *P*<0.05) but not in the UCH cohort (both *P*>0.1).

Subgroup Analyses

Observed 30-day survival increased incrementally across the lactate and blood pH groups in patients with and without ACS (Figure 5A) or CA (Figure 5B). For patients with ACS, both higher lactate and lower blood pH were associated with higher adjusted 30-day mortality when considered individually either as continuous or dichotomized variables (Table 4); effect sizes were generally smaller for patients without ACS. For patients with CA, both higher lactate and lower blood pH were associated with higher adjusted 30-day mortality when considered individually either as continuous or dichotomized variables (Table 5); effect sizes were generally smaller for patients without CA.

DISCUSSION

Main Findings

This 2-center cohort study identifies strong and independent associations of blood lactate levels and blood pH with short-term mortality in patients with CS,

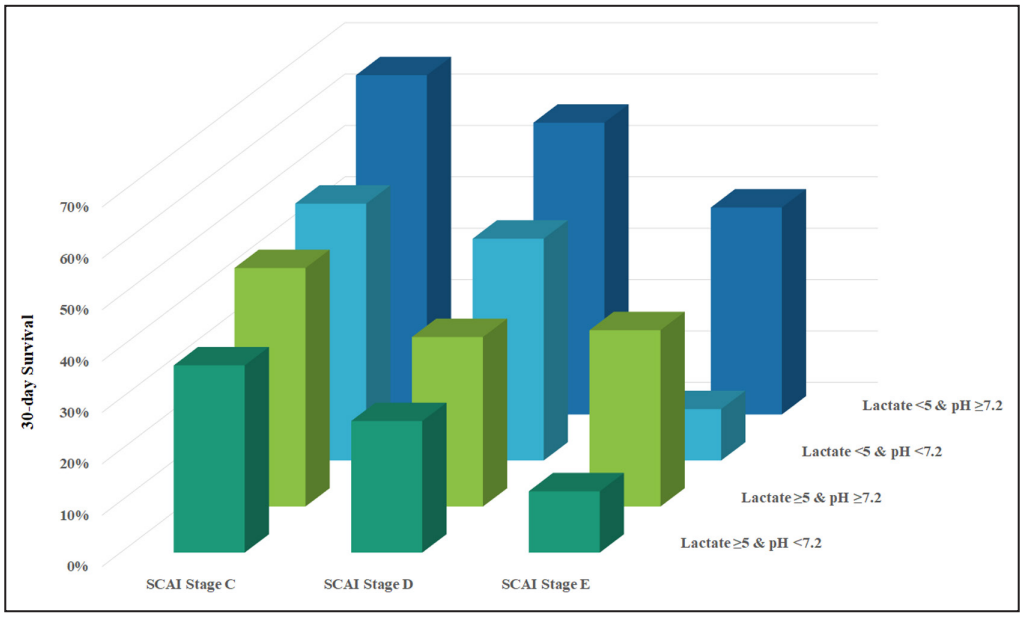

Figure 4. Observed 30-day survival in cardiogenic shock patients as a function of SCAI shock stage, admission pH and admission lactate level.
Note that all patients with SCAI shock stage B had a lactate level <5 mmol/L and were excluded from this analysis. SCAI indicates Society for Cardiovascular Angiography and Intervention.

including those with and without ACS or CA. This effect was present even when accounting for the severity of CS using the SCAI shock classification, which is notable because lactate levels were used to define the SCAI shock stages in both cohorts. Despite substantial differences in the clinical characteristics of the cohorts reflecting higher shock severity in the UHZ cohort, the associations between lactate levels and blood pH and survival were remarkably consistent in these 2 large, unselected cohorts of patients with CS from various etiologies. These findings suggest that both pH and lactate concentrations should be considered to estimate mortality in patients with CS, independent from shock severity per se. Because these commonly available laboratory biomarkers provide added risk stratification on top of shock severity, it may be useful to incorporate these variables into clinical definitions of the SCAI shock stages.

Lactate and Mortality in Cardiogenic Shock

Our finding that an elevated lactate ≥5 mmol/L is strongly associated with short-term mortality is consistent with the published literature.[10] Lactate levels are an essential marker of hypoperfusion that have been incorporated into the 2 most widely used CS risk stratification scores.[20,21] Lactate levels are a major predictor of mortality in patients with CS and have recently been identified as one of the most important blood biomarkers for predicting CS outcomes.[22–25] Although both lactate levels and blood pH were strongly associated with mortality individually, the relationship was more robust for lactate when both were incorporated into the same multivariable model. This implies that the severity of lactic acidosis, reflecting the magnitude and duration (area under the curve) of hypoperfusion, is the more important physiologic variable. This mirrors a prior analysis of patients with CS from an overlapping MCR cardiac intensive care unit cohort, which found that the lactate level alone outperformed a composite acidosis score including blood pH, base excess, and anion gap.[8] Lactic acidosis is a critical diagnostic criterion for hypoperfusion used widely to assign the SCAI shock stage, as in our study.[5–7,10–12] Nonetheless, patients with CS with higher lactate levels are more likely to die in every SCAI shock stage, implying that lactate levels provide a graded relationship with mortality risk beyond other measures of shock severity.[6–9,12] Patients with CS with severe lactic acidosis in a given SCAI shock stage are at elevated risk and might be more appropriately considered as having a higher SCAI shock stage.

pH and Mortality in Cardiogenic Shock

The blood pH and severity of systemic acidemia reflect the integration of pathologic acid-base disturbances with adaptive homeostatic buffer mechanisms and the ability of the respiratory system to compensate. The association between blood pH and mortality in patients with CS has not been examined extensively.

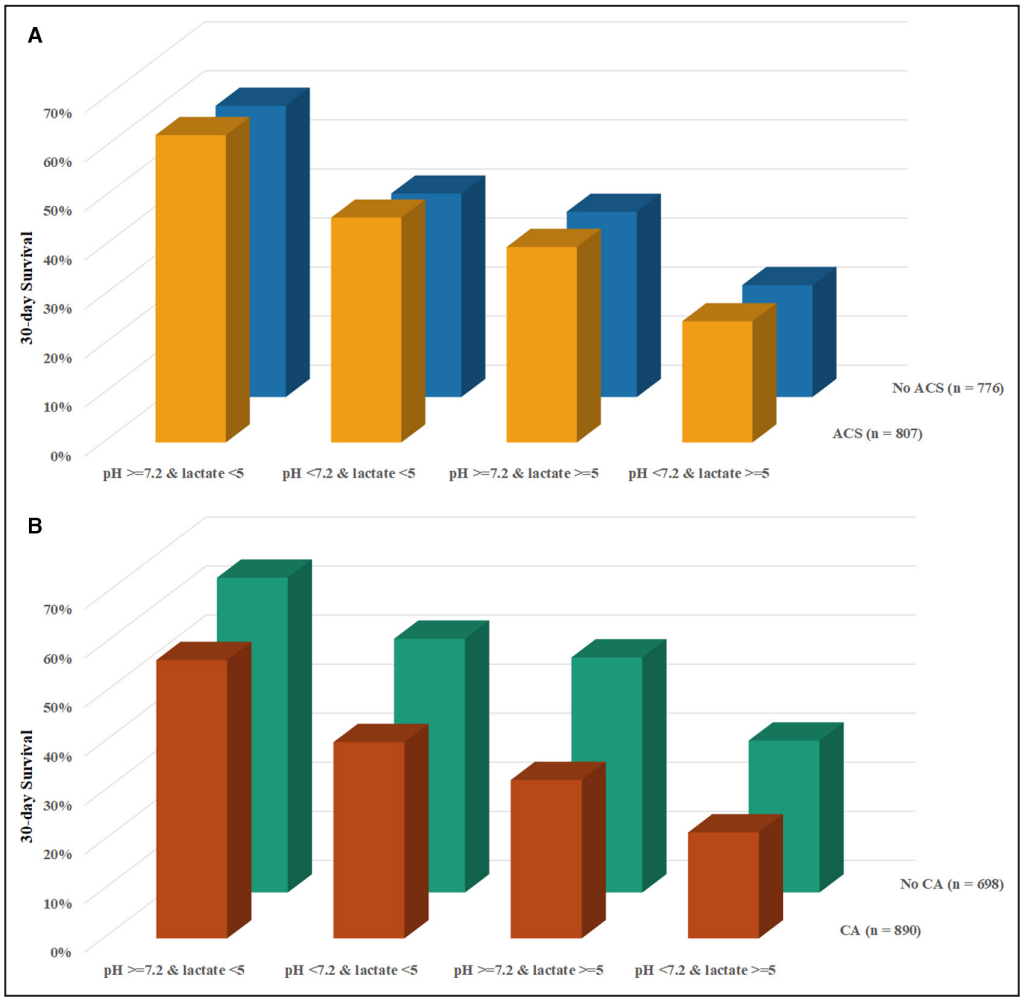

Figure 5. Observed 30-day survival in patients with cardiogenic shock as a function of admission pH and admission lactate level groups in patients with and without ACS (A) or CA (B) in the combined cohort.
ACS indicates acute coronary syndrome; and CA, cardiac arrest.

Prior studies have focused primarily on patients following CA and patients receiving extracorporeal membrane oxygenator support, finding that a lower blood pH is an important adverse prognostic variable.[26,27] A recent analysis in the MCR CS population found that a composite laboratory assessment of acidosis (including pH, anion gap, and base deficit) was highly associated with short-term mortality in patients with CS. A low blood pH was one of the strongest predictors of adjusted in-hospital mortality (other than lactate level).[8] Prior analyses have demonstrated that lactate levels rise and blood pH drops as the severity of CS worsens (defined by rising SCAI shock stage), highlighting the interrelationship between the severity of shock and the magnitude of acidosis.[5]

Overall, severe systemic acidemia with a low blood pH in patients with CS likely reflects the inability of the respiratory system and endogenous buffering mechanisms to compensate for acid-base derangements including lactic and nonlactic acidosis. Respiratory acidosis (hypercarbic respiratory failure) appeared to be a major contributor to low blood pH in our cohort, particularly for patients without elevated lactate levels. Potential contributors to hypercarbic respiratory failure in patients with CS may include increased physiologic dead space from chronic lung disease, acute lung injury, and pulmonary vascular disease in addition to compromised lung perfusion from CS itself. These noncardiovascular disease processes may confer an adverse prognosis in patients with CS, explaining in part the association between acidemia and mortality and highlighting the importance of inadequate compensation for metabolic acidosis attributable to respiratory failure as a determinant of poor prognosis in CS. Although lactate appeared to be a better overall predictor of mortality, patients with CS with a lower blood pH were more likely to die independent of their shock severity; this was less apparent in SCAI shock stage

Table 4. Adjusted Hazard Ratio and 95% CI Values for Blood pH as a Predictor of 30-Day Mortality in Patients With and Without ACS in Each Cohort Using Multivariable Cox Proportional Hazard Analysis*

Group	Mayo Clinic Rochester		University Heart Center Hamburg	
	With ACS	Without ACS	With ACS	Without ACS
Lactate (per 1 mmol/L)	1.140 (1.090–1.193)	1.078 (1.024–1.135)	1.085 (1.049–1.122)	1.063 (1.037–1.089)
Lactate ≥5 mmol/L	2.269 (1.578–3.264)	1.941 (1.242–3.033)	1.545 (1.117–2.139)	1.498 (1.152–1.950)
Blood pH (per 0.1 unit)	0.716 (0.626–0.819)	0.807 (0.685–0.951)	0.832 (0.761–0.908)	0.883 (0.821–0.949)
Blood pH <7.2	2.274 (1.602–3.226)	1.763 (1.136–2.735)	2.098 (1.516–2.903)	1.500 (1.127–1.997)

ACS indicates acute coronary syndrome.

*Adjusted for age and sex; Society for Cardiovascular Angiography and Intervention shock stage; number of comorbidities (hypertension, diabetes, stroke, myocardial infarction, chronic kidney disease); use of vasoactive drugs and mechanical ventilation on admission; inpatient use of percutaneous coronary intervention or temporary mechanical circulatory support; preceding cardiac arrest; admission heart rate, systolic blood pressure, and estimated glomerular filtration rate.

B, presumably caused by the presence of nonlactic metabolic and respiratory acidosis, which may be less harmful. The patients with the worst outcomes were those who simultaneously manifested both marked lactic acidosis and severe systemic acidemia, particularly in SCAI shock stage E. This suggests that the severity of lactic acidosis coupled with an impaired homeostatic response leading to severe systemic acidemia is particularly detrimental. Notably, the observed survival for patients in SCAI shock stage E appeared worse for those with low blood pH than those with high lactate levels. As we attempt to develop an evidence-based definition of hemometabolic CS using laboratory variables, these data suggest that both high lactate levels and low blood pH should be incorporated into the definition to reflect both severe hypoperfusion and failing homeostatic mechanisms.[8,19]

Hypoperfusion and Hemometabolic Shock

While the severity of lactic acidosis is clearly an important prognostic marker in CS, it remains uncertain how to use this information to tailor therapy. Impaired lactate clearance (defined as a persistently elevated or rising lactate over time) may be an even more powerful prognostic marker than an elevated admission lactate level alone.[22,28] Indeed, both MCR and UHZ incorporated a rising lactate level into our definitions of SCAI shock stage D, and patients in SCAI shock stage D had substantially higher mortality than patients with lower CS severity.[5–9] For this reason, worsening lactic acidosis in patients with CS should trigger an escalation of therapy to alleviate ongoing hypoperfusion. Severe systemic acidemia is known to compromise the cardiovascular response to catecholamines and therefore may directly contribute to worsening or refractory shock; this explains the high prevalence of low blood pH among patients in SCAI shock stage E.[29,30]

Hypoperfusion causes systemic acidemia directly via lactic acidosis and often causes kidney injury that further compromises acid-base homeostasis and buffering of the metabolic acid load; in addition, respiratory failure is common and can further impair compensation. These metabolic derangements contribute to a worsening shock state termed *hemometabolic shock*.[8,17–19] Breaking this shock-acidosis-shock vicious cycle using alkali therapy (such as sodium bicarbonate) to reverse systemic acidemia seems logical, but this approach remains controversial and has not been clearly demonstrated to improve outcomes in

Table 5. Adjusted Hazard Ratio and 95% CI Values for Blood pH as a Predictor of 30-Day Mortality in Patients With and Without Preceding CA in Each Cohort Using Multivariable Cox Proportional Hazard Analysis*

Group	Mayo Clinic Rochester		University Heart Center Hamburg	
	With CA	Without CA	With CA	Without CA
Lactate (per 1 mmol/L)	1.121 (1.073–1.171)	1.046 (0.994–1.101)	1.065 (1.042–1.089)	1.087 (1.038–1.139)
Lactate ≥5 mmol/L	2.216 (1.543–3.183)	1.645 (1.034–2.615)	1.615 (1.256–2.076)	1.355 (0.938–1.956)
Blood pH (per 0.1 unit)	0.741 (0.647–0.849)	0.819 (0.695–0.996)	0.868 (0.818–0.921)	0.887 (0.769–1.024)
Blood pH <7.2	1.910 (1.369–2.665)	1.840 (1.144–2.961)	1.675 (1.324–2.120)	1.849 (1.110–3.079)

CA indicates cardiac arrest.

*Adjusted for age and sex; Society for Cardiovascular Angiography and Intervention shock stage; number of comorbidities (hypertension, diabetes, stroke, myocardial infarction, chronic kidney disease); use of vasoactive drugs and mechanical ventilation on admission; inpatient use of percutaneous coronary intervention or temporary mechanical circulatory support; acute coronary syndrome; admission heart rate, systolic blood pressure and estimated glomerular filtration rate.

critically ill patients.[29,31] Greater benefits of alkali may be observed in patients with acute kidney injury, and we anticipate that patients with CS with lower blood pH might more likely to benefit.[31] Alternatively, adjustments in mechanical ventilator settings to improve alveolar ventilation and clear carbon dioxide may be necessary. For this reason, routine measurement of arterial pH (ideally a full arterial blood gas analysis) in addition to the lactate level is appropriate for initial risk stratification and management of patients with CS. A therapeutic trial of alkali therapy can be considered for patients with CS with severe systemic acidemia from metabolic acidosis if they are not responding appropriately to standard doses of vasopressors, but future studies are need to determine the benefit of this approach.[18,30]

Strengths and Limitations

The strengths of the analysis are its inclusion of 2 independent, large, unselected cohorts of patients with CS. Independent validation in prospective cohorts is warranted. The thresholds for categorized analysis were taken from clinical experience rather than calculating optimal cutoff values.[10] The fact that lactate level and blood pH were predictors of mortality when considered as continuous parameters validates their relevance. While it is tempting to speculate on the mechanisms leading to early death, the study merely describes associations. It remains entirely unclear whether interventions targeting blood pH or lactate levels can improve outcomes in CS. Ideal interventions would target upstream drivers of hemodynamic and metabolic compromise (ie, hypoperfusion) rather than their consequences, such as lactic acidosis and systemic acidemia. While the analysis of 2 large cohorts validates our findings, performing separate analyses within each cohort has some shortcomings, such as decreased statistical power compared with combining the cohorts. We did not have data on treatments for acidosis, nor did we have comprehensive data regarding all measurements reflecting acid-base balance or serial measures of acidosis; we combined both arterial and venous lactate and pH measurements, leading to some variability.

In conclusion, severe lactic acidosis and systemic acidemia are important predictors of short-term mortality in patients with CS independent of the severity of shock using the SCAI shock stages. Patients with CS and higher lactate level or lower blood pH are more likely to die across the spectrum of shock severity. As measured by the lactate level, the severity of hypoperfusion appears more important for predicting mortality than the extent of intrinsic compensation, as measured by the blood pH. Arterial pH and lactate levels should be routinely measured in patients with CS and reported in clinical studies. The presence of severe lactic acidosis or severe systemic acidemia should be considered risk modifiers that can identify high-risk patients when added to the SCAI shock classification.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Figures S1–S4

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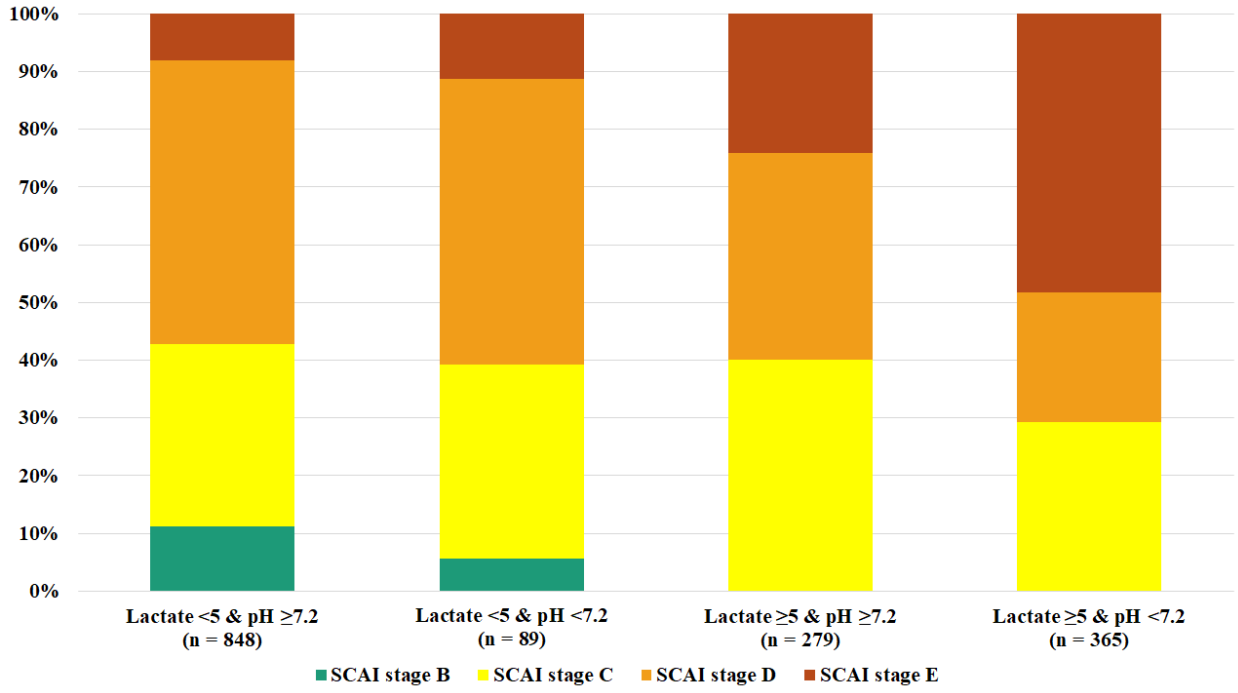
SUPPLEMENTAL MATERIAL

Figure S1. Distribution of SCAI shock stages as a function of lactate and blood pH groups (a), and distribution of lactate and blood pH groups as a function of SCAI shock stages (b). No patients in SCAI shock stage B had a lactate level ≥5 mmol/L.



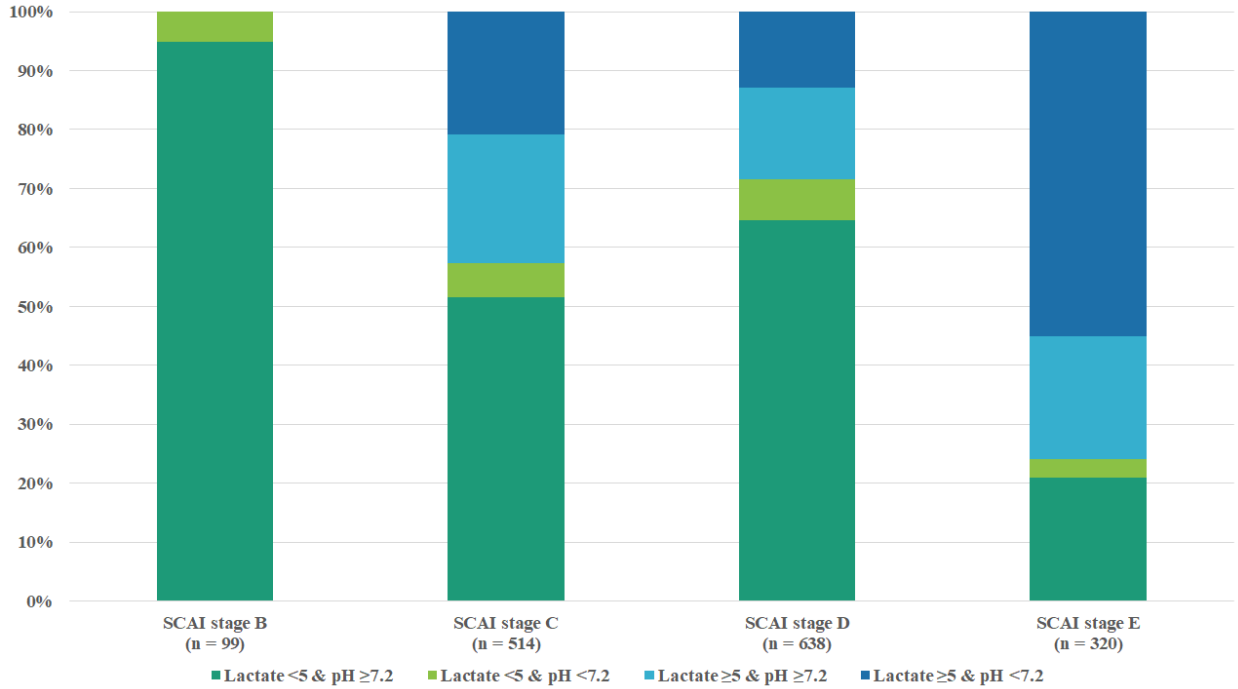


Figure S2. Kaplan-Meier 30-day mortality curves of patients with versus without a lactate level ≥5 mmol/L in the Mayo Clinic Rochester (MCR) cohort (a) and University Heart Center Hamburg (UHZ) cohort (b).

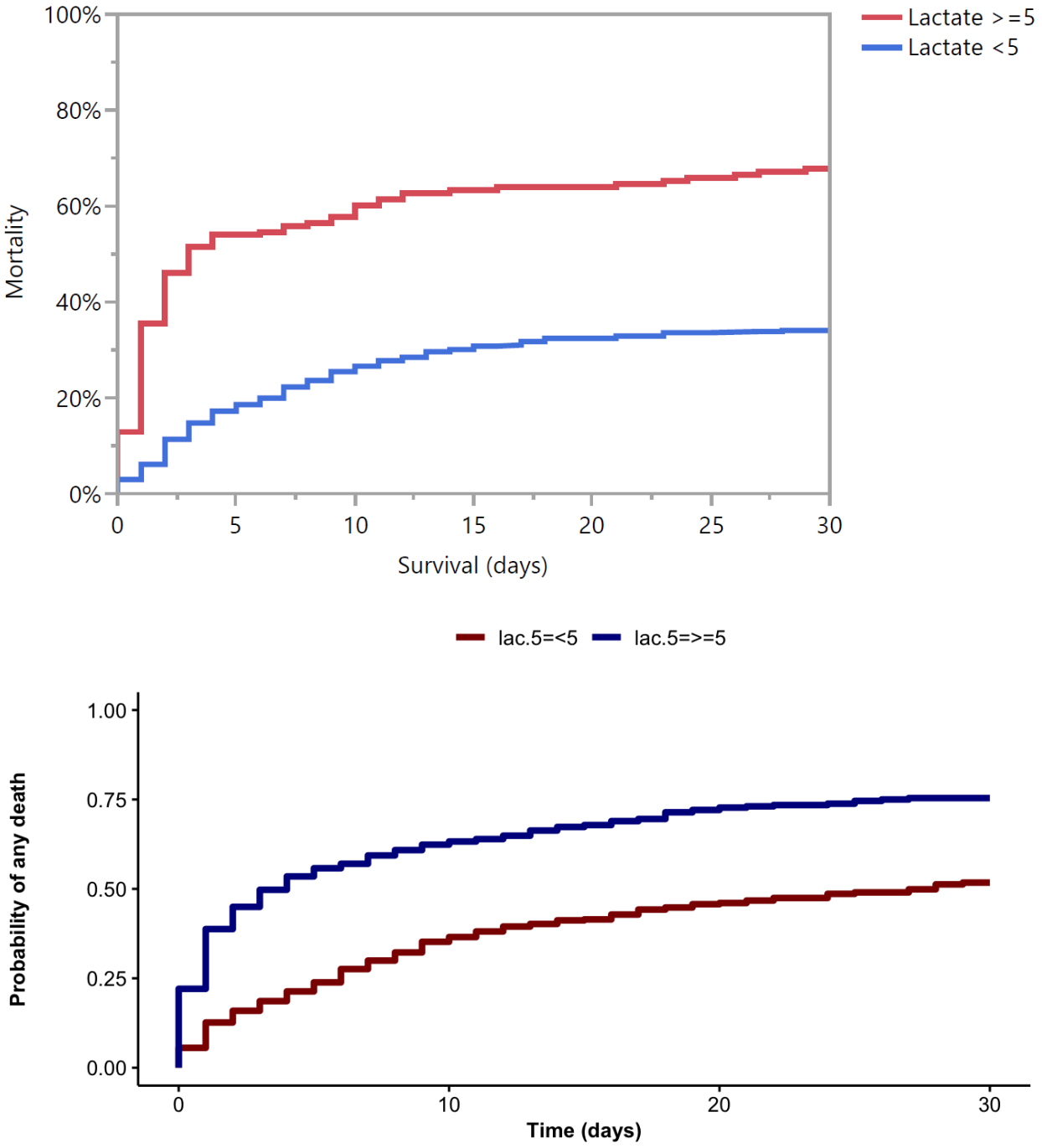


Figure S3. Kaplan-Meier 30-day mortality curves of patients with versus without a blood pH <7.2 in the Mayo Clinic Rochester (MCR) cohort (a) and University Heart Center Hamburg (UHZ) cohort (b).

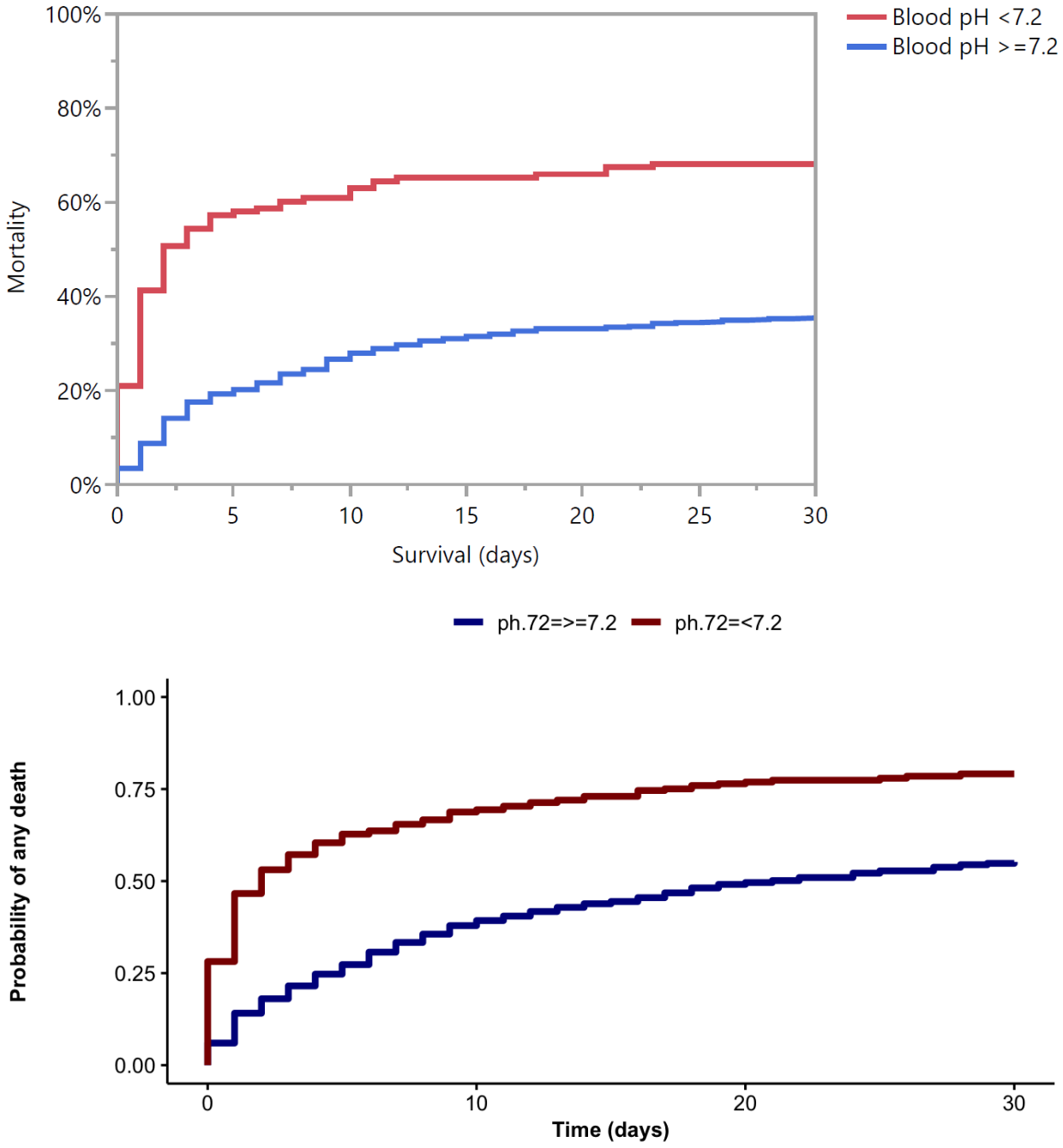


Figure S4. Kaplan-Meier 30-day mortality curves of patients divided into groups based on lactate level ≥5 mmol/L and blood pH <7.2 in the Mayo Clinic Rochester (MCR) cohort (a) and University Heart Center Hamburg (UHZ) cohort (b).