CHEST

In Patients With Sepsis, Initial Lactate Clearance Is Confounded Highly by Comorbidities and Poorly Predicts Subsequent Lactate Trajectory

To the Editor:

Serum lactate clearance, defined as a 10% drop in lactate over 2 h, commonly is used and recommended by guidelines to assess therapeutic response to resuscitation in sepsis.[1,2] Yet, its physiologic and prognostic significance is understood incompletely.[3] Lactate clearance is confounded by comorbidities (liver and renal dysfunction), which themselves predict adverse outcomes. It is unknown how much of the prognostic value of lactate clearance actually is attributable to these comorbidities. Further, although overall lactate trajectory throughout hospitalization predicts mortality rates in critically ill patients,[4] no study has determined whether initial lactate clearance predicts overall lactate trajectory in hospitalized patients with sepsis.

Patients and Methods

We conducted a retrospective cohort study and screened 22,074 subjects who were admitted to the University of Michigan Hospital from 2015 through 2019 who met validated surveillance criteria for sepsis.[5] We included adult patients who were admitted through the ED who had clinical suspicion of infection (evidenced by blood culture acquisition, new initiation of IV antibiotics, and 4 consecutive days of antibiotics), fewer than two serum lactate measurements (the first within 72 h of admission and a repeat 2 to 12 h later), and serum lactate > 2 mM within 72 h. We excluded patients who had been transferred from an outside facility. Per convention,[1,2] we initially defined lactate clearance as a 10% drop in lactate in 2 to 12 h. We fit a mixed-effects exponential decay model to estimate the aggregate rate of change in lactate among patients who did and did not achieve lactate clearance. We fit a multivariable logistic regression model that incorporated clinical covariates known to impact lactate metabolism (age, sex, cirrhosis, and end-stage renal disease) to determine whether lactate clearance independently predicted 90-day hospital mortality rates. We also compared 2- to 12-h lactate clearance to a previously validated 24-h change in peak lactate.[6]

Results

We identified 4,775 patients in the screening cohort with elevated lactate levels and at least two lactate measurements. Of these, 2,963 patients (62%) met the lactate clearance threshold, and 1,812 patients (38%) did not (Table 1). Those who met the lactate clearance threshold had lower Acute Physiology and Chronic Health Evaluation and Sequential Organ Failure Assessment scores, less renal disease, and less liver disease than subjects who did not. Individuals who met the lactate clearance threshold had a lower 90-day hospital mortality rate (15.9%) compared with individuals who did not (21.8%). In multivariable analysis, the presence of cirrhosis was associated with an average marginal effect of a 10.6% increase in absolute mortality rate. In contrast, the impact of lactate clearance was approximately one-half the magnitude and associated with an average marginal effect of a 5.4% reduction in absolute 90-day mortality rate (Table 1; $P < .001$).

Both groups' lactate trajectories during hospitalization were highly variable (Fig 1). Compared with those who did not achieve lactate clearance, individuals who did achieve lactate clearance actually exhibited slower rates of overall lactate clearance during their initial 72 h of admission, which is a difference that was statistically significant but clinically small ($P < .001$; 4.8% slower rate of decay).

We next asked whether the relatively poor prognostic performance of lactate clearance was attributable to the arbitrary cutoff of 10%. We built a univariable logistic regression model using lactate clearance (% of initial) as a continuous variable to predict 90-day mortality rate. Using receiver operator characteristic analysis and the Youden-Index to identify an optimal lactate clearance, we determined an optimal cutoff of 31%. Yet, when we compared the predictive power of the optimal 31% cutoff with the arbitrary 10% cutoff, we found that regardless of threshold, lactate clearance remained poorly predictive of 90-day mortality rate (areas under the curve, 0.54 and 0.52, respectively).

TABLE 1] Patient Characteristics and Results of Multivariable Logistic Regression Model

Variable	Individuals Who Did Not Meet the Lactate Clearance Threshold (N = 1,812)	Individuals Who Met the Lactate Clearance Threshold (N = 2,963)	*P* Value
Patient Characteristics[a]			
Age, mean (SD), y	61.18 (16.62)	60.86 (16.63)	.514
Male sex	1,010 (55.7)	1,712 (57.7)	.168
White race	1,472 (81.7)	2,414 (81.6)	.903
Acute Physiology and Chronic Health Evaluation IV, mean (SD)	92.72 (28.80)	90.13 (25.90)	.005
Sequential Organ Failure Assessment, mean (SD)	5.57 (3.06)	4.72 (2.77)	< .001
Cirrhosis	213 (11.7)	256 (8.7)	.001
End-stage renal disease	501 (27.6)	714 (24.1)	.001
Coronary artery disease	307 (16.9)	508 (17.2)	.855
Congestive heart failure	498 (27.5)	757 (25.6)	.124
Active malignancy	332 (18.3)	543 (18.3)	.999
Metastatic malignancy	180 (9.9)	335 (11.3)	.133
Initial lactate, mean (SD)	3.24 (2.88)	4.08 (2.68)	< .001
Peak lactate, mean (SD)	5.12 (4.00)	4.52 (3.07)	< .001
Absolute Mortality Rate			
90-d hospital mortality rate	396 (21.79)	472 (15.86)	< .001
Marginal Effect on Absolute Mortality Rate,[b] % (95% CI)			
Lactate clearance	−5.44 (−7.61 to −3.26)		< .001
Cirrhosis	10.60 (7.45 to 13.76)		< .001
End-stage renal disease	0.05 (−1.94 to 2.98)		.68
Age (decade of life)	2.20 (1.4 to 2.70)		< .001
Male sex	0.04 (−2.14 to 2.23)		.96

Data are presented as No. (%) unless otherwise indicated.
[a]Medical comorbidities were based on Charlson comorbidity index and identified with *International Classification of Diseases, 10th Revision*, codes.
[b]Calculated from logistic regression model with an outcome of 90-day mortality rate and covariates of lactate clearance, cirrhosis, and end-stage renal disease, age, and sex.

Finally, we compared short-term lactate clearance (2 to 12 h) with a previously validated metric of lactate clearance: 24-h change in peak lactate greater or less than 19%.[6] We found that this 24-h metric outperformed initial lactate clearance regardless of the cutoff used for lactate clearance (area under the curve, 0.64 vs 0.52-0.54).

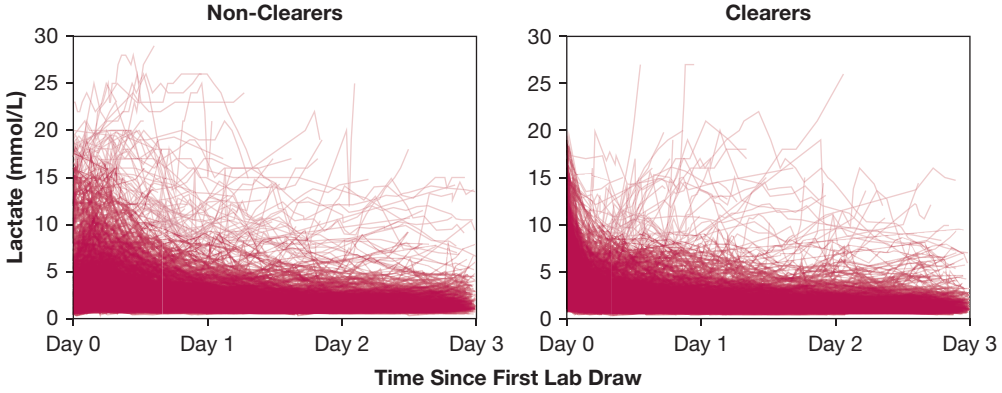

Figure 1 – *Lactate trajectories for individual patients grouped by initial lactate clearance. Clearers = individuals who met the lactate clearance threshold; non-clearers = individuals who did not meet the lactate clearance threshold.*

Discussion

In this study that analyzed the prognostic significance of lactate within a large group of patients with sepsis, the prognostic significance of initial lactate clearance was highly confounded by patient comorbidities, specifically cirrhosis. The prognostic significance of lactate clearance on absolute 90-day mortality rate was roughly one-half of that of cirrhosis, which implies that much of the prognostic utility of early lactate clearance is due to confounding by patient comorbidities. We also discovered wide variability in serum lactate trajectories that were predicted poorly by initial lactate clearance. Compared with initial lactate clearance, 24-h change in peak lactate level was a superior predictor of 90-day mortality rate, though this measurement, of course, is unavailable for guiding initial resuscitation or determining eligibility for clinical trials of early sepsis management.

Our findings emphasize the importance of interpreting lactate clearance within its broader clinical context and caution against overreliance on this single marker to guide resuscitation efforts. Patient 24-h change in peak lactate demonstrates superior predictive power compared with short-term lactate clearance, which suggests that clinicians should focus on longer-term lactate trends as a more accurate reflection of a patient's underlying physiologic condition and prognosis. Our results indicate that initial lactate clearance offers limited prognostic information beyond baseline medical comorbidities and does not reliably predict a patient's subsequent lactate trajectory. These findings contribute to the growing body of evidence that suggests that the utility of lactate clearance as a resuscitation goal in both clinical practice and research may warrant reevaluation.

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DOI: https://doi.org/10.1016/j.chest.2023.04.023

Funding/Support

This study was funding by National Institutes of Health (R01HL144599 to R. P. D., K24HL159247 to R. P. D., T32HL007749 to R. C., R01HL158626 to M. W. S., K01HL136687 to M. W. S., and R01LM013325 to M. W. S.).

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Author contributions: R. M., M. N., M. W. S., R. P. D., and R. C. designed the analyses. R. M., M. N., and R. C. performed clinical data abstraction, adjudication, and model building. R. M. wrote the first draft, and all authors participated in the revision of the manuscript. All authors approve of the final version of the manuscript.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Disclaimer: This manuscript does not represent the views of the Department of Veterans Affairs or the US government. This material results from work supported with resources and use of Ann Arbor VA Medical Center facilities.

Ethics Statement: This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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