References and Literature Grading Is Lactate Measurement in the Emergency Department Valuable as a Predictor of Poor Outcomes in Adult Patients with Sepsis?

Sepsis?		-		
Reference	Grade	Rank	Comment	Support for:
Lokhandwala, S., et al., <i>Absolute lactate value vs relative reduction as a predictor of mortality in severe sepsis and septic shock.</i> Journal of Critical Care, 2017. 37 : p. 179-184.	D	Adequate	Retrospective study; only patients w/lactate > 4 Persistent lactate > 4mmol/dL or < 20% clearance associated w/increased mortality	Initial Lactate: Did not address Lactate clearance: Supportive
Paquet, A.L., et al., <i>Agreement between</i> arterial and venous lactate in emergency department patients: A prospective study of 157 consecutive patients. European Journal of Emergency Medicine, 2018. 25 (2): p. 92- 96.	С	Adequate	Small prospective study Primary objective to compare arterial & venous lactate Both lactate sources had AUC of 0.67 predicting hospital death or ICU admission > 72 hrs	Initial Lactate: Supportive Lactate clearance: Did not address
Chen, YX. and CS. Li, <i>Arterial lactate</i> <i>improves the prognostic performance of</i> <i>severity score systems in septic patients in</i> <i>the ED.</i> American Journal of Emergency Medicine, 2014. 32 (9): p. 982-986.	С	Adequate	Small prospective study; arterial lactate Arterial lactate AUC of 0.79 to predict 28-day mortality	Initial Lactate: Supportive Lactate clearance: Did not address
Datta, D., et al., <i>Arterial lactate levels in an emergency department are associated with mortality: a prospective observational cohort study.</i> Emergency Medicine Journal, 2015. 32 (9): p. 673-677.	С	Good	Large prospective study; 747 patients ORs for 30-day death compared with lactate ≥4 were 0.125 (95% Cl 0.068 to 0.229) for lactate <2 and 0.273 (95% Cl 0.140 to 0.533) for lactate 2=<4	Initial Lactate: Supportive Lactate clearance: Did not address
Hwang, S.Y., et al., <i>Association between hemodynamic presentation and outcome in sepsis patients</i> . Shock, 2014. 42 (3): p. 205-210.	С	Adequate	Sepsis registry; stratified into cryptic shock (CS), cryptic to overt shock (COS) & overt shock (OS) Did not assess patients w lactates < 4 w/ normotension Odds ratio (OR) for in- hospital mortality of 0.17 (95% CI, 0.07 - 0.40; P	Initial Lactate: Supportive Lactate clearance: Did not address

Filho, R.R., et al., <i>Blood Lactate Levels</i> <i>Cutoff and Mortality Prediction in Sepsis-</i> <i>Time for a Reappraisal? a Retrospective</i> <i>Cohort Study.</i> Shock, 2016. 46 (5): p. 480- 485.	C	Good	< 0.01) for the CS group and 0.83 (95% CI , 0.46 - 1.49; P = 0.54) for COS group compared w/ OS group Retrospective study; 443 patients Predict 28-day mortality: Lactate level > 2.5 AUC 0.70; (95% CI, 0.62- 0.79)	Initial Lactate: Supportive Lactate clearance: Did not address
Alsolamy, S., et al., <i>Diagnostic accuracy of</i> a screening electronic alert tool for severe sepsis and septic shock in the emergency department. BMC medical informatics and decision making, 2014. 14 : p. 105.	D	Poor	Small retrospective study; 60 patients w/ SIRS or sepsis patients; multiple biomarkers Lactate associated w/ mortality (AUC=0.778; p<0.0001).	Initial Lactate: Supportive Lactate clearance: Did not address
Singer, A.J., et al., <i>Diagnostic</i> characteristics of a clinical screening tool in combination with measuring bedside lactate level in emergency department patients with suspected sepsis. Acad Emerg Med, 2014. 21 (8): p. 853-7.	С	Good	Observational trial; 248 patients Initial lactate associated w/ sepsis severity (p < 0.001), ICU admission (odds ratio [OR] = 2.01; 95% CI = 1.53 to 2.63), and need for vasopressors (OR = 1.54; 95% CI = 1.13 to 2.12)	Initial Lactate: Supportive Lactate clearance: Did not address
Cheng, H.H., et al., <i>Difference between</i> elderly and non-elderly patients in using serum lactate level to predict mortality caused by sepsis in the emergency department. Medicine (Baltimore), 2018. 97 (13): pe0209.	D	Good	Large retrospective trial; 7,087 patients Compared lactate between elderly (>/=65 years) and non-elderly (<65 years) patients Higher adjusted mortality with lactate >/=4.0 (OR 4.98 and 5.82; P < .01, respectively) and lactate 2 - 4 (OR, 1.57 and 1.99; P < .01, respectively)	Initial Lactate: Supportive Lactate clearance: Did not address
Milzman, D., et al., <i>Early determination of outcomes for sirs vs qSOFA in ED sepsis patients</i> . Critical Care Medicine, 2016. 44 (12): p. 435.	с	Poor	Retrospective study; 256 patients Presenting lactate > 2.0 (mortality 11%) and L > 4.0 (mortality 30%).	Initial Lactate: Supportive Lactate clearance: Did not address

Walker, C.A., et al., Early lactate clearance in septic patients with elevated lactate levels			Small retrospective study; 106 patients	Initial Lactate: Did not address
admitted from the emergency department to intensive care: Time to aim higher? Journal of Critical Care, 2013. 28 (5): p. 832-837.	С	Poor	Hazard ratio for death w/ LC 36% or less was 7.33 (95% confidence interval, 2.17-24.73; P =.001).	Lactate clearance: Supportive
			Small prospective observational study; 111 patients	Initial Lactate: Did not address
Nguyen, H.B., et al., <i>Early lactate clearance is associated with improved outcome in severe sepsis and septic shock.</i> Critical Care Medicine, 2004. 32 (8): p. 1637-1642.	С	Outstanding	Survivors compared w/ non-survivors had a LC of 38.1 +/- 34.6 vs. 12.0 +/- 51.6%, respectively (p =.005).	Lactate clearance: Supportive
			LC had inverse relationship with mortality (p =.04); 11% decrease likelihood of mortality for each 10% increase in LC	
Leisman, D.E., et al., <i>Early sepsis bundle</i> <i>compliance for non-hypotensive patients</i> <i>with intermediate versus severe</i> <i>hyperlactemia.</i> American Journal of Emergency Medicine, 2017. 35 (6): p. 811-	D	Good	Retrospective study; 2,417 patients Initial lactate > 4 (OR=1.99, CI=1.51-	Initial Lactate: Supportive Lactate clearance: Did not address
818.			2.63) for mortality Small RTC; 62 patients	Initial Lactate:
Tian, H.H., et al. <i>The effect of early goal lactate clearance rate on the outcome of septic shock patients with severe pneumonia.</i> 2012. 24 , 42-45	С	Poor	ICU LOS of 10% and 30% LC groups significantly shorter than control (10% group 7.94 +/- 6.00, 30% group 7.51 +/- 3.99, control group 11.31 + 5.97, both P<0.05).	Did not address Lactate clearance: Supportive for ICU LOS & 28-day mortality
			The three groups had no differences in 7-day mortality rate, but 28- day mortality of 10% and 30% LC groups significantly lower than control	
Contenti, J., et al., <i>Effectiveness of arterial,</i> venous, and capillary blood lactate as a sepsis triage tool in ED patients. American	с	Adequate	Small prospective study; 103 patients Evaluated arterial, venous and capillary	Initial Lactate: Supportive Lactate clearance:
Journal of Emergency Medicine, 2015. 33 (2): p. 167-172.			samples associated w/ mortality	Did not address

April, M.D., et al., <i>Emergency department</i> septic shock patient mortality with refractory hypotension vs hyperlactatemia: A retrospective cohort study. American Journal of Emergency Medicine, 2017. 35 (10): p. 1474-1479.	С	Good	0.76±0.05, and 0.75±0.05 for VBL, ABL, and CBL, respectively; P<.01) Observational study; 202 patients with septic shock with hypotension or initial lactate ≥ 4 Mortality was 10.9% among 101 patients w/ isolated hypotension, 24.4% among 41 patients with isolated lactate ≥ 4 and 28.3% among 60 patients with both (p=0.01). Logistic regression analyses yielded in- hospital mortality OR for lactate ≥ 4 of 2.9 (95% Cl 1.2-7.4) Large retrospective study; 985 patients	Initial Lactate: Supportive Lactate clearance: Did not address Did not address
Fernando, S.M., et al., <i>Helpful Only When</i> <i>Elevated: Initial Serum Lactate in Stable</i> <i>Emergency Department Patients with</i> <i>Sepsis Is Specific, but Not Sensitive for</i> <i>Future Deterioration.</i> Journal of Emergency Medicine, 2018.	D	Good	Composite outcome (death, ICU > 24 h, intubation, vasopressors for > 1 h, or NIPPV for > 1 h) within 72 h. Initial lactate ≥ 4.0 specificity of 97% (95%, CI 94–100%), sensitivity of 27% (95% CI 18– 37%) Positive and negative LR of 10.7 (95% CI 6.3– 18.3) and 0.8 (95% CI 0.7–0.9), respectively. Lactate ≥ 2.0 had sensitivity of 67% (95% CI 55–76%) and specificity of 66% (95% CI 63–69%), with positive and negative LR of 2.0 (95% CI 1.7–2.3) and 0.5 (95% CI 0.4– 0.7).	Lactate clearance: Did not address

Thomas-Rueddel, D.O., et al., Hyperlactatemia is an independent predictor of mortality and denotes distinct subtypes of severe sepsis and septic shock. Journal of Critical Care, 2015. 30 (2): p. 439.e1-439.e6.	с	Good	Secondary analysis of a prospective trial; 988 patients w/lactate > 4 Lactate > 4 on 28-day mortality (P < .001) (OR 3.0, (95% Cl, .1-4.1)	Initial Lactate: Supportive Lactate clearance: Did not address
Su, H., et al. (2016) Impact of initial lactate level on ED management of patients with sepsis: a multicenter retrospective cohort study.	D	Good	Multicenter retrospective study; 2,082 patients ICU admission: 25.4 % in normal lactate group to 54.5 % in high lactate group (p < 0.05). Unadjusted in-hospital mortality for normal, low, intermediate and high lactate group was 13.8 %, 21.7 %, 32.9 % and 57.2 %, respectively	Initial Lactate: Supportive Lactate clearance: Did not address
Dettmer, M., C.V. Holthaus, and B.M. Fuller, The impact of serial lactate monitoring on emergency department resuscitation interventions and clinical outcomes in severe sepsis and septic shock: An observational cohort study. Shock, 2015. 43 (1): p. 55-61.	С	Adequate	Retrospective study; 243 patients Compared serial lactate (SL) monitoring to no SL; LC was not reported. Lack of SL was independently associated with mortality (adjusted OR, 2.09; 95% CI 1.12 -3.89). SL showed greater improvement in 24-h SOFA scores (1.16 vs. 0.19; P = 0.03), decreased ICU LOS (4.6 vs. 6.0; P = 0.04), and more ventilator-free (19.9 vs. 16; P = 0.05) and vasopressor-free (21.6 vs. 17.9; P = 0.02) days.	Initial Lactate: Supportive Lactate clearance: Did not address
Heffner, A. and C. Karvetski, <i>Incidence and outcome factors in emergency department septic shock due to urinary infection.</i> Critical Care Medicine, 2016. 44 (12): p. 448.	С	Good	Prospective multicenter trial of 1,084 patients All source of sepsis was UTI Initial lactate was independently associated with hospital death. (OR 1.18; 95%	Initial Lactate: Supportive Lactate clearance: Did not address

			CI: 1.02-1.36)	
Driessen, R.G.H., et al., <i>The influence of a change in septic shock definitions on intensive care epidemiology and outcome: comparison of sepsis-2 and sepsis-3 definitions.</i> Infectious Diseases, 2018. 50 (3): p. 207-213.	С	Good	Prospective study of 643 patients Only initial lactate values ≥6 was significantly associated with increased ICU mortality. Initial lactate < 6 was not associated with ICU mortality	Initial Lactate: Supportive Lactate clearance: Did not address
Lee, S.M., et al., Lactate Clearance and Vasopressor Seem to Be Predictors for Mortality in Severe Sepsis Patients with Lactic Acidosis Supplementing Sodium Bicarbonate: A Retrospective Analysis. Plos one, 2015. 10 (12).	D	Adequate	Retrospective study; 109 patients 6-hour, 24-hour, and 48- hour lactate clearance (HR: 4.00, 95% CI: 1.31- 12.22) were significantly associated with mortality	Initial Lactate: Did not address Lactate clearance: Supportive
Bhat, S. R., et al. (2015). "Lactate clearance predicts survival among patients in the emergency department with severe sepsis." <u>Western Journal of Emergency Medicine</u> 16 (7): 1118-1126.	D	Good	Retrospective trial; 207 patients 28-day mortality rates were 15.2% in the LC group and 36.1% in the non-LC group (p<0.01). Vasopressor support was initiated more often in the non–LC group (61.1%) vs. LC (36.8%, p<0.01) and mechanical ventilation used in 66.7% of non-LC group and 36.3% in LC group (p=0.001)	Initial Lactate: Did not address Lactate clearance: Supportive
Lee, S. W., et al. (2008). "Lactic acidosis not hyperlactatemia as a predictor of in hospital mortality in septic emergency patients." <u>Emergency Medicine Journal</u> 25 (10): 659-665.	С	Poor	Small prospective study; 126 patients Assessing the relationship of pH and lactate with respect to in-hospital mortality. Patients with lactic acidosis had significantly higher hospital mortality than patients with normal pH and normal lactate	Initial Lactate: Supportive Lactate clearance: Did not address
Song, J. E., et al. (2016). "Mortality risk factors for patients with septic shock after implementation of the surviving sepsis	D	Good	Retrospective study; 436 patients	Initial Lactate: Supportive

campaign bundles." <u>Infection and</u> <u>Chemotherapy</u> 48 (3): 199-208.			Initial lactate independent risk for 28- day mortality OR 1.346 (95% CI, 1.083-1.673)	Lactate clearance: Did not address
Arnold, R. C., et al. (2009). "Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis." <u>Shock</u> 32 (1): 35-39.	С	Good	Prospective multicenter trial 166 patients Mortality 60% for non- LC vs. 19% for LC (P < 0.001) Non-LC independent predictor of death OR 4.9 (95% CI, 1.5-15.9)	Initial Lactate: Did not address Lactate clearance: Supportive
Wacharasint, P., et al. (2012). "Normal- range blood lactate concentration in septic shock is prognostic and predictive." <u>Shock</u> 38 (1): 4-10.	A	Outstanding	Secondary analysis of RTC; 1,134 patients with septic shock Initial lactate < 1.4 and ≥ 4.4 associated with decreased and increased 28 day mortality.	Initial Lactate: Supportive Lactate clearance: Did not address
Puskarich, M. A., et al. (2011). "Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock." <u>Resuscitation</u> 82 (10): 1289-1293.	A	Outstanding	Secondary analysis of RTC; 300 patients No difference in hospital mortality between cryptic shock (CS; normotensive with lactate > 4) with overt shock (OS; persistent hypotension) Hospital mortality 20% (95% CI 11-34) in CS group and 19% (95% CI 15-25) in OS group, difference of 1% (95% CI -10 to 14; log rank test p=0.81)	Initial Lactate: Supportive Lactate clearance: Did not address
Chambers, K. A., et al. (2018). "Outcomes of severe sepsis and septic shock patients after stratification by initial lactate value." <u>World Journal of Emergency Medicine</u> 9 (2): 113-117.	D	Adequate	Retrospective study; 338 patients. Initial lactic acid level of ≥ 4 was independently associated with increased mortality	Initial Lactate: Supportive Lactate clearance: Did not address
Vorwerk, C., et al. (2009). "Prediction of mortality in adult emergency department patients with sepsis." Emergency Medicine	D	Adequate	Retrospective study; 307 patients.	Initial Lactate: Supportive

<u>Journal</u> 26 (4): 254-258.			Initial lactate \geq 4 had sensitivity of 49.1% (95% Cl 35.1%-63.2%) and specificity of 74.3% (95% Cl 64.8%-82.3%) for 28-day mortality	Lactate clearance: Did not address
Capp, R., et al. (2015). "Predictors of patients who present to the emergency department with sepsis and progress to septic shock between 4 and 48 hours of emergency department arrival." <u>Critical Care Medicine</u> 43 (5): 983-988.	D	Good	Retrospective study of 1,316 patients Lactate ≥ 4 had OR, 5.30; (95% CI, 2.59- 10.84) associated with progression to septic shock within 48 hours	Initial Lactate: Supportive Lactate clearance: Did not address
Aluisio, A. R., et al. (2016). "The prognostic role of non-critical lactate levels for in- hospital survival time among ED patients with sepsis." <u>American Journal of</u> <u>Emergency Medicine</u> 34 (2): 170-173.	D	Poor	Retrospective trial; 197 patients LC median survival was 24 days (95% CI, 5-32). For patients with increasing LAC median survival was 7 days; 95% CI, 4-11, P = .04).	Initial Lactate: Did not address Lactate clearance: Supportive
Chang, W. and Y. Yang (2017). "Prognostic utility of the combined SOFA score, lactate, procalcitonin and C-reactive protein in severe sepsis." <u>Intensive Care Medicine</u> <u>Experimental</u> 5 (2).	D	Poor	Retrospective study; 124 patients Lactate drawn before resuscitation and antibiotic administration 28-day mortality: AUC for initial lactate 0.67	Initial Lactate: Supportive Lactate clearance: Did not address
García-De La Torre, A., et al. (2017). "Quartiles of lactate concentration in sepsis and mortality." <u>Intensive Care Medicine</u> <u>Experimental</u> 5 (2).	D	Adequate	Retrospective study; 780 patients Median initial lactate higher in non-survivors 2.6 [1.8-3.73] vs. 4.21 [2.6-6.86], p < 0.001. AUC for initial lactate was 0.75 (95% CI: 0.69- 0.81) with an optimal cut-off value of 3.7 (76.3% sensitivity and 62% specificity) to predict hospital mortality.	Initial Lactate: Supportive Lactate clearance: Did not address
Trzeciak, S., et al. (2007). "Serum lactate as a predictor of mortality in patients with infection." Intensive Care Medicine 33 (6):	D	Good	Post-hoc analysis prospectively study; 1,177 patients	Initial Lactate: Supportive

970-977.				
			Outcome measures included acute-phase (≤ 3 days) death and in- hospital death In-hospital mortality was 15%, 25%, and 38% for initial lactate of < 2.0,	Lactate clearance: Did not address
			2.1-3.9 and > 4 respectively.	
			Retrospective study; 8,310 patients	Initial Lactate: Supportive
Shetty, A. L., et al. (2018). "Serum lactate cut-offs as a risk stratification tool for in-			Composite outcome: hospital mortality and/or prolonged ICU stay ≥72 hours	Lactate clearance: Did not address
hospital adverse outcomes in emergency department patients screened for suspected sepsis." <u>BMJ open</u> 8 (1).	D	Good	OR for combined AE outcome were 2.71 (95% CI 2.05-3.57), 2.65 (95% CI 2.29-3.08), 3.10 (95% CI 2.71-3.53) and 3.89 (95% CI 3.36-4.50) for initial lactate above 1, 2, 3 and 4 respectively.	
			Retrospective study; 830 patients	Initial Lactate: Supportive
Mikkelsen, M.E., et al., Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock.	с	Good	Non-shock: Initial lactate associated w/ mortality (OR = 4.87, p < 0.001)	Lactate clearance: Did not address
Critical Care Medicine, 2009. 37 (5): p. 1670-1677.			Shock Intermediate (OR = 3.27 , p = 0.022) and high lactate (OR = 4.87 , p = 0.001) also associated w/ mortality.	
Dadeh, et al (2016). "Serum lactate levels			Prospective study of 131 patients	Initial Lactate: Supportive
as a prognostic predictor of septic shock in emergency department patients with systemic inflammatory response syndrome (SIRS) at Songklanagarind hospital." Journal of the Medical Association of <u>Thailand</u> 99 (8): 913-918.	С	Poor	Initial lactate > 36 mg/dL associated with 28-day mortality (odds ratio [OR] = 4.29, 95% Cl, 1.19-15.55) and w/ progression to shock (p = 0.013)	Lactate clearance: Did not address
Oedorf, K., et al. (2017). "Serum Lactate	С	Poor	Prospective study; 488	Initial Lactate:

Predicts Adverse Outcomes in Emergency Department Patients With and Without Infection." West J Emerg Med 18 (2): 258-			patients with & without infection	Supportive
266.			Deterioration rates by lactate level: < 2.5, 26% (95% CI: 21-30%); 2.5-4.0, 52% (42 - 63%); >4.0, 72% (59 -85%)	Lactate clearance: Did not address
			Lactate > 4 independent predictor of deterioration for patients with infection (OR 4.8, 95% CI: 1.7 - 14.1	
Musikatavorn, K., et al., Venous lactate in predicting the need for intensive care unit and mortality among nonelderly sepsis patients with stable hemodynamic.	с	Adequate	Retrospective study; 392 patients Initial lactate not associated with 30-day mortality	Initial Lactate: Not supportive for mortality; Supportive for increased need for supportive care.
American Journal of Emergency Medicine, 2015. 33 (7): p. 925-930.		Auequale	Initial lactate (>=2 mmol/L) associated with vasopressor or mechanical ventilation use	Lactate clearance: Did not address
Mahmoodpoor, A., et al., Which one is a better predictor of ICU mortality in septic patients? Comparison between serial serum lactate concentrations and its removal rate. Journal of Critical Care, 2018. 44 : p. 51-56.	с	Poor	Prospective study of 82 patients Non-survivors had higher admission initial lactate (P = 0.033)	Initial Lactate: Supportive Lactate clearance: Did not address
			Pre-planned analysis of an RTC; 187 patients	Initial Lactate: Supportive
Puskarich, M.A., et al., Whole blood lactate			Predicting survival: AUC of initial lactate, 0.64; for relative lactate clearance, 0.67 and lactate clearance rate, 0.58	Lactate clearance: Supportive Lactate normalization: Supportive
kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. CHEST, 2013. 143 (6): p. 1548-1553.	A	Outstanding	Lactate clearance \geq 50% (OR, 4.0; 95% CI, 1.6-10.0). Lactate clearance \geq 10% was not an independent predictor	
			Lactate normalization was strongest predictor of survival (adjusted OR, 5.2; 95% CI, 1.7-15.8),	

Abbreviations: CI, NPV, AUC, ROC, OR, LC, ICU. All patients were septic unless otherwise reported. Unless otherwise stated, lactate normalization refers to a final lactate of < 2 mmo/L and low, intermediate and high lactate levels refer to < 2, >2 to <4 and \geq 4 mmol/L.

References

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