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Letters to the Editor

☐ COMMENTS ON "HELPFUL ONLY WHEN ELEVATED: INITIAL SERUM LACTATE IN STABLE EMERGENCY DEPARTMENT PATIENTS WITH SEPSIS IS SPECIFIC, BUT NOT SENSITIVE FOR FUTURE DETERIORATION"

☐ **To the Editor:**

We share the concerns expressed by Fernando et al. on early identification of septic patients at risk of deterioration in the emergency department (ED) (1).

The authors aimed to test the ability of initial serum lactate in predicting future devterioration among initially stable ED patients. Additionally, they sought to determine any differences between those who deteriorated and those who did not.

The results showed that initial lactate ≥ 4 mmol/L had a specificity of 97%, but a sensitivity of 27% for predicting deterioration, with positive and negative likelihood ratios of 10.7 and 0.8, respectively. A lower threshold of lactate (≥2 mmol/L) had a sensitivity of 67% and specificity of 66%, with corresponding positive and negative likelihood ratios of 2.0 and 0.5, respectively.

Ryoo et al. found that lactate ≥ 2 mmol/L and lactate clearance are both useful targets in patients with septic shock, defined by Sepsis-3 (2). Serum lactate level at 6 h can be an easier and more effective tool for prognosis of septic shock patients who were treated with protocol-driven resuscitation bundle therapy. Both lactate and lactate clearance were associated with mortality after adjusting for confounders (odds ratio 1.27; 95% confidence interval [CI] 1.21–1.34 and odds ratio 0.99; 95% CI 0.989–0.995, respectively), but lactate had a significantly higher prognostic value than lactate clearance (area under the receiver operating characteristic [AUROC] 0.70 vs. 0.65; $p < 0.01$).

The study published by Cheng et al. demonstrates the ability of serum lactate level to predict the mortality of patients with sepsis in the ED, with an increased risk if the lactate level was > 2 mmol/L and > 4 mmol/L in non-elderly and elderly patients, respectively (3).

In another study, unselected patients who arrived in the ED and were admitted to the hospital, a serum lactate level > 2.6 mmol/L predicted 30-day in-hospital mortality with positive and negative predictive values of 20.8% and 93.5%, respectively (4). That low positive predictive value and high negative predictive value indicate that serum lactate test might be an effective screening tool.

Furthermore, Shetty et al. found a significantly increased risk for intensive care unit stay of at least 72 h or death in hospital with increasing lactate threshold values (5). They considered that initial serum lactate ≥ 2 mmol/L was more appropriate than ≥ 4 mmol/L for identification of an increased risk of death.

In other recent retrospective study, Jung et al. found that the combined the quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) and lactate level score was superior to qSOFA alone (AUROC 0.754 vs. 0.717, respectively; $p = 0.039$) in predicting mortality in patients who presented to the ED and required emergency gastrointestinal surgery for a complicated intra-abdominal infection (6).

The study by Fernando et al. has some strengths, one of them is that there were no endpoints between patients discharged at 72 h (1). Moreover, patients who were discharged within 72 h were contacted directly by telephone to ensure they had not achieved one of the study endpoints. There were no patients lost to follow-up in those discharged at 72 h.

This study has several limitations; there were 648 (35.6%) patients excluded due to lactate being drawn > 2 hours from triage or not drawn, declined participation, or incorrectly enrolled. That means that there could have been selection bias and it is difficult to predict the direction of such an impact.

Moreover, the authors could have performed a propensity score analysis in order to correct selection biases.

There is a confounding factor that has not been taken into consideration. Patients were included in the study when they satisfied Systemic Inflammatory Response Syndrome (SIRS) criteria, which have their own sensitivity and specificity, so the results given by Fernando et al. in sensitivity analysis are for the combination of SIRS and lactate (1).

On the other hand, one-third of patients who deteriorated did not have an initial elevated lactate > 2 mmol/L. In those patients, qSOFA could have been helpful in identifying those at high risk for deterioration.

Fernando et al. concluded that high ED lactate is predictive of subsequent deterioration from sepsis within 72 h (1).

We believe that serum lactate level is specific, with a high negative predictive value, so it should be used to

select patients with sepsis who could be discharged safely from the ED.

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☐ To the Editor:

We thank Dr. Úbeda-Iglesias and colleagues for their comments on our paper (1). They have raised some interesting points. We do agree that initial serum lactate certainly does have a role in the disposition of emergency department (ED) patients presenting with suspected infection. However, the utilization method of this biomarker is very important, and it is here where we have some concerns related to the comments made by Úbeda-Iglesias et al.

We agree that a high initial serum lactate is an ominous sign. The studies cited by these authors all suggest that a high serum lactate is associated with increased risk of deterioration or death. They include studies of patients with suspected sepsis, those with septic shock, as well as studies that more broadly investigate all patients presenting to the ED (2–4). All of these studies found that elevated lactate was associated with mortality. Indeed, this is similar to our study, where a lactate $\geq$ 4.0 mmol/L was associated with a positive likelihood ratio of 10.7 for future deterioration. However, it is important to note that none of the studies cited by Úbeda-Iglesias and colleagues concluded that ED lactate could be utilized for safely discharging patients from the ED. In fact, the study by Park et al. found that the sensitivity of a serum lactate level of even $\geq$ 2.7 mmol/L only had a sensitivity of 56.7% for mortality. We similarly found that a lactate $\geq$ 2.0 mmol/L had a sensitivity of 67.1% for future deterioration (1). In other words, one-third of patients who deteriorated within 72 h had normal lactate initially. Thus, we would vigorously disagree with Úbeda-Iglesias et al. and their assertion that "an initially normal serum lactate (i.e., < 2.0) may be used to discharge patients with suspected infection."

When using any clinical tool for predicting subsequent deterioration in the ED (whether it be a laboratory value, an imaging test, or a clinical decision rule), it is important that this tool should have very high sensitivity, as a false negative would result in a poor outcome (i.e., a patient who is discharged home when they should not have been). Therefore, in the ED, specificity of the tool matters relatively less, because while false positives are undesirable, the consequences are not as dire as false negatives. For this reason, accuracy metrics that weight sensitivity and specificity equally (such as the area under the receiver operating characteristic curve) are misleading, as poor sensitivity can be masked by higher specificity (5).

The authors also suggest that the quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score may be added to serum lactate to aid in the discharge of patients with sepsis (6). However, our group found that qSOFA has poor sensitivity, particularly in the ED, and especially when compared to Systemic Inflammatory Response Syndrome (SIRS) criteria (7,8). Our study effectively combined the SIRS criteria with serum lactate and found that this did not result in a sufficient sensitivity

Conflict of Interest—Andrew J. E. Seely holds patents related to multiorgan variability analysis, and has shares in Therapeutic Monitoring Systems, a company whose mission is to help deliver waveform-based, variability-directed clinical decision support products to the bedside to improve care.