SERUM ANION GAP PREDICTS LACTATE POORLY, BUT MAY BE USED TO IDENTIFY SEPSIS PATIENTS AT RISK FOR DEATH: A COHORT STUDY

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INTRODUCTION

Lactate is a common cause of anion gap metabolic acidosis, and increases In lactate are associated with increased anion gap and decreased serum bicarbonate

OBJECTIVE

The purpose of this study is to test whether serum bicarbonate or anion gap can be used to predict elevated lactate or mortality in emergency department (ED) patients with sepsis, and define thresholds that may predict elevated lactate and mortality.

METHODS:

Retrospective diagnostic-validation study of adults with sepsis, severe sepsis, or septic shock treated in a Midwestern university ED between January 1, 2010 and December 31, 2015.

Serum lactate, bicarbonate, and anion gap were measured at the time of admission

Three outcomes were defined for this study to correspond with the outcome being predicted:

lactate >4 mmol/L (LACT4)

lactate >2 mmol/L (LACT2)

in-hospital mortality (MORT)

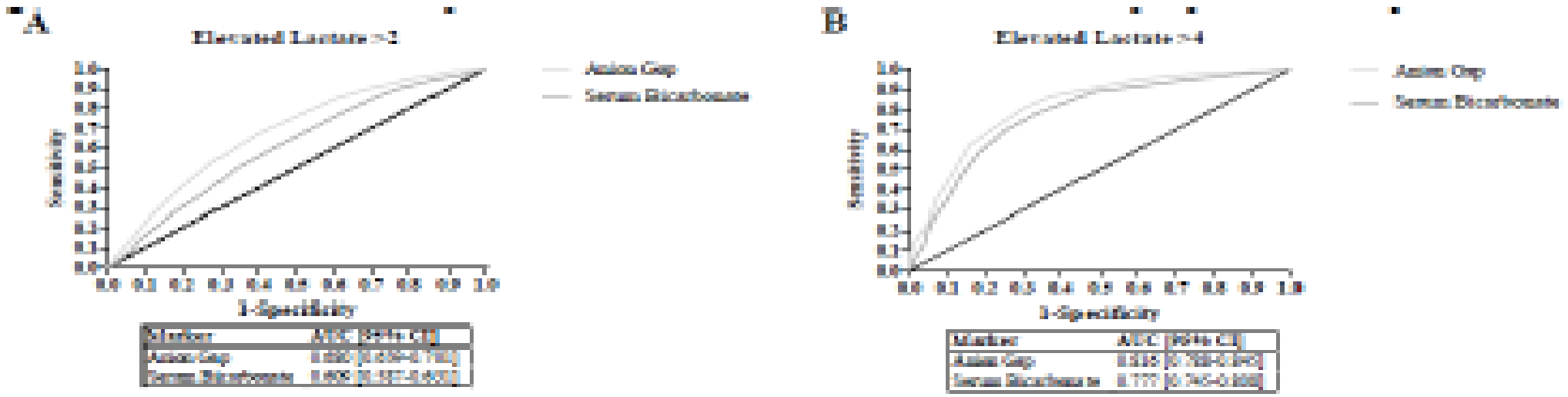
RESULTS

There were 4,159 ED visits that met the definition of sepsis and had the necessary laboratory components

The prevalence of LACT2 was 36% and LACT4 was 9%.

Figure 2. ROC Curve analysis of elevated lactate and mortality b

derivation set



With an outcome of LACT2, the area under the curve was 0.609 [95% CI: 0.587-0.631] for serum bicarbonate and 0.680 [95%CI: 0.659-0.701] for anion gap

Anion gap predicted lactate>2 better than bicarbonate

anion gap predicted lactate>4 better than lactate>2

With increasing serum bicarbonate levels (toward normal), the corresponding sensitivity measures rose while specificity measures declined

Table 1. Summary of derivation set test characteristics by elevated lactate threshold[1]

	Elevated Lactate [>2 mmol/L]						Elevated Lactate [>4 mmol/L]					
Serum Bicarbonate Threshold	Sens.	Spec.	LR+	LR-	Youden	Dist. ULC	Sens.	Spec.	LR+	LR-	Youden	Dist. ULC
16	12.9	94.7	2.434	0.920	0.076	0.873	30.0	94.3	5.263	0.742	0.243	0.702
17	17.1	92.7	2.342	0.894	0.098	0.832	38.8	92.1	4.911	0.664	0.309	0.617
18	23.1	89.9	2.287	0.855	0.130	0.776	51.5	89.0	4.682	0.545	0.405	0.497
19	28.5	85.9	2.021	0.832	0.144	0.729	57.3	84.6	3.721	0.505	0.419	0.454
20	36.1	79.3	1.744	0.806	0.154	0.672	66.5	77.9	3.009	0.430	0.444	0.401
21	44.2	71.5	1.551	0.780	0.157	0.627	74.2	70.0	2.473	0.369	0.442	0.396
22	55.4	60.5	1.403	0.737	0.159	0.596	81.5	58.6	1.969	0.316	0.401	0.453
23	65.9	49.8	1.313	0.685	0.157	0.607	86.2	47.3	1.636	0.292	0.335	0.545
24	73.9	37.7	1.186	0.692	0.116	0.675	89.6	35.9	1.398	0.290	0.255	0.649
25	82.2	27.6	1.135	0.645	0.098	0.746	93.5	18.4	1.146	0.353	0.119	0.819
26	87.4	19.7	1.088	0.640	0.071	0.813	95.4	12.7	1.093	0.362	0.081	0.874
	Elevated Lactate [>2 mmol/L]						Elevated Lactate [>4 mmol/L]					
Anion Gap Threshold	Sens.	Spec.	LR+	LR-	Youden	Dist. ULC	Sens.	Spec.	LR+	LR-	Youden	Dist. ULC
12	80.9	39.2	1.331	0.487	0.201	0.637	93.1	34.6	1.424	0.199	0.277	0.658
13	71.6	53.5	1.540	0.531	0.251	0.545	88.5	47.9	1.699	0.240	0.364	0.534
14	60.1	67.3	1.838	0.593	0.274	0.516	84.2	61.8	2.204	0.256	0.460	0.413
15	48.3	77.4	2.137	0.668	0.257	0.564	76.2	72.8	2.801	0.327	0.490	0.361
16	39.4	85.1	2.644	0.712	0.245	0.624	69.2	81.0	3.642	0.380	0.502	0.362
17	31.3	89.8	3.069	0.765	0.211	0.695	62.3	86.8	4.720	0.434	0.491	0.399
18	24.5	92.6	3.311	0.815	0.171	0.759	52.7	90.5	5.547	0.523	0.432	0.482
19	20.4	94.7	3.849	0.841	0.151	0.798	46.2	93.0	6.600	0.578	0.392	0.543
20	15.9	95.9	3.878	0.877	0.118	0.842	40.0	95.0	8.000	0.632	0.350	0.602

Anion gap predicted LACT4 with greater discrimination than LACT2;

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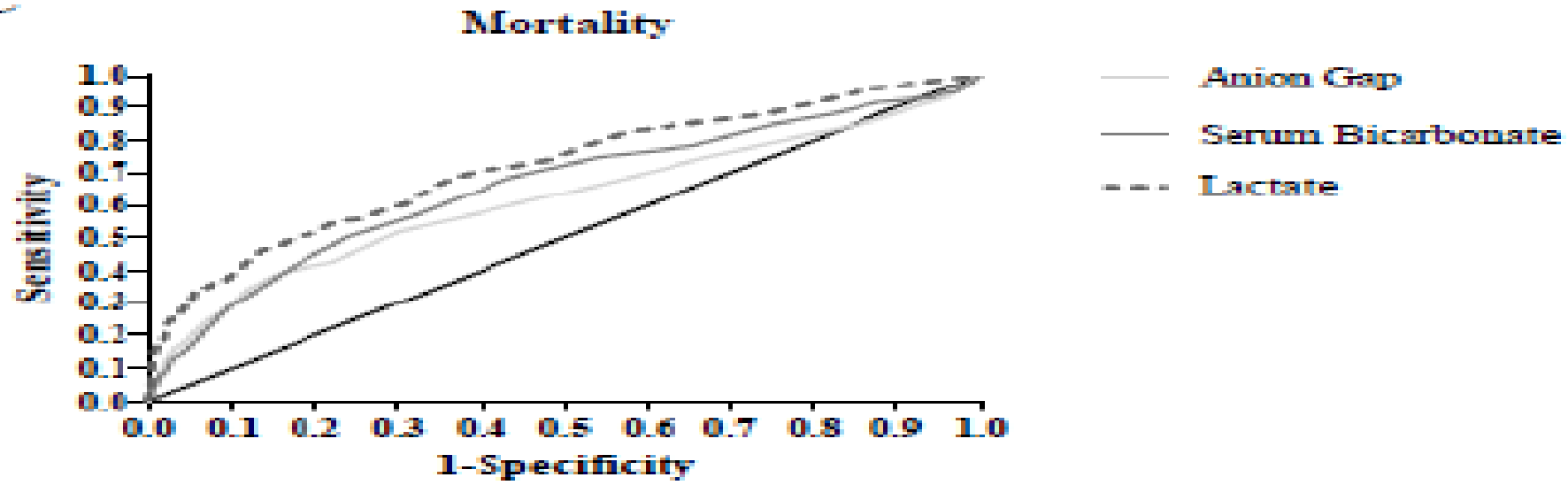


Marker	AUC [95% CI]
Anion Gap	0.615 [0.569-0.661]
Serum Bicarbonate	0.656 [0.614-0.698]
Lactate	0.717 [0.677-0.756]

In predicting mortality, the area under the curve was
0.656 [95%CI: 0.614-0.698] for serum bicarbonate,
0.615 [95%CI: 0.569-0.661] for anion gap,
and 0717 [95%CI: 0.677-0.756] for lactate

the anion gap cut point (≥20 mEq/L) more effectively predicted LACT4 than LACT2 (e.g. sensitivity of 45.9% vs. 19.4%, respectively).

Although anion gap was inferior to LACT4, it performed similarly to LACT2 in predicting mortality.

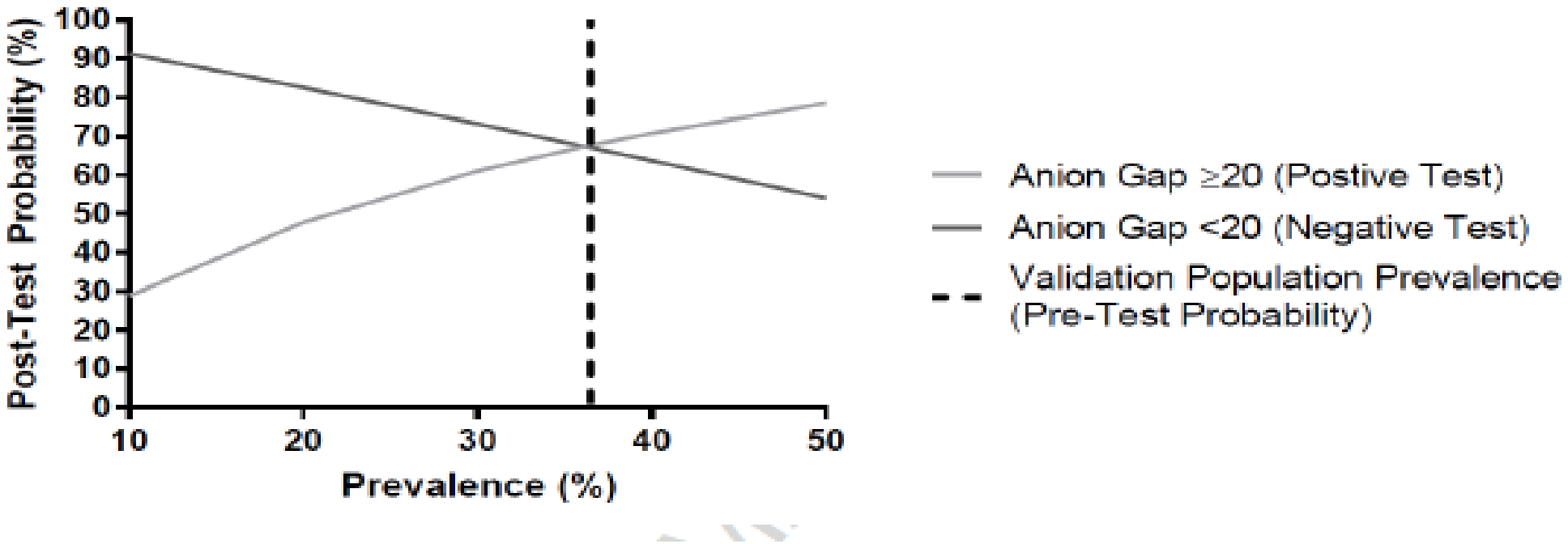
Table 2. Validation set performance characteristics for predicting elevated lactate and mortality

Outcome	Lactate [>2 mmol/L]	Lactate [>4 mmol/L]	Mortality		
Threshold	Anion Gap [≥20 mEq/L]	Anion Gap [≥20 mEq/L]	Lactate [>2 mmol/L]	Lactate [>4 mmol/L]	Anion Gap [≥20 mEq/L]
Measure[1]	Value [95% CI]	Value [95% CI]	Value [95% CI]	Value [95% CI]	Value [95% CI]
Sens	0.194 [0.160-0.231]	0.459 [0.373-0.547]	0.703 [0.609-0.786]	0.378 [0.288-0.475]	0.252 [0.175-0.344]
Spec	0.947 [0.930-0.961]	0.935 [0.919-0.948]	0.665 [0.638-0.691]	0.926 [0.911-0.940]	0.909 [0.893-0.925]
PPV	0.678 [0.595-0.754]	0.434 [0.351-0.519]	0.156 [0.125-0.191]	0.311 [0.234-0.396]	0.196 [0.134-0.270]
NPV	0.672 [0.645-0.698]	0.941 [0.926-0.953]	[illegible] [0.947-0.974]	0.944 [0.930-0.956]	[illegible] [0.917-0.946]
LR+	3.670 [2.630-5.122]	7.019 [5.310-9.278]	2.096 [1.[illegible]8-2.840]	5.135 [3.772-6.990]	2.768 [[illegible]922-3.986]
LR-	0.851 [0.813-0.891]	0.579 [0.495-0.676]	0.447 [0.[illegible]09-0.489]	0.671 [0.580-0.777]	0.823 [[illegible]737-0.918]

[1] Sens. = Sensitivity; Spec. = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value; LR+ = Positive Likelihood Ratio; LR- = Negative Likelihood Ratio

Anion gap predicted mortality similar to lactate>2 [LR+ 2.768 vs. LR+ 2.09; LR- 0.823 vs. 0.447]

Figure 3. Positive and negative predictive values for anion gap in predicted elevated lactate (>2 mmol/L), given various prevalence (pre-test probability) of elevated lactate in the target population



DISCUSSION

Our results indicate that neither serum bicarbonate nor anion gap are adequate Substitutes for directly measuring lactate.

Lactate can be elevated in the absence of elevation of the anion gap, and there are many other reasons for the anion gap to be elevated in the absence of hyperlactatemia.

A prior papers simply report concordance between biomarkers without reporting associations with clinical outcomes.

In this report, it has been reported that this relationship is poor, yet it has been shown that anion gap predicts mortality

lactate should continue to be measured directly where laboratory capability exists or can be implemented

Patients diagnosed with infection who also have an elevated anion gap should be treated aggressively, because most of these patients actually have severe sepsis with an increased risk of death

If serum anion gap is used, however, the utility of this test is a function of pre-test probability. In this population, patients who had an anion gap ≥20 mmol/L had a probability ofbLACT2 of 68%, whereas an anion gap less than this threshold is associated with an elevated lactate of 32%.

As the prevalence changes, the post-test probability changes as well. This fact makes the accurate assessment of pre-test risk assessment important,

and several tools have been studied to aid in this risk stratification.

A patient with an elevated anion gap (like the patients in our study) is twice as likely to have an elevated lactate and has mortality three times higher

LIMITATIONS

A single-center study based on retrospective records

They have not adjusted the anion gap for other factors that could increase or decrease the “baseline” anion gap other than lactate (e.g., albumin, ethanol).

CONCLUSIONS

Anion gap and serum bicarbonate poorly predict changes in lactate, but they do predict patients with infection who have increased mortality. In resource-limited settings where lactate is not immediately available, anion gap may be useful to further risk stratify patients for ongoing sepsis care.