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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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ABSTRACT

Purpose: (1) 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 (2) to define thresholds that may predict elevated lactate and mortality.
Methods: Retrospective diagnostic-validation study of adults with sepsis treated in a 60,000-visit Midwestern university ED (2010–2015). In the derivation sample, 8 experts selected thresholds based on objective measures to optimize clinical utility. Test performance was reported using likelihood ratios (LR +/−) in the validation cohort.
Results: We included 4159 patients. Anion gap predicted lactate > 2 better than bicarbonate [ROC AUC 0.680 vs. 0.609], and anion gap predicted lactate > 4 better than lactate > 2 [ROC AUC 0.816 vs. 0.680]. In the validation cohort, anion gap ≥20 mEq/L had LR + for lactate > 2 of 3.670 (2.630–5.122), lactate > 4 of 7.019 (5.310–9.278), and mortality of 2.768 (1.922–3.986). Anion gap predicted mortality similar to lactate > 2 [LR + 2.768 vs. LR + 2.09; LR − 0.823 vs. 0.447].
Conclusions: Anion gap and serum bicarbonate poorly predict changes in lactate and mortality. In resource-limited settings where lactate is unavailable, anion gap ≥20 mEq/L may be used to further risk-stratify patients for ongoing sepsis care, but lactate remains a preferred biomarker.

1. Introduction

1.1. Background

Sepsis affects over one million Americans annually and is responsible for 17% of all in-hospital deaths [1,2]. It costs more than $20 billion a year, making it one of the most expensive life-threatening conditions in the U.S. [3]. Aggressive early therapy has been shown to improve survival,[4] but early diagnosis remains difficult. Serum lactate measurement is an important aspect of identification and risk stratification for sepsis patients.[5,6] Lactate values over 4 mmol/L confer significantly increased mortality [7], and lactate clearance toward normal levels is associated with reduced mortality [6,8]. Furthermore, increased attention has been focused on early lactate measurement, since lactate >2.0 mmol/L has been defined as an inclusion criterion for the CMS-endorsed SEP-1 Sepsis Early Management Bundle [9].

1.2. Importance

Unfortunately, many low-volume and rural emergency departments (EDs) lack the capability to measure serum lactate rapidly (i.e., 28% of hospitals in a rural 29-hospital cohort in our region do not have the ability to measure lactate) [10], which may compound the already significant challenge in diagnosing and risk stratifying patients with severe infection. Rural patients have increased mortality [11], and even patients transferred to high-volume centers continue to suffer worse

Abbreviations: LACT2, lactate >2 mmol/L; LACT4, lactate >4 mmol/L; MORT, in-hospital mortality.

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outcomes [12]—likely owing to multifactorial aspects of resource-limited care. In hospitals without rapid lactate availability, clinicians currently use non-lactate serum biomarkers (such as serum bicarbonate) to assess organ perfusion and severity of illness [13]. Prior studies have shown poor correlation between lactate and other serum biomarkers, but these studies used traditional cut-off values for serum anion gap and bicarbonate, rather than defining useful biomarker thresholds based on disease-specific data [14-17]. They also limited their analysis to predicting lactate, rather than predicting more clinically relevant endpoints.

1.3. Goals of this investigation

Lactate is a common cause of anion gap metabolic acidosis, and increases in lactate are associated with increased anion gap and decreased serum bicarbonate. The purpose of our study was to test the hypotheses that serum bicarbonate or anion gap can be used [1] to predict elevated lactate and [2] to predict mortality in patients with suspected infection, and [3] to determine test thresholds of bicarbonate and anion gap (if any) that could be used in clinical practice. We performed this analysis by using a combination of statistical measures and a modified Delphi method to select a threshold of test values beyond which abnormal lactate and mortality would be predicted.

2. Methods

2.1. Study setting, population, and source

This study was a retrospective derivation-validation study of adults with sepsis, severe sepsis, or septic shock treated in a 60,000-visit Midwestern university ED between January 1, 2010 and December 31, 2015. Sepsis was defined using a combination of a previously validated diagnosis code-based approach of identifying infection and organ failure [International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) codes] [18] as well as explicit sepsis-specific diagnostic codes (ICD-9 codes 785.52, 995.91, 995.92, 998.02), evaluated from hospital discharge diagnoses. These records were matched to patients who were admitted from the ED and had laboratory tests conducted, including a basic metabolic panel (for bicarbonate and anion gap measurement) and serum lactate thereby representing a consecutive sampling of all patients who met these criteria. These diagnoses and patients were purposely selected to be broadly inclusive (sepsis, severe sepsis, and septic shock), including the full severity of illness for which screening lactate might be ordered, rather than just selecting the most severely ill cohort of patients with severe sepsis or admitted to ICUs as previous studies have [1,2,4,8,11]. Further, cases were defined using a historical sepsis definition rather than the more contemporary Sepsis-3 definition, because these older definitions remain in place for the purposes of billing and coding [19]. Despite the absence of lactate in the revised sepsis definition (although it remains in the septic shock definition), it remains an element of the CMS-endorsed SEP-1 sepsis resuscitation quality measure.

All patient records that met the following inclusion criteria were included: age ≥ 18 years, hospital admission, qualifying sepsis ICD-9 and -10 diagnosis codes, serum lactate, bicarbonate, and anion gap measured at the time of admission. Data were extracted from the electronic medical record by automated query into a data set for analysis. Cases with incomplete or uninterpretable data (i.e. records with errors, missing, or non-numerical data) were excluded. No manual chart review was performed for this study. When multiple laboratory studies existed for a given ED visit, the first order was used in the analysis. For patients with multiple ED visits for sepsis, only the earliest ED visit was retained for the analysis. Patients who did not have laboratory testing performed in the ED were also excluded (e.g., many of these patients were transferred into the university ED and laboratory studies were not repeated). This study was approved by the local institutional review board under waiver of informed consent, and the study is reported in accordance with the Standards for Reporting Diagnostic Accuracy Studies statement (STARD) [20].

2.2. Data collection

All patient records that met the following inclusion criteria were included: age ≥ 18 years, hospital admission, qualifying sepsis ICD-9 diagnosis codes, serum lactate, bicarbonate, and anion gap measured at the time of admission. Data were extracted from the electronic medical record by automated query into a data set for analysis. Cases with incomplete or uninterpretable data (i.e. records with errors, missing, or non-numerical data) were excluded. No manual chart review was performed for this study.

2.3. Diagnostic testing and outcomes

Blood for the basic metabolic panel and lactate measurement was collected on ED arrival for included patients by standard practice and analyzed using an ABL Flex analyzer (Radiometer®) instrument. Laboratory results were reported in the electronic medical record as clinical data and tests were most often completed at the same time, thereby limiting clinical interventions and gaps in time between test results. Reference and index results were analyzed as an aggregate independently of additional clinical information. Three outcomes were defined for this study to correspond with the outcome being predicted: lactate >4 mmol/L (LACT4), lactate >2 mmol/L (LACT2), and in-hospital mortality (MORT). None of the lactate values reported in this study were measured using point-of-care testing.

2.4. Derivation analysis

The data were divided into a derivation set and an independent validation set. The derivation set was generated by selecting two-thirds of the entire data using a simple random sample function. The derivation cohort was used for initial screening of the accuracy of the predictor variables and selection of the threshold values, and the validation cohort was used for reporting test characteristics based on selected threshold values. Initially, receiver operating characteristics (ROC) curves were analyzed for each continuous predictor (bicarbonate and anion gap) on each outcome (LACT2, LACT4, MORT). The results from the derivation set were reviewed by a panel of eight experts [4 board-certified emergency physicians, 3 board-certified critical care physicians (2 of whom were also board-certified in emergency medicine), an emergency medicine clinical pharmacist, and a research scientist with a PhD in Epidemiology] using a modified Delphi method to determine whether bicarbonate or anion gap performed well enough to proceed with threshold selection. To determine objective clinical rationale for identifying bicarbonate and anion gap thresholds, we calculated the following measures for each threshold value for each outcome: sensitivity, specificity, positive and negative likelihood ratios, the Youden index, and the distance to the top left corner (DLC) of the ROC curve. The Youden index and the DLC were used to identify the point of maximal discrimination for each predictor test. We used this technique with clinical experts because we felt it may be preferable to prioritize sensitivity or specificity to guide threshold selection, and statistical measures alone are unable to make this judgment.

2.5. Selection of threshold values

Using a modified Delphi method, each investigator independently determined whether threshold selection should proceed and a formal vote was conducted, with discussion until consensus was achieved. If the expert panel agreed to proceed with threshold selection, each individual independently identified a threshold based on clinical interpretation of the summary measures. The expert panel reported their pre-

selected threshold values using the same modified Delphi method. Members discussed their selection and priorities in choosing a threshold, then each member independently selected another threshold, reporting the new thresholds to the group. This process was repeated iteratively until consensus was achieved. This method was selected to minimize the impact of influential team members and recognize the importance of dissenting views, but ultimately consensus was sought to incorporate each of the team member's perspective in aggregate. Threshold values selected from the derivation set were carried forward into the validation phase.

2.6. Validation analysis

After threshold values were selected, we analyzed the same test performance characteristics on the remaining validation dataset (1/3 of total cases randomly selected) for each outcome using the threshold values. The study protocol prevented the team from changing the threshold values based on the results of the validation data set. Final measures presented included the sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values, with 95% confidence intervals. For the purposes of comparison with bicarbonate and anion gap, lactate thresholds were also evaluated in their ability to predict mortality. All analyses were conducted using SAS v.9.4 (SAS Institute, Cary, NC) and SPSS v.24.0 (IBM Corp, Armonk, NY).

3. Results

3.1. Patient characteristics

There were 4159 ED visits that met the definition of sepsis and had the necessary laboratory components [Fig. 1], with a prevalence of LACT2 of 36% and LACT4 of 9%. Males accounted for approximately 53% of the visits, and there was an overall median age of 61 years [IQR: 49–72 years]. Median hospital length-of-stay was 5 days [IQR: 3–9 days]. Most patients were discharged to home (50%), and the mortality in this cohort was 8%. Although this mortality is lower than most studies of patients with severe sepsis, it is consistent with studies of patients with lactate measured in EDs with suspected sepsis (the sepsis-screened population). As laboratory tests were based on blood samples, no adverse events resulted from either the reference or index tests in this population.

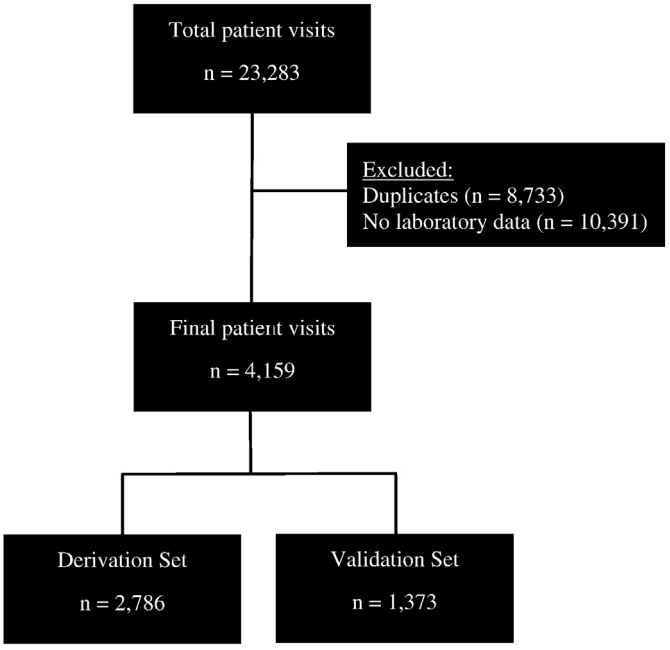

Fig. 1. Flow chart of study subjects.

3.2. Derivation set findings

With LACT2 and LACT4, approximately 36% and 9% were identified as positive for elevated results, respectively. 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 [Fig. 2A and B]. With increasing serum bicarbonate levels (toward normal), the corresponding sensitivity measures rose while specificity measures declined [Table 1]. Anion gap predicted LACT4 with greater discrimination than LACT2; for example, with an anion gap measure ≥20 mEq/L, the positive likelihood ratios were approximately 3.9 and 8.0 for LACT2 and LACT4, respectively [Table 1]. 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 0.717 [95%CI: 0.677–0.756] for lactate [Fig. 2C].

3.3. Decision to proceed

After careful inspection of the ROC curve analysis and the tables of test characteristics, the members of the expert panel discussed whether using serum bicarbonate or anion gap as a marker of illness severity was superior to disregarding those values. The expert panel achieved consensus that the test characteristics were relatively marginal and that increasing hospital capability to include lactate measurement was preferable. The expert panel also felt, however, that such a marginal test, if thresholds prioritizing specificity were selected, could supplement clinical evaluation better than practicing without the guidance of these tests. Because other clinical criteria (vital signs, etc.) were viewed as more sensitive than specific[21], anion gap was viewed as being most useful in specificity.

Because anion gap predicted lactate better than serum bicarbonate, the expert panel elected to select an anion gap threshold alone. Each investigator submitted an anion gap threshold, then using the modified Delphi method, the investigators achieved threshold consensus by discussion and iterative voting. The panel selected an anion gap threshold ≥20 mEq/L.

3.4. Validation set findings

Diagnostic test characteristics were similar in the independent validation data set. Similar to the derivation set, 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. A summary of the validation set test performance characteristics of elevated lactate and mortality outcomes are presented in Table 2.

3.5. Impact of prevalence on post-test probability

Lastly, we conducted an analysis of the impact of prevalence (pre-test probability) on post-test probability using the threshold selected from the derivation set. Fig. 3 shows this relationship, using data from the validation cohort.

4. Discussion

Lactate has been an important risk stratification tool for severe infection since the 1990s [22], and lactate has continued to play a role in sepsis risk stratification [23,24]. It has also been used to measure the adequacy of resuscitation, and lactate clearance has been used to replace other markers of oxygen delivery (ScVO2) [23]. Many low-volume EDs do not have this test immediately available [10], which hampers clinicians' ability to provide guideline-adherent screening and care for

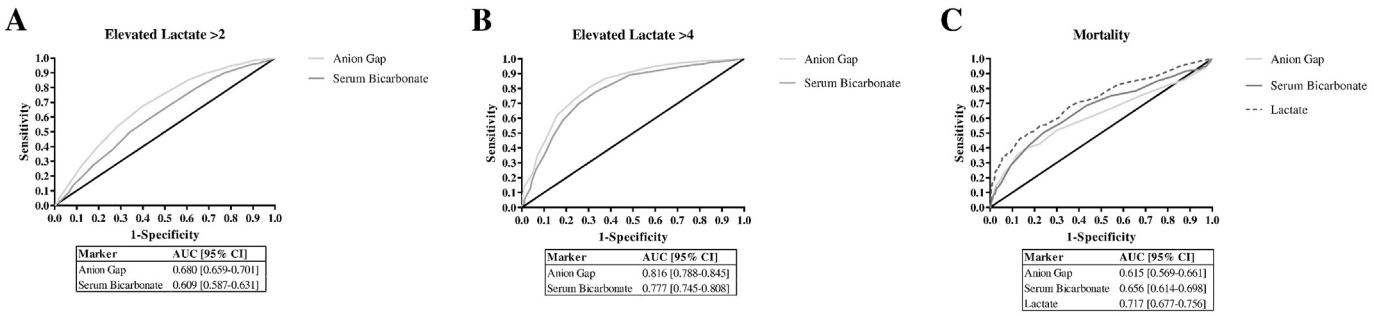

Fig. 2. ROC Curve analysis of elevated lactate and mortality by laboratory marker in derivation set.

sepsis patients [13]. It also may explain higher guideline nonadherence in patients transferred for sepsis care and hospital admission [25]. Clinicians continue to use serum bicarbonate and anion gap to identify patients with tissue hypoperfusion, but no test has replaced direct measurement of serum lactate.

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 [5,16,26]. Although this finding has been reported previously [14-17], these prior papers simply report concordance between biomarkers without reporting associations with clinical outcomes. In our report, we have also reported that this relationship is poor, yet we also show that anion gap predicts mortality (albeit not as well as lactate). Knowing that many clinicians in low-volume and rural EDs are currently using alternative biomarkers for sepsis risk stratification, our report quantifies the utility of these tests and proposes a model for how these tests might be used.

Our study has several limitations. First, it is a single-center study based on retrospective records. While this allows for a very large number of records and precise estimates of test characteristics, it also limits variation in the machines used to measure the biomarkers. Second, we have included only those for whom infection was diagnosed and for those with complete laboratory records. This was done to limit the list of alternative diagnoses that might contribute to elevations in the anion gap. This closely mirrors the population in which these findings would be most applicable, but it also might make the test seem more useful than it would be in a more undifferentiated population. It also includes a broader spectrum of illness severity than strictly including severe sepsis alone would – and it more closely mirrors the population in which the findings would likely be applied. Additionally, we 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). While this could improve the diagnostic utility of this test, we were concerned that adjusting for all of these factors could overstate the utility of our test compared with the manner in which it is used in clinical practice. Alternatively, a delta-anion gap could be used to apply our findings in clinical practice. Finally, allowing a cohort of clinicians to select the threshold value has shifted the threshold value selected toward increased specificity. While others may prioritize statistical parameters differently, we felt that allowing clinical judgment of a group of independent clinicians to guide the selection of the statistical threshold would improve the relevance of test characteristics in the final validation sample.

Despite these limitations, our findings are different from previous findings in two ways. First, the patient population includes a wider

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

Serum Bicarbonate Threshold	Elevated Lactate [>2 mmol/L]						Elevated Lactate [>4 mmol/L]					
	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

Anion Gap Threshold	Elevated Lactate [>2 mmol/L]						Elevated Lactate [>4 mmol/L]					
	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
21	12.8	97.2	4.571	0.897	0.100	0.872	33.1	96.4	9.194	0.694	0.295	0.670

[a] Sens. = Sensitivity; Spec. = Specificity; LR+ = Positive Likelihood Ratio; LR− = Negative Likelihood Ratio; Youden = Youden Index; Dist. ULC = Distance to Upper Left Corner of Graph.

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[a]	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]	0.962 [0.947–0.974]	0.944 [0.930–0.956]	0.933 [0.917–0.946]
LR+	3.670 [2.630–5.122]	7.019 [5.310–9.278]	2.096 [1.548–2.840]	5.135 [3.772–6.990]	2.768 [1.922–3.986]
LR−	0.851 [0.813–0.891]	0.579 [0.495–0.676]	0.447 [0.409–0.489]	0.671 [0.580–0.777]	0.823 [0.737–0.918]

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

cohort of ED patients who presented with infection. This contrasts with studies that enroll patients only in a surgical ICU [15] or in an unselected ED population [16]. By including a wide range of illness severity diagnosed with infection, we have attempted to replicate the population in which this test might be used. The main criticism of measuring lactate surrogates is that other non-lactate organic acids can elevate the anion gap, and that buffering can act to normalize anion gap even in the presence of lactate [27,28].

Second, we selected a threshold for lactate to predict pathology in this setting. The clinicians who selected this threshold intentionally chose a threshold value that was more restrictive because of how this test was likely to be used. In many settings, ordering this test may be triggered by abnormal vital signs or other triggers suggesting systemic infection. While these triggers are imperfect, they often trigger aggressive interventions and simultaneously suffer from alarm fatigue [29,30]. We justified our threshold selection with the recognition that anion gap and bicarbonate are currently being used in clinical practice, but without an evidence-based threshold. We also felt that identifying a potential sepsis patient based on this threshold should reasonably prompt additional therapy, monitoring, and careful placement in the hospital – actions that could not be strongly recommended for a less specific test.

Recent data from a predominantly rural state suggests that the majority of patients with sepsis and septic shock are transferred between hospitals [12]. One large rural sepsis quality improvement network has made recommendations for bicarbonate thresholds to predict hyperlactatemia [31], specifically because of the number of rural hospitals that are unable to measure lactate. Recent diagnostic guidance from the Centers for Medicare and Medicaid Services has renewed interest in intermediate levels of lactate elevation (lactate >2.0 mmol/L), since it qualifies patients for completion of the SEP-1 sepsis quality care bundle [32]. For all of these reasons, an overly sensitive but nonspecific application of diagnostic tests can have far-reaching consequences on sepsis care and rural health systems that were considered in the selection of this threshold.

So how should this test ultimately be used? First, lactate should continue to be measured directly where laboratory capability exists or can be implemented. It remains a superior test. In the absence of lactate availability, though, anion gap can be used to predict poor clinical outcomes. 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. Antibiotics, hemodynamic resuscitation, attentive monitoring, and perhaps transfer to a high-volume center should not be withheld simply because a formal diagnosis of severe sepsis cannot be made. Our analysis demonstrates that these patients are still very ill.

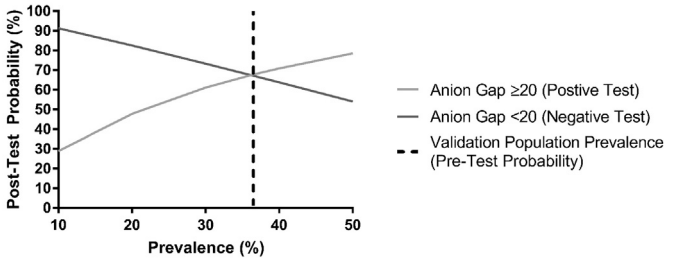

Fig. 3. Positive and negative predictive values for anion gap in predicted elevated lactate (>2 mmol/L), given various prevalence (pre-test probability) of elevated lactate in the target population.

If serum anion gap is used, however, the utility of this test is a function of pre-test probability. In our population, patients who had an anion gap ≥20 mmol/L had a probability of LACT2 of 68%, whereas an anion gap less than this threshold is associated with an elevated lactate of 32%. As shown in Fig. 3, 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 [33-35].

Another important point is that these tests continue to be risk stratification tools and not diagnostic tools. In fact, the utility of lactate measurement is in predicting mortality, and we have shown that elevated anion gap also predicts mortality. 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. Future work should continue to focus on characteristics that identify patients who will benefit most from aggressive sepsis resuscitation, and biomarkers likely play an important role in defining this cohort.

5. 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. Future work should continue to identify strategies to improve sepsis care in rural and low-volume EDs, and to better identify a group of sepsis patients for whom aggressive early care is most valuable.

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Conflicts of interest

None.

Author contributions

NMM, BF, KKH, and AA designed the study. BAF, BF, RDP, SQS, and BS provided expertise in the interpretation of the data. NMM, KKH, BF, and JPV was responsible for managing the data and provided oversight of statistical analyses. NMM, JPV, and KKH had full access to the data set and analyzed the data. NMM and JPV drafted the manuscript, and all

authors contributed substantially to its revision. NMM takes responsibility for the paper as a whole.

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