

Procalcitonin and Lactic Acid: A Review of Predictive Value in Septic Patients

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Received: March 26, 2019; Published: May 30, 2019

Abstract

Introduction: Sepsis is a major cause of morbidity and mortality around the globe. Early identification and intervention is crucial to ensuring better patient outcomes. Several biomarkers, such as procalcitonin (PCT) and lactic acid (lactate), have shown promise for clinical decision-making to identify sepsis early and direct patient care.

Objective: Evaluate the predictive value of PCT and lactate, independently and in combination, among septic patients.

Methods: A literature review was conducted through PubMed of published studies between 2007-2017.

Results: Studies demonstrate that lactate significantly aids in the evaluation of sepsis severity and mortality. In the assessment of PCT, studies report improved utility for early identification of bacterial infection and de-escalation of antibiotics. Few studies examined a combined PCT+Lactate index, which some methods showed promise for enhanced predictive value for outcomes in septic patients.

Conclusion: The combination of these biomarkers potentially offers synergistic utility in the early evaluation of patients with sepsis and septic shock.

Keywords: Procalcitonin; Lactate; Sepsis; Prognostic; Biomarker; Emergency Department

Background

According to the SEP-3 definition, sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Early identification and appropriate risk stratification can be very challenging even for the most skilled clinicians. PCT is a precursor of the hormone calcitonin and is typically synthesized by thyroid C cells. In normal physiologic conditions, PCT levels are low (< 0.5 ng/ml). However, during a bacterial infection and systemic inflammatory response syndrome (SIRS), PCT is synthesized in various extra-thyroidal tissues increasing by 100,000 fold due to the release of pro-inflammatory cytokines stimulated by the presence of bacterial toxins, which in turn causes elevated levels of PCT in the blood (> 0.5 ng/ml). Substantial literature has been published on the utility of PCT as a prognostic marker in septic patients. Prior research has examined PCT as a biomarker that distinguishes bacterial sepsis from viral and non-infectious systemic inflammatory response syndrome (SIRS) [2,3]. It has also been shown that PCT kinetics are particularly useful in determining the severity of infection and effectiveness of antimicrobial therapy [1], which has allowed clinicians to set PCT thresholds to guide antibiotic stewardship [4].

Lactate has been extensively utilized as a marker of tissue perfusion in critically ill patients. In normal physiologic conditions, blood lactate levels are typically between 0.5 - 1 mmol/L being produced by anaerobic metabolism in various organs and tissues [5]. However, in critically ill patients, persistent levels > 2 mmol/L are indicative of poor tissue perfusion and worse patient outcome. Patients with levels

that rise > 4 mmol/L are at particularly high risk of mortality regardless of shock state [2]. Prior research has stated that lactate concentrations are of particular prognostic value in predicting septic shock and mortality in septic patients [5]. Based on this work, clinicians have implemented lactate normalization goals in managing septic patients through their sepsis care bundles as supported by the “Surviving Sepsis” guidelines [6]. There is limited data or clinical utility in using lactate levels to de-escalate antibiotics as compared to PCT.

Many studies have been published evaluating PCT and lactate as independent predictors of sepsis identification and patient outcomes. However, little clinical data exists focusing on the utility of combining both biomarkers. Cochon, *et al.* [7] applied a Bayesian statistical model to PCT and lactate utility with results that suggested incorporating a lab panel including both PCT and lactate in risk assessment of potentially septic patients. In a complex disease process like sepsis, no single biomarker has been proven to be the gold standard for septic patients. Rather, there has been a recent exploration of combining various markers implicated in sepsis. PCT and lactate may have potential for risk stratification and triage protocols in the emergency department and may help inform tailored treatments. Examining the effect of PCT and lactate within these sepsis populations allows for the comparison of the predictive ability of both biomarkers.

This review seeks to address two key questions. First, what prognostic utility do PCT and lactate levels present independently within the same patient population based on previously published literature? Second, is there potential value in correlating these markers to enhance predictive ability?

Methods

This narrative review entails a broad literature search using PubMed key terms. We found studies that examined predictive value of both markers by using different combinations of search terms that included “PCT” OR “procalcitonin” AND “lactate” OR “lactic acid” AND “roc” OR “receiver operating curve” AND “regression” AND “sepsis”. The timeframe was limited to studies published between 2007 - 2017. Original clinical studies that reported on both PCT and lactate data were included in this narrative review. Studies that only included one of the markers were removed. Research that did not include full text in English were excluded. Systematic reviews and meta-analyses were also excluded. No restriction was placed on the patient population (ex: pediatric or adult) nor hospital setting (ex: ICU, emergency department, operating room). Studies were categorized according to the primary outcomes measured, which encompassed severity of sepsis and mortality. 41 original research articles were included for qualitative synthesis.

Based on diagnosis and severity outcomes, studies were categorized into “Bacteremia”, “Sepsis”, and “Septic Shock”. Studies that did not qualify specifically for any of the above were included in a “General Infection” category.

For mortality outcomes, studies were categorized into “28/30-Day Mortality”, “Poor Outcomes”, “In-Hospital/ICU Mortality”, and “Other Mortality Measures”. Those studies that focused on 28 or 30-day mortality were placed in the “28/30-Day Mortality” group. Other research that focused on ICU admission and/or mortality as a primary outcome were designated to the “Poor Outcome” category. Studies that examined in-hospital or specific ICU related mortality were put in the “In-Hospital/ICU Mortality” group. The major distinction between the latter two groups is that the former includes those patients that were admitted to the ICU but did not necessarily expire. The last category encompassed those studies whose primary outcome did not fit into the other three designations.

To compare the utility of the biomarkers across studies, outcomes were assessed based on the receiver operating characteristic (ROC) with area under the curve (AUC). This measure indicates the ability of the biomarker to discriminate between those with and without the outcome of interest.

Results

Diagnosis and severity

For diagnosis and severity of sepsis, twenty research articles were synthesized into the following categories: “General Infection”, “Bacteremia”, “Sepsis”, and “Septic Shock” (Table 1).

Outcome	# of Studies	Study Design(s)	PCT AUC Range*	Lactate AUC Range*	Conclusions
General Infection	1	Observational (Retrospective)	NR**	NR**	PCT is effective at identifying infection onset early. Lactate levels are significant in infection, and failure to meet lactate clearance goals result in further severity.
Bacteremia	6	Observational (Prospective, Retrospective)	0.790 - 0.993	0.710 - 0.844	PCT is able to differentiate bacteremia from non-infectious etiology. Lactate is inconsistent.
Sepsis	10	Observational (Prospective, Retrospective), Case-Control	0.640 - 0.966	0.570 - 0.781	PCT and lactate levels significantly elevated in septic patients. However, PCT more reliably differentiates sepsis.
Septic Shock	3	Observational (Prospective, Retrospective)	0.740 - 0.840	0.690 - 0.890	PCT and lactate range from moderate to strong predictors of septic shock and organ failure.

Table 1: Summary of PCT and lactate utility with diagnosis and severity.

General infection

Only one study was designated for this group due to a primary outcome of infectious complications in a population of trauma patients [8]. Infectious complications had a broad definition that included pneumonia, blood stream infections (BSI), urinary tract infection (UTI), SIRS, and sepsis onset. Area under the curve (AUC) values were not reported but a receiver operating curve was displayed as a figure. Elevated early PCT levels and inadequate clearance of lactate ($p = 0.032$, $p = 0.013$, respectively) were statistically significant markers in identifying both septic and non-septic infectious complications among trauma patients.

Bacteremia

Six studies showed that PCT was superior to lactate in terms of differentiating bacteremia from non-bacteremia patients based on the AUC values [9-14]. In a population of patients identified with urinary tract infections, PCT achieved an AUC of 0.993 (CI: 0.987 - 1.0) compared to lactate with an AUC of 0.844 (CI: 0.785 - 0.904) for predicting bacteremia [9]. Juutilainen, *et al.* [10] reported that in patients with neutropenic fever after chemotherapy, elevated PCT levels were associated with bacteremia (AUC = 0.690 (CI: 0.510 - 0.860)) and more specifically with gram-negative bacteremia (AUC = 0.77 (CI: 0.560 - 0.980)). Another study showed that PCT (AUC = 0.790 (CI: 0.70 - 0.890)) and lactate (AUC = 0.760 (CI: 0.650 - 0.870)) were of equivalent value in assessing bacteremia in critically ill children [11]. Two studies suggested that the predictive value of lactate was limited in the setting of bacteremia [10,12]. In particular, lactate levels were significant ($p < 0.005$), but upon incorporation into a multivariate model, lactate was rendered insignificant ($p = 0.192$) for predicting blood stream infection [12]. Lactate was of no significance with any endpoints in Juutilainen, *et al* [10]. Across all studies evaluated, PCT was considered a strong predictor of bacteremia, while lactate was inconsistent in predictive value. None of these studies correlated PCT with the time to onset of positive blood cultures.

Sepsis

Ten studies evaluated PCT as a predictive marker of sepsis [15-24] with the majority of studies (9/10) concluding significant utility in differentiating bacterial sepsis from a non-bacterial etiology. In the same nine studies, lactate was considered a weak to moderate indicator of sepsis and was always inferior to PCT. This was demonstrated by the comparison of ROC curves as indicated by four studies that reported both PCT and lactate AUC values. This is consistent with clinical management where we see poor specificity of lactate to just sepsis.

In a population of patients presenting to the ICU with suspicion of sepsis, PCT had an AUC value of 0.918 ($p < 0.001$) and lactate displayed a value of 0.663 ($p = 0.004$) in distinguishing sepsis from systemic inflammation without a clear bacterial etiology [15]. Ljungstrom, *et al.* [16] found a moderate distinction between each individual marker with an AUC value of 0.640 (CI: 0.610 - 0.670) for PCT and 0.570 (CI: 0.540 - 0.600) for lactate in predicting bacterial sepsis.

For a sample of burn patients whose total burn surface area exceeded 15%, PCT and lactate AUC values were 0.717 ($p < 0.05$) and 0.649 ($p < 0.05$) in predicting sepsis onset, respectively [17]. Park, *et al.* [18] found that PCT (AUC = 0.923 (CI: 0.873 - 0.957)) was superior to lactate (AUC = 0.781 (CI: 0.714-0.840)) in differentiating septic and non-septic patients but both were still clinically significant.

The relationship between PCT and lactate levels was consistent in eight studies with PCT being superior to lactate in early sepsis diagnosis across populations ranging from general ICU admissions, post-operative wards, and burn victims.

Septic Shock

Three studies examined the relationship of PCT and lactate primarily with respect to septic shock. One study evaluated the development of septic shock in patients with pyogenic liver abscess and found that lactate was a strong predictor of septic shock [25]. In the same study, PCT was shown to be associated with an increased rate of septic shock, but overall not statistically significant ($p = 0.058$). Another study examining the utility of sphingosine-1-phosphate as a biomarker in the development of septic shock in general ICU patients reported moderate prognostic values for both PCT (AUC = 0.740 (CI: 0.640 - 0.840)) and lactate (AUC = 0.690 (CI: 0.580 - 0.810)) [26]. The third study examined biomarker utility in predicting septic shock, which found that initial lactate (AUC = 0.890 (CI: 0.820 - 0.960)) was a more reliable predictor [27]. PCT was still of strong clinical significance as indicated by an AUC value of 0.840 (CI: 0.770 - 0.920). In general, both PCT and lactate present consistent utility as predictors of septic shock.

Mortality

For mortality-related outcomes, twenty-one studies were placed into the following categories: "28/30-Day Mortality", "Poor Outcome", "In-Hospital/ICU Mortality", and "Other Mortality Measures" (Table 2).

Outcome	# of Studies	Study Design(s)	PCT AUC Range*	Lactate AUC Range*	Conclusions
28/30-Day Mortality	10	Observational (Prospective, Retrospective)	0.377 - 0.713	0.660 - 0.837	Lactate is a consistently strong predictor of mortality outcome. PCT is considered a weak to moderate predictor depending on patient population.
Poor Outcome (ICU admission or Mortality)	2	Observational (Prospective), Case-Control	0.584 - 0.664	0.629 - 0.679	PCT and lactate are both moderate indicators of ICU admission and/or mortality outcome.
In-Hospital/ICU Mortality	6	Observational (Prospective, Retrospective), RCT	0.380 - 0.707	0.712 - 0.910	PCT levels are significantly different between survival groups but provide weak prognostic value. Lactate maintains strong utility across disease severity in risk stratifying mortality.
Other Mortality Measures	3	Observational (Prospective, Retrospective)	0.830**	0.700 - 0.749	Lactate is a good predictor of 7-day mortality but not 90-day mortality. PCT has a strong ability to predict 90-day mortality.

Table 2: Summary of PCT and lactate utility with mortality.

*PCT and Lactate ranges based on studies that explicitly reported ROC values.

**No range available due to only 1 study reporting PCT ROC values.

28/30-day mortality

Ten studies evaluated the prognostic value of PCT and lactate with respect to 28/30-day mortality assessment [14,28-36]. In general, PCT was found to have moderate to limited utility in predicting mortality. There was some indication that PCT was predictive of mortality

in patients with severe sepsis or septic shock [28-30]. A percentage change PCT from baseline levels yielded an AUC of 0.760 (CI: 0.670 - 0.850), suggesting that a fall in PCT levels was associated with a favorable outcome at 28 days in severe sepsis and septic shock patients [28]. According to Choe, *et al.* [29], low PCT levels (< 0.25 ng/mL) were also associated with a favorable outcome with an odds ratio of 0.43 (CI: 0.19 - 0.98). Higher PCT levels did not reflect a significantly higher mortality. Viallon, *et al.* [30] compiled a multivariate model with and without PCT which resulted in an increase in AUC from 0.939 to 0.985 as a predictor of mortality in sepsis patients, however this was found to be statistically insignificant ($p = 0.066$).

In contrast, lactate was consistently reported as a strong predictor of mortality across the spectrum of disease severity. Suárez-Santamaría, *et al.* [31] found an AUC of 0.781 (CI: 0.707 - 0.855) for lactate as a predictor of 28-day mortality. Brodska, *et al.* [32] found a similar ROC curve value (AUC = 0.805 ($p < 0.001$)) further underscoring the strong predictive ability of lactate. One study found peak PCT and lactate levels to be relatively equivalent in predicting mortality in surgical patients with complicated intra-abdominal infections with an AUC value of 0.650 (CI: 0.479 - 0.821) and 0.674 (CI: 0.537 - 0.810), respectively [33]. There is strong evidence supporting the prognostic value of lactate with regards to mortality, whereas PCT lacks consistency in this outcome measure.

Poor outcome

Two studies examined poor outcome as a primary result, which was defined as mortality and/or ICU admission. PCT (AUC = 0.584 (CI: 0.473 - 0.690)) and lactate (AUC = 0.629 (CI: 0.518 - 0.731)) were considered of similar weak to moderate utility in predicting poor outcome in cancer patients with sepsis [37]. Another study presented PCT and lactate with moderate abilities to predict severe outcome and described increased value in combining these markers with patients admitted to the emergency department with the suspected infection [38]. PCT and lactate had AUC values of 0.664 (CI: 0.594 - 0.724) and 0.679 (CI: 0.604 - 0.731) respectively in predicting poor outcome. PCT and lactate, on the whole, are moderate predictors of mortality and/or ICU admission.

In-hospital/ICU mortality

In all six studies included, lactate was considered a strong indicator of in-hospital and ICU-specific mortality as indicated by respective AUC reported [39-44]. Only two of these studies found utility for PCT on inpatient mortality [39-40]. In an intervention study of septic shock patients receiving veno-venous hemofiltration, a significant elevation of PCT levels, as well as CRP and kynurenic acid, was a consistent trend in non-surviving patients ($p < 0.05$) [39]. A similar observation was made in a population of secondary peritonitis patients ($p < 0.001$) [40]. All other studies found PCT to be a poor marker for assessing potential in-hospital mortality risk [41-44].

Other mortality measures

Two studies assessed 7-day mortality and one study examined 90-day mortality with respect to PCT and lactate levels. These mortality metrics presented different conclusions. Lactate was considered an insignificant measure of 90-day mortality, whereas PCT possessed strong predictive utility based on AUC metrics [45]. For the studies assessing 7-day mortality, high lactate levels and inefficient lactate clearance were predictive of mortality [46,47]. PCT served no utility in these studies.

Combined utility of PCT and lactate

Six studies combined both PCT and lactate as a predictive measure (Table 3). It is important when assessing these combination methods that there is sufficient statistical rigor to properly assess a PCT+Lactate index but also be clinically applicable to medical practice. While the value of strong statistical models is important, there can be limitations to incorporating further complexity into a fast paced emergency department.

Study	Outcome	Combined Method	Combination v. Independent	Limitations
Phua., <i>et al.</i> (2008)	28-Day Mortality	Logistic Regression	Higher mortality rates were associated with patients having increases of both markers as opposed to increase of one or none.	Only 69% of patients with proven infections; small sample size; septic shock focus
Freund., <i>et al.</i> (2012)	Mortality and/or ICU admission	Logistic Regression	When considering both elevated PCT and lactate levels, patients had an increased risk of ICU admission and/or mortality compared to independent markers.	Selection bias of only patients with both PCT and lactate measurements; Single-center; Physician bias of diagnostic decisions
Suarez-de-la-Rica., <i>et al.</i> (2015)	28-Day Mortality	Dummy Variable ^a	Peak levels of each marker combined together achieved superior mortality prediction.	Retrospective analysis
Peschanski., <i>et al.</i> (2016)	30-Day Mortality	BLC Method ^b	There was no difference in predictive value of mortality.	Retrospective analysis; no severity scoring; no adjustment for antibiotic therapy prior, during, or after ER admission; Lactate not measured in all patients
Nellis., <i>et al.</i> (2016)	Bacteremia	Logistic Regression	Enhanced sensitivity and specificity of bacteremia resulted from combining markers.	Retrospective analysis; small sample size; niche sample of pediatric cancer patients; co-morbidities not considered (malnutrition, immunodeficiency, kidney disease)
Ljungstrom., <i>et al.</i> (2017)	Sepsis	Linear Discriminant Analysis ^d	Composite biomarkers were comparable to PCT in identifying sepsis but superior to both individual markers in severe forms of sepsis.	Used strict definition of bacterial sepsis which could exclude infectious patients without being microbiologically proven; Could be too oversimplified to use linear models

Table 3: Methods used in combining PCT and lactate.

^aDummy Variable: Concomitant peak lactate and peak PCT levels with designated cut-off values incorporated into one variable (0-1 range).

^bBest Linear Combination: Creates a formula to combine PCT and lactate based on their coefficient of covariance in the study population.

^dLinear Discriminant Analysis: Function that produces a score (Z) calculated from discriminant coefficients and independent markers.

Three of the six studies focused on 28/30-day mortality as the primary outcome of interest. Two of these studies reported improvement in predictive utility for mortality when examining both markers together. Suarez-de-la-Rica., *et al.* [33] found similar enhanced predictive ability when considering peak levels of both PCT and lactate. The combination yielded an odds ratio of 99.11 (CI: 5.21 - 1885.97), which far exceeded both independent PCT (OR = 11.28 (CI: 1.80 - 70.20)) and lactate (OR = 8.86 (CI: 1.51 - 52.10)) in predicting mortality. Phua., *et al.* [35] saw higher rates of mortality when there was an increase in both markers (86.7%) compared to an increase in one marker (22.7%) or neither marker (20.7%). Only one study found that the combination of PCT and lactate was not particularly useful in enhancing predictive value [36]. The resulting combination (AUC = 0.633 (CI: 0.533 - 0.726)) failed to produce a maximal ROC curve compared to PCT alone ($p = 0.061$). This study had many limitations. The study was restricted to patients with high PCT, the sample size was small ($n = 188$) and there was a limited number of patients that had lactate levels measured. This study did show that when patients had elevation of both PCT and lactate above cutoff values, patients had unfavorable outcomes. Therefore, they concluded the two biomarkers could be potentially useful in very high risk patients.

Freund., *et al.* [38] was the only study that primarily examined severe outcome, defined as mortality and/or ICU admission. The authors found that the combination of PCT and lactate most notably enhanced specificity (0.93 (CI: 0.90 - 0.95)), positive predictive value

(PPV) (0.56 (CI: 0.42 - 0.69)) and positive likelihood ratio (PLR) (4.54 (CI: 2.86 - 7.27)). When considering independent PCT, specificity, PPV and PLR were 0.75 (CI: 0.70 - 0.79), 0.35 (CI: 0.28 - 0.44), and 2.00 (CI: 1.53 - 2.59), respectively. For lactate, these diagnostic variables were 0.76 (CI: 0.72 - 0.81), 0.39 (CI: 0.32 - 0.47), and 2.31 (CI: 1.78 - 2.98), respectively.

The two remaining studies examined disease onset, bacteremia, and sepsis, and found significant improvement in predictive value with the combination of PCT and lactate. Nellis, *et al.* [11] combined abnormal lactate (> 2 mmol/L) levels with PCT at varying thresholds (0.2, 0.5, 1, 2, 5, 10 ng/mL). At each PCT threshold, specificity and PPV were improved with the addition of abnormal lactate. For example, at a PCT of > 0.5 ng/mL, the specificity improved from 48.7% to 87.2% and PPV increased from 20.4% to 41.2%. Ljungstrom, *et al.* [16] examined combined utility of PCT, lactate, and a few additional markers, such as C-reactive protein and neutrophil-lymphocyte count ratio, with respect to sepsis diagnosis. For identifying sepsis, the composite marker (AUC = 0.700 (CI: 0.670 - 0.730)) was comparable to PCT (AUC = 0.680 (CI: 0.650 - 0.710)) with both being greater than lactate (AUC = 0.570 (CI: 0.540 - 0.600)). However, in predicting more severe forms of sepsis, the composite marker (AUC = 0.850 (CI: 0.820 - 0.880)) significantly exceeded independent PCT and lactate (p < 0.05).

Discussion

As evidenced by this review, substantial literature exists in evaluating PCT and lactate as useful predictive markers in sepsis. PCT and lactate levels provide useful information when it comes to risk stratifying patients and improving clinical outcomes, but the utility of each marker varies depending on the specified outcome (Table 4).

	Outcome	Early Detection	Infection	Disease Severity	Mortality
Marker	PCT	++	++	+	+/-
	Lactate	-	+/-	+	++
	PCT+Lactate	NR	++	+	++

Table 4: General biomarker assessment based on literature review.

Level of evidence as indicated by literature: Strong (++), Moderately consistent (+), No association (-), Inconsistent (+/-), Not reported (NR).

What prognostic value do PCT and lactate, as independent markers, have among septic patients? PCT is particularly valuable in detecting sepsis early, differentiating bacterial and non-bacterial systemic inflammation, and determining disease severity. The kinetic profile of PCT contributes to its strengths with its rapid escalation during a bacterial infection [48]. However, PCT has shown inconsistencies in predicting patient mortality. Lactate, on the other hand, is a strong predictor of mortality and disease severity. Nonetheless, lactate is unable to differentiate infectious and non-infectious etiology effectively and does not inform on appropriate antibiotic stewardship efforts.

What is the best way to combine these markers and is there clinical application? One of the major challenges for researchers is deciding on what multi-marker approach is best to translate several markers into one index. All six studies that examined this combination sought to develop a single score and threshold for a PCT+Lactate index using various different methods. The methods included logistic regression, dummy variable, best linear combination, and linear discriminant analysis.

Logistic regression was leveraged for three studies, and although statistically useful, it's clinical application is limited. It allows researchers to input multiple independent variables to estimate the probability of an outcome, whether mortality or disease onset. However, considering multiple markers in the same logistic model does not mean that the values are "combined" in the traditional sense. Rather, the independent variables are adjusting for their respective presence in the model based on the outcomes of interest. Phua, *et al.* [35], Freund, *et al.* [38] and Nellis, *et al.* [11] all found enhanced predictive value when considering both PCT and lactate levels, which contributes to further investigation of combined utility. However, other metrics may be better suited for clinical use.

The dummy variable combined peak PCT and lactate values if they both exceeded a certain threshold, but if one or neither marker made it above the threshold, no value was inputted leaving a binary range of values from 0 to 1 [33]. In this study, the PCT cutoff point was

exceedingly elevated at 100 ng/mL, with the lactate cutoff point of 1.8 mmol/L. This model was based on specific cut-off values that are relevant to the study population, but they may not be generalizable to all septic patients. Additionally, there is a lack of statistical rigor incorporated into the dummy variable. Further research is needed to establish proper thresholds to incorporate into a combination metric.

The other methods including logistic regression, the best linear combination, and linear discriminant analysis, all strive to develop a linear equation to combine the values of PCT and lactate using different statistical approaches. The best linear combination method provides a more statistically rigorous approach to risk stratifying the integration of these markers. In the Peschanski, *et al.* [36] study, the combination equation based on the study population coefficient of variance was the following: $\text{PCT (ug/L)} + 0.025 \times \text{lactate (mmol/L)}$. This equation could be taken a step further by examining the change in PCT+ lactate score with respect to potential patient outcomes. It provides improved statistical rigor, however, the linear equation is developed and validated on a specific population that may not extend the accuracy to external populations. External validation is necessary to determine if this method will hold its value at other locations.

Linear discriminant analysis is used by Ljungstrom, *et al.* [16] as a means to combine PCT, lactate, and two other biomarkers. Like the best linear combination method, this model offers simplicity while also being mathematically robust. The resulting discriminant function produced a Z-score derived from four independent markers and discriminant coefficients. The composite marker score was then compared to independent markers in the identification of bacterial sepsis.

The scoring and best linear combination equation approaches have significant limitations in their clinical application of combining PCT and lactate. Both would need to be studied further to enhance their generalizability across septic patients and develop proper clinical utility with a PCT+Lactate index as studies using these methods were restricted to smaller sample sizes (< 200), rendering them susceptible to skewed data and weaker conclusions. On the other hand, linear discriminant analysis, as Ljungstrom, *et al.* [16] have described, is a variable combination that can easily be incorporated into clinical use. Additionally, the study was strengthened by a large sample size ($n > 1,500$) to be better generalized to all septic patients.

The question then becomes how should these markers be measured? Rather than utilizing absolute levels of each marker, addressing the change or clearance in PCT and lactate levels appears to be the best approach at enhancing predictive value and improving patient outcomes. Some studies, like Billeter, *et al.* [8], Lee, *et al.* [46] and Wang, *et al.* [34], each used lactate clearance from baseline instead of absolute concentrations of the marker to assess patient outcomes, which produced strong predictive utility. Specifically, Lee, *et al.* [34] found that initial and max lactate values were not significant amongst survival groups. Rather, change in lactate levels at specific time intervals (6, 24, and 48 hours) from baseline reflected 7-day survival outcome ($p < 0.001$). Lactate levels at 24 and 48 hours compared to baseline yielded AUC of 0.749 (CI: 0.606 - 0.892) and 0.782 (CI: 0.647 - 0.917), respectively, leading the authors to conclude that lactate clearance from baseline levels at discrete time points was a better indicator of survival. With PCT, other authors used the change in PCT from baseline as opposed to independent PCT levels [10,19,20,24,28,35]. For example, a key secondary outcome for Lavrentieva, *et al.* [24] in burn patients measured effectiveness of sepsis treatment in evaluating PCT and change in PCT. A decrease in PCT over three days of treatment reflected therapy effectiveness with an AUC of 0.988 (CI: 0.960 - 1.030) compared to PCT on day three with an AUC of 0.860 (CI: 0.69-1.030). Charles, *et al.* [20] identified a similar trend in PCT kinetics over three days to be indicative of survival (OR = 2.94 (CI: 1.22 - 7.09)) in ICU patients with documented sepsis. PCT is an inconsistent predictor of mortality, which could be improved by incorporating lactate. The same reasoning goes for lactate with respect to determining the presence of bacterial infection and utilizing PCT in the diagnosis. PCT and lactate are readily available from lab testing, which makes this combination a potentially useful and financially reasonable option to inform a physician's overall clinical evaluation.

Further research with sufficiently large sample sizes ($n > 1,000$) should investigate and validate the value of combining PCT and lactate measurements to evaluate their change in levels over time. Specifically, serial measurements of both markers should be obtained with clinical outcomes (i.e. sepsis diagnosis, mortality, etc.) documented for each subject admitted to an emergency care unit with suspicion of sepsis. The next step would then be to assess outcomes corresponding to the change in PCT and lactate levels from baseline over time.

Lastly, as discussed previously it seems to be the most useful and generalizable to combine the markers using linear discriminant analysis to yield a combination score. This will provide a direct comparison of combined utility against individual biomarkers. The combination can be further assessed through the establishment of threshold values of the integrated PCT+Lactate index and comparing them to established cutoff levels of independent PCT and lactate in clinical practice as described by Ljungstrom., *et al* [16]. By evaluating the change in the combination score, PCT and lactate can be maximally enhanced with their strengthened predictive values and thereby improve clinical outcomes for septic patients.

Limitations

Overall, the body of literature is very heterogeneous due to sample sizes, patient populations, biomarker thresholds (i.e. PCT cut-offs ranging from 4.3 to 32.5 ng/mL [36]), lack of uniformity in measuring PCT and lactate values, and different outcomes measures (i.e. mortality, septic shock, etc.). Despite these challenges, trends emerged from levels of PCT and lactate with patient outcomes of interest.

Further limitations exist to this narrative review. The PubMed search was not fully systematic in terms of extensive inclusion and exclusion criteria. Geographic flexibility was permitted with studies based in various settings across the globe (i.e. U.S., Spain, Thailand, Sweden, etc.), which have different health systems that could potentially impact generalizability. All populations, adult and pediatric, and varying sources of infection were included as long as both PCT and lactate data was reported. This could also potentially affect generalizability. Also, not all studies excluded or examined the use of antibiotics and amount of fluids received in the patient population, which could thereby potentially affect PCT values. Additionally, all of the studies measured lactic acid and PCT levels, but none of the studies measured the compliance and use of treatment bundles, such as the early administration of intravenous fluids and antimicrobials. No other markers such as CRP and IL-6 were considered for this review, although they were discussed in several of the studies. Lastly, there were only a few studies that focused specifically on combining PCT and lactate levels with respect to patient outcomes. These studies only considered linear combinations whereas a non-linear approach may be more appropriate.

Conclusion

Sepsis is a disease process that can result in multi-organ dysfunction and death unless detected early. The key to early detection of sepsis is a keen clinical sense with respect to history and physical exam findings, imaging, and various laboratory values but can be assisted through biomarkers, such as PCT and lactate. PCT can be very useful when it comes to early detection of bacterial infection, while lactate has demonstrated to be helpful in patients with septic shock and as a predictor of mortality. When the two biomarkers are combined, it seems that their predictive utility is enhanced by addressing their independent weaknesses. Future research should consider both absolute marker levels at discrete time points and the change of marker levels over time to accurately reflect predictive value.

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