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Disease heterogeneity and risk stratification in sepsis-related occult hypoperfusion: a retrospective cohort study

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Abstract

Purpose—Occult hypoperfusion is associated with increased mortality in patients with sepsis.

We sought to determine the practice patterns and outcomes of patients with sepsis-related occult hypoperfusion and introduce a potential method for risk-stratification.

Materials and Methods—Single-center retrospective study of normotensive patients presenting to an urban tertiary care Emergency Department (ED) with lactate ≥ 4 mmol/L and suspected infection. Chi-square testing, Spearman, and Wilcoxon coefficients were used to compare binary, parametric, and non-parametric data, respectively. Patients were divided into four groups based on lactate clearance (<4 mmol/L) and the presence of respiratory distress while in the ED; outcomes were compared using chi-square and analysis of variance.

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Competing Interests:

The authors declare that they have no competing interests.

Author's Contributions:

SL, AM, TG, RL, MNC and MWD participated in the design of the study. SL, RL, TG and AM gathered and analyzed the data. MNC and MWD supervised the data gathering and analysis. SL, AM and TG performed the statistical analysis. SL and AM drafted the manuscript. All authors read and approved the final manuscript.

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Results—Median initial lactate was 4.7 mmol/L [IQR 4.2–6.4] and 34/73 (45.2%) exhibited respiratory distress. Hyperlactatemia resolved in 67.1% (49/73) of patients. Mortality was 23.3% (17/73) and 19.1% (14/73) required vasopressors. In patients with lactate clearance and without respiratory distress (n=27), mortality was 0% and none required vasopressors. In patients with persistent hyperlactatemia and/or respiratory distress (n=46), 30.4% required vasopressors and the mortality was 37.0% (p<0.01 and p<0.01, respectively).

Conclusions—Patients defined as having occult hypoperfusion comprise a heterogeneous group with a varied degree of illness severity. Identifying those with low risk for clinical deterioration may be important for titration of care.

Keywords

Sepsis; occult hypoperfusion; lactate clearance; mortality; vasopressor

Introduction

Occult hypoperfusion, defined by elevated serum lactate without hypotension, has been associated with significantly increased mortality[1, 2]. Serum lactate may represent a more accurate measure of tissue hypoperfusion than vital signs alone and has been suggested as both a method for risk stratification[3, 4] and a target for resuscitation strategies[5, 6]. In prior work by our group, we have found serum lactate is significantly associated with mortality even after adjusting for age and systolic blood pressure[1]. Similarly, Mikkelsen et al. found that among patients with severe sepsis without evidence of shock, a serum lactate 4mmol/L was associated with a mortality of 31.8%[2]. These findings have been echoed in the surgical and trauma literature where elevated lactate is seen as predictive of poor outcomes even in the absence of clinical shock[7–9]. Given the high mortality associated with occult hypoperfusion in patients with suspected infection, clinical practice guidelines recommend quantitative resuscitation guided by a central venous catheter (CVC) for all patients with suspected sepsis and a lactate 4mmol/L[10].

The use of this definition of occult hypoperfusion without consideration of other-organ injury and/or an overall clinical assessment of the patient may have unintentionally led to classification of a heterogeneous group of patients as having ‘occult hypoperfusion.’ While it is clear that patients identified by the currently accepted definition of occult hypoperfusion have high mortality, the existing evidence lacks the granularity to determine whether there exists a subset of patients in this heterogeneous population who are at low risk for clinical deterioration. For example, clinical experience suggests that a septic patient with respiratory failure requiring mechanical ventilation has a higher risk of mortality than one who exhibits no evidence of respiratory compromise even if both patients are normotensive with elevated initial lactate measurements. Despite this discrepancy, most of the existing evidence places them in the same risk stratum and would define both as occult. The application of one treatment model to a heterogeneous group of patients may result in inappropriately titrated care to the given illness severity and patient profile. This could lead to unnecessary invasive procedures as well as the misallocation of health care resources for patients who are unlikely to benefit from them. Clearly, more evidence is needed to guide clinicians in how best to risk stratify patients with occult hypoperfusion.

We sought to determine the patterns in physician decision-making and outcomes for a cohort of patients with elevated lactate without hypotension, and when those same patients are divided into more homogenous categories by using respiratory distress and/or failure (i.e., other-organ injury) and lactate clearance.

Materials and Methods

Study Design

This was a single-center retrospective study of patients presenting to an urban tertiary care center between 2008 and 2009. Informed consent was waived as the study was a retrospective chart review. The Institutional Review Board (IRB) at Beth Israel Deaconess Medical Center (BIDMC) approved the study.

Patient Selection

The electronic medical records (EMR) of all patients who had an initial lactate measured on arrival at the BIDMC emergency department were screened for inclusion in the study. Those patients with an initial serum lactate of 4.0mmol/L or higher were identified and their medical records reviewed. Patients with an initial serum lactate $\geq$ 4.0mmol/L, a suspected source of infection based on clinical judgment of the treating physician and later verified by review of the electronic medical record by the use of antimicrobials, and absence of hypotension throughout their emergency department stay were ultimately selected for further analysis.

Data Collection

Patient demographics, co-morbid conditions, initial vital signs and laboratory test results were collected and managed using REDCap, Version 4.3.5[11]. The presence or absence of respiratory distress was determined by a review of the EMR. The amount of intravenous fluid received while in the emergency department was similarly determined. The hospital course of all enrolled patients were reviewed to identify those who had a CVC placed, those who required vasopressors, and ultimately to determine patient outcomes.

Definitions

Hypotension was defined by systolic blood pressure SBP<90 mm Hg. Lactate clearance was defined by reduction of hyperlactatemia (second lactate measurement < 4mmol/L). Respiratory distress was defined by respiratory rate >30, need for non-invasive positive pressure ventilation, or intubation with mechanical ventilation. A respiratory rate >30 was chosen *a priori* as one definition of respiratory distress as it is our institutional standard for our hospital rapid response program[12].

Outcomes

Outcomes of interest included need for vasopressors within 72 hours and in-hospital mortality. Additional factors investigated with regard to care practice variation in occult hypoperfusion included the rate of CVC placement and ICU admission. The composite

primary outcome is defined as the need for vasopressors within 72 hours and/or in-hospital mortality.

Statistical Analysis

Simple descriptive statistics were used to summarize the study population. Continuous variables are presented as means with standard deviations (SD) or median with inter-quartile ranges [IQR] depending on normality of the data. Categorical data are presented as frequencies with percentages. Chi-square testing was used to compare binary variables. Spearman and Wilcoxon coefficients were used to compare parametric and non-parametric data respectively.

Patients were divided into four groups based on whether there was a decrease in lactate to <4 mmol/L and whether they exhibited respiratory distress in the ED. Analysis of Variance (ANOVA) calculations were used to compare outcomes across the four groups. All analysis was performed using JMP Pro, a component of SAS (Cary, NC). A p-value < 0.05 was considered significant.

Results

76 patients were included in the study. One patient was excluded due to having a pre-existing central venous catheter and one was excluded after the goals of care transitioned to comfort-focused care. An additional patient was excluded for a systolic blood pressure <90 subsequently during their ED stay. The average patient age was 68.2 years (± 18.6) and 57.5% were male. 56.1% of patients were admitted to the intensive care unit with the remainder admitted to the non-ICU wards. The median initial lactate was 4.7 [IQR 4.2–6.4] and the median time between lactate measurements was 157 minutes [IQR 97.3–280.3]. Respiratory distress was present in 33/73 patients (45.2%) with 9 requiring mechanical ventilation, 1 requiring non-invasive positive pressure ventilation, and 23 with tachypnea (respiratory rate ≥ 30). Patients received an average of 2.8L of intravenous fluids in the ED. Overall 19.1% of patients ultimately required vasopressor support and the mortality rate for the entire cohort was 23.3%. Nearly 22% of patients had a CVC placed while in the ED with an additional 11.0% ultimately requiring CVC placement in the ICU during their hospital stay. See Table 1 for baseline characteristics.

Overall, patients with respiratory distress in the ED more frequently required vasopressors (30.3% vs. 10%, $p=0.03$). Mortality was 33.3% in those with respiratory distress as compared to 15% in those without respiratory distress, however this did not reach statistical significance ($p=0.06$). Patients with respiratory distress were more likely to be admitted to the intensive care unit (69.7% vs. 45.0%, $p=0.03$). The absence of respiratory distress had a negative predictive value for the composite outcome of in-hospital mortality and/or need for vasopressors within 72 hours of 85% (95% CI=0.70–0.94). See Table 2 for details.

Patients with a persistently elevated lactate ≥ 4 mmol/L more frequently required vasopressor support (37.5% vs. 10.2%, $p<0.01$) and mortality rates were higher (50% vs. 10.2%, $p<0.01$). Lactate clearance to <4 mmol/L after administration of intravenous fluids had a negative predictive value of 85.7% (95% CI= 0.73–0.94) for the composite outcome of in-

hospital mortality and/or need for vasopressors within 72 hours. Furthermore, patients with a persistently elevated lactate $\geq 4\text{mmol/L}$ were more likely to be admitted to the intensive care unit (75.0% vs. 46.9%, $p=0.02$). There was no difference in amount of intravenous fluid administered between the two groups (3.06 vs. 2.63, $p=0.14$). See Table 3 for details.

The study cohort was further segmented into four groups based on the presence or absence of respiratory distress and presence or absence of lactate clearance (subsequent serum lactate $<4\text{mmol/L}$).

In patients with persistently elevated lactate $>4\text{mmol/L}$ and respiratory distress ($n=11$), 45% required vasopressors and the mortality rate was 55%. Among this group, 45% of patients received a CVC in the ED, 9% had a CVC subsequently placed while in the intensive care unit, and 82% were admitted to the ICU. In patients with lactate clearance to $<4\text{mmol/L}$ and respiratory distress ($n=22$), mortality was 22.7% and 22.7% of patients subsequently required vasopressors. 18.2% had a CVC placed in the ED, 18.2% had a CVC placed in the ICU, and 63.6% were admitted to the ICU. Those patients with persistently elevated lactate $\geq 4\text{mmol/L}$ but no respiratory distress ($n=13$) had a mortality rate of 46% and 31% of patients required vasopressors; among these patients, 31% had a CVC placed in the ED, 23% had a CVC placed in the ICU, and 69% were admitted to the ICU. None of patients who cleared lactate to $<4\text{mmol/L}$ and did not have respiratory distress ($n=27$) had a CVC placed in the ICU or required vasopressors and the overall mortality rate was 0%. Furthermore, only 33% of these patients were admitted to the ICU. The difference in mortality rate and vasopressor requirement between all four groups was statistically significant ($p<0.01$ and $p<0.01$, respectively). There was no statistically significant difference between groups with regard to initial creatinine ($p=0.09$). There was no difference in the volume of fluid resuscitation between groups ($p=0.65$). See Figures 1–3 for details.

Patients in the former three groups were compared with those patients in group four (who had no respiratory distress and cleared lactate to $<4\text{mmol/L}$) using a combined end-point of need for vasopressors and mortality. In patients who had either persistent hyperlactatemia $\geq 4\text{mmol/L}$ and/or respiratory distress, 30.4% required vasopressors and the mortality rate was 37.0%. This compares to 0% in both categories for group four ($p<0.01$ and $p<0.01$, respectively). The absence of respiratory distress combined with lactate clearance had a negative predictive value of 100% (95% CI=0.87–1.0) for the composite outcome.

Discussion

While hyperlactatemia was associated with both high mortality and high rate of vasopressor use within 72 hours (23.3% and 19.1%, respectively), we found a subset of patients in whom clinical deterioration was low. Our population, consisting of normotensive septic patients further stratified by presence of respiratory distress (i.e. other organ injury) and presence of lactate clearance to $<4\text{mmol/L}$, illustrated that there is significant variability within the broad category of what has traditionally been defined as sepsis-related occult hypoperfusion.

In our cohort, 89.8% of patients who exhibited lactate clearance to $<4\text{mmol/L}$ did not require vasopressors, indicating that lactate clearance may be a valuable tool in predicting

clinical deterioration and need for hemodynamic support, which is consistent with prior studies[13, 14]. Of note, we (and others) have previously found that a substantial percentage of patients with overt shock requiring vasopressor support may have normal lactate levels[15, 16]. Synthesizing these two findings will require additional study but may represent patient-level differences in those who initially present with and without lactate elevation (so-called lactate expressors versus non-lactate expressors) in those who present with overt hypotension.

Although prior studies have chosen to define lactate clearance as a 10% reduction in serum lactate[14, 17], we chose *a priori* to define lactate clearance as a subsequent lactate <4mmol/L in order to simplify decision making for providers with a dichotomous metric to determine tissue hypoperfusion. In our current study, 8/73 patients failed to clear their lactate by at least 10%, thus limiting this parameter to a very small number of patients. Additionally, intuition leads one to believe that if a patient presented with a lactate of 6.0, a subsequent lactate of 5.4 after resuscitative efforts would indicate that the patient still may have inadequate perfusion even though lactate cleared by 10%. We did not seek to determine which definition of lactate clearance is superior, however this raises an interesting question that warrants further study.

While initial lactate and lactate clearance are clearly valuable indicators of severity of illness, it has been postulated that presence of respiratory distress has significant prognostic value. Others have found that peak respiratory rate[18] and tachypnea[19] correlate with mortality. In their prospective observational study, Bossink, et al. found an average peak respiratory rate of 28–33 in patients with clinical infection, and found that peak respiratory rate was associated with progression to overt shock[18]. We used a respiratory rate ≥ 30 as part of our definition of respiratory distress as it is part of our institution-wide rapid response system[12]. In our study, patients who presented with respiratory distress were much more likely to require vasopressors and the mortality trended higher. While some may assert that the association between respiratory distress and clinical deterioration may be confounded by acidosis, we would argue that respiratory distress is an important proxy for acidosis, indicating that these patients may not actually be occult. While the absence of hypotension may be reassuring, organ dysfunction indicated by respiratory distress should be a warning to the clinician that there is inadequate perfusion.

Relying on either lactate clearance or the absence of respiratory distress would not have adequately risk-stratified patients in our population. Ten percent of patients with lactate clearance to <4mmol/L subsequently required vasopressors and 8.2% required CVC placement in the ICU. Within this group, mortality was 10.2%. Likewise, 10% of patients without respiratory distress subsequently required vasopressors with 7.5% requiring a CVC be placed in the ICU. Furthermore, mortality in this group was 15%. In isolation, neither metric definitively identified which patients would not require hemodynamic support with vasopressors nor patients in whom mortality was low. In our cohort, lactate clearance to <4mmol/L in combination with the absence of respiratory distress, however, did reliably predict which patients were unlikely to need hemodynamic support with vasopressors and have low mortality. In the 27 patients without respiratory distress and who subsequently had lactate clearance, mortality was 0% and none required vasopressors.

Current guidelines suggest that patients presenting with a lactate ≥ 4 and suspected infection have a CVC placed for guidance of resuscitation regardless of blood pressure [10]. This practice has been called into question as a result of the recent publication of the ProCESS trial, which showed no statistically significant change in mortality despite a statistically significant difference in the rate of central venous cannulation and ICU admissions in patients with severe sepsis and septic shock[20]. However, over 50% of patients in the control arm of the study still had a central line placed therefore making definitive conclusions difficult with regards to specific treatment recommendations. Our data reveals that the population of patients with occult hypoperfusion as traditionally defined has significant heterogeneity, and the combination of lactate clearance plus respiratory distress status may help differentiate risk of deterioration within this population. The finding of substantial clinical heterogeneity within this population suggests that a “one-size fits all” approach to recommendations (for example, all patients with lactate > 4 mmol/L need a central line) may be inadequate for management. We do not intend for our method of risk stratification to replace clinical judgment, but rather to assist with the triage of patients with occult hypoperfusion within a busy emergency department. Our current study strengthens a growing argument that purely algorithmic protocols based on a patient’s initial laboratory data (i.e., only an initial lactate) without consideration of other factors may lead a clinician to place patients in an inappropriate risk strata. For example, among patients who cleared their lactate and did not present in respiratory distress, 33% (9/27) patients were admitted to the intensive care unit and none of these patients required vasopressors within 72 hours and mortality was 0%. If our findings were validated in future studies, perhaps clinicians would feel more confident triaging patients to less resource intensive settings. Conversely, if future studies verified the risk of deterioration in our highest risk strata, our method of risk stratification may alert clinicians to a higher risk population and thus supplement their clinical judgment. This may reflect an area where clinical judgment does not adequately capture those at very high or very low risk and the method of risk stratification presented here may be useful. Future recommendations with regards to CVC or other approaches to care such as ICU admission, should consider patient heterogeneity. Moreover, our findings (if validated in prospective multicenter investigations) could provide potential means for risk stratifying patients and assisting in decision-making around titration of care.

As demonstrated in our study, significant care practice variations exist with regard to CVC placement and ICU admission in occult hypoperfusion. For example, in what we defined as the lowest risk group (0% progression to vasopressors and mortality), 89% of patients did not have a central venous catheter placed. Moreover, of these patients, 66.7% were admitted to the wards as opposed to the intensive care unit, and none received a CVC or required vasopressors during their admission. The care plan within the lowest risk strata could potentially reflect titration of care based on clinical judgment but this remains unknown in a retrospective study.

Notably, patients stratified by the presence or absence of respiratory distress and lactate clearance had no significant differences in IV fluid resuscitation volume in the ED. Although we have identified a low-risk population, it is essential to remember that all patients who presented with occult hypoperfusion received high-volume resuscitation and close clinical monitoring. Our data suggests that monitoring for respiratory distress (i.e.

organ failure) and the adequacy of resuscitation (through repeat venous lactate measurements) may assist in risk-stratification and in determining ED disposition. However, one limitation of this observation with retrospective data is that a small percentage of patients may have developed hypotension while in the emergency department, thus driving a change from the initial care plan. Therefore, future prospective study will be necessary to answer this question. Moreover, our study may help to inform future clinical judgment in that we are now identifying key risk factors within this heterogeneous population that can be incorporated into clinical triage decisions.

The ability to accurately predict which patients will not undergo clinical deterioration has important implications. Our data suggest that significant heterogeneity exists within the population that has been labeled as having occult hypoperfusion. By predicting clinical deterioration and better risk stratification, patients can be appropriately triaged both in terms of need for ICU level (or more intensive) monitoring as well as need for more aggressive care such as invasive monitoring. Further prospective analysis can both confirm our current observations and/or potentially test titrated care pathways for this population.

Conclusions

Among a cohort of patients with suspected infection who present with hyperlactatemia and without hypotension, often referred to as ‘occult hypoperfusion,’ mortality was high. However, within this seemingly homogenous group, there exists significant variability with regard to the risk of clinical deterioration, which may be discernable by ability or failure to clear lactate, or the presence or absence of respiratory distress. Further prospective study is warranted to validate these findings as well as determine whether respiratory status and lactate levels may be used to guide clinical decisions about the role of invasive hemodynamic monitoring or need for ICU level monitoring in patients with sepsis.

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Abbreviations

ANOVA	Analysis of variance
CI	Confidence interval
CVC	Central venous catheter
ED	Emergency department
EMR	Electronic medical record
ICU	Intensive care unit
IQR	Inter-quartile range

IRB	Institutional review board
OR	Odds ratio
RD	Respiratory distress
SD	Standard deviation

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Key Messages

- Mortality and need for vasopressors is high in patients with elevated lactate despite normal systolic blood pressure
- Normotensive patients with elevated lactate are not homogenous
- Respiratory distress and lactate clearance are valuable tools in identifying risk of clinical deterioration

Figure 1.
 Patient Flowchart
 RD: respiratory distress

Figure 2.
Vasopressors within 72 hours stratified by lactate clearance, respiratory distress

Figure 3.
In-hospital mortality stratified by lactate clearance, respiratory distress

Baseline characteristics^{ab}

Table 1

	Persistently elevated lactate + RD	Lactate clearance + RD	Persistently elevated lactate + no RD	Lactate clearance + no RD	Overall
No. (%)	11 (15.1)	22 (30.1)	13 (17.8)	27 (37.0)	73
Demographics					
Age (years)	73.5 ± 17.4	75.7 ± 12.3	58.9 ± 17.0	64.5 ± 21.6	68.2 ± 18.6
Sex (% male)	54.5	63.6	53.8	55.6	57.5
Co-morbidities					
Diabetes	6 (54.5)	7 (31.8)	6 (46.2)	9 (33.3)	28 (38.4)
Coronary artery disease	1 (9.1)	9 (36.4)	3 (23.1)	6 (22.2)	18 (24.7)
Congestive heart failure	1 (9.1)	7 (31.8)	3 (23.1)	3 (11.1)	14 (19.1)
Chronic kidney disease	2 (18.2)	3 (13.7)	3 (23.1)	2 (7.4)	10 (13.7)
End-stage renal disease	0 (0)	0 (0)	3 (23.1)	3 (11.1)	6 (8.2)
Cirrhosis	0 (0)	1 (4.5)	3 (23.1)	0 (0)	4 (5.5)
Malignancy	2 (18.2)	3 (13.6)	2 (15.4)	7 (25.9)	14 (19.2)
Suspected Source of Infection					
Respiratory	9 (81.8)	11 (50.0)	8 (61.5)	8 (29.6)	36 (49.3)
Urine	1 (9.1)	4 (18.2)	1 (7.7)	7 (25.9)	13 (17.8)
Gastrointestinal	0 (0)	5 (22.7)	3 (23.1)	5 (18.5)	13 (17.8)
Skin	0 (0)	0 (0)	0 (0)	5 (18.5)	5 (6.8)
CNS	1 (0)	2 (9.1)	1 (7.7)	0 (0)	4 (5.5)
Bacteremia	0 (0)	0 (0)	0 (0)	2 (7.4)	2 (2.7)
Initial Vital Signs					
Temperature (°C)	37.9 [36.8–39.0]	36.9 [36.4–39.2]	37.9 [36.8–39.4]	36.9 [36.4–37.8]	37.2 [36.6–38.6]
Heart rate (beats per minute)	115.7 ± 18.0	115.0 ± 30.4	107.8 ± 20.6	104.7 ± 17.8	110.0 ± 22.9
Mean arterial pressure (mm Hg)	98.5 ± 20.5	99.1 ± 19.5	90.7 ± 16.8	93 ± 19.8	95.1 ± 19.4
IV fluid (liters)	3.25 ± 1.3	2.70 ± 1.6	2.90 ± 2.5	2.56 ± 1.1	2.8 ± 1.6
Respiratory distress	11 (100)	22 (100)	0 (0)	0 (0)	33 (45.2)
Vasopressors within 72 hours	5 (45)	5 (22.7)	4 (31)	0 (0)	14 (19.1)

	Persistently elevated lactate + RD	Lactate clearance + RD	Persistently elevated lactate + no RD	Lactate clearance + no RD	Overall
Hospital length of stay (days)	4 [1–6]	7 [4.75–12.25]	7 [5–10]	4 [2–9]	5 [2.5–9.5]
In-hospital mortality	6 (54.5)	5 (22.7)	6 (46.2)	0 (0)	17.0 (23.3)
Lactate measurements					
Initial lactate (mmol/L)	6.6 [4.8–9.2]	4.35 [4.2–4.7]	7.1 [6.0–7.9]	4.3 [4.1–4.8]	4.7 [4.2–6.4]
Second lactate (mmol/L)	6.8 [4.6–7.4]	2.6 [2.1–3.4]	5.3 [4.7–5.7]	2.1 [1.5–3.1]	3.2 [2.0–4.6]
Lactate clearance <4mmol/L	0 (0)	23 (100)	0(0)	27 (100)	49 (67.1)
Lactate clearance 10%	6 (54.6)	22 (100)	10 (76.9)	27 (100)	65 (89.0)
Time between lactate values (minutes)	173 [64–189]	144 [102.8–268.7]	173 [89.5–308]	141.5 [95–353.8]	157 [97.3–280.3]
Initial Creatinine (mg/dl)	1.8 [1.3–2.6]	1.2 [0.9–1.9]	1.7 [1.3–3.1]	1.3 [0.9–1.6]	1.4 [1.0–2.1]
Initial Creatinine (excluding ESRD) (mg/dl)	1.8 [1.3–2.6]	1.2 [0.9–1.9]	1.4 [1.2–2.1]	1.3 [0.9–1.6]	1.3 [0.9–2.0]
Central venous catheter placement					
No CVC	5 (45.4)	14 (63.8)	6 (46.2)	24 (88.9)	49 (67.1)
CVC in ED	5 (45.4)	4 (18.1)	4 (30.8)	3 (11.1)	16 (21.9)
CVC in ICU	1 (9.1)	4 (18.1)	3 (23.1)	0 (0)	8 (11.0)
Central venous pressure					
Patients with documented initial CVP	3	4	4	1	12 (50.0)
Initial CVP measurement (mm Hg)	5 [4–6]	9 [4.25–10.75]	11.5 [10–18.3]	2 [2]	9 [4.25–10.75]
ICU admission	9 (81.8)	14 (63.6)	9 (69.2)	9 (33.3)	41 (56.1)

^a All continuous variables are expressed as medians [inter quartile range] or mean±SD depending on normality of data. Categorical data is expressed as n (frequency).

^b CVC: Central venous catheter; ED: Emergency department; ICU: Intensive care unit; CVP: Central venous pressure

Table 2Comparison based on respiratory distress^{abc}

	Overall	Respiratory distress	No respiratory distress	P value
N	73	33	40	
ICU admission	41/73 (56.2%)	23/33 (69.7%)	18/40 (45.0%)	0.03
CVC in ED	16/73 (21.9%)	9/33 (27.3%)	7/40 (17.5%)	0.32
CVC in ICU	8/73 (11.0%)	5/33 (15.2%)	3/40 (7.5%)	0.30
IV fluid (liters)	2.8	2.88	2.68	0.71
Vasopressors within 72h	14/73 (19.2)	10/33 (30.3%)	4/40 (10%)	0.03
In-hospital mortality	17/73 (23.3%)	11/33 (33.3%)	6/40 (15%)	0.06
Composite outcome	20/73 (27.4%)	14/33 (42.4%)	6/40 (15%)	<0.01

^a All continuous variables are expressed as means. Categorical data is expressed as n (frequency).

^b CVC: Central venous catheter; ED: Emergency department; ICU: Intensive care unit

^c Composite outcome: Vasopressors within 72 hours and/or In-hospital mortality

Table 3Comparison based on lactate clearance to $<4\text{mmol/L}^{abc}$

	Overall	Persistently elevated lactate ($\geq 4\text{mmol/L}$)	Lactate clearance ($<4\text{mmol/L}$)	P value
N	73	24	49	
ICU Admission	41/73 (56.2%)	18/24 (75.0%)	23/49 (46.9%)	0.02
CVC in ED	16/73 (21.9%)	9/24 (37.5%)	7/49 (14.3%)	0.03
CVC in ICU	8/73 (11.0%)	4/24 (16.7%)	4/49 (8.2%)	0.29
IVF (liters)	2.8	3.06	2.63	0.14
Vasopressors within 72h	14/73 (19.2)	9/24 (37.5%)	5/49 (10.2%)	<0.01
In-hospital mortality	17/73 (23.3%)	12/24 (50%)	5/49 (10.2%)	<0.01
Composite outcome	20/73 (27.4%)	13/24 (54.2%)	7/49 (14.3%)	<0.01

^a All continuous variables are expressed as means. Categorical data is expressed as n (frequency).

^b CVC: Central venous catheter; ED: Emergency Department; ICU: Intensive care unit

^c Composite Outcome: Vasopressors within 72 hours and/or In-Hospital Mortality