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NEPHROLOGY & UROLOGY | RESEARCH ARTICLE

Serum lactates and acute kidney injury in patients with sepsis: A cohort analysis

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Abstract: Granting the association of lactates with mortality has been largely documented in critically ill patients with sepsis, its association with the development of acute kidney injury (AKI) in this setting is not well established. We aimed to analyze the association of serum lactates at intensive care unit (ICU) admission with the occurrence AKI in a cohort of critically ill septic patients. Materials and methods: This study is retrospective including 457 adult patients with sepsis admitted to the Division of Intensive Medicine of the Centro Hospitalar Lisboa Norte (Lisbon, Portugal) between January 2008 and December 2014. The Kidney Disease Improving Global Outcomes (KDIGO) classification was used to diagnose and classify patients developing AKI within the first week of hospitalization. Logistic regression analysis was employed to determine factors associated with AKI development. Data were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was defined as a p-value < 0.05. Results: AKI occurred in 87.5% of patients with a maximum KDIGO category (19.5% with stage 1, 22.6% with stage 2 and 45.4% with stage 3). Serum lactates were higher among patients developing AKI as compared with non-AKI patients (mmol/L 29.9 ± 25.7 vs. 18.6 ± 9.3, p = 0.001; unadjusted OR 1.04 (95% CI 1.02–1.07), p = 0.001; adjusted OR 1.03 (95% CI 1.01–1.06), p = 0.024), and they were progressively higher in accordance with AKI severity (stage 1, 24.5 ± 18.7; stage 2, 25.5 ± 16.9; stage 3, 34.6 ± 30.7; p = 0.001). Conclusions: Serum lactates at ICU admission were independently associated with the occurrence of AKI in critically ill patients with sepsis.

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José António Lopes is a professor at the Faculty of Medicine of the University of Lisbon and a recognized specialist in nephrology field. Its clinical activity is focused on the approach and treatment of acute renal injury and acute in chronic kidney disease, also directs the hospitalization sector of Hospital Santa Maria, the largest hospital in Portugal. He has developed a recognized work in the area of acute renal injury, in its definition and diagnosis. Leads a research team in the field of nephrology, providing other clinicians, such as Miguel Gonçalves and colleagues, to develop interesting studies and contributing to new knowledge.

PUBLIC INTEREST STATEMENT

Acute Kidney Injury (AKI) it's a high prevalence problem in patients hospitalized, but especially in the intensive care unit (ICU). Serum lactate, often elevated in this context, is assumed in current knowledge as an important form of monitoring and prognostic importance in critically ill patients. Although physiologically interrelation with the kidney, its role as a risk factor for AKI has not been studied very sparingly. Therefore, we analyze the impact of serum lactates on the occurrence of AKI in a cohort of critically ill septic patients, and we find that serum lactates at ICU admission were independently associated with the occurrence of AKI. This finding may make it possible to identify these patients earlier.

1. Introduction

The primary cause of acute kidney injury (AKI) in intensive care units (ICU) is sepsis. It is well known that those patients suffering non-septic AKI are clinically different from those with AKI of septic origin. In reality, septic AKI is linked to higher disease severity scores at admission into the ICU, an increased necessity for vasoactive drugs, non-renal organ failure, requirement for mechanical ventilation, extended ICU and hospital stay, increased in-hospital mortality and a higher probability of recovery of renal function at discharge from hospital (Bagshaw et al., 2007; Uchino et al., 2005). Consequently, it is crucial that both the nephrologist and the intensivist display a deep understanding and purview of septic AKI, not only as a means to ensure correct diagnoses, but also to aid in fundamental treatment decisions, follow-up strategies and, ultimately, assist in the prediction of patient outcome.

Serum lactate has been widely considered as an important biomarker for the evaluation of hemodynamic status in the critically ill patient. Since lactate is a sensitive biomarker of global and regional hypoperfusion, lactate can be used as a marker of ongoing hypoperfusion that may contribute to continuing development of AKI (Zhang & Ni, 2015). Despite the fact that the deleterious impact of raised serum lactates on mortality has been broadly reported in critically ill septic patients (Moskowitz et al., 2016; Singer et al., 2016), the association of serum lactates with the development of AKI in sepsis is still not well defined.

The purpose of this study was to analyze the association of serum lactates at ICU admission with the occurrence of AKI in a cohort of critically ill patients admitted to this department with a diagnosis of sepsis. To achieve this aim, we cross-examined data from a retrospective study in which we studied a cohort of critically ill patients admitted with sepsis to the ICU and in which the primary objective was to compare the diagnostic sensitivity and prognostic ability of the standard classifications for AKI, namely the 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications (Pereira et al., 2016).

2. Methods

This study is retrospective in nature and inclusive of all patients with sepsis admitted between January 2008 and December 2014 to the Division of Intensive Medicine of the Centro Hospitalar Lisboa Norte (Lisbon, Portugal), an academic and referral center serving a population of 3,000,000 inhabitants.

2.1. Participants

All eligible patients were selected by consultation of the ICU patient admission register. Adult patients (≥18 years of age) with a diagnosis of sepsis at admission to the Division of Intensive Medicine were included. Sepsis was defined by current criteria in agreement with the third international consensus definitions for sepsis and septic shock (Singer et al., 2016). Exclusion criteria were clearly defined and encompassed the following: (i) chronic kidney disease (CKD) patients already on renal replacement therapy; (ii) patients who required and underwent renal replacement therapy one week prior to admission to the ICU; and (iii) patients who were discharged or died less than two days after ICU admission.

2.2. Variables and data sources

Patient variables were collected from individual handwritten and electronic clinical records. Analyzed variables included patient demographic characteristics (gender, age, ethnicity and body weight), comorbidities [presence of hypertension, diabetes mellitus, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), cirrhosis and/or malignancy], primary diagnosis on

admission (medical vs. surgical), source of infection, biochemical parameters [pH, serum lactates, serum hemoglobin and serum albumin at ICU admission, as well as daily serum creatinine (SCr)], urine output (UO), disease severity score according to the Simplified Acute Physiologic Score (SAPS) II (Le Gall, Lemeshow, & Saulnier, 1993) and as determined by the worst variables recorded during the first 24 h, fluid balance, vasopressor use, need for mechanical ventilation and requirement of renal replacement therapy. Hypertension was diagnosed according to the seventh report of the Joint National Committee (Chobanian et al., 2003) and diabetes mellitus was diagnosed according to the American Diabetes Association criteria (2009). CVD was considered as present whenever a history of chronic heart failure of any etiology, cardiac ischemic disease, cerebrovascular disease and/or peripheral arterial disease was documented and COPD included both emphysema and chronic bronchitis. For CVD and COPD, a previous diagnosis on clinical records was considered adequate for the confirmation of this diagnosis. The outcome measure was development of AKI.

The KDIGO classification based on both serum creatinine (SCr) and urine output (UO) criteria was used to diagnose and classify patients developing AKI within the first week of ICU hospitalization (Lameire, Kellum, & Aspelin, 2012). The criteria that culminated in the worst classification was used and the maximum KDIGO stage was recorded. SCr is determined at least once daily and UO is recorded on an hourly basis for all patients as per protocol in this ICU. For determination of baseline SCr values, pre-admission SCr (SCr within the previous three months) was considered and accepted. When these values were unavailable, baseline SCr was estimated from the MDRD equation (Manjunath, Sarnak, & Levey, 2001), considering the lower limit of a normal baseline glomerular filtration rate (GFR) of 75 mL/min/1.73 m^2. Hourly urine output was registered and available for all patients, and the urine output value within 6 h periods was considered to identify and classify AKI, as proposed.

2.3. Statistical methods

Categorical variables were reported as the total number and percentage of cases for each category, while continuous variables were presented as the mean ± standard deviation. Student's t-test was used to compare normally distributed continuous variables, Mann–Whitney U test was used to compare non-normally distributed continuous variables and chi-square test was used to compare categorical variables. Univariate and multivariate logistic regression analysis was applied to determine risk factors for AKI. Only variables with statistical significance in the univariate analysis were included in the multivariate analysis model (enter model). Data were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Model fit was assessed by the goodness-of-fit test and discrimination was assessed by the area under the receiver operating characteristic (AUROC) curve. Statistical significance was defined as a *p*-value < 0.05. Statistical analysis was performed with the statistical software package SPSS for windows (version 21.0; SPSS, Chicago, IL, USA).

3. Results

3.1. Participants

After investigation of the ICU patient admission register, 723 patients were included as potentially eligible. Of these, 266 were excluded based on the following criteria: 122 had stage 5 CKD on regular renal replacement therapy and 144 had been hospitalized for a period less than 48 h. No patients required renal replacement therapy in the week foregoing ICU admission. Hence, we examined a final cohort of 457 patients. Baseline characteristics of the selected population, and the clinical and demographic characteristics of the patients according to AKI development are shown in Table 1.

Pre-admission SCr was obtainable in 185 patients (40.6%) and in the outstanding cases [*n* = 272(59.4%)] estimation using the MDRD formula, assuming a baseline estimated GFR of 75 mL/min/1.73 m^2, was required. AKI occurred in 87.5% of patients with a maximum KDIGO category

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Table 1. Demographic and clinical characteristics of patients according to the baseline characteristics and the development of acute kidney injury				
Characteristic	**Value**	**KDIGO classification**		
		No AKI (*n* = 57)	**AKI (*n* = 399)**	***p* value**
Age (year)	64.1 ± 16.4	64.1 ± 17.4	64.1 ± 16.0	0.994
Gender (Male)—*n* (%)	264 (57.9)	35 (61.4)	229 (57.4)	0.566
Race (Caucasian)—*n* (%)	433 (94.7)	54 (94.7)	379 (95.0)	0.936
Weight (kg)—mean ± SD	76.2 ± 18.2	70.9 ± 14.3	77.0 ± 18.6	0.019
Co-morbidities—*n* (%)				
Hypertension—*n* (%)	212 (46.5)	30 (50.2)	182 (45.6)	0.320
Diabetes—*n* (%)	103 (22.6)	15 (26.3)	88 (22.1)	0.472
CVD—*n* (%)	125 (27.4)	14 (24.6)	111 (27.8)	0.606
COPD—*n* (%)	38 (8.3)	5 (8.8)	33 (8.3)	0.898
Cirrhosis—*n* (%)	18 (3.9)	1 (1.8)	17 (4.3)	0.363
Neoplasia—*n* (%)	109 (23.9)	13 (22.8)	96 (24.1)	0.836
Medical admission—*n* (%)	253 (55.5)	31 (54.4)	222 (55.6)	0.859
Infection source—*n* (%)				
Abdominal—*n* (%)	187 (41.0)	19 (33.3)	168 (42.1)	0.208
Respiratory—*n* (%)	138 (30.3)	16 (28.3)	122 (30.6)	0.700
Kidney—*n* (%)	57 (12.5)	14 (24.6)	43 (10.8)	0.003
Skin—*n* (%)	34 (7.5)	2 (3.5)	32 (8.0)	0.225
Others—*n* (%)	26 (5.7)	6 (10.5)	20 (5.0)	0.093
Unknown—*n* (%)	14 (3.1)	0 (0.0)	14 (3.5)	0.151
SAPS II—mean ± SD	49.4 ± 17.3	42.8 ± 15.6	50.4 ± 17.3	0.002
Baseline SCr (mg/dl)*—mean ± SD	1.3 ± 0.6	1.4 ± 0.7	1.3 ± 0.6	0.185
Lactates (mg/dl)—mean ± SD	28.6 ± 24.5	18.6 ± 9.3	29.9 ± 25.7	0.001
pH—mean ± SD	7.32 ± 0.1	7.35 ± 0.1	7.32 ± 0.1	0.011
Hemoglobin (g/dl)—mean ± SD	10.4 ± 2.0	10.0 ± 1.7	10.5 ± 2.0	0.078
Serum albumin (g/dl)—mean ± SD	1.9 ± 0.6	2.1 ± 0.6	1.9 ± 0.6	0.003
Mechanical ventilation—*n* (%)	350 (76.6)	41 (8.9)	309 (77.4)	0.357
Vasopressors—*n* (%)	316 (69.4%)	26 (45.6)	290 (72.7)	<0.001
Fluid balance (liters)—mean ± SD	4.5 ± 5.7	4.6 ± 5.5	3.6 ± 6.9	0.18
RRT—*n* (%)	108 (23.7)		108 (27.1)	
LOS in hospital (days)—mean ± SD	37.1 ± 39.4	39.5 ± 44.8	36.7 ± 38.6	0.625
LOS in ICU (days)—mean ± SD	10.0 ± 10.0	9.8 ± 10.3	10.0 ± 10.0	0.881
ICU mortality—*n* (%)	108 (23.7)	7 (12.3)	101 (25.3)	0.030
In-hospital mortality—*n* (%)	153 (33.6)	10 (17.5)	143 (87.5)	0.006

(19.5% with stage 1, 22.6% with stage 2 and 45.4% with stage 3). Median time to AKI development was 2 days (1 to 8 days). One-hundred and eight patients (23.7%) underwent renal replacement therapy (8.3% intermittent hemodialysis, 76% continuous venovenous hemodiafiltration, and 15.7% both). Three hundred and sixteen patients (69.8%) had septic shock criteria. Patients diagnosed with AKI were more likely to have significantly higher SAPS II values (*p* = 0.002) and to require

vasopressors ($p < 0.001$) when compared to patients who did not develop AKI. Lower serum pH and albumin values were also more frequently found among AKI patients ($p = 0.011$ and $p = 0.003$, respectively). AKI developed more frequently in patients with urinary tract infections ($p = 0.003$).

3.2. Serum lactates and AKI

Serum lactates were higher among patients developing AKI as compared with non-AKI patients (mmol/L 29.9 ± 25.7 vs. 18.6 ± 9.3, $p = 0.001$; unadjusted OR 1.04 (95% CI 1.02–1.07), $p = 0.001$) (Table 1), and they were progressively higher according to increasing AKI severity (stage 1, 24.5 ± 18.7; stage 2, 25.5 ± 16.9; stage 3, 34.6 ± 30.7; $p = 0.001$). In multivariate analysis, serum lactates at ICU admission were independently associated with the occurrence of AKI (adjusted OR 1.03 (95% CI 1.01–1.06), $p = 0.024$) (Table 2). The ROC curve of AKI for in-hospital mortality was 0.645 (95% CI 0.577–0.713); $p < 0.001$).

Table 2. Univariate and multivariate analysis of factors associated with acute kidney injury				
	AKI			
	Unadjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Demographics				
Age	1.00 (0.98–1.02)	0.094		
Male	0.85 (0.48–1.50)	0.567		
Caucasian	1.053 (0.30–3.66)	0.936		
Body weight	1.02 (1.01–1.04)	0.019	1.02 (1.01–1.04)	0.037
Co-morbidities				
Hypertension	0.76 (0.43–1.32)	0.321		
Diabetes	0.79 (0.42–1.50)	0.473		
CVD	1.18 (0.62–2.25)	0.606		
COPD	0.94 (0.35–2.51)	0.898		
Cirrhosis	2.492 (0.33–19.09)	0.379		
Neoplasia	1.04 (0.75–1.44)	0.836		
Medical admission	1.05 (0.60–1.84)	0.859		
Infection source				
Abdominal	1.45 (0.81–2.61)	0.210		
Respiratory	1.13 (0.61–2.09)	0.700		
Kidney	0.37 (0.19–0.73)	0.004	0.43 (0.20–0.91)	0.028
Skin	2.40 (0.56–10.29)	0.239		
Others	0.45 (0.17–1.17)	0.101		
SAPS II	1.03 (1.01–1.05)	0.002	1.01 (0.90–1.03)	0.690
Baseline SCr	0.76 (0.50–1.15)	0.188		
pH	0.02 (0.01–0.4)	0.012	0.11 (0.03–3.90)	0.226
Lactates	1.04 (1.02–1.07)	0.001	1.03 (1.01–1.06)	0.024
Hemoglobin	1.14 (0.99–1.32)	0.078		
Serum albumin	0.51 (0.33–0.81)	0.004	0.70 (0.43–1.15)	0.162
Mechanical ventilation	1.34 (0.72–2.50)	0.358		
Septic shock (need of vasopressors)	3.17 (1.80–5.59)	0.0001	2.39 (1.23–4.64)	0.010

4. Discussion

In this retrospective study including 457 critically ill patients with sepsis, we established that serum lactates at ICU admission were independently associated with AKI.

Previous studies on septic patients have only investigated the impact of lactate and its change on mortality (Casserly et al., 2015). Nonetheless, considering that lactate is a sensitive biomarker of not only global but also regional hypoperfusion (Jones & Puskarich, 2009), serum lactate can theoretically be used as a marker of ongoing hypoperfusion that may eventually contribute to ongoing development of AKI. As far as we know, lactate has never been studied for its independent association with AKI in septic patients. In fact, although higher levels of serum lactates have been reported to occur in patients with AKI as compared with non-AKI patients, an independent association of serum lactates with AKI has not yet been described. In an observational cohort study, Plataki and colleagues aimed to evaluate predictors of AKI (defined by RIFLE based on SCr and urine output) by enrolling 390 patients with septic shock. Although they found higher levels of serum lactate in AKI patients compared to those patients not developing AKI (2.3 vs. 1.9, mmoL, $p = 0.01$), serum lactates were not independently associated with AKI in this cohort (Plataki et al., 2011).

Recent studies on AKI in patients undergoing cardiac surgery have also established an association between serum lactates and risk of AKI (Lopez-Delgado et al., 2013; Zhang & Ni, 2015). However, in this specific setting, serum lactates can be influenced by various factors during and after cardiopulmonary bypass. During cardiopulmonary bypass, hyperlactatemia may arise from: (1) administration of Ringer's lactate solution (priming pump); (2) low-perfusion pressure secondary to distributive shock; and (3) type-B hyperlactatemia (frequently associated with hyperglycemia). Inversely, the majority of the causes of hyperlactatemia resulting from an inadequate oxygen supply can be identified following the cardiopulmonary bypass phase, including left/right pump dysfunction and/or distributive shock (Zhang & Ni, 2015). The pathogenesis of AKI in septic patients is, however, distinct from that of AKI in patients undergoing cardiac surgery. While low renal blood flow during cardiopulmonary bypass in cardiac surgery, with consequent renal oxygenation impairment may eventually trigger renal failure, and the production and release of several pro inflammatory mediators, such as interleukins, TNFα and other metabolites can lead to membrane damage of the renal tubular epithelium (Friedrich et al., 2017; Wanderer & Rathmell, 2017), sepsis-induced AKI can occur in the setting of normal or even increased renal blood flow. In sepsis, AKI is characterized by heterogeneous areas of colocalized listless peritubular blood flow and tubular epithelial cell oxidative stress, rather than by acute tubular necrosis or apoptosis. Evidence has also revealed that inflammation, diffuse microcirculatory flow irregularities and cell bioenergetic adaptive responses to injury are vital pathophysiologic mechanisms that may explain the development of sepsis-induced AKI (Gomez et al., 2014). Epithelial cells of the kidney may have the ability to respond to initial inflammatory injury by activating energy regulatory pathways as a means to preserve energy balance, and limit oxidative damage from dysfunctional mitochondria (Gómez, Jin, & Kellum, 2015).

The causes of hyperlactacidemia in sepsis are also different from those in cardiac surgery patients. Epinephrine-dependent stimulation of the β2-adrenoceptor increases the glycolytic flux both directly and indirectly by enhancing activity of the sarcolemmal Na+, K+-ATPase (which consumes great quantities of ATP)in the hyperdynamic stage of sepsis (Levy, Desebbe, Montemont, & Gibot, 2008). In inflammatory states, aerobic glycolysis can also be driven by cytokine-dependent stimulation of cellular glucose uptake (Taylor, Faragher, & Evanson, 1992). In global or localized tissue hypoxia, lactate is overproduced and underutilized as a result of compromised mitochondrial oxidation. Even if systemic oxygen delivery is not low enough to induce generalized hypoxia, microcirculatory dysfunction can cause regional tissue hypoxia and hyperlactatemia (Ince, 2005; Kraut & Madias, 2014). Hyperlactatemia can also result from aerobic glycolysis, representing stimulated glycolysis that is contingent on other factors besides tissue hypoxia. Activated in response to stress, aerobic glycolysis is an effective, albeit inefficient, mechanism for the rapid generation of ATP (Levy et al., 2008). Additionally, there are many sources of lactate in sepsis aside from hypoperfusion-induced tissue hypoxia. For example, non-hypoxemic causes include catecholamine-driven accelerated glycolytic

flux, stimulation of sodium-potassium adenosine triphosphatase pump activity, and inhibition of pyruvate dehydrogenase, along with decreased lactate metabolism by the liver (Garcia-Alvarez, Marik, & Bellomo, 2014).

In the present study, serum lactate was independently associated with AKI diagnosed within the first two days of ICU stay. Taking this into consideration, we hypothesize that hyperlactacidemia can be an early marker of the underlying renal lesion conditioning a reduced renal uptake of lactate and metabolization or can appear as an adaptive response to conserve energy balance as a result of limitation of oxidative damage due to dysfunctional mitochondria. It is important to recall that the native kidney is second only to the liver in eliminating lactate from the circulation and metabolizing it (Bellomo, 2002).

In the present study, some limitations have to be recognized. Firstly, the single-centre and retrospective nature of the study with a small cohort of patients may compromise, at least in part, the results of our study. Secondly, other factors contributing to elevation of serum lactates, such as presence of liver failure and medications (i.e. metformin) were not evaluated. Third, the percentage of caucasian patients could limit the generalization of this study.

Regardless of these limitations, our study has numerous notable strengths. To the best of our knowledge, this is the first study evaluating the association between lactate and AKI in septic patients in an ICU. Moreover, despite the retrospective nature of the study, most of the studied variables were registered as part of routine clinical practice on a daily basis and made accessible for analysis.

5. Conclusion

In a cohort of critically ill septic patients, serum lactates at ICU admission were independently associated with AKI occurrence.

Author notes

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