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High serum lactate level may predict death within 24 hours

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Abstract: Background: Unexpected death within 24 hours of admission is a real challenge for the clinician in the emergency room. How to diagnose these patients and the right approach to prevent sudden death with 24 hours is still an enigma. The aims of our study were to find the independent factors that may affect the clinical outcome in the first 24 hours of admission to the hospital.

Methods: We performed a retrospective study defining unexpected death within 24 hours of admission in our Department of Medicine in the last 6 years. We found 43 patients who died within 24 hours of admission, and compared their clinical and biochemical characteristics to 6055 consecutive patients who were admitted in that period of time and did not die within the first 24 hours of admission. The parameters that were used include gender, age, temperature, clinical and laboratory criteria for SIRS, arterial blood lactate, and arterial blood pH.

Results: Most of the patients who died within 24 hours had sepsis with SIRS. These patients were older (78.6±14.7 vs. 65.2±20.2 years [p<.0001]), had higher lactate levels (8.0±4.8 vs. 2.1±1.8mmol/L [p<.0001]), and lower pH (7.2±0.2 vs. 7.4±0.1 [p<.0001]). Logistic regression analysis found that lactate was the strongest independent parameter to predict death within 24 hours of admission (OR 1.366 [95% CI 1.235-1.512]), followed by old age (OR 1.048 [95% CI 1.048-1.075] and low arterial blood pH (OR 0.007 [CI <0.001-0.147]). When gender was analyzed, pH was not an independent variable in females (only in males).

Conclusions: The significant independent variable that predicted death within 24 hours of admission was arterial blood lactate level on admission. Older age was also an independent variable; low pH affected only males, but was a less dominant variable. We suggest use of arterial blood lactate level on admission as a bio-marker in patients with suspected sepsis admitted to the hospital for risk assessment and prediction of death within 24 hours of admission.

Keywords: Lactate, SIRS

1 Background

Death within the first 24 hours of admission in the medical ward is still an enigma. We expect grave prognosis for patients who are admitted with an acute myocardial infarction (AMI) or severe septic shock, but patients who are admitted without these extreme conditions and die within the first 24 hours are still an unsolved mystery for the clinician in the emergency department and in the department of medicine.

Several studies investigated different scores that could predict 28-day mortality and the ability to use them in the emergency department. In a study where the mortality in emergency department sepsis (MEDS), confusion, urea, respiratory rate, blood pressure, age>65 (CURB-65), acute physiology and chronic health evaluation II (APACHE II), rapid acute physiology score (RAPS), and rapid emergency medicine score (REMS) scores were studied, it was found that MEDS and CURB-65 scores were the most adequate and feasible tools for the prediction of 28-day mortality

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[1]. Another study tried to predict mortality by using emergency department sepsis score for in-hospital mortality and did not find definite results [2]. The effectiveness of the APACHE II, SAPS, and SOFA scoring systems was evaluated to predict death in hematological patients admitted to the ICU and found that SAPS II score was the only independent risk factor of patients' in-hospital deaths in multivariate analysis [3].

We decided to study those patients who died within the first 24 hours of admission and were admitted to the general internal medicine department without an AMI or septic shock, and try to define clinical and biochemical characteristics that could define those patients in order to find a bio-marker that would warn the clinician in the emergency department that this specific individual is at high risk of death within 24 hours and should get special monitoring and be admitted in the ICU.

2 Methods

This was a retrospective study that investigated death within 24 hours of admission to the general internal medicine ward. We found 43 patients who were admitted to the department and died unexpectedly within 24 hours of admission. In order to find the independent variables that could characterize them and distinguish them from other patients, we compared their clinical and laboratory data to 6055 patients who were admitted to the general internal medicine ward in the last 3 years and survived the first 24 hours of hospitalization.

We used statistical tests such as Chi-square test and logistic regression analysis to predict death within 24 hours.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the my institutional review board.

3 Results

Patients who died within the first 24 hours were older (78.6±14.7 vs. 65.2±20.2 years [p<.0001]), had higher lactate levels (8.0±4.8mmol/L vs. 2.1±1.8mmol/L [p<.0001]), and a more acidic pH (7.2±0.2 vs. 7.4±0.1 [p<.001]).

Most of the patients who died in the first 24 hours had an infection with a positive systemic inflammatory response syndrome (SIRS) (86% of all patients), most had coronary artery disease (CAD) documented by an old MI or coronary intervention (93%), many were hypertensive per history (67%), had type 2 diabetes mellitus (DM) (37%), half had renal failure (53%), and 58% had recurrent hospitalizations in the last year.

Thirty-eight patients (88%) had high levels of lactate and 28 patients (65%) had pH lower than 7.1 (Table 1).

No gender differences were observed in this group of patients except for age (females were older – 84.2±12.7 years, males 75.9±15.0; p=.04). No gender difference was observed in relation to temperature, heart rate, lactate, pH, and blood pressure measurements. No significant difference was observed between genders in relation to SIRS, CAD, type 2 DM, HTN, renal failure, recurrent hospitalizations, lactate level, and pH.

Comparing the group of patients who died within the first 24 hours to controls, we found that patients who died in the first 24 hours were older (males 75.9±15.0 vs. 63.5±19.9 years [p=.0009]; females 84.2±12.7 vs. 66.9±20.3 years [p=.0002]). Lactate level was higher in those patients (males 7.6±4.3 vs. 2.2±1.8mmol/L [p<.0001]), females 8.6±5.7 vs. 2.1±1.8mmol/L [p=.0008]), and the pH level was lower (males 7.2±0.2 vs. 7.4±0.1 [p<.0001]), females 7.2±0.2 vs. 7.4±0.1 [p=.011]). Interestingly, the pCO2 was 55.6±25.4 in men and 48.7±20.6 in women (p=0.172).

Logistic regression analysis showed that the strongest independent variable that could predict death within 24 hours of admission was blood lactate (for male patients Odds Ratio (OR) 1.325 [95% Confidence Interval (CI) 1.176-1.495], for female patients 1.548 [95% CI 1.376-1.740]); then

Table 1: Unexpected Death within 24 Hours; Clinical and Biochemical Data.

	Males (%)	Females (%)	p value
Number	29	14	
Age	75.9±15.0	84.2±12.7	.04
SIRS[a]	25 (86%)	12 (86%)	NS
CAD[b]	23 (79%)	12 (86%)	NS
DM[c]	11 (38%)	5 (36%)	NS
HTN[d]	18 (62%)	11 (78%)	NS
RF[e]	17 (58%)	6 (42%)	.05
RH[f]	18 (62%)	7 (50%)	NS
Lactate>2	25 (85%)	13 (93%)	NS
pH<7.1	20 (69%)	8 (57%)	NS

[a] SIRS – systemic inflammatory response syndrome
[b] CAD – coronary artery disease
[c] DM – diabetes mellitus
[d] HTN – hypertension
[e] RF – renal failure
[f] RH – recurrent hospitalization

Table 2: Analysis of Difference between Patients by Outcome and Gender.

	Males		Females	
	Survivors	**Died**	**Survivors**	**Died**
Number	3118	29	2937	14
p value		<.0001		<.0001
Age	63.5±19.9	75.9±15.0	66.9±20.3	84.2±12.7
p value		.0009		.0002
Lactate	2.2±1.8	7.6±4.3	2.1±1.8	8.6±5.7
p value		<.0001		<.0008
pH	7.4±0.1	7.2±0.2	7.4±0.1	7.2±0.2
p value		<.0001		.0115

Odds Ratios

Age	1.043 (95% CI 1.013-1.075)	1.085 (95% CI 1.023-1.151)
Lactate	1.325 (95% CI 1.176-1.495)	1.548 (95% CI 1.376-1.740)
pH	<0.001 (95% CI <0.001-0.015)	

old age (for males OR 1.043 [95% CI 1.013-1.075], for females 1.085 [95% CI 1.023-1.151]); and pH (for males OR of <0.001 [95% CI <0.001-0.015]). pH did not have any independent effect in females (Table 2).

4 Discussion

The most significant independent variable that could predict death within 24 hours of admission to the general internal medicine department was lactate level. Levels higher than 2 mmol/L (the cutoff point in our study) predicted a grave outcome; the higher the level the worse the outcome and a higher probability of death within 24 hours of admission. The second significant independent variable was old age. Old age could predict a worse outcome according to our study. Blood pH (pH lower than 7.1) had a predictive value only in male patients, not in females, and showed that male patients admitted with sepsis and SIRS who also had a pH level lower than 7.1 had a high chance to die within 24 hours of admission. It could be that the mechanism is a more complex acid base disturbance in this group of patients, and it could be that the real culprit here is not the lactic acidosis but the mixed respiratory and metabolic acidosis that could explain the independent variable of pH in men but not in women.

The purpose of this study was to try to define a biomarker that could guide the clinician in the emergency room and in the general ward that there is a high risk patient who is now in danger and should be treated more aggressively and should be transferred to the intensive care department.

Blood lactate concentration reflects a balance between production and uptake of lactate in tissues, and the normal level is between 0.5 and 1.8mM. It is formed by reduction of pyruvate, and metabolized by oxidation to pyruvate in a reaction catalyzed by the cytosolic NAD-dependent lactate dehydrogenase. Pyruvate is metabolized to carbon dioxide and water in the mitochondria by oxidation and it is part of the energy production of the respiratory chain. If pyruvate production exceeds the capacity of oxidative metabolism, pyruvate is diverted to lactate. Lactate is released from tissues with a proton, and excessive lactate production may cause lactic acidosis. Uptake of lactate occurs mainly in the heart, where it is used for energy purposes, and the liver, where it is a precursor for glucose formation.

A meta-analysis that reviewed the literature found that blood lactate monitoring is useful for risk assessment in patients admitted acutely to the hospital and the trend is especially valuable in predicting in-hospital mortality [4]. The main difference between this study and ours is the research population. In this study patients were already hospitalized in the ICU. In our study all patients who died within 24 hours were admitted to the general medicine ward and their death was unexpected. On admission they were not considered "patients at high risk" and were not transferred to the ICU. Another study examined lactate clearance for death prediction in severe sepsis or septic shock patients during the first 24 hours in ICU after initial resuscitation [5]. Even though we aren't talking about the same population of patients, still it is important to learn that in those intensive care septic shock patients who had already been treated intensively, lactate clearance was the best parameter associated with 28-day mortality and the authors of this study recommended that a protocol of

lactate clearance directed therapy should be considered in septic patients even after the golden hours [5]. Among undifferentiated children with SIRS, early hyperlactemia (>4 mmol/L) was significantly associated with increased risk of organ dysfunction, resuscitative therapies, and critical illness. Adding lactate level to the current clinical assessment may improve early identification of pediatric patients with sepsis requiring intensive care, and thus may prevent death in high risk patients [6].

Admission lactate >2mM was found to be an independent predictor of mortality in adults admitted to the ICU [7]. Odds Ratio (OR) for mortality increased from 1.94 to 10.89 dependent on the level of lactate (in comparison to patients with lactate level lower than 2mmol/L). Another study supported these findings and demonstrated a significant effect of elevated lactate level on admission (above 2.0mmol/L) on mortality in unselected ICU patients [8,9]. Other studies have shown the importance of elevated admission lactate on in-hospital mortality [10-20].

Blood lactate monitoring for risk assessment in the critically ill patient is still controversial. Some of the inconsistent data relates to the different screening methods – one measurement, several measurements, arterial or venous blood, peripheral or capillary blood. Sustained high lactate levels in ICU patients demonstrated by serial measurements have shown to be predictive of in hospital mortality [20-22]. In most of the studies the cut-off point was 2.0mmol/L. Jansen et al. assessed blood lactate at the site of injury and at the hospital, and found that mortality was higher in patients with lactate >3.5mmol/L at the site of injury or at admission to the hospital compared to patients with lactate level below 3.5mmol/L [11]. Prehospital lactate level had a better predictive prognostic value than vital signs such as blood pressure [23]. More than that, lactate-guided treatment (by giving erythrocytes, dobutamine, and fluids) lowered the in-hospital mortality significantly [24]. No significant difference was observed between peripheral arterial and venous blood lactate; the highest correlation was found between the radial artery and a peripheral vein. 20 Other studies supported these findings [24, 25].

5 Summary

Our study, evaluated by logistic regression, analyzed the independent variables that could predict death within 24 hours of admission for patients admitted with an infectious disease but without septic shock or severe sepsis. If we have to choose the most important and significant variable, then lactate level on admission higher than 2mmol/L predicted death within 24 hours of admission. The higher the lactate level, the higher the probability to die within 24 hours.

We also found that old age is another independent variable for death within 24 hours of admission.

We suggest measuring lactate level in the emergency department in order to improve the risk assessment and triage of patients admitted with an infectious disease, especially in older patients (older than 70 years).

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Conflict of interest: Authors state no conflict of interest

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