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PhD THESIS

**LACTATE LEVEL OR LACTATE CLEARANCE AS A GOOD
PREDICTOR FOR THE PROGNOSIS OF PATIENTS WITH
SEPTIC SHOCK**

A B S T R A C T

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INTRODUCTION

Sepsis syndromes, particularly septic shock, involve complex immune responses to infection, leading to significant morbidity and high mortality rates. The immune response activates both pro-inflammatory and anti-inflammatory pathways, causing endothelial damage and initiating coagulation and complement cascades. This vascular damage results in severe symptoms such as capillary leakage. The balance between these responses determines patient outcomes, from recovery to severe morbidity or death.

The EPIC II study (2009) identified gram-negative bacteria as the leading cause of sepsis in intensive care units, responsible for 62% of cases, with gram-positive bacteria accounting for 47%. Key pathogens include *Staphylococcus aureus*, *Pseudomonas*, and *Escherichia coli*, primarily infecting the respiratory system, bloodstream, and genitourinary tract. Over one-third of sepsis patients lack positive culture results. Mortality rates vary by bacterial type and infection site, with gram-negative infections generally more fatal. High mortality rates are seen in bacteremia and pneumonia caused by *Acinetobacter* and *Pseudomonas*, with *Pseudomonas* pneumonia reaching up to 70%. Multidrug-resistant organisms like MRSA and VRE now cause 25% of sepsis cases. Viruses and parasites account for only 2% to 4% of cases. Risk factors include diabetes, cancer, chronic organ diseases, immunosuppressive conditions, trauma, surgeries, and prolonged hospital stays.

Septic shock, marked by severe circulatory failure, demands rapid prognostic assessment. Lactate levels are crucial biomarkers for assessing septic shock severity, indicating poor tissue oxygenation and metabolic stress. Traditionally seen as a by-product of anaerobic metabolism, lactate is now recognized as resulting from stress-induced hypermetabolism during shock, making its measurement valuable for clinical assessment. Effective lactate clearance, the reduction rate of lactate levels after resuscitation, is associated with improved outcomes in septic shock patients, providing real-time feedback on patient status and treatment efficacy. Incorporating lactate level and clearance monitoring into septic shock treatment protocols offers essential information for timely decision-making, potentially improving patient outcomes. Ongoing research aims to establish these parameters as standards in septic shock management. This study investigates the predictive value of lactate levels and lactate clearance as biomarkers for septic shock prognosis, aiming to enhance early diagnosis and optimize therapeutic interventions in intensive care settings.

AIM OF THE STUDY

The primary aim of this study is to investigate the predictive value of lactate levels and lactate clearance as biomarkers for determining the prognosis of patients with septic shock. Given the high mortality and severe morbidity associated with septic shock, early and accurate prognostic assessment is crucial for effective management and therapeutic interventions. This research focuses on understanding how lactate levels and their rate of clearance can serve as dynamic indicators of patient status and treatment efficacy.

Specifically, the study aims to:

- Evaluate lactate levels as prognostic markers: assess the utility of initial lactate levels measured at ICU admission and their correlation with patient outcomes, including mortality, length of ICU stays, and overall recovery.
- Investigate lactate clearance rates: analyze the rates at which lactate levels decrease following initial resuscitation and how these rates are associated with improved outcomes in septic shock patients.
- Compare COVID-19 and Non-COVID-19 Patients: examine the differential impact of COVID-19 on lactate dynamics, given the unique metabolic challenges introduced by the virus. This comparison aims to highlight any distinct prognostic implications for patients with COVID-19-related septic shock versus those with septic shock from other causes.
- Identify risk factors: Determine additional patient-specific factors, such as comorbidities and demographic characteristics, that may influence lactate levels and clearance, thereby affecting prognosis.

By addressing these objectives, the study aims to enhance the understanding of septic shock pathophysiology and support the development of more effective, evidence-based interventions in critical care settings.

MATERIALS AND METHODS

This study was conducted in the Emergency Department (ED) of the County Emergency Hospital Resita, Romania. The study period was from January 2021 to December 2022. During this period, we evaluated a total of 990 patients diagnosed with septic shock. This PhD thesis was based on three pillars, each of them representing a study stage of the analyzed problem and a subchapter of this work. Thus, each sub-chapter and study presented an individual methodology.

RESULTS

LACTATE LEVELS AND CLEARANCE: KEY PREDICTORS OF PROGNOSIS FOR COVID-19 AND NON-COVID-19 SEPTIC SHOCK PATIENTS IN THE EMERGENCY DEPARTMENT

Our study included 114 patients aged 23–91 years presenting with septic shock at the Emergency Department, divided into non-COVID-19 (Group 1, 23 patients) and COVID-19 (Group 2, 91 patients) groups. Key findings include:

- Demographics:** The average age was 67 years in the non-COVID-19 group and 71 years in the COVID-19 group ($p = 0.031$). The gender distribution was similar, with 74% male in the non-COVID-19 group and 73% male in the COVID-19 group ($p = 0.712$).
- Comorbidities and Complications:** Heart failure was more prevalent in COVID-19 patients (9%) compared to non-COVID-19 patients (4%) ($p = 0.045$). Cardiovascular diseases were more frequent in non-COVID-19 patients (91%) compared to those with COVID-19 (29%) ($p = 0.021$). Obesity was more common in non-COVID-19 patients (30%) compared to COVID-19 patients (18%) ($p = 0.031$). Multi-organ failure was significantly higher in the COVID-19 group (10%) compared to the non-COVID-19 group (4%) ($p = 0.001$).
- Laboratory Parameters:** COVID-19 patients had higher initial lactate levels (6.2 ± 2.9 mmol/L) compared to non-COVID-19 patients (4.7 ± 2.6 mmol/L) ($p = 0.001$). This pattern persisted at 6, 24, and 48 hours with p -values of 0.021, 0.037, and 0.046, respectively. Procalcitonin levels were significantly higher in COVID-19 patients (17.2 ± 3.7 ng/mL) compared to non-COVID-19 patients (9.7 ± 4.1 ng/mL) ($p = 0.049$).
- Lactate Clearance:** Lactate clearance at 24 hours was better in non-COVID-19 patients ($p = 0.017$). Effective lactate clearance was associated with improved survival outcomes.
- Clinical Outcomes:** The overall 30-day mortality rate was 37%, higher in COVID-19 patients (42%) compared to non-COVID-19 patients (25%). Survivors had significantly lower initial lactate levels (1.5 ± 0.4 mmol/L) and higher lactate clearance rates ($33 \pm 15\%$) compared to non-survivors (2.5 ± 0.5 mmol/L and $24 \pm 9\%$) (lactate levels $p = 0.001$, clearance rates $p = 0.002$).
- Predictive Value:** Higher initial lactate levels were significant predictors of 30-day mortality (OR = 0.60, $p < 0.001$). Each 10% increase in lactate clearance decreased the odds of 30-day mortality by 20% (OR = 0.44, $p = 0.002$).
- Survival Analysis:** Kaplan-Meier survival curves indicated that effective lactate clearance within the first 24 hours correlated with improved survival outcomes.
- Etiologies of Septic Shock:** Non-COVID-19 patients: 40% had bacterial pneumonia, 30% had intra-abdominal infections. COVID-19 patients: mostly viral pneumonia with secondary bacterial

infections, higher mortality (42%) compared to non-COVID-19 patients (25%). In conclusion, the study highlights the significant prognostic value of lactate levels and clearance in septic shock patients, particularly in those with COVID-19, underscoring the importance of early lactate monitoring in improving patient outcomes.

RISK ASSESSMENT OF VENOUS THROMBOEMBOLISM AMONG SEPTIC SHOCK PATIENTS: SINGLE VERSUS CONCURRENT INSERTION OF CENTRAL VENOUS CATHETERS

The study analyzed 114 patients with septic shock, a majority of whom were elderly males and had COVID-19. The femoral vein was the preferred site for central venous catheter (CVC) insertion in 62.3% of cases, and two concurrent CVCs were placed in 52.6% of patients. Continuous veno-venous hemodiafiltration (CVV-HDF) was required in 41.7% of patients, and anticoagulants were administered to 86.8% of patients due to high Caprini risk scores.

The study found that higher Caprini risk scores were associated with venous thromboembolism (VTE) ($p < 0.001$) but not with mortality ($p = 0.377$). The femoral vein was the most common CVC insertion site, and patients with two concurrent CVCs had higher Caprini scores. VTE occurred more frequently in COVID-19 patients with two CVCs (26.6% vs. 7.4%; $p = 0.006$) and was significantly associated with the placement of two CVCs ($p = 0.041$). No significant difference in ICU stay length was found between COVID-19 patients with one or two CVCs.

Logistic regression identified the Caprini risk score as a significant predictor of VTE but not of in-hospital mortality. The study highlights the increased risk of VTE in patients with higher Caprini scores and those with two concurrent CVCs, emphasizing the need for careful monitoring and potential preventive measures in these high-risk groups.

LACTATE LEVEL AND LACTATE CLEARANCE - GOOD PREDICTORS FOR THE PROGNOSIS OF SEPTIC SHOCK PATIENTS WITH ACUTE KIDNEY INJURY REQUIRING CONTINUOUS RENAL REPLACEMENT THERAPY

The study compared baseline characteristics and clinical outcomes between survivors and non-survivors of septic shock among 114 patients. Significant differences were found in the

prevalence of COVID-19 and neurologic disease, which were higher in non-survivors. Non-survivors also had significantly higher levels of CRP, procalcitonin, and lactate at ICU admission and at 6- and 24-hours post-admission, while lactate clearance was significantly lower in non-survivors. Logistic regression analysis indicated that increased lactate clearance at 24 hours significantly decreased mortality, whereas higher CRP levels and older age increased mortality risk.

Subgroup analysis on patients with pulmonary septic shock receiving renal replacement therapy (RRT) revealed that increased lactate levels at 6 and 24 hours were associated with higher mortality in the plasmapheresis group but not in the CVVHDF group. ROC curve analysis identified lactate levels and lactate clearance at ICU admission, 6 hours, and 24 hours as strong predictors of mortality, with specific cutoff points providing high sensitivity and specificity.

Overall, the study highlights the prognostic value of lactate levels and clearance in predicting survival in septic shock patients, particularly emphasizing the differences in outcomes based on the type of RRT received.

CONCLUSIONS

This study highlights the significant role of lactate levels and clearance as prognostic indicators in septic shock, with a specific focus on the differences observed between COVID-19 and non-COVID-19 patients. Through comparative analysis, we found that lactate dynamics have unique implications for predicting patient outcomes, particularly in the context of the COVID-19 pandemic. By advocating for early and diligent lactate monitoring, our research enhances the understanding of septic shock prognostics and encourages further exploration of these insights across diverse patient populations.

The use of two concurrent central venous catheters (CVCs) in the ICU for patients with septic shock is rare but can be beneficial despite the associated risks. Our findings indicate an increased risk of venous thromboembolism (VTE) when two CVCs are placed in the same vein, though this risk appears to be more related to the nature of the second catheter used for continuous veno-venous hemodiafiltration (CVV-HDF) rather than its mere presence. Importantly, neither mortality rates nor the length of ICU stays increased due to the presence of two CVCs.

Understanding the impact of lactate levels and clearance in patients undergoing renal support procedures is crucial for optimizing care and improving outcomes. By elucidating the

relationship between lactate dynamics, renal function, and morbidity rates, healthcare providers can better tailor interventions to enhance lactate clearance and mitigate associated risks in this vulnerable patient population.

In our study, we used lactate levels and clearance as predictors of outcomes, markers to initiate therapy, and measures to monitor treatment adequacy. We measured lactate parameters at 1, 6, and 24 hours, and assessed lactate clearance between 1-6 hours and 6-24 hours in patients with pulmonary septic shock. Our findings showed that 24-hour lactate levels and clearance after the initiation of continuous renal replacement therapy (CRRT) were significantly associated with 24-hour mortality in patients with pulmonary septic shock and acute kidney injury.

Our study reaffirms the association between lactate levels and mortality rates in patients with pulmonary septic shock. However, further research is needed to determine the causality between lactate levels and mortality and to establish more precise guidelines for the clinical use of lactate monitoring in managing septic shock.