Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 03, 2023

EVALUATING THE ASSOCIATION OF INITIAL BLOOD LACTATE LEVELS WITH MORTALITY AND RESULTANT SEPTIC SHOCK IN NON- SHOCK SEPTIC SUBJECTS

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Conflict of Interest: None
Type o study: Original Research Paper
Date of submission: 23 February 2023
Date of acceptance: 10 March 2023
Date of publication: 30 March 2023

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ABSTRACT

Background: Increased levels of blood lactate have shown adverse outcomes as mortality where assessing blood lactate levels is vital in each subject with septic shock and severe sepsis as it can lead to tissue hypoxia and hypoperfusion.

Aim: The present study aimed to assess the association of initial blood lactate levels with mortality and resultant septic shock in non-shock septic subjects.

Methods: The present retrospective study assessed 224 subjects with sepsis admitted to a non-critical department and with the initial levels of serum lactate in the emergency ward. The subjects with hyperlactatemia of any other etiology were not considered for the study.

Results: The most common cause of sepsis was pneumonia in 44.5% (n=213) of subjects. More iv fluid was administered in Group II with high lactate levels compared to the low lactate group with $p<0.001$. Also, iv fluid of >1500ml was administered in 24 subjects from Group II and 6 subjects from group I with $p<0.001$. A high frequency of initial positive hemoculture was seen in 30 subjects of Group II compared to 13 subjects from Group I ($p=0.00$. 3 days of septic shock was seen in 5 subjects from Group I which was significantly lower compared to Group II where it was reported in 23 subjects with $p<0.001$. 28 days mortality was reported in 40 subjects from Group II compared to 10 subjects from Group I ($p<0.001$).

Conclusion: Septic shock and high mortality are associated with initial blood lactate levels of ≥2 mmol/L in subjects with non-shock sepsis. Mortality in subjects can be better predicted with more accuracy with other predictive scores and composites of blood lactate levels.

Keywords: Mortality, non-shock, sepsis, shock, serum lactate

INTRODUCTION

Sepsis is a syndromic condition causing life-threatening organ dysfunction resulting from a dysregulation in the host response to severe infection that can result in either early sepsis or more severe septic shock.[1] The sepsis-3 task force in 2016 recommended using the sepsis-related SOFA score as the diagnostic criteria for sepsis as it can predict the mortality rates with high accuracy and lesser errors. However, the SOFA score has a few limitations as the need for multiple lab assessments which may not be suitable in subjects presenting with early sepsis, mainly when the subject first present to the emergency department.[2]

The SOFA score was first introduced as a screening method for subjects who are not admitted to ICU (intensive care unit). The SOFA score is a relatively simple method. However, despite being simple, previous literature data has shown that it has poor sensitivity when used in sepsis subjects not admitted to the ICU and in the emergency department.[3] To judge the adverse outcomes in subjects with early sepsis at the emergency department, initial blood lactate levels can be reliable predictors. An increase in the levels of blood lactate is associated with poor outcomes including mortality.[4]

It has been recommended by the sepsis bundle to measure the blood lactate levels in all subjects with septic shock and severe sepsis as it can result in tissue hypoxia and hypoperfusion. In subjects where initial blood lactate levels are >2 mmol/L, it is considered a cut-off for hemodynamic resuscitation.[5] Despite its mention in previous literature data, the utility of the lactate levels is still highly unknown owing to the inclusion of septic shock and severe sepsis in the previously conducted literature data.[6] The present study aimed to evaluate the association of initial blood lactate levels with mortality and resultant septic shock in non-shock septic subjects.

MATERIALS AND METHODS

The present retrospective clinical study aimed to evaluate the association of initial blood lactate levels with mortality and resultant septic shock in non-shock septic subjects. The study population was taken from the subjects admitted to the institute.

All subjects were assessed initially at the emergency department followed by detailed history and clinical examination to assess the infection source. The qSOFA and Systemic inflammatory response syndrome criteria were assessed following the conventional protocols taken from the surviving sepsis campaign bundle.[7] In subjects where laboratory tests and arterial blood gases were assessed, the complete SOFA score was evaluated.

Initial management and laboratory investigations included intravenous fluid administration, empiric broad-spectrum antibiotics, venous blood lactate levels, and hemoculture. Before admitting the subject, each subject was reassessed to confirm the diagnosis made.

The study included subjects admitted to the non-critical department with sepsis diagnosis and of age 18 years or more was included in the study. The exclusion criteria were subjects with concurrent metformin use, seizure during the presentation, cardiac arrest or shock, and subjects where blood lactate levels were not assessed.

Sepsis was considered in subjects having confirmed or suspected infection and meeting the qSOFA or SIRS criteria or both or more. Systemic inflammatory response syndrome criteria were scored from 0-4 which was considered with two or more of these

a) white blood cell counts greater than 12,000 or less than 4000 cells/mm3 or more than 10% band forms
b) heart rate greater than 90 beats/minute
c) temperature greater than 38°C or less than 36°C
d) respiratory rate greater than 20 breaths/minute or PaCO2 less than 32 mm Hg

The qSOFA scores were from 0-3 including the systolic blood pressure of 100 mm Hg or less, abnormal mental status (Glasgow coma scale score of 14 or less), and a respiratory rate of 22 breaths/minute or greater. Septic shock was considered as persistent hypotension needing vasopressors for maintenance of serum lactate levels of >2 mmol/L and mean arterial pressure of ≥65mmHg.

The data for the study were collected from the previous records of the institute. The components assessed for SOFA score, qSOFA, and SIRS criteria were 3 days septic shock status, 28 days mortality, initial effective antibiotic regarding the microbiological results, time to initial antibiotic at the emergency department, amount of iv fluid during the emergency department stay, microbiologic data, site of infection, source of infection, and blood lactate levels.

The high blood lactate group was considered for initial blood lactate levels of >2 mmol/L. Depending on the "hour-1 bundle" of the surviving sepsis campaign bundle, the cut-off point was taken as 2 mmol/L. Depending on the recommendation and guidelines, the cut-point value of each tool was taken as ≥2 for qSOFA and SIRS both.[8]

The outcomes assessed primarily was 28 days mortality and secondarily was 3 days subsequent in-hospital septic shock.

The data gathered were analyzed statistically using the SPSS software version 21.0 and the Mann-Whitney U test. The level of significance was taken at $p<0.05$.

RESULTS

The present retrospective study assessed 224 subjects where the subjects were divided into two groups of 100 subjects with blood lactate <2 mmol/L making Group I and 124 subjects with blood lactate ≥2 mmol/L forming Group II. The mean age of subjects in Group I and II were 71.7±3.12 and 70.2±2.48 years respectively which was non-significant with p=094. There were 39 and 61 males in Groups I and II respectively which was significantly higher in Group II with p=0.02. The Glasgow coma scale was 8 and oxygen saturation was 94.2% in both groups. In group I, 8 subjects and in Group II, 15 subjects presented with hypotension. Mean arterial pressure, diastolic blood pressure, systolic blood pressure, and respiratory rates had a non-significant difference in the two groups with respective p-values of 0.64, 0.75, 0.22, and 0.26, whereas, heart rate was significantly higher in Group II with p=0.001 and the temperature was higher in Group I with p=0.01. Cancer and cirrhosis were significantly higher in Group II with p=0.007 and 0.03, whereas immunocompromised state, renal disease, diabetes, CVA, CHF, and CAD were comparable in the two groups with p=0.09, 0.07, 0.43, 0.920.95, 0.74, and 0,46 respectively as shown in Table 1.

Concerning the site of infection, intraabdominal infection was higher in Group II with 15 subjects compared to Group I with 6 subjects with p=0.01. The other sites, unknown sites, UTI, and pneumonia were comparable in two groups with p=0.72, 0.34, 0.26, and 0.16 respectively. The infection was hospital-acquired in 42 subjects of group I and 59 subjects of Group II with p=024. SOFA score was 2 and 3 in Group I and II with p=0.002, qSOFA≥2 score was 25 and 42 in groups I and II respectively with p=0.03, and SIRS≥2 was 95 and 118 in groups I and II respectively with p=0.95. In laboratory parameters, arterial blood gas examination was done in 63 subjects from Group I and 79 subjects from group II with p=074Total bilirubin and WBC counts were significantly higher in Group II with p<0.001 and 0.006 respectively. Platelet counts and hemoglobin levels were comparable in the two groups with p=0.23 and 0.05. The lactate levels were 1.35 mmol/L in Group I and 3,05 mmol/L in Group II with p<0.001 (Table 1).

It was seen that more iv fluid was administered in Group II with high lactate levels compared to the low lactate group with p<0.001. Also, iv fluid of >1500ml was administered in 24 subjects from Group II and 6 subjects from group I with p<0.001. More antibiotics were initially administered in Group II at a higher frequency compared to Group I. However, the difference was statistically non-significant with p=0.25. Within 60 minutes, antibiotics were administered to 74 subjects of Group II and 58 subjects of Group I with p=0.76. A high frequency of initial positive hemoculture was seen in 30 subjects of Group II compared to 13 subjects from Group I which was significant with p=0.003 as depicted in Table 2.

Concerning the study outcomes, it was seen that 3 days of septic shock was seen in 5 subjects from Group I which was significantly lower compared to Group II where it was reported in 23 subjects with p<0.001. For the 28 days mortality, it was reported in 40 subjects from Group II compared to 10 subjects from Group I. This difference was statistically significant with p<0.001 as shown in table 3.

DISCUSSION

The present retrospective study aimed to evaluate the association of initial blood lactate levels with mortality and resultant septic shock in non-shock septic subjects. The study assessed 224 subjects and the subjects was divided into two groups 100 subjects with blood lactate <2 mmol/L making Group I and 124 subjects with blood lactate ≥2 mmol/L forming Group II. The mean age of subjects in Group I and II were 71.7±3.12 and 70.2±2.48 years respectively which was non-significant with p=094. There were 39 and 61 males in Groups I and II respectively which was significantly higher in Group II with p=0.02. The Glasgow coma scale was 8 and oxygen saturation was 94.2% in both groups. In group I, 8 subjects and in Group II, 15 subjects presented with hypotension. Mean arterial pressure, diastolic blood pressure, systolic blood pressure, and respiratory rates had a non-significant difference in the two groups with respective p-values of 0.64, 0.75, 0.22, and 0.26, whereas, heart rate was significantly higher in Group II with p=0.001 and the temperature was higher in Group I with p=0.01. Cancer and cirrhosis were significantly higher in Group II with p=0.007 and 0.03, whereas immunocompromised state, renal disease, diabetes, CVA, CHF, and CAD were comparable in the two groups with p=0.09, 0.07, 0.43, 0.920.95, 0.74, and 0,46 respectively. These data were compared to the previous studies of Maitra S et al[9] in 2018 and Hwang SY et

al[10] in 2018 where authors assessed subjects with demographics comparable to the previous studies.

It was seen that the site of infection, intraabdominal infection was higher in Group II with 15 subjects compared to Group I with 6 subjects with p=0.01. The other sites, unknown sites, UTI, and pneumonia were comparable in two groups with p=0.72, 0.34, 0.26, and 0.16 respectively. The infection was hospital-acquired in 42 subjects of group I and 59 subjects of Group II with p=024. SOFA score was 2 and 3 in Group I and II with p=0.002, qSOFA≥2 score was 25 and 42 in groups I and II respectively with p=0.03, and SIRS≥2 was 95 and 118 in groups I and II respectively with p=0.95. In laboratory parameters, arterial blood gas examination was done in 63 subjects from Group I and 79 subjects from group II with p=074Total bilirubin and WBC counts were significantly higher in Group II with p<0.001 and 0.006 respectively. Platelet counts and hemoglobin levels were comparable in the two groups with p=0.23 and 0.05. The lactate levels were 1.35 mmol/L in Group I and 3,05 mmol/L in Group II with p<0.001. These disease characteristics were similar to the data described by Filho RR et al[11] in 2016 and Nichol AD et al[12] in 2010 where authors described similar disease characteristics as reported in the present study.

The study results showed that more iv fluid was administered in Group II with high lactate levels compared to the low lactate group with p<0.001. Also, iv fluid of >1500ml was administered in 24 subjects from Group II and 6 subjects from group I with p<0.001. More antibiotics were initially administered in Group II at a higher frequency compared to Group I. However, the difference was statistically non-significant with p=0.25. Within 60 minutes, antibiotics were administered to 74 subjects of Group II and 58 subjects of Group I with p=0.76. A high frequency of initial positive hemoculture was seen in 30 subjects of Group II compared to 13 subjects from Group I which was significant with p=0.003. These results were consistent with the previous studies of Krishna U et al[13] in 2009 and Hwang TS et al[14] in 2020 where authors reported more administration of iv fluid and more antibiotic consumption in subjects with higher lactate levels compared to subjects with low lactate levels.

On assessing the study outcomes, it was seen that 3 days of septic shock was seen in 5 subjects from Group I which was significantly lower compared to Group II where it was reported in 23 subjects with p<0.001. For the 28 days mortality, it was reported in 40 subjects from Group II compared to 10 subjects from Group I. This difference was statistically significant with p<0.001. these results were in agreement with the findings of Baumann BM et al[15] in 2020 and Shetty A et al[16] in 2017 where authors reported higher mortality rates and septic shock in subjects with high lactate levels as in the present study.

CONCLUSION

Considering its limitations, the present study concludes that in subjects with early sepsis, the assessment of the blood lactate levels and its cut-off at or above 2 mmol/L is a reliable predictive factor of the 28 days mortality and progression to the septic shock. Also, assessing the initial blood lactate levels can increase the adequate prediction of qSOFA and SIRS.

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TABLES

Characteristic	**Blood lactate <2 mmol/L (n=100)**	**Blood lactate ≥2 mmol/L (n=124)**	**p-value**
Mean age (years)	71.7±3.12	70.2±2.48	0.94
Gender (Male)	39	61	**0.02**
Glasgow coma scale	8	8	**0.01**
Oxygen saturation percentage	94.2	94.2	0.54
Presenting with hypotension	8	15	0.1
Vitals			
Mean arterial pressure (mm Hg)	90.2	90.9	0.64
Diastolic BP (mm Hg)	70.2	71.2	0.75
Systolic BP (mm Hg)	126.2	125.2	0.22
Respiratory rates (breath/min)	24.2	24.2	0.26
Heart rate (beats/min)	104.7	110.2	**0.001**
Temperature (C)	38.4	38.2	**0.01**
Comorbidity			
Immunocompromised	10	7	0.09
Cancer	24	43	**0.007**
Cirrhosis	3	8	**0.03**
Renal disease	15	11	0.07
Diabetes	20	22	0.43
Cerebrovascular accident	20	24	0.92
Congestive heart failure	13	16	0.95
Coronary artery disease	8	9	0.74
COPD	11	17	0.46
Infection site			
Unknown	22	23	0.34
Other	6	7	0.72
Intraabdominal infection	6	15	**0.01**
UTI	15	24	0.26
Pneumonia	51	56	0.16
Source (hospital-acquired)	42	59	0.24
Clinical predictive scores			
SOFA score	2	3	**0.002**
qSOFA ≥2	25	42	**0.03**
SIRS ≥2	95	118	0.95
Laboratory parameters			
Arterial blood gas	63	79	0.74
Lactate level mmol/L	1.35	3.05	**<0.001**

Total bilirubin (mg/dl)	0.55	0.85	**<0.001**
Creatinine (mg/dl)	1.04	1.04	-
Platelet count (X 10^3/mm3)	238.3	225.2	0.23
WBC count (cells/mm3)	10,310	12,745	**0.006**
Hemoglobin (gm/dl)	10.6	11.2	0.05

Table 1: Demographic and disease characteristics of the study subjects

Parameter	**Blood lactate <2 mmol/L (n=100)**	**Blood lactate ≥2 mmol/L (n=124)**	**p-value**
Initial antibiotic effectiveness	29	45	0.57
Initial positive hemoculture	13	30	**0.003**
Antibiotics within 1st hour	58	74	0.76
Antibiotic receiving time (minutes)	48.2	46.7	0.74
Initial antibiotic administration	93	119	0.25
IV fluid ≥1500ml	6	24	**<0.001**
IV fluid volume (ml)	150	250	**<0.001**

Table 2: Initial management of study subjects in the emergency department

Outcomes	**Blood lactate <2 mmol/L (n=100)**	**Blood lactate ≥2 mmol/L (n=124)**	**p-value**
3 days of septic shock	5	23	**<0.001**
28 days mortality	10	40	**<0.001**

Table 3: Primary and secondary outcomes of the study subjects