Original Article

Serum Lactate Level as a Predictor of Outcome in Patients with Septic Shock

Rupak Bhandari, R Bhandari, M Paudel, GB Malla
Department of General Practice and Emergency Medicine, BPKIHS, Dharan

Abstract

Background: Sepsis and Septic shock are a common presentation in the Emergency Department with high morbidity and mortality. Serum lactate level increases substantially in the patients with septic shock. The objectives of this study were to determine serum lactate levels at the time of presentation, find out the outcome and correlate lactate levels with the outcome in the patients with septic shock.

Methods: It is a prospective cross-sectional study of patients presenting to the Emergency, who met the criteria for septic shock defined by Surviving Sepsis Guidelines 2012. Patients' demographics, co-morbidity, triage vitals, laboratory and radiological parameters were recorded. The primary outcome was mortality and secondary outcomes were duration of stay in hospital and complications, if any, developed during hospital stay.

Results: Eighty-four cases were enrolled, with male to female ratio of 1:1. Mean age was 46.40±19.59 years. The significant variables were: serum lactate ($p<0.001$), pH level ($p= 0.001$), serum creatinine ($p= 0.002$) and INR level ($p= 0.001$). Serum lactate was the significant factor that correlated with mortality after applying multivariate regression analysis (OR= 2.75, CI= 0.890- 4.041, $p= 0.001$).

Conclusion: Initial serum lactate level is independently associated with mortality of the patients presenting to ED with septic shock.

Keywords: Sepsis, Septic shock, Lactate, Emergency.

Background

Sepsis and septic shock are frequently encountered life threatening conditions in the emergency. They are the major health problems affecting millions of people around the world, killing one in four each year.[1,2] Its most common victims are children, immuno-compromised individuals and the elderly.[2] Common sites of sepsis are respiratory tract, urogenital tract, gastrointestinal tract, skin and wounds. Extremes of age, comorbidities such as diabetes mellitus, liver cirrhosis, cardio-pulmonary disease and immunosuppression are high risk factors for sepsis.[3] Effective management of septic shock includes early recognition of inadequate tissue perfusion and timely resuscitation to reverse the effects. The cognizance of factors which predict the outcome can help in early recognition and prompt management to reduce morbidity and mortality related to septic shock. Hyperlactatemia is the cardinal finding of septic shock where serum lactate level exceeds 2mmol/L.[4,5] Lactic acidosis occurs when serum lactate exceeds 2mmol/L and pH is less than 7.35. Type-A lactic acidosis occurs in association with clinical evidence of poor tissue perfusion or oxygenation of blood (e.g. Hypotension, cyanosis, cool and mottled

Address for correspondence
Dr. Rupak Bhandari
Dept. of General Practice & Emergency Medicine
BP Koirala Institute of Health Sciences, Dharan
Email: rupakbhandari@gmail.com

periphery).[6] Serum lactate has been shown to be a useful early marker of mortality in septic shock in different western studies.[7-10] There are limited data regarding the issue in our setup. In recent times, it is easy and quick to obtain the reports of serum lactate levels in our hospital. Hence, the study was conducted to determine the levels of serum lactate in patients presenting to our emergency department (ED) with septic shock and find out the association of lactate levels with outcome of the patient.

Method

B. P. Koirala Institute of Health Sciences (BPKIHS) is a university hospital which is one of the largest tertiary care centers of Eastern Nepal. The hospital hosts over 125 patients per day in an 80 bedded ED. A prospective cross-sectional observational study was conducted at ED from 14th April 2013 to 13th April 2014 enrolling the patients of septic shock as defined by Surviving Sepsis Guidelines 2012. Patients who were referred to other center, left against medical advice (LAMA), who absconded and who were not willing to participate in study were excluded from the study.

The study was approved by Institutional Ethical Review Board (IERB) of the hospital.

Previous year's hospital data showed a total of 100 cases of septic shock at ED with 55% in-hospital mortality. Taking the confidence interval at 95% and level of precision to 80%, we calculated our sample size to be 78. We allowed 10% data for subset analysis, and hence kept the sample size to 84.

Study Procedure

Patients who presented to the ED in fluid-resistant shock state meeting at least two of the SIRS criteria and having suspected of definite focus of sepsis (either clinically or radiologically) were included in the study. Demographics including age, gender and co-morbidity of the patient were noted. The vital parameters including pulse, blood pressure, respiratory rate, temperature, and consciousness level and oxygen saturation were recorded on the arrival. Arterial blood sample was collected for pH and serum lactate levels whereas venous blood samples were collected for hemoglobin, total leukocyte count, platelets count, blood sugar, urea and creatinine level, serum bilirubin, albumin, INR level along with two sets of blood culture and urine culture. Chest radiography was done in all of the patients. Other radiological or blood investigations were carried out on case to case basis. Arterial blood gas analysis was repeated within 6 hours of presentation. Patients were followed up in ward (medical/ surgical) or ICU till discharge or death of the patient or 28 days of admission whichever is earlier.

Outcome measures

The primary outcome measure was survival/ non-survival. Secondary outcome measures were duration of hospital stay and complications encountered during hospital stay. The complications included acute respiratory failure requiring intubation, acute kidney injury, acute hepatic failure, coagulopathy and deteriorated mental status.

Data analysis

Data were recorded in Microsoft Excel version 2007 and analyzed using SPSS version 11.5. The continuous variables with normal distribution were expressed as mean ± SD and were compared using Student's t-test. Continuous variables with asymmetric distribution were expressed as median and inter-

quartile range and were compared using the non-parametric Mann–Whitney U-test, for independent samples. In the case of categorical variables, Pearson's chi-square test and Fisher's exact test were used to analyze differences in proportions. The statistically significant variables associated with the outcome in the univariate analysis were then subjected to multiple logistic regression analysis to adjust for the potential confounders.

Results

A total of 84 cases were included in the study with male: female ratio of 1:1. Mean age was 46.4 ± 19.59 years. Respiratory tract was the most frequent focus of sepsis (54.8%), followed by urogenital tract (14.3%). Median duration of hospital stay was 6 days (IQR 3.00 – 9.00 days). The initial lab parameters of the patients with septic shock are shown in table 1. The factors associated with mortality are compared among survivors and non-survivors in table 2.

Table 1: Initial Lab Parameters of the patients with septic shock

Characteristics	Category	Frequency	Percentage	Mean ± SD/ Median (IQR)*
Lactate, mmol/L (N= 84)	<4.0	70	83.33	2.81 ± 1.351
	≥4.0	14	16.67	
pH (N= 84)	<7.35	32	38.10	7.36 ± 0.106
	7.35-7.45	42	50.00	
	>7.45	10	11.90	
Hb, g/dL (N= 84)	<10	31	36.90	10.67 ± 3.004
	≥10	53	63.10	
WBC, per mm^3 (N= 84)	<4000	5	5.95	14000 (9125 – 20750)*
	4000 – 12000	26	30.95	
	>12000	53	63.10	
Platelet Count, per mm^3 (N= 84)	<100000	38	45.24	113500 (64250 – 203000)*
	≥100000	46	54.76	
Random Blood Sugar, mg/dL (N= 84)	≤140	60	71.43	112 (86.25 – 152.50)*
	>140	24	28.57	
Creatinine, mg/dL (N= 84)	≤2	57	67.85	1.3 (0.70-2.80)*
	>2	27	32.15	
Serum Albumin, mg/dL (N = 76)	<3.5	58	76.32	2.97 ± 0.629
	≥3.5	18	23.68	
Total Bilirubin, mg/dL (N = 76)	≤4	69	90.79	1.2 (0.80 – 1.9)*
	>4	7	9.21	
INR (N = 71)	≤1.5	31	43.66	1.57 (1.26 – 1.96)*
	>1.5	40	56.34	

*Non-Paramteric samples expressed as median with inter-quartile range (25th – 75th percentile)

Table 2: Factors associated with mortality in patients with septic shock

Characteristics	Survivors (N= 58)	Non-survivors (N = 26)	P-Value
Age, mean ± SD, years	43.26 ± 18.446	53.42 ± 20.623	*0.027*
GCS, mean ± SD	14.81 ± 0.736	14.31 ± 1.517	*0.043*
Heart Rate, mean ± SD, beats/min	104.62 ± 19.601	107.62 ± 16.425	0.499
Respiratory Rate, mean ± SD, cycles/min	25.43 ± 6.25	25.77 ± 4.942	0.808
Temperature, mean ± SD, °F	99.302 ± 2.271	98.79 ± 1.674	0.309
Systolic BP, mean ± SD, mm Hg	74.31 ± 9.005	70.38 ± 9.157	0.070
MAP, mean ± SD, mm Hg	55.69 ± 8.189	52.95 ± 8.344	0.162
SpO_2, mean ± SD, %	92.03 ± 7.865	85.23 ± 9.889	*0.001*
LABORATORY PARAMETERS			
pH, mean ± SD	7.38 ± 0.083	7.30 ± 0.131	*0.001*
Lactate, mean ± SD, mmol/L	2.43 ± 0.893	3.65 ± 1.779	*0.000*
Hemoglobin, mean ± SD, g/dL	10.82 ± 3.280	10.34 ± 2.294	0.497
Total Leukocyte Count, median (IQR), per mm^3	13850 (8900-21125)	14050 (10300-19600)	0.824*
Platelets, median (IQR) , per mm^3	113500 (64750-202250)	114000 (63500-226500)	0.670*
Blood Sugar, median (IQR), mg/dL	112 (87.25-137.75)	107 (84-185)	0.523*
Creatinine, median (IQR), mg/dL	1.0 (0.675-1.925)	2.2 (1.55-3.43)	*0.002**
Albumin, mean ± SD, g/dL, N = 76	3.07 ± 0.613	2.73 ± 0.615	*0.029*
Total Bilirubin, median (IQR), mg/dL, N = 76	1 (0.8-1.7)	1.3 (0.90-3.60)	*0.049**
INR, median (IQR), N= 71	1.43 (1.24-1.61)	1.78 (1.52-2.61)	*0.001**
Blood Culture, N=63	4 (6.35)	3 (4.76)	0.279
COMPLICATIONS DURING HOSPITAL STAY			
Need For Intubation, n (%)	8 (13.8)	25 (96.2)	*0.000*
Coagulopathy, n (%)	7 (12.1)	15 (57.7)	*0.000*
Acute Kidney Injury, n (%)	15 (25.9)	20 (76.9)	*0.000*
Hepatic Failure, n (%)	8 (13.8)	8 (30.8)	0.067
Altered Consciousness, n (%)	6 (10.3)	14 (53.8)	*0.000*
Hospital Stay, median (IQR)	7 (4.00-10.25)	1 (1-3.25)	*0.000**

*Mann Whitney U test was applied for non-parametric variables

The final multiple logistic regression analysis model included the statistically significant variables associated with outcome in the univariate analysis. After adjusting all the potential confounding factors, serum lactate level was still significantly associated with in-hospital mortality (OR= 2.75, CI= 0.890- 4.041, p= 0.001). The other factors significantly associated were serum total bilirubin and INR at presentation. Multiple logistic regression analysis of the confounding factors is shown in table 3.
The area under receiver-operating characteristic (ROC) curve was 0.721 (0.588– 0.855, P= 0.001) as shown in table 4 and figure 1; and the cutoff value of serum lactate with the best diagnostic accuracy was found to be 2.45 mmol/L which gave a sensitivity of 73.1% and specificity of 58.6%.

Table 3: Multiple logistic regression analysis of the confounding factors

Variable	Odd's Ratio	95% Confidence Interval	P-value
Age	0.02	0.958-1.039	0.070
GCS	0.27	0.436-1.616	0.341
SpO_2	0.94	0.882-1.043	0.050
pH	0.16	0.000-1780.557	0.005
Serum Lactate	2.75	0.890-4.041	*0.001*
Serum Creatinine	0.44	0.839-1.427	0.315
Serum Albumin	0.68	0.134-2.267	0.056
Serum bilirubin	3.77	0.996-2.205	*0.016*
INR	1.02	0.695-3.107	0.003

Table 4: Area under the receiver-operating characteristics curve

Area Under the Curve

Area	SE	P	95% CI	
			Lower Bound	Upper Bound
0.721	0.068	0.001	0.588	0.855

SE: Standard Error; CI: Confidence Interval

Discussion

Anecdotal evidence suggests sepsis to be a common presentation in emergency department of Nepal. But only a few studies were found that touched upon the subject of shock in ED and ICU. This study is the first to investigate the cases of septic shock in the ED of Nepal. Basnet B et al found 23.1% of the cases with triage score of 2 presenting to the ED of BPKIHS had shock at presentation.[11] Lakhe S et al published a study of 28 cases in the ICU of a private hospital in Kathmandu. He found 10.7% had sepsis, 89.3% had severe sepsis and 82% had septic shock. The mortality rates of the cases were 0%, 39% and 47 % respectively.[12] This study showed a mortality of 30.9% in contrast to the study by Lakhe S et al.[12] The difference in mortality may represent a population which is from different geographical region and different ICU admission criteria.

Another multicentric prospective observational study from India by Todi S et al[13] was conducted in four ICUs enrolling 5478 patients. The study showed 16.5% of the cases had severe sepsis. The in-hospital mortality of those cases was 65%. Similar mortality rate was found in diverse setting done by Lee et al[14] (26.9%), Mikkelsen ME et al[15] (37.8%) and van Beest P et al[9] (26.7%). Higher mortality was seen however in the studies by Rivers E[10] (42.3%), Kang YR et al[16] (48%), Nguyen H et al[17] (42.3%).

The mean age group of the cases of septic shock presenting to our ED was 46.4 ± 19.59 years which is lower as compared to the studies by van Beest et al[9] (61), Nguyen H et al[17] (64.9), Kang YR et al[16] (62) and Lee SW et al[14] (61).

M: F ratio of 1:1 in our study was almost similar in most studies.[8,10,12,15,17] Mean MAP in this study was 54.84 ± 8.28 mmHg. Most other studies show higher MAP ranging from 68 to 77 mmHg.[9,14,15,17] The higher MAP in their studies might be because of inclusion of the cases of severe sepsis along with septic shock. Mean pH at presentation in our study was 7.36 ± 0.18. Similar figure is seen with Nguyen H et al[17] (7.33 ± 0.18) and Lee SW et al[14] (7.35).

This study found the respiratory tract infection and urogenital tract infection contributed 69% of septic shock cases presenting to ED. This is a similar percentage to that reported by various studies of sepsis.[8,9,12,14,15,17] One study by Kang YR et al[14] showed abdominal infection as the most common focus of sepsis. The contrast in foci in this study may be due to the fact that their sample included the cases with hepatic dysfunction only. The other common foci of sepsis shown in their study were respiratory and urogenital tract which is similar to our study.

Respiratory failure (39.3%) and acute renal failure (41.7%) were the most frequent complications developed during the hospital stay in our study. Mikkelson ME et al[15] showed renal (43.4%) and neurological complication (34.2%) as the most frequent ones.

The elevated lactate level has been shown to be adversely associated with outcome in various studies.[4,5,7–10,18,19] However, various cut offs range for lactate have been used. This study used a lactate cut off range of ≥ 4 mmol/L to differentiate sepsis and severe sepsis and found a significant association with mortality in our population ($p<0.001$). This cut-off has been the most commonly used value in different researches.[7–10,18] Others have used a cut off values as low as 2.0 mmol/L[4,5] and as high as 5 mmol/L[14] and shown to have positive association with mortality.

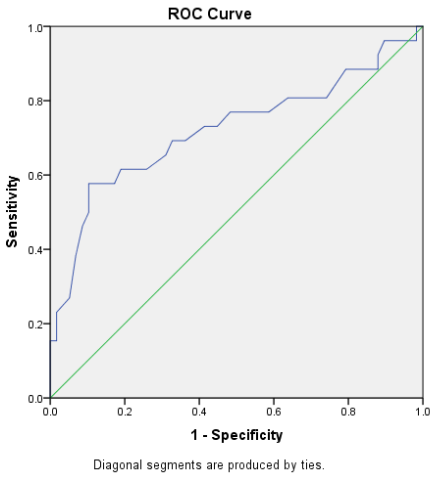

Figure 1: Receiver-operating characteristics curve for the performance of serum lactate as a predictor of mortality in septic shock

This study used the arterial lactate level, as it is the practice in the hospital. ABG are reported

early and can give other supportive data like oxygenation, acid base balance, electrolyte values and glucose. Different studies by various authors suggest the agreement between arterial and venous lactate levels.[20,21] Recently, there is a move away from ABG to VBG which is less painful and can give comparable information.

With a single measurement of lactate concentration, it may be difficult to predict the outcome, more so with the hepatic and/ or renal failure. Kang YR et al[16] found that the initial lactate level was independently associated with in-hospital mortality in septic shock patients with hepatic dysfunction. In patients with chronic kidney disease (CKD), the serum lactate level might be elevated due to impaired lactate clearance.[22] However, the number of patients with CKD or hepatic failure in this study was too small to confound the association between the elevated serum lactate level and mortality.

Although there are numerous other tools for predicting outcome in patients with septic shock such as severity of illness scoring systems and clinical prediction rules, these types of multivariate indices may be cumbersome for routine clinical use by the clinicians at bedside. In contrast, lactate measurement is a relatively simple test that can be obtained easily. The simplicity of use of serum lactate can make it a useful bedside tool for risk stratification of the patients with septic shock.[8]

Bedside clinical acumen of a clinician still remains vitally important for assessment of mortality risk although serum lactate correlates well with mortality.[8] Hence, the clinicians should use lactate measurement as an auxiliary test, not a primary one.

There are several limitations to this study. As shown by many researches, serial measurements of the lactate clearance over time may be a better predictor of outcome in septic shock.[17,18,23] Serial measurement of lactate clearance could not be done in our study. The reason was mostly financial constraints, as the patients have to pay for the investigations.

Conclusion

Initial serum lactate level is independently associated with mortality of the patients presenting to ED with septic shock. Thus, measurement of initial serum lactate level could be a good predictor of outcome in patients with septic shock.

Acknowledgement

The authors gratefully acknowledge Mr. Dharanidhar Baral for his tremendous effort during statistical analysis of the study.

Funding: None.

Ethical approval: The study was approved by the Institutional Ethical Review Board, BPKIHS.

Conflicts of interest: The authors declare there is no competing interest related to the study, authors, other individuals or organizations.

Contributors: Rupak Bhandari proposed the study and wrote the first draft. All authors read and approved the final version of the paper.

References

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis

and septic shock: 2012. Crit Care Med. 2013 Feb; 41(2): 580-637.

2. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004 Mar; 32(3): 858-73.
3. Munford RS. Severe Sepsis and Septic Shock. In: Kasper DL, Fauci AS, Hauser SL, et al (eds.) Harrison's Principles of Internal Medicine. 19th edition. McGraw Hills; 2015. Chap 325, p.1751-1759.
4. Khosravani H, Shahpori R, Stelfox HT, Kirkpatrick AW, Laupland KB. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. Crit Care. 2009 Jan; 13(3): R90.
5. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Crit Care. 2010 Jan; 14(1): R25.
6. Kraut JA, Madias NE. Lactic Acidosis. Ingelfinger JR (editor). N Engl J Med 2014; 371: 2309-19.
7. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. Ann Emerg Med. 2005 May; 45(5): 524-8.
8. Trzeciak S, Dellinger RP, Chansky ME, Arnold RC, Schorr C, Milcarek B, et al. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med. 2007 Jun; 33(6): 970-7.
9. Van Beest PA, Mulder PJ, Oetomo SB, van den Broek B, Kuiper MA, Spronk PE. Measurement of lactate in a prehospital setting is related to outcome. Eur J Emerg Med. 2009 Dec; 16(6): 318-22.
10. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. New England Journal of Medicine. 2001; 345(19): 1368-77.
11. Basnet B, Bhandari R, Moore M. Initial resuscitation for Australasian Triage Scale 2 patients in a Nepalese emergency department. Emerg Med Australas. 2012 Aug; 24(4): 430-4.
12. Lakhey S, Karki B, Shrestha B, Shakya S, Pandey S. Sepsis: a private hospital experience in Nepal. ICU Post. 1(1): 46-8.
13. Todi S, Chatterjee S, Sahu S, Bhattacharyya M. Epidemiology of severe sepsis in India: an update. Crit Care. 2010; 14(Suppl 1): P382
14. Lee SW, Hong YS, Park DW, Choi SH, Moon SW, Park JS, et al. Lactic acidosis not hyperlactatemia as a predictor of in hospital mortality in septic emergency patients. Emerg Med J. 2008 Oct; 25(10): 659-65.
15. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med. Society of Critical Care Medicine and Lippincott Williams & Wilkins; 2009 May; 37(5): 1670-7.
16. Kang YR, Um SW, Koh WJ, Suh GY, Chung MP, Kim H, et al. Initial lactate level and mortality in septic shock patients with

hepatic dysfunction. Anaesth Intensive Care. 2011 Sep; 39(5): 862-7.

17. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004 Aug; 32(8): 1637-42.
18. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, et al. Multicenter Study of Early Lactate Clearance As a Determinant of Survival in Patients With Presumed Sepsis. Shock. 2009 Jul; 32(1): 35-9.
19. Jansen TC, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systematic health technology assessment. Crit Care Med. 2009 Oct; 37(10): 2827-39.
20. Middleton P, Kelly AM, Brown J, Robertson M. Agreement between arterial and central venous values for pH, bicarbonate, base excess and lactate. Emerg Med J. 2006 Aug; 23(8): 622-4.
21. Gallagher EJ, Rodriguez K, Touger M. Agreement between peripheral venous and arterial lactate levels. Ann Emerg Med. 1997 Apr; 29(4): 479-83.
22. Leverve X, Mustafa I, Novak I, Krouzecky A, Rokyta R, Matejovic M, et al. Lactate metabolism in acute uremia. J Ren Nutr. 2005 Jan; 15(1): 58-62.
23. Jat KR, Jhamb U, Gupta VK. Serum lactate levels as the predictor of outcome in pediatric septic shock. Indian J Crit Care Med. 2011 Apr; 15(2): 102-7.