Prognostic Significance of Clinical Profile, Biochemical Markers with Special Reference to Serum Lactate Dehydrogenase (LDH) Level in Sepsis and Its Correlation with Survival of the Patient

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ABSTRACT

BACKGROUND

Sepsis is a potentially life threatening medical emergency. It should be diagnosed at the earliest and treated effectively to prevent mortality. Therefore, there is a need for parameters which are simple, reliable and cost effective which help in predicting the prognosis and help in managing the patient with sepsis more efficaciously.

METHODS

A total of seventy patients, 42 male and 28 female patients, over a period of one year, who fulfilled the inclusion and exclusion criteria was included in the study. In this study various clinical variables and biochemical markers including serum lactate dehydrogenase (LDH) were compared among survivor and non–survivor groups and analysed.

RESULTS

In this study out of 70 patients, 36 patients [51.4 %] expired. Various clinical variables and biochemical markers including serum LDH [on day 1 & day 3], were compared among survivor and non–survivor groups and analysed. Pulse rate, mean arterial pressure (MAP), total leucocyte count, renal function test (RFT), liver function test (LFT), day 3 LDH levels and requirement of ventilator support showed statistically significant difference among the survivor and non-survivor groups.

CONCLUSIONS

Despite the recent medical advances, sepsis is a multiorgan disease with significant mortality. Hence, we need simple and effective parameters which are essential in assessing the prognosis and in guiding the treatment protocols. This study focused on simple clinical and biochemical parameters with special reference to LDH, which helped us in predicting the mortality.

KEYWORDS

Markers, Serum LDH, Sepsis, Survival

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BACKGROUND

The understanding of sepsis has undergone a tremendous change and hence has resulted in favourable outcomes with respect to mortality. This has been possible because of the better understanding of the pathogenesis, advances in the pharmacotherapy and antimicrobials.

The ability to objectively estimate patient risk for mortality or other important outcomes is a new undertaking for clinical research. Assessment of the clinical and biochemical parameters of patient with sepsis, helps us in guiding the overall management and ultimately predicting the outcome.

The clinical and prognostic significance of elevated serum LDH in sepsis remains to be defined. In this study we intend to predict the outcome in patients with sepsis by calculating the serum LDH level on day 1 and day 3 of admission and corroborate with the final outcome of the treatment.

METHODS

This was a cross-sectional study undertaken in the Karnataka Institute of Medical Sciences, Hubli after the approval from the ethical committee. This study was carried out from 1st July 2014 – 30th June 2015 and 70 patients were included in the study.

The patients with sepsis as defined by the 2001 Society of Critical Care Medicine (SCCM) / European Society of Intensive Care Medicine (ESICM) / American College of Clinical Pharmacology (ACCP) / American Thoracic Society (ATS) / (Surgical Infection Society) SIS International Sepsis Definitions Conference were included in the study. The detailed history, Clinical examination and all relevant laboratory investigations were done. In the present study, the conditions were defined according to the standard practice and based on relevant literature.

All the patients of sepsis, who fulfilled the inclusion and exclusion criteria admitted to KIMS, Hubli were being prognosticated on the basis of various clinical and biochemical parameters with special reference to serum LDH level on day 1 and day 3. We analysed various profiles between two groups; survivor group which included the patients who were successfully discharged after the recovery and the non-survivor group which include the patients who died.

Inclusion Criteria

Patients admitted to the intensive care unit (ICU) and who remained for a minimum of 4 hours with evidence of sepsis fulfilled by at least 2 of the 4 criteria mentioned below were included in the study.[1,2]

- Oral temperature greater than 38^0 C (100.4^0 F) or less than 36^0 C (96.8^0 F)
- Heart rate greater than 90 beats per minute
- Respiratory rate (RR) greater than 20 breaths per minute or arterial carbon dioxide tension (PaCO2) lower than 32 mm of Hg.
- White blood cell (WBC) count greater than 12,000 / µL or less than 4000 / µL

Exclusion Criteria

Patients with -

- Age < 18 years.
- Trauma.
- Chronic kidney injury.
- Liver cirrhosis.
- Haemolytic anaemia.
- Malignancy.
- Burn injuries.
- Admitted with or suspicion of acute myocardial ischemia.

Statistical Analysis

Data was entered in Microsoft (MS)-Excel and analysed in Statistical Package for the Social Sciences (SPSS) V21. Descriptive statistics were represented with percentages, mean with SD. Chi-square test, independent t-test and logistic regression analysis was done. $P < 0.05$ was considered as statistically significant.

RESULTS

70 patients who fulfilled the inclusion and the exclusion criteria admitted in the Karnataka Institute of Medical Sciences, Hubli, were enrolled in the study. The mean age of the study population was 58.14 + / - 11.22 years. Of which mean age of the male patients was 57.31 + / - 10.93 years. The mean age of the female patients was 59.39 + / - 11.73 years.

Out of the 70 patients selected for the study, 60 % were males and 40 % were females.

Out of the 70 patients selected for the study, 34 patients survived and 36 patients died, which accounted for 48.6 % of survivors and 51.4 % of non-survivors. Non-parametric chi-square test was used and x^2 was calculated to be 0.057 and the P-value was found to be 0.81 which was statistically insignificant.

Comorbidities	Outcome: Survivors (N = 34) Number	%	Deaths (N = 36) Number	%	χ2	P-Value
Hypertension						
Present	9	26.5	19	52.8	5.04	.02
Absent	25	73.5	17	47.2		
Diabetes Mellitus						
Present	6	17.6	24	66.7	17.15	< .001
Absent	28	82.4	12	33.3		
T2DM & HTN						
Both	2	5.9	12	33.3	19.4	< .001[F]
Either	11	32.4	19	52.8		
Neither	21	61.8	5	13.9		

Table 1. Relationship of Comorbidities with Outcome

Pearson chi-square used, F indicates Fisher's exact test used, P-value < 0.05 was significant

In the study population [Table 1], among the survivors 26.5 % were hypertensive and among the non-survivors, 52.8 % were hypertensive. Here, Pearson chi-square test

was used, x^2 was found to be 5.04. The P-value was 0.02 which was statistically significant.

In the study population, among the survivors, 17.6 % were diabetic and among the non-survivors, 66.7 % were diabetic. Here, Pearson chi-square test was used, x^2 was found to be 17.15. The P-value was < 0.001 which was statistically significant.

Among the survivors, 5.9 % had both diabetes and hypertension and among the non-survivors, 33.3 % had both diabetes and hypertension. Pearson chi-square test was used, x^2 was found to be 19.4. The P-value was calculated to be < 0.001 using Fisher's exact test, which was statistically significant.

Laboratory Parameters	Outcome				χ^2	P-Value
	Survivors (N = 34)		Deaths (N = 36)			
	Number	%	Number	%		
Liver Function Test (Serum Bilirubin)						
Normal	14	41.2	2	5.6	12.58	< .001
Deranged	20	58.8	34	94.4		
Renal Function Test (Serum Creatinine)						
Normal	12	35.3	0	0.0	15.33[F]	< .001
Deranged	22	64.7	36	100.0		

Table 2. Relationship of LFT and RFT with Outcome

Pearson chi-square used, F indicates Fisher's exact test used, P-value < 0.05 was significant

The liver function test [Table 2], mainly considering the patient's serum bilirubin was found to be deranged in 58.8 % of the survivors and 94.4 % of the non-survivors. The serum total bilirubin level (mg / dL) was higher among non-survivors compared to the survivors (4.74 + / - 2.98 vs. 2.62 + / - 1.84). Pearson chi-square test was used, x^2 was found to be 12.58. The P-value was calculated to be < 0.001 which was statistically significant.

Renal function test [Table 2], accounting mainly to serum creatinine was analysed. Serum creatinine was deranged in 64.7 % survivors and among 100 % of non-survivors. The mean serum creatinine was high among non-survivors compared to the survivors (7.35 + / - 3.87 vs. 2.64 + / - 1.78). Pearson chi-square test was used, x^2 was found to be 15.33. The P-value was calculated to be < 0.001 which was statistically significant.

Ventilator Support	Outcome		P-Value
	Survivors	Non-Survivors	
Yes	3 (8.8 %)	29 (80.6 %)	< 0.001
No	31 (91.2 %)	7 (19.4 %)	

Table 3. Intervention Done - Ventilator Support

Non-parametric χ^2 used; P-value < 0.05 was significant

Variables	Survivors		Deaths		T-Value	P-Value
	Mean	SD	Mean	SD		
Pulse rate (per minute)	107.38	7.22	123.92	10.24	7.7	< .001
Systolic BP (per mmHg)	86.12	3.61	76.33	5.94	8.2	< .001
Diastolic BP (per mmHg)	53.59	5.61	46.22	6.04	5.2	< .001
MAP (per mmHg)	64.4	4.4	56.2	5.4	6.8	< .001
Temperature (in °F)	100.84	.60	101.99	.89	6.3	< .001
Respiratory rate (per min)	27.41	6.43	29.39	6.01	1.3	.189
Total count (* 10^6 per mm^3)	177.26	42.09	234.12	65.30	4.3	< .001
LDH day 1 (in units)	1149.88	206.037	1311.94	302.66	2.6	.01
LDH day 3 (in units)	1071.35	198.56	1545.39	270.37	8.3	< .001

Table 4. Association of Quantitative Variables with Outcome

Independent t-test used, P-value < 0.05 was significant

In the study population, [Table 3] 32 patients were put on mechanical ventilator. Patients who had severe respiratory distress and those who were not maintaining O_2 saturation despite high flow oxygen were intubated and connected to mechanical ventilation. Among those people, 9.4 % were survivors and 90.6 % were non-survivors. The P-value was calculated to be 0.001 which was statistically significant.

The pulse rate [Table 4] was more than 90 in all patients. The mean pulse rate among the survivors was 107.38 + / - 7.22, and among the non-survivors it was 123.92 + / - 10.24. The t-value was found to be 7.7. The P-value was calculated to be < 0.001 which was statistically significant. This shows that the pulse rate was comparatively higher in the non-survivor group.

In the study group, [Table 4] the mean systolic blood pressure among the survivors was 86.12 + / - 3.61 mmHg. and among the non-survivors it was 76.33 + / - 5.94 mmHg. The t-value was calculated to be 8.2 and the P-value was calculated to be < 0.001 which was statistically significant. This signifies that the systolic blood pressure of the non-survivors was lesser than that of the survivor group.

In the study group, [Table 4] the mean diastolic blood pressure among the survivors was 53.59 + / - 5.61 mmHg. and among the non-survivors it was 46.22 + / - 6.04 mmHg. The t-value was calculated to be 5.2 and the P-value was calculated to be < 0.001 which was statistically significant. This signifies that the diastolic blood pressure of the non-survivors was lesser than that of the survivors.

In the study group, the mean arterial pressure among the survivors was 64.4 + / - 4.4 mmHg whereas, among the non-survivors it was 56.2 + / - 5.4 mmHg which was significantly lower than the survivor group. The t-value was calculated to be 6.8 and the P-value was found to be < 0.001 which was statistically significant. This signifies that the non-survivor group had significantly lower mean arterial pressure compared to the survivor group.

The body temperature of all patients were more than 98 degree F. The mean body temperature of the survivors was 100.84 + / - 0.60 and among the non-survivors was 101.99 + / - 0.89. The t-value was found to be 6.3. The P-value was calculated to be < 0.001 which was statistically significant. This shows that, the body temperature was higher among the non-survivors.

The respiratory rate was more than 16 in all patients. The mean respiratory rate was 27.41 + / - 6.43 among the survivors and 29.39 + / - 6.01 among the non-survivors. The t-value was calculated to be 1.3. The P-value was found to be 0.189 which was statistically insignificant. This shows that the respiratory rate does not affect the prognosis much. However, non-survivors had higher respiratory rate compared to the survivor group.

In the study population all patients had leucocytosis (WBC count > 11,000 / cu.mm). The mean WBC counts among survivors were 177.26 + / - 42.09, and among non-survivors were 234.12 + / - 65.30. The t-value was calculated to be 4.3. The P-value was found to be < 0.001 which was statistically significant. This shows that the non-survivors had increased WBC count compared to the survivors.

In the study population [Table 5], serum LDH level was calculated on day 1 and day 3. The mean serum LDH level on day 1 among the survivors was 1149.88 + / - 206.037, and among non-survivors was 1311.94 + / - 302.66. The t-value was calculated to be 2.6 and the P-value was

calculated to be 0.01 which was statistically significant. This indicates that the non-survivors group had increased levels of serum LDH on day 1 compared to the survivor group. The mean serum LDH level on day 3 among survivors was 1071.35 + / - 198.56 and among the non-survivors was 1545.39 + / - 270.37. The t-value was found to be 8.3 and the P-value was calculated to be < 0.001 which was statistically significant. This shows that the serum LDH level on day 3 was higher in non-survivors compared to the survivor group.

Variables	B	Adjusted Odd's Ratio	95 % CI Lower Limit	95 % CI Upper Limit	P-Value
LDH day 1	.019	1.001	1.000	1.003	.001
LDH day 3	.025	1.025	1.012	1.039	< .001

Table 5. Multivariate Regression of Factors Associated with Outcome

Outcome variable is death compared to survival, a - adjusted for age, sex, HTN, DM, LFT, RFT, urine output, adjusted R^2 = 65.5 %, P-value < 0.05 is significant

The above table shows the multivariate logistic regression model taking outcome variable as non-survival compared against survivors. Adjusting to variables like age, sex, hypertension, diabetes, LFT, RFT, urine output, one unit raise in LDH level on day 1 individually increased the odds of death by 1.001 times, whereas one unit rise in LDH level on day 3 individually increased the odds of death by 1.025 times which is statistically significant (P < .05).

DISCUSSION

This was a descriptive study conducted to analyse the clinical profile of sepsis patients in KIMS, Hubli and to measure the biochemical markers with special references to serum LDH level on day 1 and day 3 to predict the mortality in such patients. 70 patients satisfying the inclusion and the exclusion criteria were enrolled into the study over a period of 1 year.

Mortality

An analysis of a large sample from major United States (US) medical centers reported the incidence of severe sepsis as 3 per 1000 population. Of these patients, 51.1 % were admitted to an intensive care unit. Mortality was 28.6 % overall ranging from 10 % in children to 38.4 % in the elderly.[3] As per another study, sepsis accounted for about 10 % of all ICU admissions.[4]

Gaiski et al.[5] reported an in-hospital mortality rate ranging from 14.7 % to 29.9 % after their multicentre study across Pennsylvania USA. The study noted a wide range in the difference in the incidence of mortality in severe sepsis.

Of the 70 patients in our study, 34 patients (48.6 %) survived and 36 patients (51.2 %) succumbed to sepsis. The mortality rate was 51.2 %. Though the mortality rate was alarmingly high, similar results have been obtained from studies in India. Desai et al.[6] had 48% mortality rate and Todi et al.[7] had 54.1 % mortality rate. A Turkish study had 54.5 % mortality rate.[8]

	Duman A et al.[8] (N = 44)	Desai et al.[6] (N = 50)	Todi et al.[7] (N = 1344)	Present Study (N = 70)
Mortality	54.5 %	48 %	54.1 %	51.2 %

Table 6. Comparison of Mortality Rate in Sepsis among Different Studies

Clinical Predictors of Mortality

All patients had temperature above 96.8º F. Hypothermia was not observed in any patient. The mean temperature among the survivors was 100.84 + / - 0.60 and among the non-survivors it was 101.99 + / - 0.89 (P = < 0.001) which was statistically significant. This showed that the patient with higher temperature had less chances of survival.

The mean pulse rate was much higher among non-survivors (123.92 v / s 107.38, P = < 0.001). There was also minimal difference in the mean respiratory rate. It was higher in non-survivor group (29.39 v / s 27.41, P = 0.189). However, P-value was not significant in this condition, increased respiratory rate was seen among non-survivors compared to the survivors. This shows that tachycardia and tachypnoea could be useful markers to assess the severity of infection and outcome of the patient.

The mean systolic BP, the mean diastolic BP and the mean arterial pressure (in mmHg) was higher in survivors (86.12 vs. 76.33, P-value = < 0.001; 53.59 vs. 46.22, P-value = < 0.001; 64.4 vs. 56.2, P-value = < 0.001 respectively) compared to the non-survivors, which was statistically significant. This showed that the patients with lower blood pressure had increased rates of mortality.

Among the haematological parameters, the mean WBC count was lower (177.26 v / s 234.12, P = < 0.001) among survivors, compared to the non-survivor group which was statistically significant. This showed that the increased total count is an important predictor of mortality. Renal dysfunction is known to change the clinical course of a patient in sepsis. Our study showed statistically significant differences in the serum creatinine among the two groups. The mean serum creatinine was higher in the non-survivor group (7.35 v / s 2.64, P = < 0.001) which was statistically significant. The deteriorating renal parameters could be assessed by clinically assessing and monitoring the urine output. Fall in the urine output can precede biochemical parameters. The difference in the mean urine output was highly significant in survivors (1850 ± 550.0) and non-survivors (780.50 ± 720.60), the P-value being < 0.001, which was statistically significant. Neveu et al.[9] in 1996, after a multicentric study in France concluded that sepsis induced acute renal failure occurred more commonly in older patients (mean age: 62.2 versus 57.9 years, P < 0.02) and had an inclusion a higher acute physiology and chronic health evaluation (APACHE) II (29.6 versus 24.3, P < 0.001), than patients with non-septic acute renal failure. They had a higher need for mechanical ventilation (69.1 % versus 47.3 %, P < 0.001), hospital mortality was higher in patients with septic acute renal failure (74.5 %) than in those whose renal failure did not result from sepsis (45.2 %, P < 0.001).[9]

Oppert et al.[10] in 2008, after their study on 415 patients with septic renal failure concluded that acute renal failure was an independent risk factor for mortality in severe sepsis and septic shock.[10]

As it is clear from the above discussion, the findings from our study concurs with the study by Oppert et al. and Naevu et al. So, we strongly conclude that presence of acute kidney injury (AKI) is a significant risk for mortality in septic shock patients.

Acute hepatic dysfunction occurs in septic shock patients in previous normal liver functions. The mean serum bilirubin among the survivors and non-survivors were 2.62 + / - 1.84 and 4.74 + / - 2.98. The P-value was < 0.001 which was statistically significant. This suggests that occurrence of liver dysfunction in sepsis patients was higher in the non-survivor group.

Gimson et al.[11] in their article stated that the hepatic dysfunction in sepsis is multi-factorial due to combination of hypoxic hepatitis, congestion, cholestasis and toxin mediated liver injury. The outcome of such patients was poor if it was associated with other organ dysfunction like coagulopathy, renal and cardiac dysfunction.[11]

The serum LDH level (in IU / L) was higher among the non-survivor group, compared to the survivor group. The mean serum LDH level on day 1 and day 3 among the survivors were 1149.88 and 1071.35. The mean serum LDH level on day 1 and day 3 among the non-survivors was 1311.94 and 1545.39. In Joe. G. Zein et al.[12] death was associated with a higher LDH level (656 ± 79; P < 0.001 vs. 369 ± 72 U / L). LDH levels that are increasing 48 hours after ICU admission (observed in 37 of 82 patients) were sensitive (0.72) and specific (0.77) in predicting mortality. In a Turkish study, by Duman A et al. the exitus group, who are all non-survivors had higher level of serum LDH compared to the survivor group (373.0 vs. 235.0; P < 0.02).

In a study by Aharon Erez et al.[13] the mean admission and maximal serum LDH in the LDH groups were 1025.3 and 1168.9 IU / L.

CONCLUSIONS

Serum LDH level in sepsis patients on day 3 of admission was significantly higher compared to that of day 1 in the non-survivor group than the survivor group. The survivors had a decline in serum LDH level on day 3 compared to the day 1 level. Serial LDH monitoring daily, will definitely increase the reliability of predicting the outcome of patients admitted with sepsis.

Basic parameters like pulse rate, MAP, total leucocyte count, RFT, LFT and requirement of ventilator support all showed statistically significant correlation with mortality of sepsis. Sepsis is a multiorgan disease with significant mortality. Hence, we need simple and effective parameters which are essential in assessing the prognosis and in guiding the treatment protocols. This study focused on simple clinical and biochemical parameters [special reference to LDH], which helped us in predicting the mortality.

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