The Use of Laboratory and Physiological Parameters in Predicting Mortality in Sepsis Induced Hypotension and Septic Shock Patients attending The Emergency Department

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SUMMARY

Introduction: In this study, we sought to determine whether laboratory and physiological parameters can be useful in predicting mortality in patients with sepsis-induced hypotension and septic shock.

Methodology: This prospective cohort study was carried out in the emergency department at an academic medical center. A total of 51 patients met enrollment criteria during the study period and 41 of them were included in the study. Inclusion criteria were patients 18 years old or older, diagnosed to have either sepsis-induced hypotension or septic shock and investigated sepsis marker (blood lactate and leukocytes) measured. Other physiological variables were also measured in this study. The main outcome measure was 30-day mortality. Kaplan-Meier, Log-rank and Cox's methods were used for statistical analysis using SPSS version 12.0.1.

Results: 61% were diagnosed to have sepsis-induced hypotension and 39% were diagnosed with septic shock. Twenty two (54%) deaths occurred within the 30 day follow up. The overall mean blood lactate level and leukocyte counts were 3.52 mmol/L (SD=2.29) and 11.37 x 109 (SD=6.38) respectively. A Cox Proportional Hazard Analysis revealed an increase in blood lactate levels in the ED was associated with an increased risk of death (B=0.35, HR=1.45, 95% CI 1.22, 1.73, p<0.001). However no significant correlation between the physiological parameters and the 30-day mortality. Patients with septic shock state prior to initial presentation has a lower 30 day survival compared to any other septic conditions.

Conclusion: Our results support blood lactate level as a promising risk stratification tool when compared with leukocytes counts and other physiological parameters. The multivariate analysis showed that for every increment of lactate value of 1 mmol/L, the hazards of dying are expected to increase by 1.5 times (p<0.001).

KEY WORDS:
Sepsis, Septicemic Shock, Serum Lactate, Leucocyte Count

INTRODUCTION

Physicians define sepsis as a combination of infection and physiologic conditions referred to collectively as "systemic inflammatory response syndrome (SIRS)" criteria [1]. These criteria include changes in temperature, heart rate, respiratory function and white blood cell count. The criteria permits rapid and standardize identification method for patients with sepsis. Sepsis is defined by the presence of either septicemia (pathogens or their toxins in the blood); bacteremia (bacteria in the blood); or disseminated fungal infection [2]. More severe forms of sepsis include sepsis-induced hypotension, severe sepsis and septic shock. This severe form of sepsis results from intensely activated immune response that sets off cascade of events. Patients with sepsis-induced hypotension and septic shock need to be recognized and treated early and appropriately to ensure an optimal outcome. There are, however, many potential problems with regards to recognition of sepsis at an early stage. These patients are usually detected through abnormal vital signs. Unfortunately, abnormal vital signs are often late manifestation and cannot identify early tissue hypoperfusion [3]. This results in the delay in identifying early signs of sepsis, and hence delay in initiating care and an overall poorer outcome.

We attempted a study to find out whether initial laboratory tests and physiological parameters measured in the emergency department during the initial assessment would determine and predict mortality later after the admission. We also analyzed the 30-day survival for patients presented to the emergency department with sepsis induced and septic shock patients.

MATERIALS AND METHODS

This was a prospective cohort study over a twelve month period from November 2008 until October 2009 carried out in the emergency department of a teaching hospital which is a regional tertiary care centre with an attendance rate exceeding 60,000 patients per year. The study was approved by the department board review and hospital ethics committee in September 2008 (reference USMKK/PPP/JEPeM [204.4 (2.4)].

The source population was all patients diagnosed with sepsis-induced hypotension and septic shock admitted within the

study period. Routine blood investigation was carried out according to departmental standard operating procedure. The department had instituted a clinical practice protocol whereby a serum lactate level need to be obtained in patients suspected of having sepsis. The serum lactate level was taken once diagnosis of sepsis made prior to aggressive resuscitation. This practice was carried out by emergency physicians, nurses and medical assistants who worked shift hours in the department. The researcher did not interfere in the decision to take blood lactate and leukocyte measurements by the treating doctor. The researcher also did not interfere with the treating doctors' decision on patient disposal. These patients then received the same standard of care as for other patients who were not enrolled in the study. Researcher or research assistant obtained consent once the managing doctor has determined that the patients were in sepsis-induced hypotension or septic shock and both blood lactate and leukocytes were measured.

Blood for lactate were then analyzed using the ABLTM 700 Radiometer™ machine made in Denmark operated by ABLTM 700™ Series Software Version 3.5. Other readings such as serum pH, serum bicarbonate level and base excess were also analyzed using the same instrument and sample. These parameters were analyzed using the iron selective electrode (ISE) principle. The machine was available in the emergency department laboratory. Other parameters such as systolic blood pressure, pulse rate and heart rate were recorded on the PROPAQ™ CS vital signs monitoring instrument. Other relevant data (age, gender, random blood sugar, temperature and others) were also recorded in the data collection form. Patients were divided into sepsis-induced hypotension and septic shock. Patients with sepsis-induced hypotension were identified by the presence of at least 2 or more SIRS criteria with systolic pressure <90mmHg or MAP <70mmHG and responsive to 20ml/kg fluid challenge. On the other hand, patients with presumed sepsis accompanied by at least 2 or more SIRS criteria with systolic pressure <90mmHg or MAP <70mmHg and nonresponsive to 20ml/kg fluid challenge were characterized as septic shock. We had to choose the above mentioned cut off value of the blood pressure in order to allow for a more objective selection of patients. All patients' outcomes were obtained from the medical records thirty days after being resuscitated in ED. Telephone follow up were conducted when patients' outcome in 30 days could not be obtained from medical records or in cases where follow-up appointments were not arranged or patients died at places other than the study center. Patients who were lost during follow-up or withdrew from the study were also noted. We chose 30 days as cut off point for survival or mortality because the principal investigator arbitrarily chose it based on the majority of other survival studies which had chosen 30 days as a cut off point.

Sample size was calculated by using "Power and Sample" (PS) program software copyrighted by William D. Dupont and Walton D. Plummer.
Independent t-tests: α = 0.05 (5% level of significance); β (Power) = 0.80
δ (A difference in population mean) = 2; σ (standard deviation) = 3.6 ; Based on the study by (N . Shapiro 2005) m (ratio between group) = 1
Two mean formula (mortality or survival) for sample calculation was used to obtain the sample calculation, hence sample size (expected mortality or survive) will be minimum of 37 patients.

Categorical data with 2 variables (gender and types of sepsis) were analyzed using Kaplan-Meier survival analysis to estimate survival probability. Log-Rank test was used to describe the significant difference of survival time. Statistical significance was defined as $p < 0.05$. Multivariate Cox proportional hazards regression was then used to assess the relationship described by Simple Cox regression, Kaplan-Meier and Log-Rank test. The flow chart in Figure 1 summarizes the method of this study.

RESULTS
During the period of this study, 51 patients were identified as having sepsis induced hypotension and septic shock. Nine of them had to be excluded due to few reasons (lactate or leukocyte level unavailable, unwilling to consent and age less than 18 years old). Total of 42 patients were enrolled during the study period. These patients were then followed for 30 days following admission. Of these, 1 patient was lost from follow-up.

The patient demography and laboratory parameters are as shown in Table I. During the study, more than half of the patients (61%) were diagnosed with septic shock. The majority of patients were diagnosed with pneumonia followed by urosepsis and cellulitis. Other causes were typhoid, febrile neutropenia secondary to acute lymphocytic leukemia, dengue hemorrhagic fever, pancreatitis and perforated viscus. This study also demonstrated that most deceased patients with sepsis-induced hypotension and septic shock (16 out of 22 deaths) occurred within the first 3 days. Within the deceased (22 patients), 15 patients diagnosed to have septic shock and 7 with sepsis-induced hypotension. By reading across from 0.5 on the vertical scale in the cumulative survival proportion, there was an intersection point in the Kaplan-Meier curve, thus, less than 50% of such patients still survive after 30 days as shown in Figure 2.

Twelve variables were considered for inclusion in the model. These were age, gender, type of septic condition, systolic blood pressure, respiratory rate, pulse rate, lactate, leukocyte, temperature, random blood sugar, pH and base excess. Using a simple univariate Cox Proportional Hazards Model, lactate was found to be significant in predicting mortality (Table II). Results showed no significant predictive correlation between patients' leukocyte counts and mortality (B=-0.44, HR=0.96, 95% CI 0.88, 1.04, p=0.295). A backward selection procedure was used to select the final optimal model. A partial residuals graph was plotted to test for violations of the proportional hazards assumption. Since the difference was approximately zero, the proportional hazards assumption is met. The best predictive factor of death which fit the Multiple Cox Proportional Hazards Model was the serum lactate level (Table III). In other word, lactate level remains independently associated with shorter survival time after adjusting for other factors. For every increment of lactate value of 1 mmol, the hazards of dying are expected to increase by 1.5 times (B=0.35, HR=1.45, 95% CI 1.22, 1.73, p<0.001).

Table I: Values of various parameters

Parameter Minimum value	Maximum value	Mean (SD)
Lactate (mmol/L) 0.9	10.8	3.52 (2.29)
Leukocyte (X 103/L) 0.1	32.5	11.37 (6.38)
Pulse rate (beats/min) 40	201	117.22(27.96)
Respiratory rate (breaths/min) 10	47	26.95 (10.76)
Systolic blood pressure (mmHg) 55	110	83.12 (11.09)
Temperature (oC) 36.0	41.0	37.7 (1.14)
Random blood sugar (mmol/L) 3.9	24.6	15.36 (5.02)
pH 6.98	7.56	7.36 (0.11)
Base excess -16.8	35.5	-1.71 (10.36)

Table II: Prognostic factors of patient with sepsis-induced hypotension and septic shock by Simple Cox proportional hazards model

Variable	Regression coefficient (b)	Wald	Crude Hazards ratio (95% CI)	p-value
Age	0.00	0.02	1.00 (0.98,1.029)	0.882
Systolic blood pressure	0.04	2.53	1.04 (0.99,1.09)	0.111
Pulse rate	0.02	5.80	1.02 (0.99,1.40)	0.061
Respiratory rate	0.20	0.69	1.02 (0.97,1.07)	0.407
Lactate	0.35	16.95	1.42 (1.20,1.67)	<0.001
Leukocyte	-0.04	1.10	0.96 (0.88,1.04)	0.295
Temperature	0.14	0.55	1.15 (0.80,1.65)	0.460
pH	-2.73	2.00	0.65 (0.00,2.93)	0.160
Base excess	-0.04	1.06	0.96 (0.90,1.04)	0.304
Random blood sugar	0.03	0.47	1.03 (0.95,1.12)	0.493

Table III: Prognostic factors of patient with sepsis-induced hypotension and septic shock by Multiple Cox proportional hazards model

Variable	Regression coefficient (b)	Wald	Adjusted Hazards ratio (95% CI)	p-value
Lactate	0.35	17.34	1.45 (1.22,1.73)	<0.001

Backward stepwise cox proportional hazards regression model applied

Log-minus-log plot, hazard function plot and partial residuals were applied to check the model assumption
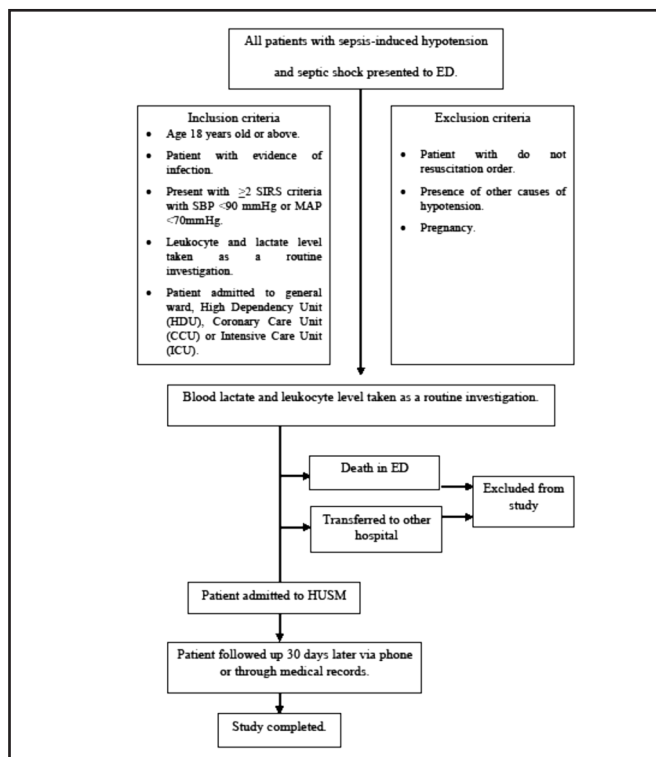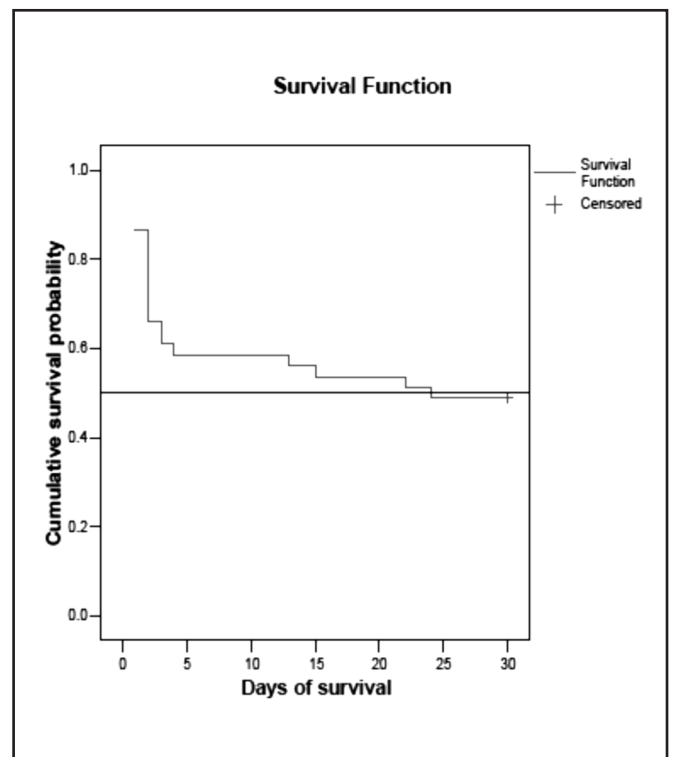

Fig. 1: Flow chart of the study.

Fig. 2: Kaplan-Meier curve showing survival probability following ED admission for all patients in the study.
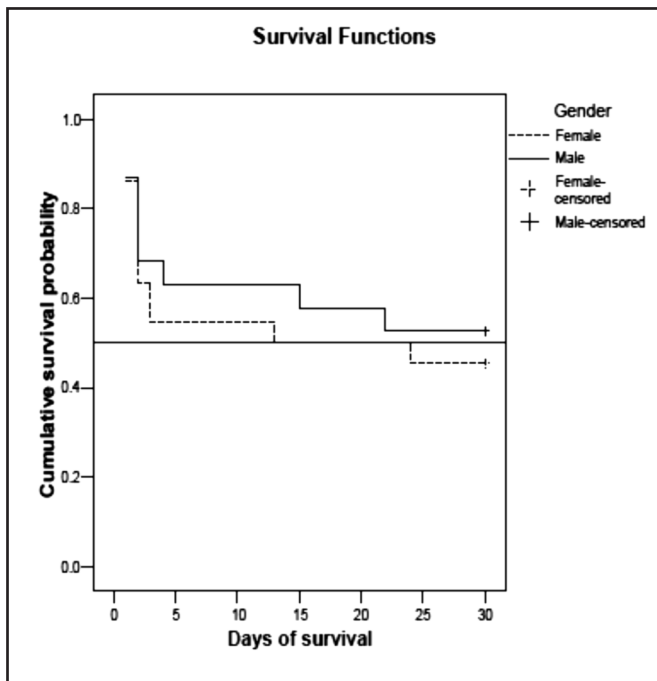
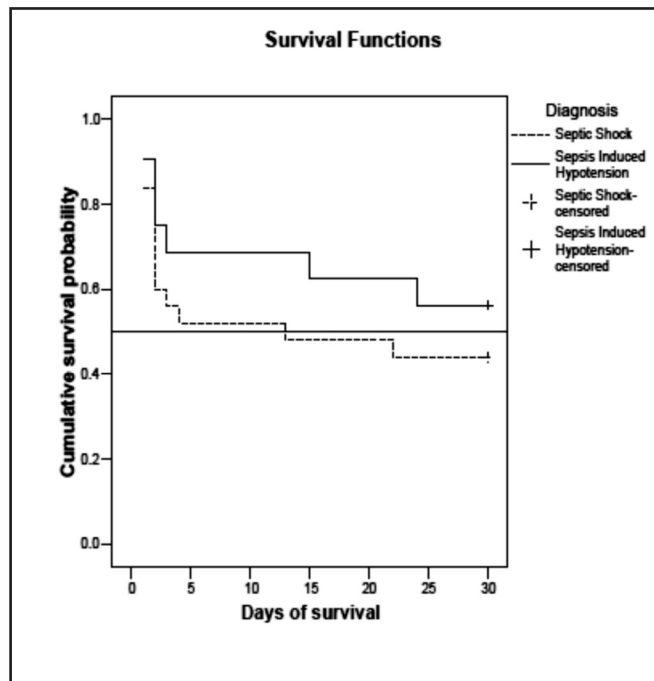**Fig. 3:** Kaplan-Meier curve showing survival probability of patients by gender.

Fig. 4: Kaplan-Meier curve showing survival probability of patients with sepsis induced hypotension and septic shock.

DISCUSSION

Infection related illnesses have been responsible for significant mortality and morbidity world-wide [4,5]. Sepsis is defined by the presence of either septicemia (pathogens or their toxins in the blood); bacteremia (bacteria in the blood); or disseminated fungal or Candida infection. More severe forms of sepsis include sepsis-induced hypotension, severe sepsis and septic shock. This severe form of sepsis results from intensely activated immune response that sets off a cascade of events. In this study, more than half of the patients were diagnosed with septic shock as compared with sepsis-induced hypotension. Most patients with sepsis-induced hypotension and septic shock died by the end of 30 days follow up. Some researcher emphasize that longterm mortality following sepsis is high. Fewer than half of patients who experience severe sepsis were alive at the end of one year (6) and their mortality was also documented as 51.4% at 1 year and 74.2% at 5 years [7]. Others showed that 2 year survival outcome of severe sepsis alone was 44.9% [8,9,10].

It is imminent that sepsis and shock need to be identified early to assist in treatment and prevent subsequent physiological deterioration. Numerous laboratory tests and markers (procalcitonin, C-reactive protein, elevated sedimentation rate, etc.) have been proposed to assist in predicting mortality in patients with infection [11,12,13]. To date, no single or combination of tests or markers exists for a reliable predictor of sepsis. Since early detection of infection and tissues hypoperfusion is subtle, an accurate blood marker is needed. Leukocytes play an essential role in the host immune response to severe infections. For decades, leukocyte counts have been known to increase in an event of infection [14,15]. Although it serves as one of the diagnostic markers for severe sepsis, it is not widely accepted as a predictor of mortality [16]. In our study, simple Cox Regression analysis showed for every increment of 1 (X 10^3/l) in leukocytes count, the hazard of dying is reduced by 0.957 %. These numbers do not show a significant correlation in predicting 30-day mortality in patients with sepsis-induced hypotension and septic shock in our sample population. It is well known that several confounding factors contribute to blood leukocyte counts. Even a non-infective cause such as stress in trauma, burn and inflammation can cause alteration in their values [17,18]. Therefore it is not surprising that our data showed no significant correlation to this parameter in predicting mortality in our patients. This finding also correlates with another study that found leukocyte counts to have low predictive value for mortality [19].

Blood lactate was shown to be significant in predicting 30-day mortality in patients with sepsis-induced hypotension and septic shock. Further analysis in our study using the Multiple Cox Proportional Hazards Model showed similar relationship. In other words, high levels of blood lactate remain independently associated with shorter survival time after adjusting for other covariates. The adjusted multivariate analysis showed that for every increment of lactate value of 1 mmol/L, the hazards of dying are expected to increase by 1.5 times. Husain et al. in a study looking into serum lactate as predictors of mortality and morbidity observed that lactate clearance times were 22 hours, 27 hours and 50 hours respectively [20]. A group of researchers in Washington Hospital Burn Center did an investigation searching a correlation of serial serum lactate and base deficit with mortality in trauma and sepsis. They found that serum lactate was one of the variables that predict mortality. The same study also demonstrated (through logistic regression analysis) that

initial serum lactate value was separately predictive of mortality [21,22]. With regard to a serial lactate reading, Abramson et al. reported that subsequent lactate measurements (8 hours, 16 hours, 24 hours, 36 hours and 48 hours) after resuscitation in ED showed significant difference with outcome (survivors vs. nonsurvivors). His initial lactate values compared to outcome were also in conformation with our result which concluded that initial (admission) lactate readings were significant as predictors of outcome. (23,24)

When comparing between serum lactate and leukocyte counts in predicting mortality in sepsis induced hypotension and septic shock, results showed no significant prognostic correlation between patients' leukocyte counts and mortality and Multiple Cox Proportional Hazards Models showed lactate remains independently associated with shorter survival time after adjusting for other covariates. Therefore it is justified to state that in this study lactate levels were found to be superior in predicting 30-day mortality in patients with sepsis-induced hypotension and septic shock.

More commonly, the treating physicians utilize the physiological parameters to monitor the progress of patients who present with sepsis. Vital signs parameters such as blood pressure, pulse rate, oxygen saturation, respiratory rate and body temperature are commonly used in all emergency departments. Nine physiological variables were considered for inclusion in the model: systolic blood pressure, respiratory rate, pulse rate, lactate, leukocytes, temperature, random blood sugar, pH and base excess. In this study, the differences of systolic blood pressure were not significant in predicting 30 days mortality. This finding might be due to early irregular patterns of blood pressure. These irregularities can occur due to many factors. One of these could be that earlier in the process of shock, neuro-hormonal response would falsely elevate the blood pressure in the face of ongoing cellular ischemia [25,26,27].

Hyperglycemia is a common feature presence in patients with sepsis in particular [28]. Evidence suggests that tight glycemic control will improve the outcome of critically ill patients. Some studies even show that a moderate degree of hyperglycemia seems detrimental for the outcome of critically ill patients, since maintenance of normoglycemia with intensive insulin therapy has shown to improve survival and reduce morbidity in prolonged critically ill patients in both surgical and medical intensive care units [29]. However, despite the initial enthusiasm, recent studies have reported that strict glycemic control with intensive insulin therapy failed to show a beneficial effect on mortality of patients with sepsis-induced hypotension and septic shock [30].

LIMITATION OF STUDY
Few limitations were noted during the conduct of the study which include:

I. Similar survival analysis studies should be done with a long-term follow up to assess both mortality and morbidity of patients with sepsis-induced hypotension and septic shock. In our study, 30-day outcome was chosen merely as a logistic considering the timeline given for the researcher to complete this study.

II. This study merely focused on serum lactate and leukocytes in determining the survival of sepsis patients. However we are aware that there are so many other sepsis markers that can be measured but due to lack of funding, we were unable to perform such laboratory tests.

III. This is just a single center trial that focused sepsis patients in an emergency department of a one tertiary center.

IV. Our study just focused on a 30-day mortality of sepsis patients as an outcome. We did not perform a much longer survival analysis, morbidity and most important cost analysis of therapy and to re-evaluate the continuing use of the approach in a changing therapeutic environment.

V. The investigators managed to obtain 42 samples for the study. The general rule for multivariate analysis, which is not strict, mentions about a minimum sampling of 100 to 200 and 5 subjects per variable. However the investigators are currently placing an effort to continue the study in order to achieve acceptable number of subjects

CONCLUSION
In this study, lactate level was found to be superior to leukocyte levels and physiological parameters in predicting 30-day mortality in patients with sepsis-induced hypotension and septic shock. Serum lactate should remain one of important biomarkers in predicting survival among sepsis patients presenting to the emergency department.

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