Intensive Care Med (2002) 28:1613–1618
DOI 10.1007/s00134-002-1501-5

ORIGINAL

Jakob B. Seidelin
Ole H. Nielsen
Jens Strøm

Soluble L-selectin levels predict survival in sepsis

Received: 30 January 2002
Accepted: 7 August 2002
Published online: 21 September 2002

J.B. Seidelin (✉) · O.H. Nielsen · J. Strøm
Department of Gastroenterology C,
Herlev Hospital,
and Department of Anesthesiology,
Glostrup Hospital,
University of Copenhagen, Denmark
e-mail: jakse@herlevhosp.kbhamt.dk
Fax: +45 44944056

Abstract *Objective:* To evaluate serum soluble L-selectin as a prognostic factor for survival in patients with sepsis. *Design:* A prospective study of mortality in patients with sepsis whose serum levels of sL-selectin were measured on admission to an intensive care unit (ICU) and 4 days later. Follow-up data on mortality were obtained from the Danish Central Office of Civil Registration. *Setting:* A tertiary referral university hospital ICU in Copenhagen. *Patients:* Sixty-three patients meeting the criteria for ystemic inflammatory response syndrome (SIRS) with a suspected or verified infection in one or more major organs, and 14 control subjects. *Measurements and results:* On admission to the ICU the Simplified Acute Physiology Score (SAPS) II was calculated, and relevant microbial cultures were performed. Mortality was registered at various follow-up points: 7 days after admission, at discharge from hospital, and 3 and 12 months after admission. Serum sL-selectin levels were significantly lower in the patients than in the controls. Sepsis nonsurvivors had significantly lower levels than survivors. Efficiency analysis and receiver operation characteristics showed that the ideal cutoff point for sL-selectin as a test for sepsis survival was 470 ng/ml. The accumulated mortality in patients with subnormal sL-selectin levels on admission was significantly increased. No correlation was found between clinical or paraclinical markers, including SAPS II and sL-selectin, and no relationship to the microbial diagnosis was found. *Conclusions:* Serum sL-selectin is a predictor of survival in patients with sepsis. Those admitted with low sL-selectin (<470 ng/ml) are characterized by a high mortality within the subsequent 12-month period.

Keywords CD62 · L-selectin · Mortality · Simplified Acute Physiology Score II · Sepsis · Systemic inflammatory response syndrome

Introduction

Nontraumatised patients with severe life-threatening infectious diseases account for a significant number of those in intensive care units (ICU). Sepsis is marked by a generalized activation of the immune system clinically seen as the systemic inflammatory response syndrome (SIRS), which is characterized by hyperthermia or hypothermia, tachycardia, tachypnea, and abnormal leukocyte counts with an increased percentage of circulating immature leukocytes [1]. A wide range of microbial compounds, such as endotoxin and bacterial DNA motifs, are known to be capable of activating immunocompetent cells via Toll-like receptors, thereby causing secretion of pro-inflammatory cytokines, including interleukin 1, tumor necrosis factor α, interleukin 12, and interferon γ [2]. Systemic administration of these cytokines brings about a SIRS/sepsislike syndrome in animals and hu-

mans [3, 4]. In addition to their systemic effects, pro-inflammatory cytokines and other cytotoxic metabolites produced by extravasated and activated leukocytes may cause organ failure by their cytotoxicity, and thus be responsible for the progression of sepsis from SIRS to the multiple organ dysfunction syndrome (MODS) and eventually death [5, 6].

The extravasation is regulated by cell adhesion molecules localized on the surface of leukocytes and endothelial cells, for instance, selectins, integrins, and members of the immunoglobulin superfamily. These cell adhesion molecules are up-regulated on endothelial cells by stimulation of proinflammatory cytokines and chemokines [7, 8]. Binding of the cell adhesion molecules permits anchorage and rolling of the leukocytes along the endothelial cell lining and subsequent diapedesis into the underlying tissue. Human L-selectin is a cell adhesion molecule of the selectin family, which is expressed on all leukocytes except T helper cells and chemokine-activated cells. L-selectin is involved in the early binding and rolling of leukocytes on endothelial cells [8]. Upon chemokine activation of the leukocytes L-selectin is shed by specific proteolysis, and the extracellular part is released as soluble sL-selectin [8, 9, 10]. The function of L-selectin could therefore be crucial for the accumulation of leukocytes in tissues during sepsis, thus reflecting the level of MODS in these patients [11].

Since MODS is associated with high morbidity and mortality, it was the aim of this study to investigate whether sL-selectin levels reflected the morbidity and mortality of sepsis, and subsequently whether sL-selectin could be a surrogate marker of the severity of the syndrome. In order to test the effectiveness of sL-selectin as an outcome predictor, its predictability of overall survival was compared with the Simplified Acute Physiology Score (SAPS) II [12].

Materials and methods

Study design and patients

A prospective study was designed to evaluate the predictive value of sL-selectin levels on the mortality and morbidity of sepsis, defined as SIRS and a suspected or confirmed underlying infection on admission to the ICU. During the course of 17 months, 63 patients who met the diagnostic criteria for sepsis were enrolled into the study [1]. Patient characteristics are shown in Table 1. Although all patients admitted to the ICU and meeting the above criteria were eligible for enrollment, those with burns, under coronary care, or with trauma were excluded. Patients who developed sepsis during their stay in the ICU, and thus did not have sepsis on admission were also excluded from the study. Blood samples for sL-selectin analysis were taken on the day of admission, and a second blood sample was taken on day 4 in those patients remaining in the ICU (24/63). Routine clinical and paraclinical analyses were performed, including microbial analysis of blood and urine. Depending on the clinical presentation, specimens were taken from abscesses, sputum/tracheal lavage fluid, feces, peritoneal fluid, or cerebrospinal fluid for examination. Endpoints were time from ICU admission to death and length of stay in the ICU. Survival status was followed up at 12 months. Blood samples for sL-selectin analysis were obtained from 14 healthy subjects, 6 of whom had an additional blood sample taken on day 4.

Table 1 Patient characteristics at admission

	Median	25–75 percentiles
Age (years)	64	52–74
Length of stay (days)	4	2–7
Heart rate (bpm)	125	107–135
Systolic blood pressure (mmHg)	90	80–100
Temperature (°C)	38.0	37.4–38.9
FIO_2	0.5	0.4–0.8
PaO_2 (kPa)	10.4	8.3–12.5
Leukocyte count ($\times 10^9$/ml)	12	9–18
Bilirubin level (μmol/l)	12	8–18
Urinary output (l/day)	3.0	2.4–3.9
Serum urea level (mmol/l)	7.0	4.1–12.6
Serum potassium (mmol/l)	4.0	3.5–4.1
Serum sodium (mmol/l)	138	135–143
Serum bicarbonate (mmol/l)	23	21–26
Glasgow Coma Score	13	9–15

The Scientific Ethics Committee of Copenhagen County approved the study. All patients or close relatives (if patients were too ill to give their consent) gave their informed consent before participation and the project fulfilled the Helsinki II declaration with later amendments.

SAPS II score and calculation of mortality probability

SAPS II scores and mortality probability were calculated in accordance with the criteria described elsewhere [12]. The worst values within 24 h of admission to the ICU were recorded.

Serum measurements of sL-selectin

Serum (10 ml) was taken from peripheral blood and centrifuged (10 min, 1600 *g*) at ambient temperature. The samples were stored at –80°C until analysis. A sandwich enzyme-linked immunosorbent assay technique for sL-selectin assessment was used (R&D Systems, Abingdon, UK) [9]. Briefly, 100 μl 1:100 diluted serum was preincubated with a specific monoclonal sL-selectin antibody, followed by addition of polyclonal antibodies conjugated with horseradish peroxidase. Washing and aspiration removed unbound antibodies, and a colomeric reaction proportional to the serum concentration of sL-selectin was performed with a substrate specific for the enzyme (tetramethylbenzidine). Light absorbances were assessed by an automatic enzyme-linked immunosorbent assay reader (Spectra Reader, OEM Version, SLT Labs Instruments, Grödig, Austria) at 450 nm with a correction wavelength of 620 nm. The detection limit was 30 ng/ml in 1:100 dilutions, and the coefficient of variation was less than 0.10.

Epidemiological data

Registration of death and causes of death in the follow-up period were obtained from the Danish Central Office of Civil Registration.

Statistics

Nonparametric statistics was applied. For comparison of groups the Mann-Whitney rank sum test was used. The correlation between sL-selectin levels and SAPS II scores or other physiological measurements was tested by the Spearman rank order correlation coefficient. The effectiveness of sL-selectin as a test of sepsis survival was calculated as the proportion of correctly classified cases at any considered cutoff limit [13, 14]. This was calculated on the assumption that the prior probability of survival was equal to the actual probability of survival found. From this, the sL-selectin level with the maximum effectiveness was found and used as a cutoff point in the subsequent analyses. Receiver operating characteristics (ROC) curves were made to evaluate the informational value of sL-selectin as a diagnostic test of sepsis outcome. The area under the curves and nonparametric standard error were calculated [15]. Efficiency tests and ROC curves were computed by the GraphROC for Windows program [14]. Fisher's exact test was used to compare mortality frequencies in groups of patients with different levels of sL-selectin. Survival analysis was further done by Kaplan-Meier plots of patients with low or high levels of sL-selectin, as estimated from the efficiency analysis. All patients were followed for up to 12 months after closure of inclusion, and were thus only censored at the end of follow-up and record as an event if death occurred within this period. Kaplan-Meier plots were compared by the nonparametric Mantel-Cox log rank test. A significance level of 0.05 (2α) was applied. Confidence intervals were set to 95%.

Results

Patient characteristics and mortality

None of the clinical or physiological parameters predicted mortality or morbidity. Mortality data were collected at various follow-up points after admission to the ICU (Table 2). A total of 33 patients (52%) died within the 12 month follow-up period. The deaths occurred in-hospital in 17 patients (27%), all of whom died from complications to MODS.

Mortality and SAPS II score

The cumulative probability of hospital mortality was 17.3, which was thus a good estimate of the observed hospital mortality of 17 patients. Nonsurvivors had significantly higher mortality probability than had survivors ($p<0.05$). No correlation was found between the length of stay in the ICU and the SAPS II score.

sL-selectin levels and outcome

sL-selectin levels (ng/ml) were significantly lower in the sepsis group than in the control group [median (25–75 percentiles)]: 448 (366–614) (sepsis); 696 (635–828); $p<0.0003$), as seen on Fig. 1. Survivors had significantly higher sL-selectin levels than had nonsurvivors ($p<0.05$). Test efficiency was analyzed at various levels of sL-selectin to determine its ideal cutoff limit as a test of hospital survival from sepsis in order to compare these estimates with the SAPS II scores. The maximum efficiency, with priority given to good sensitivity, was found to be 0.64, with the corresponding cutoff limit of 470 ng/ml [13]. The prior probability of survival was set to be equal to the actual survival rate (73%). Sensitivity at this level of sL-selectin was 57% (43–69%) and specificity 82% (59–95%). The 470 ng/ml cutoff limit gave a positive predictive value of 90% and a negative predictive value of 41%. In subsequent analyses 470 ng/ml was used although similar analyses of ideal cutoff limits at various follow-up time points showed that the limit increased with time, starting at 280 ng/ml on day 3 and ending with 610 ng/ml at the end of follow-up.

ROC curves were plotted from the sensitivity and specificity curves computed during the cutoff limit anal-

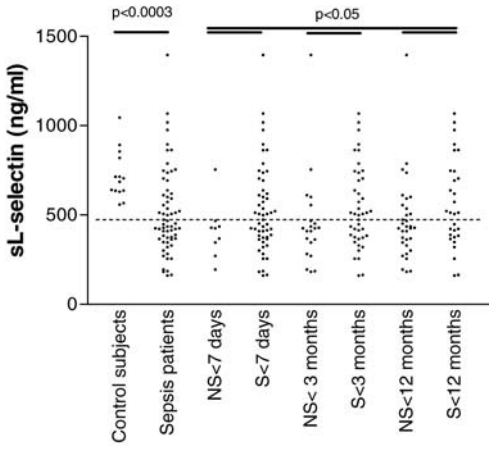

Fig. 1 sL-selectin levels in sepsis patients and control subjects. Sepsis patients had significantly lower levels of sL-selectin than healthy subjects ($p<0.0003$). Survivors (S) had significantly higher sL-selectin levels than sepsis nonsurvivors (*NS*) on admission to the intensive care unit ($p<0.05$). *Dotted line*: Cutoff limit of 470 ng/ml

Table 2 sL-selectin levels and outcome. The cutoff level of sL-selectin on the day of ICU admission was found by test of efficiency as discussed in the text. Individual contingency 2×2 tables were tested by two-tailed Fisher's exact test

	n	<470 ng/ml	>470 ng/ml	*p*
<7 days				<0.04
Dead	9	8	1	
Survived	54	26	28	
<3 months				<0.01
Dead	21	16	5	
Survived	42	18	24	
<12 months				<0.13
Dead	33	21	12	
Survived	30	13	17	

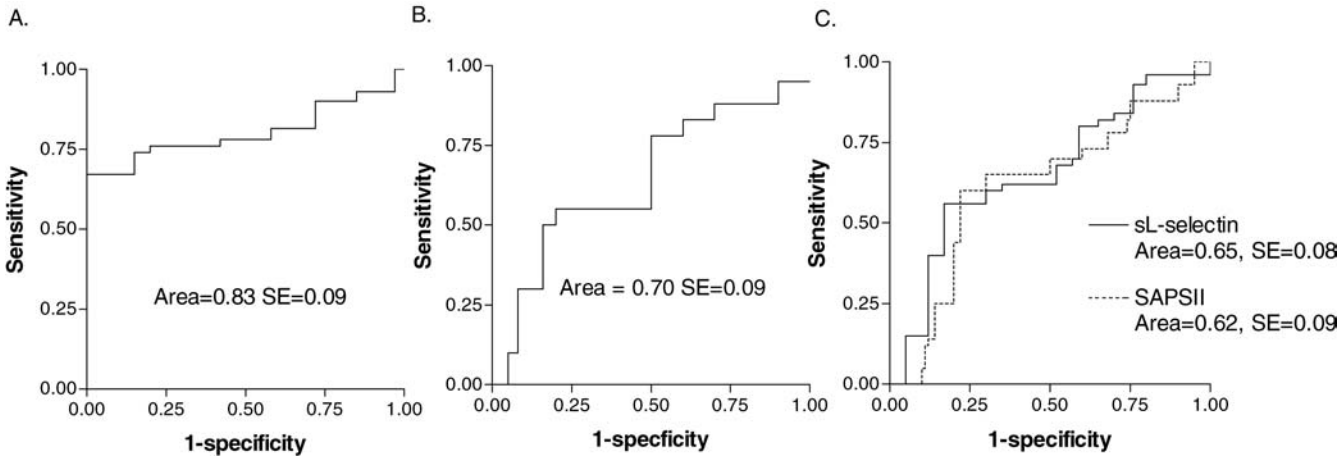

Fig. 2 Receiver operating characteristics curves of sL-selectin as a test for sepsis vs. controls (**A**), as a predictor of survival among sepsis patients 7 days after admission to the intensive care unit (**B**), and sL-selectin and SAPS II probability as a test for outcome at the end of hospital stay (**C**). Areas and standard errors are shown. sL-selectin and SAPS II have similar receiver operating characteristics in this setting ($p>0.05$)

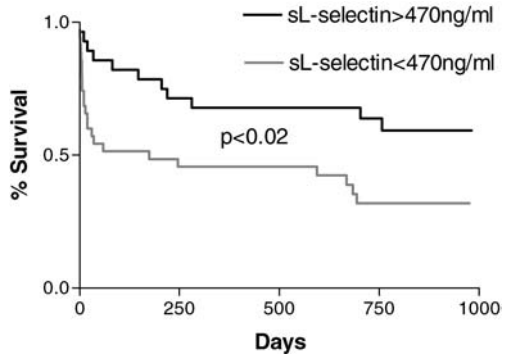

Fig. 3 Kaplan-Meier plot of patients with low vs. high sL-selectin levels. Patients with low sL-selectin had a significantly lower relative survival than patients with high sL-selectin throughout the observation period ($p<0.02$)

ysis (Fig. 2). ROC curves were generally more favorable, i.e. they had larger areas under the curve within the first weeks of sL-selectin measurement. The SAPS II probability of mortality and the sL-selectin levels had similar receiver operating characteristics ($p>0.05$). Patients with high levels of sL-selectin (i.e. over 470 ng/ml) accordingly had higher survival rates, as shown in Table 2 ($p<0.01$ at 3 months' follow-up). Within the first week 8 of 9 dying patients had sL-selectin levels below 470 ng/ml, which is below the levels detected in the control group, whereas 28 of 54 surviving patients had sL-selectin levels above the cutoff limit. Interestingly, if the same limit was used at later follow-ups, the results were similar (Table 2). Thus a high level of sL-selectin on admission further predicted higher survival rates at later hospital admissions within the subsequent 12 months' follow-up period (Table 2 and Fig. 3). There was no correlation between the length of stay in the ICU and the levels of sL-selectin (data not shown).

Generally, there was no major change in the sL-selectin concentrations of samples taken on the day of admission and those taken on day 4 (data not shown), nor was a specific pattern seen in the survivor group compared with nonsurvivors. In a single case, an initially very high sL-selectin value (1396 ng/ml on admission) decreased substantially during the next 4 days (899 ng/ml on day 4 of admission). This patient died 19 days after admission with a verified *Candida albicans* sepsis.

sL-selectin levels and physiological parameters

In order to determine whether sL-selectin levels covary with specific physiological parameters, a correlation analysis was performed with various routine physiological parameters covering inflammatory and metabolic markers, liver, respiratory, cardiac, and renal function markers. No correlation was, however, found, nor was a correlation found between SAPS II scores and sL-selectin levels (data not shown).

sL-selectin levels and infection

Whereas 70% of the enrolled patients had a significant and probable causative microbial diagnosis, the rest of the patients remained clinically septic and were treated as such, but no definite causative agent was identified. Most of the microbial diagnoses were made on multiple samples of tracheal lavage fluid or blood, some from abscesses and urine. None of the patients had positive cultures in cerebrospinal fluids, and none had human immunodeficiency virus infection. Typical pathogens and their frequencies are listed in Table 3. No specific rela-

Table 3 Microbial diagnoses in enrolled patients

Group	Typical species	Typical source	Frequency (%)
Gram-negative bacteria	*Haemophilus influenzae*, *Escherichia coli*, *Branhamella catarrhalis*, *Klebsiella pneumoniae*	Blood cultures, urine cultures, abscesses, tracheal lavage fluid	30
Gram-positive bacteria	*Streptococcus pneumoniae*, *S. aureus*, other *Streptococcus* spp.	Tracheal lavage fluid, blood cultures	19
Mixed species	As above	As above	19
H. Influenzae	Often found together with other spp.	Tracheal lavage fluid	13
Fungi	*Candida* spp.	Tracheal lavage fluid, blood culture	4

tionship was found between dominant species and sL-selectin levels. Pulmonary infections were unrelated to altered levels of sL-selectin.

Discussion

The level of serum sL-selectin is influenced by a variety of factors, for instance, leukocyte counts, leukocyte L-selectin expression, overall activation of leukocytes by proinflammatory cytokines or endotoxins, and binding of sL-selectin to ligands, either on endothelial cells activated by chemokines or on P-selectin on leukocytes [8, 16]. In general, inflammatory diseases are associated with raised sL-selectin levels, which are often correlated to disease activity, as has been shown for ulcerative colitis [17], multiple sclerosis [18], and rheumatoid arthritis [19]. Proinflammatory cytokines and bacterial products are known to stimulate leukocytes, and cause shedding of sL-selectin in animals and humans through activation of a cell surface metalloprotease [9, 10, 20]. The patients in this study had SIRS on entry into the study and were also clinically suspected of an infection in one or more major organs. Seventy percent had positive microbial cultures. The remaining very ill patients had serial blood and other relevant cultures performed, but no causative agent was found. However, it is possible that some of these patients had endotoxemia as the underlying cause of disease [21].

Sepsis patients have been shown to have a highly activated immune system [22] and could thus be expected to have elevated levels of sL-selectin. This has also been reported in patients fulfilling the SIRS criteria [23]. In this material, however, subnormal sL-selectin levels were seen, especially in nonsurvivors. Similar observations have been revealed in patients with severe traumas and multiorgan dysfunction, especially in those developing pulmonary infections [24, 25], and in patients at high risk of developing adult respiratory distress syndrome [26]. High sL-selectin levels could thus have a protective effect in patients with generalized activation of the immune system. The reason for this could be that sL-selectin has an inhibitory effect on the inflammatory response. Thus patients with SIRS and increased sL-selectin levels have a decreased homing of neutrophils in experimental skin blisters and patients with intra-abdominal infections and elevated levels of sL-selectin are at greater risk of developing nosocomial infections in remote sites [27, 28, 29]. Shed sL-selectin conserves its ability to bind to its ligands [10]. High levels of sL-selectin may therefore alter L-selectin-mediated binding of leukocytes to endothelial cells by out-competing binding of leukocyte bound L-selectin to its ligands on endothelial cells.

It has recently been shown that administration of sL-selectin to healthy mice causes a dose-dependent decrease in leukocyte endothelial interaction [11]. Whether diminished delivery of leukocytes to remote sites is beneficial or deleterious to the patient is uncertain. Decreased leukocyte homing to distant sites confers increased susceptibility to secondary infections and raised mortality in septic baboons [29, 30]. Increased and uncontrolled extravasation of leukocytes to remote sites could, on the other hand, bring about severe tissue dysfunction, which could be responsible for the progression of SIRS to sepsis and MODS [6]. This agrees with the present findings, in which the patients who succumbed to the infection died of MODS, whereas those who recovered did not develop fatal MODS. However, it remains to be established whether the recruitment of leukocytes is actually changed in septic sL-selectin low responders.

In the present study high sL-selectin levels predicted survival. The receiver operating characteristics of the probability of survival calculated from the SAPS II score and sL-selectin were similar in this study, and thus sL-selectin may serve as well as SAPS II as a predictor of sepsis hospital outcome. However, the small sample size of this material must be taken into account before applying the results to other groups of patients. In conclusion, sL-selectin is an independent predictor of short-term survival in patients with severe infection admitted for intensive care. sL-selectin seems to be a predictor of survival on an individual basis.

Acknowledgements We thank Ms. Lene Appelt, Ms. Mette Edelved, Ms. Ruth Lock, and Ms. Inge Rigtrup for their skillful technical assistance. This study was supported by a grant from Else and Mogens Wedell-Wedellsborg's Foundation.

References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 101:1644–1655
2. Read RC, Wyllie DH (2001) Toll receptors and sepsis. Curr Opin Crit Care 7:371–375
3. Kimura K, Taguchi T, Urushizaki I, Ohno R, Abe O, Furue H, Hattori T, Ichihashi H, Inoguchi K, Majima H (1987) Phase I study of recombinant human tumor necrosis factor. Cancer Chemother Pharmacol 20:223–229
4. Okusawa S, Gelfand JA, Ikejima T, Connolly RJ, Dinarello CA (1988) Interleukin 1 induces a shock-like state in rabbits. Synergism with tumor necrosis factor and the effect of cyclooxygenase inhibition. J Clin Invest 81:1162–1172
5. Aukrust P, Damas JK, Gullestad L, Froland SS (2001) Chemokines in myocardial failure – pathogenic importance and potential therapeutic targets. Clin Exp Immunol 124:343–345
6. Oberholzer C, Oberholzer A, Clare-Salzler M, Moldawer LL (2001) Apoptosis in sepsis: a new target for therapeutic exploration. FASEB J 15:879–892
7. Springer TA (1994) Traffic signals for lymphocyte recirculation and leukocyte immigration: the multistep paradigm. Cell 76:301–314
8. Tedder TF, Green NE, Miller A (1996) L-selectin function and inflammatory disease. In: Peltz G (ed) Leukocyte recruitment in inflammatory disease. Springer, Berlin Heidelberg New York, pp 165–210
9. Kishimoto TK, Kahn J, Migaki G, Mainolfi E, Shirley F, Ingraham R, Rothlein R (1995) Regulation of L-selectin expression by membrane proximal proteolysis. Agents Actions 47 [Suppl]:121–34
10. Schleiffenbaum BE, Spertini O, Tedder TF (1992) Soluble sL-selectin is present in human plasma at high levels and retains functional activity. J Cell Biol 119:229–238
11. Ferri LE, Swartz D, Christou NV (2001) Soluble L-selectin at levels present in septic patients diminishes leukocyte-endothelial cell interactions in mice in vivo: a mechanism for decreased leukocyte delivery to remote sites in sepsis. Crit Care Med 29:117–122
12. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
13. Sunderman FW Jr (1975) Current concepts of "normal values," "reference values," and "discrimination values" in clinical chemistry. Clin Chem 21:1873–1877
14. Kairisto V, Poola A (1995) Software for illustrative presentation of basic clinical characteristics of laboratory tests – GraphROC for Windows. Scand J Clin Lab Invest 55 [Suppl 222]:43–60
15. Hanley JA, McNeil BJ (1982) The meaning and the use of the area under the receiver operator characteristics (ROC) curve. Radiology 143:29–36
16. Zetterberg E, Richter J (1993) Correlation between serum level of soluble L-selectin and leukocyte count in chronic myeloid and lymphocytic leukaemia and during bone marrow transplantation. Eur J Haematol 51:113–119
17. Seidelin JB, Vainer B, Horn T, Nielsen OH (1998) Circulating L-selectin levels and endothelial CD34 expression in inflammatory bowel disease. Am J Gastroenterol 93:1854–1859
18. Mossner R, Fassbender K, Kuhnen J, Schwartz A, Hennerici M (1996) Circulating L-selectin in multiple sclerosis patients with active, gadolinium-enhancing brain plaques. J Neuroimmunol 65:61–65
19. Littler AJ, Buckley CD, Wordsworth P, Collins I, Martinson J, Simmons DL (1997) A distinct profile of six soluble (ICAM-1, ICAM-3, VCAM-1, E-selectin, L-selectin, and P-selectin) in rheumatoid arthritis. Br J Rheumatol 36:164–169
20. Jilma B, Blann A, Pernerstorfer T, Stohlawetz P, Eichler HG, Vondrovec B, Amiral J, Richter V, agner OF (1999) Regulation of adhesion molecules during human endotoxemia. Am J Respir Crit Care Med 159:857–863
21. Bates DW, Parsonnet J, Ketchum PA, Miller EB, Novitsky TJ, Sands K, Hibberd PL, Graman PS, Lanken PN, Schwartz JS, Kahn K, Snydman DR, Moore R, Black E, Platt R (1998) Limulus amebocyte lysate assay for detection of endotoxin in patients with sepsis syndrome. Clin Infect Dis 27:582–591
22. Oberholzer A, Oberholzer C, Moldawer LL (2001) Sepsis syndromes: understanding the role of innate and acquired immunity. Shock 16:83–96
23. Ahmed NA, Christou NV (1996) Decreased neutrophil L-selectin xpression in patients with systemic inflammatory response syndrome. Clin Invest Med 19:427–434
24. Kerner T, Ahlers O, Spielmann S, Keh D, Buhrer C, Gerlach M, Hofler S, Gerlach H (1999) L-selectin in trauma patients: a marker for organ dysfunction and outcome? Eur J Clin Invest 29:1077–1086
25. Stengel D, Orth M, Tauber R, Sehouli J, Hentsch S, Thielemann HK, Laun R, Ekkernkamp A (2001) Shed L-selectin (sCD62L) load in trauma patients. J Surg Res 99:321–327
26. Donnelly SC, Haslett C, Dransfield I, Robertson CE, Carter DC, Ross JA, Grant IS, Tedder TF (1994) Role of selectins in development of respiratory distress syndrome. Lancet 344:215–219
27. Tellado JM, McGowen GC, Christou NV (1993) Decreased polymorphonuclear leukocyte exudation in critically ill anergic patients associated with increased adhesion receptor expression. Crit Care Med 1993 21:1496–1501
28. Ahmed NA, McGill S, Yee J, Hu F, Michel RP, Christou NV (1999) Mechanisms for the diminished neutrophil exudation to secondary inflammatory sites in infected patients with a systemic inflammatory response (sepsis). Crit Care Med 27:2459–2468
29. Pacelli F, Doglietto GB, Alfieri S, Piccioni E, Sgadari A, Gui D, Crucitti F (1996) Prognosis in intra-abdominal infections. Multivariate analysis on 604 patients. Arch Surg 131:641–645
30. Welty-Wolf KE, Carraway MS, Ghio A, Kantrow SP, Huang YC, Piantadosi CA (2000) Proinflammatory cytokines increase in sepsis after anti-adhesion molecule therapy. Shock 13:404–409