Delta neutrophil index as a predictive marker of early mortality in gram negative bacteremia

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Despite medical advances, sepsis records still high mortality rate. To improve the treatment outcome, early detection of fatal sepsis is essential. And that is the reason why lots of researches about biomarkers of sepsis are in progress. Delta neutrophil index (DN), which corresponds to the fraction of immature granulocytes in circulating blood, could be calculated with a recent model of automatic cell analyzer (ADVIA 2120, Siemens Inc.). This study investigated the significance of DN as a predictive marker of early mortality in patients with gram negative bacteremia.

We retrospectively collected data on adult patients who admitted an urban hospital between November 2010 and March 2011, with gram negative bacteremia. Laboratory and clinical data including DN were collected at the onset of bacteremia, after 2 days (Day 3) and after 6 days (Day 7).

A total 172 patients were included in this analysis. Among the 172 patients, 17 patients died within 10 days. Elevated DN from the onset of bacteremia until day 3 could be a predictive marker of early mortality and 7.6% was the best cut off value of DN to predict early mortality in gram negative bacteremia.

Key words: delta neutrophil index, mortality, gram negative, bacteremia, sepsis

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I. INTRODUCTION

Sepsis is a common reason for hospitalization and admission to intensive care unit (ICU) and a major factor which consume the healthcare resource. The documented incidence of severe sepsis in the European Union has been estimated at 90.4 cases per 100,000 population and the estimated mortality rate from severe sepsis was between 28% and 50%[1]. An international guideline named "Surviving Sepsis Campaign" was published in 2004 and updated in 2008 by collaboration between the European Society of Critical Care Medicine, the International Sepsis Forum and the Society of Critical Care Medicine and the mortality rate was reduced from 37.0% to 30.8% over a recent 2 year period. Despite proper implementation of the evidence based guideline, sepsis still has a high mortality rate[2].

Initial appropriate antibiotic treatment is a major factor that impact on the outcome of sepsis treatment. However, it is very difficult to distinguish sepsis from other systemic inflammatory conditions because there is no rapidly available diagnostic marker with high sensitivity and specificity. For examples, microbiological culture results take more than 72 hours, and mediators such as C-reactive protein (CRP), procalcitonin and various interleukins are elevated both conditions in sepsis and noninfectious inflammatory diseases. For these reasons, there are still a lot of needs to find suitable markers which are specialized to sepsis[3-8].

The presence of immature granulocyte represents increased myeloid cell production, which is accompanied by infection or systemic inflammation[9,10]. And increase in immature granulocytes is a part of the definition of systemic inflammatory response syndrome (SIRS)[11]. But it has not been used commonly in practical field, because it requires intensive labor to count manually. Furthermore counting immature granulocytes manually is not reproducible.

Recently, some researchers have introduced delta neutrophil index (DN), which could be calculated with the results of an automatic counter (ie, ADVIA 120, Siemens, Inc.). The counter analyzes leukocyte differential count by two methods, a cytochemical myeloperoxidase(MPO) reaction and a light beam reflected from the nuclear lobularity of white blood cells(WBCs). The difference between the 2 methods was designated as DN, and the formula is as follows: DN = (the leukocyte subfraction assayed in the MPO channel by cytochemical reaction) – (the leukocyte subfraction counted in the nuclear lobularity channel by the reflected light beam). DN correlates with immature granulocytes calculated by manual counting, and has significant association with DIC scores, positive blood culture rate, and mortality in patients with suspected sepsis[12].

There are some reports on the relationship between infection and immature granulocytes, but the data is limited and lacks clinical confirmation[9,12,13]. In this study, we investigated DN as a predictive marker of mortality in patients with gram negative bacteremia and correlated to clinical factors and laboratory results associated with mortality in sepsis.

II. MATERIALS AND METHODS

1. Patient eligibility criteria

All adult patients (more than 18 years of age) with gram negative bacteremia, who were admitted to Severance hospital, a 2000 bed tertiary hospital in Korea, from November 2010 to March 2011, were screened retrospectively. Positive

blood culture with the same as previous organism recurred within 14 days of the previous event was regarded as the same episode, and the first bacteremic episode was included. Exclusion criteria are as follows.

A. Exclusion criteria

(A) Patients with subsequent episodes of bacteremia with the same organism after 14 days or with other organisms during any time of hospital treatment.

(B) Patients who were bacteremic as an outpatient or who were discharged from hospital before obtaining the results of the culture.

(C) Patients with other conditions which could affect the production of immature granulocytes[9,10]

ⓐ myelodysplastic syndromes, myeloproliferative disease such as chronic myeloid leukemia, myelofibrosis, metastatic bone marrow infiltration by a malignancy, recovery after bone marrow hypoplasia or agranulocytosis

ⓑ severe systemic inflammation such as systemic lupus erythematosus and thrombotic thrombocytopenic purpura

ⓒ acute rejection in organ transplantation

ⓓ trauma, acute bleeding and recent operation

2. Study design

We performed a retrospective case control study. To evaluate the factors associated with early mortality in gram negative bacteremia, mortality was assessed on the 10^{th} day from the onset of bacteremia. And the patients were divided into twon groups: death within 10 days group (Non-survivor) and survival after 10 days from the onset of bacteremia group (Suvivor).

We collected the laboratory data at the onset of bacteremia (day 1), after 2 days (day 3) and after 6 days (day 7) from the onset of bacteremia. The laboratory data included white blood cell (WBC) count, fraction of neutrophil, DN, platelet count, erythrocyte sedimentation rate (ESR) and CRP. DN was calculated with the blood cell analyzer (ADVIA 2120i, Siemens, Inc.) using the

formula which was introduced by former study[12]. The clinical data included Acute Physiology And Chronic Health Evaluation (APACHE) II score to measure the severity[14] and Sequential Organ Failure Assessment (SOFA) score to measure the degree of organ dysfunction were also collected on day 1, day 3 and day 7[15].

Data included age, sex, body mass index (BMI), source of infection, duration of hospital stay before the onset of bacteremia and the history of ICU stay before the onset of bacteremia were collected. And we investigated the Charlson comorbidity index to estimate underlying comorbidity condition[16]. Appropriateness of antibiotic treatment, the presence of multidrug resistant (MDR) bacterial infection and whether the infection was healthcare associated or not were also investigated.

3. Definition

The onset of bacteremia was defined as the first notification of the febrile events. The day when blood cultures were taken was regarded as the onset of bacteremia in cases with no febrile event. In cases with febrile events, blood cultures were taken at the same day of the events.

Septic shock was defined as sepsis with hypotension, despite adequate fluid resuscitation. Hypotension meant a systolic BP of $\leq$ 90mmHg or a reduction of $>$ 40mmHg from baseline in the absence of other causes of low blood pressure[11].

Inappropriate antibiotic therapy was defined as no antibiotic or no susceptibility matching antibiotic administration during 24 hour from the onset of bacteremia[17].

MDR was defined as resistance to one or more of the extended-spectrum cephalosporins, one of two aminoglycosides, and ciprofloxacin[18].

Healthcare associated infection was defined as the systemic condition resulting from an infectious agent or toxin that occurs in a patient in a health care setting, and was not found to be present or incubating at the time of admission[19].

4. Statistical analysis

Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviations (SD), and using two-sample Student's t-test to calculate the P-value in 2 groups. Categorical variables were expressed as absolute numbers and percentages, and studied by Pearson Chi-square test and Fisher's exact test. And we used linear mixed model to calculate the regression slope of the laboratory and clinical data during the 7 days and P-value between the 2 groups.

Multivariate logistic regression models were used with the factors associated with mortality in patients with bacteremia. We made 4 models and area under curve (AUC) of receiver operating characteristic (ROC) curve was calculated for each model to estimate the power of the model predicting early mortality in gram negative bacteremia. And we divided the patients in 4 groups according to the change of DN over time. We calculated the cumulative overall survival rate by Kaplan-Meier estimates, and compared the survival curves of 4 groups with Breslow test.

III. RESULTS

279 patients were screened for eligibility, and 107 patients were excluded due to recovery after agranulocytosis (in 27 cases), hematologic malignancy (in 25 cases), subsequent episode of bacteremia (in 22 cases), recent operation (in 11 cases), acute bleeding (in 10 cases), metastatic bone marrow infiltration (in 10 cases) and being discharged before obtaining the culture results (in 2 cases), leaving 172 patients for analysis. 17 patients expired within 10 days and 155 patients survived after 10 days from the onset of bacteremia. And among the 155 patients, 13 patients expired within 10 to 30 days. Mean survival period in non-survivor group was 3 days and 158 days in survivor group.

The baseline demographic data of patients are shown in Table 1. There were no

differences in age, sex and body mass index (BMI). Comorbidity according to Charlson index was higher in non-survivor than survivor (P-value = 0.018). The proportion of healthcare associated infecton and MDR bacterial infection were higher in non-survivor than survivor (P-value = 0.003 and 0.003, respectively). Admission duration before the onset of bacteremia was longer in non-survivor than survivor (P-value = 0.010). The patients who were treated in the ICU before the onset of bacteremia accounted for 29.4% in non-survivor group and 3.2% in survivor group (P-value = 0.001). The proportion of patients with septic shock was higher in non-survivor than survivor (P-value < 0.001). There was significant difference of source of infection between 2 groups (P-value < 0.001). Urinary tract infection was the most frequent source of infection in survivor (38.1%). In non-survivor, pneumonia was the most frequent source of infection (64.7%).

The predominant organisms were *Escherichia coli* (n=82, 47.7%), *Klebsiella pneumonia* (n=36, 20.9%), *Acinetobacter baumannii* (n=10, 5.8%), *Enterobacter cloacae* (n=8, 4.7%) and *Pseudomonas aeruginosa* (n=8, 4.7%) (Figure 1).

Figure 1. Microbiology of patients with gram negative bacteremia

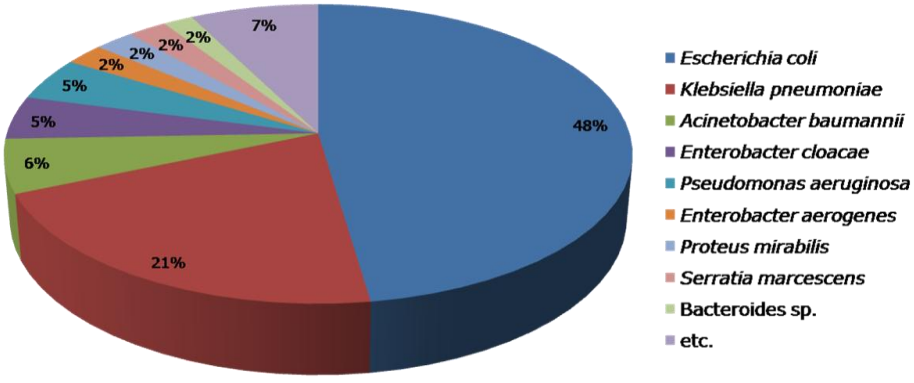


Table 1. Baseline characteristics

	Non-survivor (N=17)	Survivor (N=155)	P-value
Age* (yr)	64±15	65±13	0.804[a]
Male gender	11 (64.7)	66 (42.6)	0.122[c]
BMI* (kg/m^2)	23±4	23±4	0.437[a]
Survival period (days)	3±3	158±90	<0.001[a]
Charlson index*	5±2	3±2	0.005[a]
Health care associated infection	13 (76.5)	59 (38.1)	0.003[b]
MDR bacterial infection	9 (52.9)	28 (18.1)	0.003[c]
Appropriate antibiotics	11 (64.7)	120 (77.4)	0.367[c]
Admission duration before the onset of bacteremia* (days)	13±16	4±12	0.010[a]
History of ICU stay before the onset of bacteremia	5 (29.4)	5 (3.2)	0.001[b]
Septic shock	13 (76.5)	32 (20.6)	< 0.001[b]
Source of infection			
Urinary tract infection	2 (11.8)	59 (38.1)	
Biliary tract infection	2 (11.8)	45 (29.0)	
Intra-abdominal infection	1 (5.9)	32 (20.6)	< 0.001[b]
Pneumonia	11 (64.7)	10 (6.5)	
Etc.	1 (5.9)	9 (5.8)	

BMI, body mass index; MDR, Multidrug resistant; ICU, Intensive care unit

*Numeric variables, presented as mean±standard deviation.

All other data are presented as number (%)

[a]P-value was calculated by two-sample Student's t-test

[b]P-value was calculated by Fisher's exact test

[c]P-value was calculated by Pearson Chi-square test

Laboratory and clinical data on day 1, day 3 and day 7 are listed in Table 2 and Figure 2. There were no differences in WBC count between 2 groups during the 7 days. However, the regression slope of non-survivor (regression slope = 992) was higher than that of survivor (regression slope = -710, P-value = 0.001).

DN was higher in non-survivor on day 1 and day 3 than survivor (P-value = 0.012 and 0.003, respectively). Though DN decreased from 19% to 11% on day 7 in non-survivor group, it was still higher than survivor group without statistical significance. And the regression slope between 2 groups were difference statistically (P-value = 0.024). When divide the patients into death within 10 days group and death within 10 to 30 days group, DN was higher in death within 10 days group during the 7 days (DN in death within 10 to 30 days group; 7±6 on day 1, 3±2 on day 3 and 5±7 on day 7; P-value = 0.009, <0.001 and 0.001, respectively; not in table).

Platelet count tended to decrease during the 7 days in non-survivor and it was lower than survivor group on day 1, day 3 and day 7 (P-value = 0.003, <0.001 and <0.001, respectively).

There was no difference in CRP level between 2 groups during the 7 days. However, it had a tendency to increase in non-survivor and a tendency to decrease in survivor (regression slope = 12.88 and -10.8, respectively, P-value = 0.001).

APACHE II score was higher in non-survivor than survivor during the 7 days (P-value < 0.001). SOFA score was higher in non-survivor group also, during the 7 days (P-value <0.001, <0.001 and 0.011, respectively). And it had a tendency to increase in non-survivor and a tendency to decrease in survivor (regression slope = 0.46 and -0.22, respectively, P-value = 0.001).

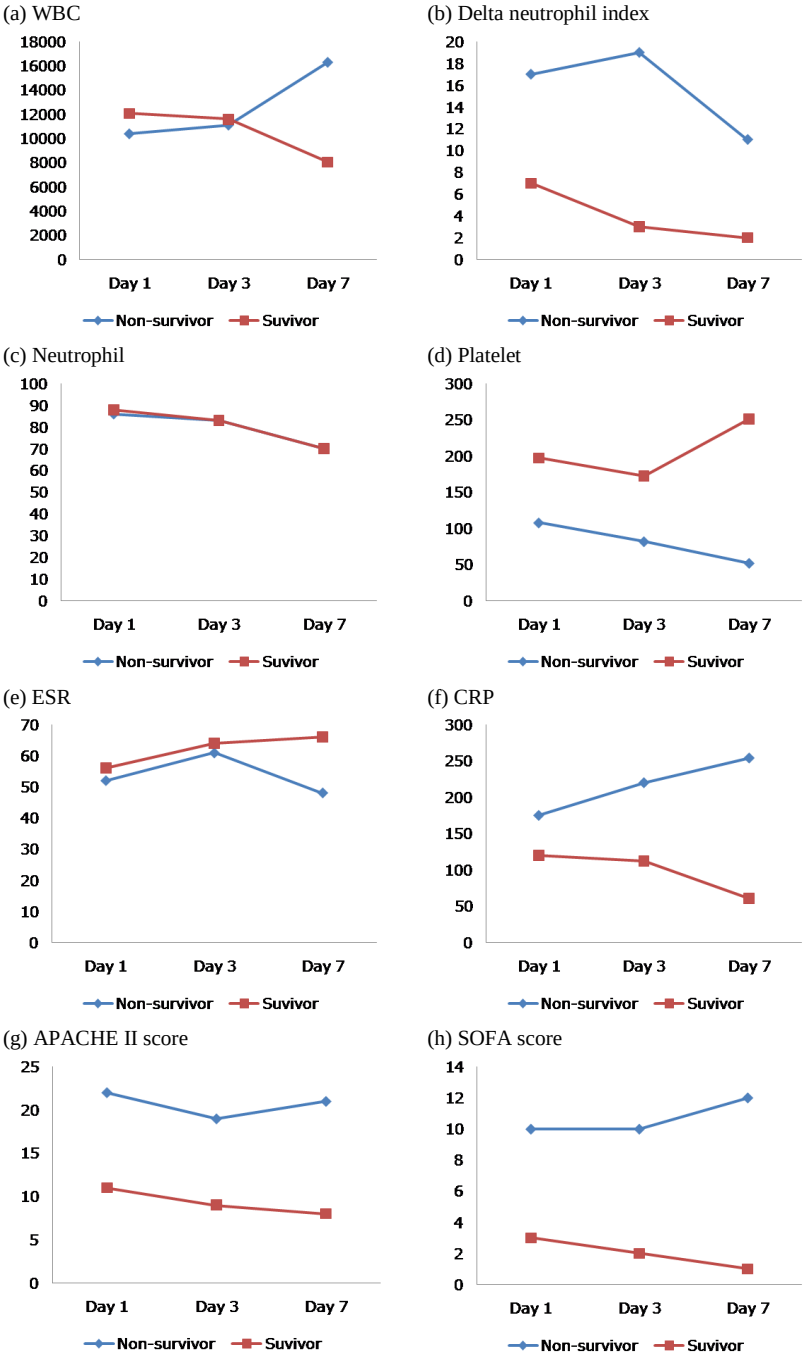
There was no difference of the value and regression slope in proportion of neutrophil and ESR between 2 groups during the 7 days and the regression slopes.

Table 2. Laboratory and clinical data on day 1, day 3 and day 7

		Non-survivor (N=17)	Survivor (N=155)	P-value
WBC (/uL)	Day 1	10411±8416	12073±6776	0.350
	Day 3	11125±8260	11585±7813	0.851
	Day 7	16310±18676	8044±3918	0.379
Regression slope		992	-710	<0.001
DN (%)	Day 1	17±15	7±8	0.012
	Day 3	19±14	3±3	0.003
	Day 7	11±8	2±3	0.070
Regression slope		-1.32	-0.36	0.024
Neutrophil (%)	Day 1	86±14	88±7	0.455
	Day 3	83±27	83±10	0.983
	Day 7	70±33	70±13	0.939
Regression slope		-2.44	-2.85	0.686
Platelet (10^3/uL)	Day 1	108±87	197±117	0.003
	Day 3	82±51	172±111	<0.001
	Day 7	52±38	251±147	<0.001
Regression slope		-10.01	9.44	0.095
ESR (mm/hr)	Day 1	52±43	56±35	0.713
	Day 3	61±30	64±31	0.885
	Day 7	48±42	66±34	0.331
Regression slope		-0.47	1.73	0.526
CRP (mg/L)	Day 1	175±159	120±104	0.181
	Day 3	220±172	112±79	0.188
	Day 7	254±146	61±64	0.077
Regression slope		12.88	-10.8	0.001
APACHE II	Day 1	22±9	11±5	<0.001
	Day 3	19±6	9±5	<0.001
	Day 7	21±7	8±4	<0.001
Regression slope		-0.25	-0.49	0.564
SOFA	Day 1	10±6	3±2	<0.001
	Day 3	10±5	2±2	<0.001
	Day 7	12±6	1±2	0.011
Regression slope		0.46	-0.22	0.001

WBC, white blood cell; DN, delta neutrophil index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment
All data are presented as mean±standard deviation. P-value was calculated by two-sample Student's t-test
P-value of the difference between the regression slope was calculated by linear mixed model

Figure 2. The trend of clinical and laboratory data during 7 days



Factors associated with early mortality (death within 10 days) in univariate analysis were assessed in multivariate logistic regression (Table 3).

The factors included in the analysis were age, gender, BMI, Charlson index, admission duration before the onset of bacteremia, the history of ICU stay before the onset of bacteremia, healthcare associated infection, MDR bacterial infection, SOFA score, platelet count at the onset of bacteremia (Platelet – day 1) and DN at the onset of bacteremia (DN – day 1) in model 1. SOFA score (OR 1.637, 95% CI 1.227-2.184, P-value = 0.001) and DN – day 1 (OR 1.074, 95% CI 1.005-1.148, P-value = 0.036) were independent factors significantly associated with early mortality in gram negative bacteremia. AUC of the ROC curve of this regression model was 0.949 (P-value < 0.001).

In model 2, one more factor was added, which was whether DN was decreased on day 3 or not. And the independent factors associated with early mortality were SOFA score (OR 2.236, 95% CI 1.241-4.029, P-value = 0.007), DN – day 1 (OR 1.163, 95% CI 1.021-1.325, P-value = 0.023) and DN – day 3 ≥ DN – day 1 group (OR 74.241. 95% CI 1.626-3389.881, P-value = 0.027). AUC of this regression model was 0.980 (P-value < 0.001).

In model 3, we substituted the platelet – day 1 for platelet – day 3. The independent factors associated with early mortality were SOFA score (OR 2.161, 95% CI 1.239-3.770, P-value = 0.007), DN – day 1 (OR 1.158, 95% CI 1.016-1.319, P-value = 0.028) and DN – day 3 ≥ DN – day 1 group (OR 58.786, 95% CI 1.297-2664.400, P-value = 0.036). AUC of this regression model was 0.983.

In model 4, we eliminated the DN – day 1 and supplemented the other factor which was whether DN – day 1 is larger than 7.6 or not. The independent factors associated with early mortality were SOFA score (OR 2.244, 95% CI 1.312-3.837, P-value = 0.003), DN – day 1 ≥ 7.6 group (OR 305.181, 95% CI 1.725-53983.520, P-value = 0.030) and DN – day 3 ≥ DN – day 1 group (OR 77.774, 95% CI 1.897-3188.046, P-value = 0.022). AUC of this regression model was 0.987.

Table 3. Multivariate analysis of factors associated with early mortality in gram negative bacteremia by logistic regression

Variables	Model 1 adjusted Odds ratio (95% CI)	Model 2 adjusted Odds ratio (95% CI)	Model 3 adjusted Odds ratio (95% CI)	Model 4 adjusted Odds ratio (95% CI)
Age (yrs)	1.052 (0.979-1.131)	1.087 (0.978-1.209)	1.097(0.983-1.224)	1.096(0.979-1.226)
Gender				
Male	1.000	1.000	1.000	1.000
Female	0.517 (0.100-2.671)	0.184 (0.012-2.747)	0.219 (0.015-3.151)	0.915 (0.061-13.802)
BMI (kg/m^2)	1.015 (0.840-1.228)	0.907(0.645-1.276)	0.895(0.638-1.256)	1.158 (0.851-1.577)
Charlson index	1.393 (0.969-2.004)	1.166(0.675-2.014)	1.239(0.693-2.213)	1.618 (0.813-3.218)
Admission duration before the onset of bacteremia (days)	0.999 (0.936-2.004)	1.008(0.928-1.095)	1.005(0.913-1.106)	0.978 (0.890-1.074)
History of ICU stay before the onset of bacteremia				
Yes	8.185 (0.178-376.135)	9.587 (0.079-1164.857)	9.377 (0.056-1578.762)	77.370 (0.193-31089.796)
No	1.000	1.000	1.000	1.000
Health care assocated infection				
Yes	2.168 (0.370-12.696)	4.358 (0.255-74.628)	3.417 (0.194-60.094)	4.179 (0.275-63.585)
No	1.000	1.000	1.000	1.000
MDR bacterial infection				
Yes	2.300 (0.377-14.015)	3.126 (0.232-42.187)	3.014 (0.218-41.608)	0.535 (0.031-9.280)
No	1.000	1.000	1.000	1.000
SOFA score	1.637 (1.227-2.184)[a]	2.236(1.241-4.029)[c]	2.161(1.239-3.770)[f]	2.244 (1.312-3.837)[i]
Platelet count – day 1 (10^3/uL)	0.997 (0.988-1.005)	1.000 (0.987-1.013)		
Platelet count – day 3 (10^3/uL)			0.994 (0.976-1.011)	0.998 (0.981-1.016)
DN – day 1 (%)	1.074 (1.005-1.148)[b]	1.163 (1.021-1.325)[d]	1.158 (1.016-1.319)[g]	
DN group				
DN 1 < 7.6%				1.000
DN 1 ≥ 7.6%				305.181 (1.725-53983.520)[j]
Trend of DN				
Day 1 > day 3		1.000	1.000	1.000
Day 3 ≥ day 1		74.241 (1.626-3389.881)[e]	58.786 (1.297-2664.400)[h]	77.774 (1.897-3188.046)[k]
AUC	0.949	0.980	0.983	0.987

BMI, body mass index; ICU, intensive care unit; MDR, multi drug resistant; SOFA, sequential organ failure assessment; DN, delta neutrophil index; CI, confidential interval; AUC, area under curve

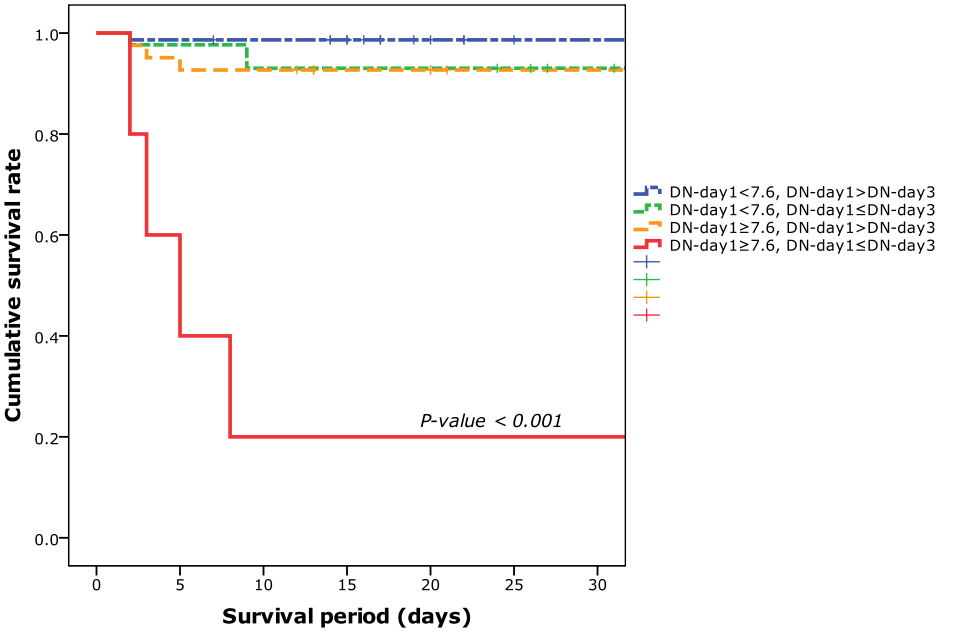
[a]P-value=0.001; [b]P-value=0.036; [c]P-value=0.007; [d]P-value=0.023; [e]P-value=0.027; [f]P-value=0.007; [g]P-value=0.028; [h]P-value=0.036; [i]P-value=0.003; [j]P-value=0.030; [k]P-value=0.022

According to the results of multivariate analysis, we divided the patients in 4 groups to evaluate the correlation between the trend of DN and early mortality in gram negative bacteremia.

The groups are DN – day 1 < 7.6% & DN – day 1 > DN – day 3 group, DN – day 1 < 7.6% & DN – day 1 ≤ DN – day 3 group, DN – day 1 ≥ 7.6% & DN – day 1 > DN – day 3 group and DN – day 1 ≥ 7.6% & DN – day 1 ≤ DN – day 3 group.

The difference of survival rate between 4 groups is shown in figure 3. The DN – day 1 ≥ 7.6% and DN – day 1 ≤ DN – day 3 group showed higher mortality rate than other 3 groups (P-value < 0.001).

Figure 3. Cumulative survival rate according to DN group in patients with gram negative bacteremia



IV. DISCUSSION

Sepsis is a major cause of mortality in world wide. To reduce the mortality from severe sepsis, an evidence based guideline known as “Surviving Sepsis Campaign (SSC)” was developed and the results were published in 2010[2]. Compliance with the guideline was rose from 10.9% to 31.3% and mortality reduced from 37.0% to 30.8% ($p < 0.001$) for 2-year period[2]. However the mortality is still high and relative mortality of sepsis in 1 year for the UK was higher than lung cancer in 2008. To limit to severe sepsis, mortality was higher than that for acute coronary syndrome or stroke[1].

To improve the treatment outcome, early detection and early treatment are essential. Therefore the role of biomarker is important to diagnose sepsis and to guide the treatment, and there are many efforts to find out more appropriate biomarker. The exact role of biomarker as predict the prognosis remains undefined. CRP and procalcitonin have been proposed, however their value has been also challenged[7]. Immature granulocyte has been known as an indicator of infectious condition, but the data are limited and have missed clinical aspect[9,12,13].

In our study, mortality rate was about 10% and it is very low than the mortality rate reported traditionally. We excluded the immune-compromised patients and complicated cases after the surgery or trauma, and it could be the cause of low mortality rate. And we limited the inclusion criteria as gram negative bacteremia, because it was difficult to distinguish true infection from contamination in gram positive bacteremia in this retrospective study.

DN was higher in non-survivor than survivor, and higher in death within 10 days than death within 10-30 days. And this trend was maintained during the 3 days from the onset of bacteremia. However there was no significant difference in DN on day 7 between non-survivor and survivor. It could be a common phenomenon that DN rises early period of sepsis and decreases rapidly regardless of the disease status. To figure out the accurate changes of DN in the course of sepsis, prospective study with larger scaled group and frequent

sampling would be needed. And the effort to reveal the pathophysiology of immature granulocyte in sepsis could be helpful.

In this study, platelet count, APACHE II score and SOFA score were different between survivor and non-survivor. And the pattern of change during the 7 days in WBC count, CRP and SOFA score were different significantly between survivor and non-survivor. Therefore, serial repetitive confirming of these factors would be useful to predict the early mortality in patients with gram negative bacteremia. However, WBC count and CRP had no difference between non-survivor and survivor on separate days. These findings suggest that the trend is more important than the absolute count in WBC count and CRP. Though there was a statistical difference in the trend of delta neutrophil index between non-survivor and survivor, the regression slopes were negative in both group and the pattern of delta neutrophil index in non-survivor group was non linear. Thus, this finding has a little significance clinically. The proportion of neutrophil and ESR did not show any meaningful outcome.

To figure out the most powerful predict marker, we made 4 different models. Platelet count was included in the multivariate model to reflect the univariate analysis. We planned to include SOFA score and APACHE II score in the model as a factor representing the degree of organ failure and the severity of disease respectively. However SOFA score and APACHE II score had strong correlation ($r = 0.695$, P-value < 0.001), and we eliminate APACHE II score from the multivariate model. Delta neutrophil index at the onset of bacteremia was an independent marker to predict early mortality in gram negative bacteremia in multivariate model. We made a model including delta neutrophil index – day 3, but DN – day 3 was not an independent marker to predict early mortality in gram negative bacteremia. However, the trend of delta neutrophil index during 3 days was confirmed as an independent marker to predict early mortality.

The relevant cut-off value of DN – day 1 to predict early mortality in gram negative bacteremia was 7.6% (sensitivity 70.6, specificity 74.2). And DN – day 1 exceeding 7.6% or not is more powerful predict marker than the absolute count of DN – day 1.

The difference of the cumulative survival rate also indicate that delta neutrophil index exceeding 7.6% at the onset of bacteremia and not decreasing during 3 days would be a predictive marker of early mortality in gram negative bacteremia.

The most powerful fact is that delta neutrophil index needs no additional time or cost. The test could be done accompanied with leukocyte differential count simultaneously. We can confirm the result of WBC, fraction of neutrophil and delta neutrophil index at the same time. Existing methods, for example, CRP needs several hours to report the result. And because of the high cost, the test is limited 2 or more times per one week in Korea, generally. The time and cost saving could be a strong benefit of delta neutrophil index. Though this study is limited to a specific analyzer (ADVIA 2120), there are additional reports about some analyzers that could count immature granulocyte[9,10,13]. Therefore immature granulocyte would be used universally in near future.

V. CONCLUSION

Delta neutrophil index is a valuable predictive marker of early mortality in gram negative bacteremia. And high mortality rate is expected in cases that have high delta neutrophil index at the onset of bacteremia and delta neutrophil index does not decrease during the 3 days from the onset of bacteremia.

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ABSTRACT (IN KOREAN)

그람 음성균에 의한 균혈증 환자에서 조기 사망 예측 인자로서의 Delta Neutrophil Index의 유용성

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의학의 발전에도 불구하고 패혈증은 여전히 높은 사망률을 기록하고 있다. 치료 성적의 향상을 위하여 조기 진단 및 치료의 시작이 중요한 것으로 알려져 있으며, 따라서 많은 연구자들이 패혈증의 진단 및 예후 예측과 관련된 인자를 찾기 위한 연구에 매진하고 있다. Delta neutrophil index (DN) 는 최근에 개발된 자동 혈구 분석기 (ADVIA 2120, Siemens.)를 이용하여 계산이 가능한 검사 방법으로, 이전의 연구자들에 의하여 말초 혈액의 미성숙 백혈구와 연관이 있는 것으로 밝혀진 바 있다. 본 연구에서는 그람 음성균에 의한 균혈증 환자에서 DN 과 조기 사망의 관련성을 밝히고자 하였다.

본 연구는 2010년 11월부터 2011년 3월까지 세브란스 병원에 입원한 환자 중 그람 음성균에 의한 균혈증이 확인된 환자를 대상으로 하였으며, 후향적으로 진행되었다. 균혈증 발생 당일 및 2일 뒤, 6일 뒤에 DN를 포함한 균혈증과 관련된 검사 및 임상적 자료를 수집하였다.

총 172명의 환자가 연구에 포함 되었으며 그 중 17명의 환자가 10일 이내에 사망하였다. 로지스틱 회귀분석 및 Kaplan-Meier 분석 결과, 균혈증 발생 당일 DN가 7.6% 이상이며 3일 이후에도 지속적으로 DN가 높은 경우 그람 음성균에 의한 균혈증 환자의 조기 사망을 예측할 수 있을 것으로 판단된다.

핵심되는 말 : Delta neutrophil index, 사망률, 그람 음성균, 균혈증, 패혈증