Delta neutrophil index as a prognostic marker in the pediatric intensive care unit

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Directed by Professor Myung Hyun Sohn

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This certifies that the Master's Thesis of
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<ABSTRACT>

Delta neutrophil index as a prognostic marker in the pediatric intensive care unit

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Purpose: The delta neutrophil index (DNI) is known to be a useful marker for diagnosing and predicting the prognosis of sepsis. The purpose of this study was to investigate the usefulness of DNI as a prognostic marker in patients within the pediatric intensive care unit (PICU), as well as its association with other prognostic factors. *Methods:* The medical records of 149 children admitted to Severance Children's Hospital PICU in Korea were analyzed retrospectively. DNI was measured from day of admission until day seven of the PICU stay. *Results:* The DNI was significantly higher in the non-survivor group (mean ± SD, 7.8 ± 9.7) than the survivor group (2.0 ± 3.1) ($p < 0.0001$). Subjects were categorized into the following three groups based on DNI: low group (<5%), intermediate group (5-10%) and high group (>10%). The percentage of survivors was lowest in the high DNI group ($p < 0.0001$). DNI had a significant correlation with ICU score, white blood cell count, hemoglobin, platelet count, CRP and aPTT. DNI at PICU admission (OR=1.118; 95% CI, 1.016–1.231; p =0.022) was found to be statistically significant for predicting mortality on multivariate logistic regression analysis. The area under the receiver operating characteristic curve of DNI for mortality was 0.673 and the cut-off value was 3.1%. Survival curves showed significantly higher survival rates in the DNI <3.1% group as compared to the ≥3.1% group ($p < 0.0001$). The mean values of DNI during the first seven days of the ICU stay were significantly higher in the non-survivor group ($p < 0.0001$). When analyzed only 109 patients who meet the criteria of sepsis or SIRS, DNI on day 6 only showed a statistically significant difference between sepsis and SIRS group (p =0.006) and DNI on the day of admission was higher in the non-survivor group vs. survivor group (p =0.045). *Conclusions:* The initial DNI level and trend are considered useful indicators for predicting prognosis in PICU patients.

Key words : Delta neutrophil index • Pediatrics • Intensive care unit • Mortality

Delta neutrophil index as a prognostic marker in the pediatric intensive care unit

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I. INTRODUCTION

The outcome of critically ill children recovering from life-threatening diseases in intensive care situations has improved due to advancing diagnostic and therapeutic methods [1]. Clinicians recognized the importance of identifying patients with the highest risk of mortality among those admitted to the pediatric intensive care unit (PICU), and of proper monitoring and appropriate intervention and treatment. They also have recognized the need to observe and treat high-risk patients more aggressively, using appropriate indicators to predict mortality.

Many studies of mortality predictors in PICU patients have been performed, and ICU scoring systems such as the Pediatric Risk of Mortality III (PRISM-III), Pediatric Index of Mortality 2 (PIM2), and Pediatric Logistic Organ Dysfunction (PELOD) have been validated and are being used in clinical practice [1-8]. In addition, studies on the association between mortality and laboratory biomarkers such as C-reactive protein (CRP), platelet count, procalcitonin, transthyretin and eosinophil count in adult ICU patients have also been performed [9-16].

The delta neutrophil index (DNI) is a parameter measured by a specific type of automated blood cell analyzer, the ADVIA2120 Hematology System (Bayer HealthCare, Diagnostics Division, Tarrytown, NY, USA), and is known to reflect circulating immature granulocytes (IG) [17]. The ADVIA2120

Hematology System is a flow cytometry-based hematologic analyzer, which has two independent white blood cell (WBC) analysis methods (peroxidase and lobularity/nuclear density channels) [18-20]. The difference between the leukocyte differentials assayed in the peroxidase channel and those measured in the nuclear lobularity channel is defined as the DNI [17].

In a previous study in adult patients with suspected sepsis, the DNI was helpful in evaluating clinical severity [17]. In another study, the DNI was elevated in patients with severe sepsis/septic shock and overt disseminated intravascular coagulation (DIC), and was proposed as a marker of disease severity in septic patients [21]. IG is also an indicator of left shift occurring due to infection, and is a meaningful discriminator of sepsis presence. It was also reported to be a predictor of infection and positive blood cultures [22,23]. In studies of infants, an increase in IG was associated with positive blood cultures [24] and DNI was significantly associated with the mortality of sepsis [25].

There have been some studies on the associations between DNI/IG and the severity of sepsis, but no research has been conducted on the relationship between these parameters and survival in critically ill children. Therefore, the purpose of this study was to investigate the usefulness of DNI in pediatric patients admitted to the PICU as a predictor of survival and prognosis, in addition to its association with other known prognostic factors.

II. MATERIALS AND METHODS

1. Patients and variables

Children under the age of 16 who were admitted to the PICU at Severance Children's Hospital, Seoul, Korea between January 2010 and August 2011 were included in this study. Patients originated from the emergency room or the general ward or operating room. The medical records of a total of 149 children were analyzed retrospectively. Patients who died or were transferred to

the general ward within 24 h after ICU admission were excluded. Collected data included patient age, sex, ICU admission diagnosis, absence or presence of mechanical ventilation within 24 h after ICU admission, length of ICU stay, steroid treatment (considered positive if given at least once), blood and urine culture results (considered positive if more than 100,000 CFU/ml of a single pathogen was identified), in addition to complete blood cell (CBC) count, coagulation parameters, erythrocyte sedimentation rate (ESR), and CRP at admission. Additionally, PRISM III [2], PIM2 [26] and PELOD scores [27] were calculated to define the severity of a patient's condition within the first 24 h of ICU admission. Survival or death was defined as vital status at ICU discharge. DNI values were recorded on the day of ICU admission and daily during the period of ICU stay, up to seven days. Patients were divided into the following three groups based on initial DNI level: <5% (115 patients), 5–10% (15 patients), and >10% (18 patients). The definitions of sepsis and systemic inflammatory response syndrome (SIRS) were according to the criteria of American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [28]. SIRS was defined as two or more of the following conditions. (1) temperature > 38 ℃ or < 36 ℃, (2) heart rate > 90 beats/min, (3) respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg, and (4) WBC count > 12,000 cells/mm 3 or < 4000 cells/mm^3. Sepsis was defined as these clinical features with evidence or suspicion of infection.

2. DNI measurement

Blood samples for DNI measurement were obtained by venipuncture or indwelling catheter. They were drawn into ethylenediaminetetraacetic acid-treated tubes and analyzed within 24 h of blood sampling. DNI was measured using an ADVIA2120 Hematology System (Bayer HealthCare, Diagnostics Division, Tarrytown, NY, USA) [18-20]. After lysis of red blood cells (RBC), a tungsten-halogen-based optical system of the peroxidase channel

measures the forward light scatter (cell size) and absorbance (stain intensity) in order to count and distinguish lymphocytes, monocytes, neutrophils, and eosinophils based on size and peroxidase content. The laser diode–based optical system of the lobularity/nuclear density channel uses acidic reagent to lyse red blood cells (RBC) and platelets and strips the cytoplasmic membrane from all of the WBCs except basophils. Cells are counted and classified according to size (basophils are recognized as the largest cells since they have a cytoplasmic membrane), lobularity and nuclear density. This channel provides valuable information about the degree of maturity of each WBC's nucleus by measuring its lobularity and density, in addition to reporting the WBC count and basophil count. The DNI can therefore be calculated using the following formula:

DNI = [the neutrophil subfraction and the eosinophil subfraction measured in the myeloperoxidase (MPO) channel by cytochemical MPO reaction] - [the polymorphonuclear neutrophil (PMN) subfraction measured in the nuclear lobularity channel by the reflected light beam] [21].

3. Statistical analysis

Categorical variables are represented as numeric values (percentages) and continuous variables as mean ± standard deviation (SD). Groups were compared by the chi-square test or Fisher's exact test for categorical variables, and the Student's t-test or ANOVA test for continuous variables, as appropriate. The associations between DNI and the ICU scoring system values and other laboratory parameters were examined using Pearson's method.

Logistic regression analysis was used to identify predictive factors for mortality. Each variable was first analyzed using univariate regression analysis, and variables with a *P*-value <0.1 were included in the multivariate logistic regression model after excluding multicollinearity. Odds ratios (OR) and 95% confidence intervals (CI) were obtained for the selected variables, and the results were adjusted for age and gender.

Receiver operating characteristic (ROC) curves and the respective area under the curve (AUC) of DNI at ICU admission for predicting mortality were calculated [29]. The Youden method [30] was used to select an "optimal" DNI level for predicting mortality. Patients were stratified into two groups according to this optimal level for analyses. Kaplan-Meier curves were constructed using these strata and compared using log-rank testing. Time courses of the mean DNI of survivors and non-survivors during the first seven ICU days were analyzed using a linear mixed model. Statistical analyses were performed using Statistical Analysis Software (SAS, version 9.2; SAS Institute; Cary, NC, USA). *P*-values < 0.05 were considered statistically significant for all analyses.

III. RESULTS

1. Analysis of all patients

A. Characteristics of the study population

A total 149 children were analyzed in this study. Among them, 103 patients survived and 46 died (mortality rate of 30.8%). Reasons for admission included respiratory (40.9%), neurological (15.4%), renal (9.4%), postoperative (8.1%), infectious (8.1%), post-resuscitation (5.4%), hepatic (2.7%) and other (10.1%).

Baseline characteristics of the study population, shown in Table 1, were compared between the survivor and non-survivor groups. The proportion of patients receiving mechanical ventilation was higher ($p = 0.014$) and the duration of ICU stay was longer in the non-survivor group ($p = 0.014$). The DNI was significantly higher in the non-survivor group (mean ± SD, 7.8 ± 9.7) than the survivor group (2.0 ± 3.1) ($p < 0.0001$). The CRP was higher ($p = 0.047$) in the non-survivor group. Scores on three different ICU scoring systems (PRISM III, PIM2 and PELOD) that evaluate the severity of the patient's condition were

Table 1 Characteristics of the study population

	Survivor group (*n* = 103)	Non-survivor group (*n* = 46)	*p*-value
Clinical characteristics			
Age, years	4.9 ± 5.4	5.4 ± 5.1	0.556
Male gender	58 (56.3)	31 (67.4)	0.203
Corticosteroids therapy	51 (49.5)	29 (63.0)	0.126
Positive blood culture	5 (4.9)	6 (13.0)	0.095
Positive urine culture	5 (5.2)	6 (14.0)	0.095
Mechanical ventilation	67 (65.0)	39 (84.8)	0.014
Length of ICU stay, days	14.3 ± 18.3	29.3 ± 38.0	0.014
ICU scoring systems			
PRISM III	7.1 ± 5.5	12.0 ± 8.6	0.001
PIM2	9.5 ± 15.6	27.4 ± 29.8	<0.0001
PELOD	7.6 ± 6.9	13.3 ± 10.6	0.001
Hematologic variables			
DNI, %	2.0 ± 3.1	7.8 ± 9.7	<0.0001
WBC, $10^3/\mu L$	14.1 ± 12.0	19.2 ± 31.2	0.289
ANC, /μL	100,12 ± 8,833	10,853 ± 9,926	0.606
Hb, g/dL	10.5 ± 2.1	10.0 ± 2.0	0.151
Platelets, $10^3/\mu L$	317.8 ± 209.1	270.3 ± 273.5	0.248
ESR, mm/hr	22.0 ± 24.2	25.6 ± 31.6	0.610
CRP, mg/L	30.3 ± 56.0	61.2 ± 85.4	0.047
Coagulation parameters			
PT, sec	13.2 ± 4.2	16.7 ± 10.5	0.032
INR	1.1 ± 0.3	1.4 ± 0.8	0.032
aPTT, sec	33.6 ± 12.1	38.9 ± 21.6	0.130
Fibrinogen, mg/dL	292.3 ± 188.2	282.0 ± 176.9	0.827
D-dimer, ng/mL	1,475 ± 3,004	4,900 ± 6,405	0.016
ATIII, %	82.4 ± 27.5	84.7 ± 46.5	0.825

ICU intensive care unit, *PRISM* pediatric risk of mortality, *PIM* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *DNI* delta neutrophil, *WBC* white blood cells, *ANC* absolute neutrophil count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PT* prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *ATIII* antithrombin III

Data are presented as the mean ± standard deviation or number of patients (percentage).

P-values are from the chi-square test or Student's t-test used to compare the difference between the survivor and non-survivor groups.

all significantly higher in the non-survivor group. Prothrombin time (PT) (p = 0.032), international normalized ratio (INR) (p = 0.032) and D-dimer (p =

0.016) were significantly higher in the non-survivor group. No significant differences were observed in age, sex, corticosteroid therapy, positive blood/urine culture rates, length of ICU stay and other laboratory data between the survivor and non-survivor groups.

B. Comparisons of patients according to DNI level at ICU admission and the relationship between DNI and other parameters

Table 2 compares characteristics among the three patient subgroups based on DNI level at ICU admission; DNI <5% (n = 116), DNI 5% to 10% (n = 15) and DNI >10% (n = 18). As DNI increased, the proportion of survivors declined ($p < 0.0001$) and the proportion of patients who received mechanical ventilation increased ($p = 0.013$). The three ICU scores also increased parallel with increasing DNI. Hemoglobin ($p = 0.031$) and platelet ($p = 0.018$) levels were lowest in the high DNI group. CRP ($p = 0.034$), PT ($p = 0.033$) and INR ($p = 0.035$) levels were highest in the high DNI group. However, WBC counts did not differ significantly among the three groups. DNI had a significant correlation with the three ICU scores ($r = 0.305$ for PRISM III, $r = 0.291$ for PIM2 and $r = 0.332$ for PELOD), as well as WBC ($r = 0.234$), hemoglobin($r = –0.187$), platelet count ($r = –0.223$), CRP ($r = 0.244$) and activated partial thromboplastin time (aPTT) ($r = 0.331$). However, DNI was not correlated with absolute neutrophil count (ANC), ESR, or PT.

C. Results of multivariate logistic regression analysis

When analyzed by univariate regression to determine predictive factors of mortality, the variables with a P-value <0.1 were mechanical ventilation (OR=2.994; 95% CI, 1.216–7.368; p =0.017), length of ICU stay (OR=1.020; 95% CI, 1.006–1.034; p =0.004), PRISM III (OR=1.111; 95% CI, 1.050–1.175; p <0.0001), PIM (OR=1.036; 95% CI, 1.017–1.056; p <0.0001), PELOD (OR=1.080; 95% CI, 1.034–1.127; p <0.0001), DNI at ICU admission

Table 2 Comparisons of study patients according to DNI level at ICU admission

	Low DNI (<5) (n = 116)	Intermediate DNI (5-10) (n = 15)	High DNI (>10) (n = 18)	p-value
Clinical characteristics				
Age, years	4.8 ± 5.3	4.0 ± 5.0	7.5 ± 5.2	0.099
Male gender	69 (59.5)	8 (53.3)	12 (66.7)	0.732
Survivors	89 (76.7)	10 (66.7)	4 (22.2)	<0.0001
Mechanical ventilation	76 (65.5)	13 (86.7)	17 (94.4)	0.013
ICU scoring systems				
PRISM III	7.7 ± 6.4	8.9 ± 6.7	14.2 ± 8.3	0.001
PIM2	11.7 ± 17.7	22.0 ± 27.2	30.8 ± 36.2	0.001
PELOD	8.3 ± 7.6	8.1 ± 7.2	17.6 ± 11.5	<0.0001
Hematologic variables				
WBC, 10^3/μL	13.9 ± 10.2	21.2 ± 19.9	22.3 ± 48.6	0.137
ANC, /μL	9,905 ± 8,117	18,948 ± 14,236	7,906 ± 9,080	0.027
Hb, g/dL	10.4 ± 2.0	10.9 ± 2.5	9.2 ± 2.1	0.031
Platelets, 10^3/μL	328.0 ± 238.1	276.4 ± 155.5	165.1 ± 190.0	0.018
ESR, mm/h	23.4 ± 26.7	7.5 ± 5.0	32.8 ± 29.0	0.167
CRP, mg/L	31.6 ± 55.6	62.9 ± 107.2	75.2 ± 86.0	0.034
Coagulation parameters				
PT, sec	13.8 ± 5.2	13.2 ± 2.4	18.4 ± 14.8	0.033
INR	1.1 ± 0.4	1.1 ± 0.2	1.5 ± 1.2	0.035
aPTT, sec	33.8 ± 13.5	38.3 ± 12.6	42.3 ± 27.4	0.097

ICU intensive care unit, *PRISM* pediatric risk of mortality, *PIM* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *WBC* white blood cells, *ANC* absolute neutrophil count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PT* prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time

Data are presented as the mean ± standard deviation or number of patients (percentage).

P-values are from the chi-square test or ANOVA test used to compare the difference between DNI groups.

(OR=1.169; 95% CI, 1.082–1.262; p <0.0001), CRP (OR=1.006; 95% CI, 1.001–1.012; p =0.028), PT (OR=1.094; 95% CI, 1.014–1.181; p =0.021) and INR (OR=2.884; 95% CI, 1.172–7.096; p =0.021). The results of multivariate logistic regression analysis of the variables that were significant on univariate analysis (mechanical ventilation, length of ICU stay, PIM, PELOD, DNI at ICU admission, CRP and PT*)*, adjusting for age and gender, are shown in Table 3. Length of ICU stay (OR=1.027; 95% CI, 1.009–1.045; p =0.003), DNI at ICU

admission (OR=1.118; 95% CI, 1.016–1.231; p =0.022) and PT (OR=1.103; 95% CI, 1.011–1.203; p =0.027) were the variables found to be statistically significant for predicting mortality on multivariate logistic regression analysis.

Table 3 Results of multivariate logistic regression analysis

Factors	OR	95% CI for OR	*P*-value
Mechanical ventilation	1.057	0.254–4.400	0.939
Length of ICU stay	1.027	1.009–1.045	0.003
PIM	1.018	0.992–1.044	0.181
PELOD	1.029	0.956–1.107	0.443
DNI	1.118	1.016 –1.231	0.022
CRP	1.005	0.998–1.012	0.147
PT	1.103	1.011–1.203	0.027

OR odds ratio, *CI* confidence intervals, *ICU* intensive care unit, *PIM* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *DNI* delta neutrophil index, *CRP* C-reactive protein, *PT* prothrombin time

D. ROC curve of DNI, comparison of survival curves according to DNI cut-off level and time courses between survivor and non-survivor groups

Figure 1 shows the ROC curve of DNI for predicting mortality. The AUC was 0.673 (95% confidence interval 0.572–0.775; p = 0.001) and the

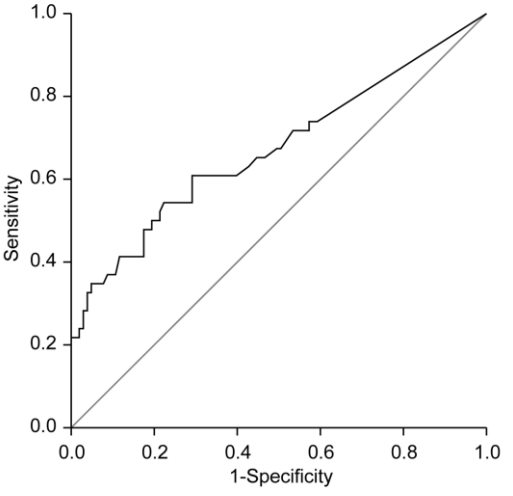

Fig. 1 Receiver operating characteristic (ROC) curve of DNI for survival prediction (AUC 0.673, 95% confidence interval 0.572–0.775).

optimal cut-off value was 3.1%. Sensitivity, specificity, negative predictive value and positive predictive value were 54.3%, 77.6%, 79.2% and 52.0%, respectively. The patients were divided into two groups according to their initial DNI levels; DNI ≥ 3.1% (n = 48) and <3.1% (n = 101). Kaplan-Meier curves demonstrating the probability of survival in each group are shown in Fig. 2. When compared using the log-rank test, patients with lower DNI levels had significantly longer survival time ($p < 0.0001$).

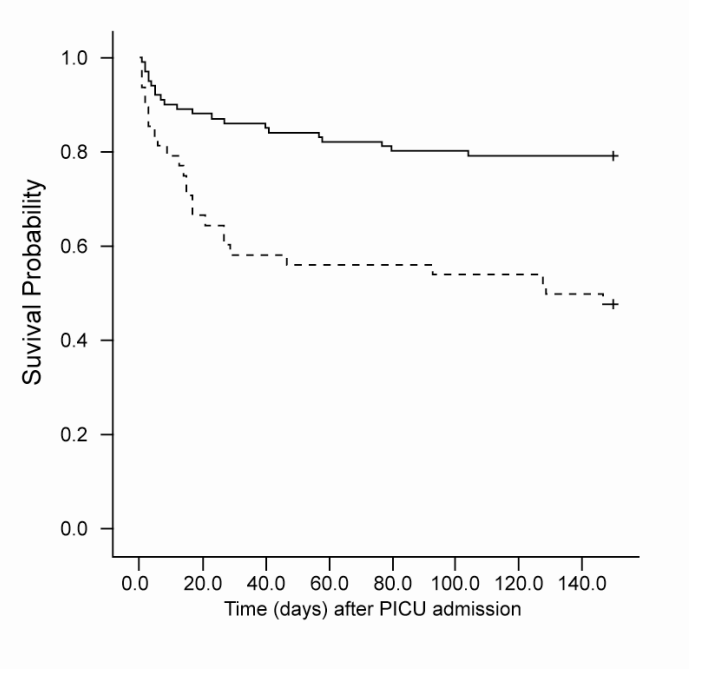

Fig. 2 Survival curves for patients with DNI <3.1% (solid line) and DNI ≥3.1% (dotted line).

Figure 3 shows DNI values (mean and standard error) in the survivor group (circle dotted line) and the non-survivor group (square dotted line) over the first seven ICU days. The mean DNI values during the first seven days of the ICU stay were consistently less than 3.1% in the survivor group and greater than 3.1% in the non-survivor group. They were also significantly higher in the non-survivor group over the entire seven day period ($p < 0.0001$).

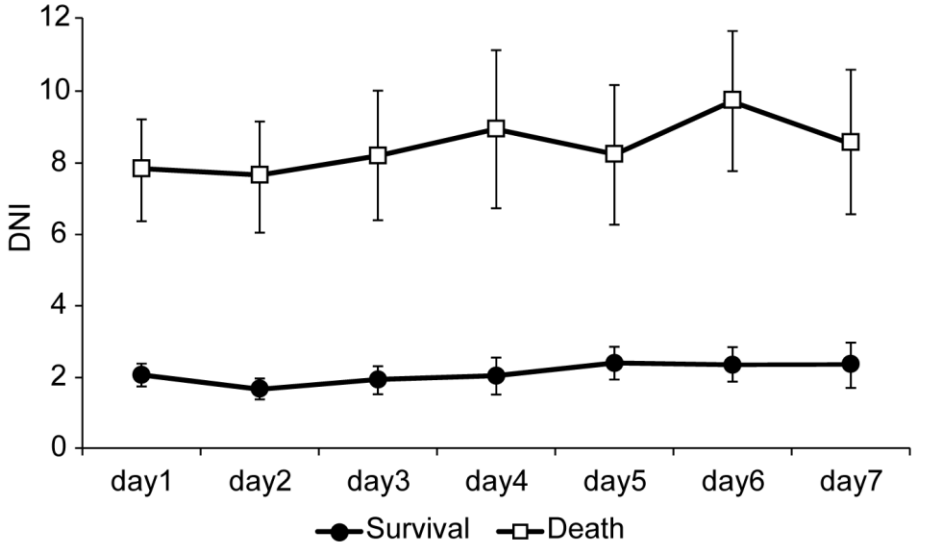

Fig. 3 Delta neutrophil index values (mean and standard error) in survivor (circle dotted line) and non-survivor (square dotted line) groups over the first seven ICU days.

2. Analysis of patients who are categorized as sepsis or SIRS

A. Characteristics of the study population

Table 4 shows characteristics of 109 patients who meet the criteria of sepsis or SIRS. Reasons for admission included respiratory (42.2%), neurological (16.5%), renal (8.3%), postoperative (8.3%), infectious (6.4%), post-resuscitation (6.4%), hepatic (3.7%) and other (8.2%). When compared sepsis group versus SIRS group, higher proportion of patients who received steroid therapy was observed ($p < 0.0001$) in the sepsis group although there were no significant differences in age and sex, and other clinical characteristics. Three ICU scores did not differ significantly between the two groups. DNI of up to 7 days from the day of admission showed generally higher average values in the sepsis group but DNI on day 6 only showed a statistically significant difference ($p = 0.006$). The values of the other laboratory parameters did not

Table 4 Characteristics of the patients with sepsis and SIRS

	Sepsis group (*n* = 75)	SIRS group (*n* = 34)	*p*-value
Clinical characteristics			
Age, years	4.6 ± 4.5	3.8 ± 5.0	0.395
Male gender	42 (56)	18 (52.9)	0.766
Survivors	51 (68)	28 (82.4)	0.120
Corticosteroids therapy	47 (62.7)	8 (23.5)	<0.0001
Positive blood culture	9 (12)	0 (0)	0.055
Positive urine culture	6 (8.7)	2 (5.9)	1.000
Mechanical ventilation	60 (80)	23 (67.6)	0.161
Length of ICU stay, days	24.5 ± 33.0	15.3 ± 19.5	0.136
ICU scoring systems			
PRISM III	7.8 ± 6.6	8.2 ± 7.0	0.731
PIM2	16.6 ± 24.6	15.7 ± 22.5	0.858
PELOD	8.0 ± 7.6	9.5 ± 9.0	0.391
DNI, %			
DNI–day 1	3.7 ± 5.9	2.3 ± 3.1	0.116
DNI–day 2	3.5 ± 6.0	1.9 ± 3.4	0.195
DNI–day 3	3.0 ± 5.0	1.7 ± 4.0	0.240
DNI–day 4	3.3 ± 6.6	1.6 ± 3.1	0.223
DNI–day 5	3.8 ± 7.7	2.4 ± 3.2	0.433
DNI–day 6	4.4 ± 6.7	1.4 ± 2.2	0.006
DNI–day 7	3.4 ± 4.8	4.3 ± 7.9	0.636
Hematologic variables			
WBC, $10^3/\mu L$	15.9 ± 12.7	17.9 ± 9.2	0.416
ANC, /μL	11,767 ± 9,897	12,653 ± 7,753	0.645
Hb, g/dL	10.7 ± 1.9	10.0 ± 2.0	0.104
Platelets, $10^3/\mu L$	326.6 ± 237.6	396.5 ± 223.3	0.150
ESR, mm/hr	23.6 ± 27.8	18.1 ± 17.8	0.406
CRP, mg/L	40.7 ± 66.7	21.4 ± 39.1	0.074
Coagulation parameters			
PT, sec	14.6 ± 8.5	13.9 ± 6.3	0.720
INR	1.2 ± 0.7	1.2 ± 0.5	0.721
aPTT, sec	34.3 ± 12.5	34.3 ± 15.4	0.996
Fibrinogen, mg/dL	263.5 ± 152.3	266.3 ± 167.6	0.961
D-dimer, ng/mL	2,451 ± 4,498	6,779 ± 7,648	0.117
ATIII, %	79.5 ± 36.4	82.6 ± 34.4	0.833

SIRS systemic inflammatory response syndrome *ICU* intensive care unit, *PRISM* pediatric risk of mortality, *PIM* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *DNI* delta neutrophil, *WBC* white blood cells, *ANC* absolute neutrophil count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein,

PT prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *ATIII* antithrombin III

Data are presented as the mean ± standard deviation or number of patients (percentage).

P-values are from the chi-square test or Student's t-test used to compare the difference between the sepsis and SIRS groups.

differ between the sepsis and SIRS groups. When compared the the DNI's time-course of 7 days after PICU admission between sepsis and SIRS groups, significant changes over time in both groups were not observed and the overall differences of values and trends between the two groups were not significant, either (Figure 4).

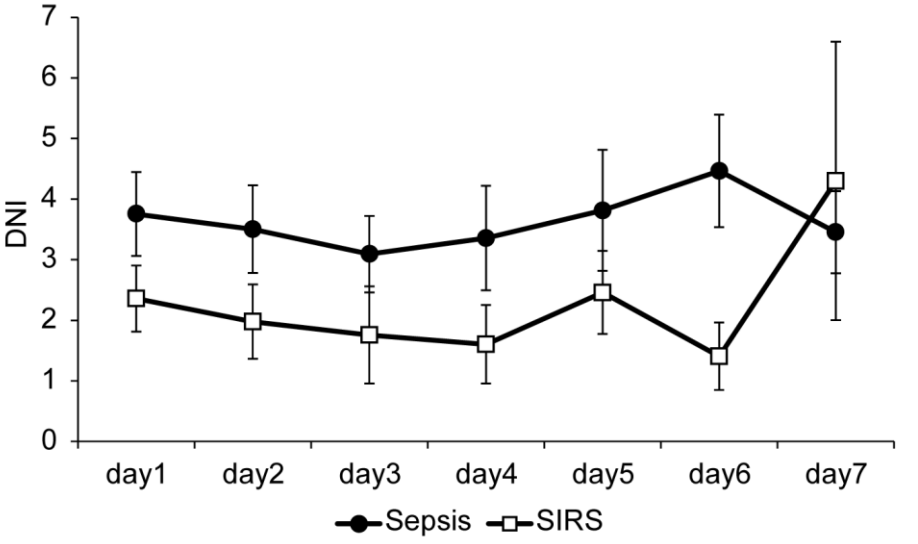

Fig. 4 Delta neutrophil index values (mean and standard error) in sepsis (circle dotted line) and SIRS (square dotted line) groups over the first seven ICU days.

Table 5 shows the results of a comparative analysis of these patients divided into survivor and non-survivor groups. The length of ICU stay was longer (p = 0.003) and PIM2 (p = 0.001) and PELOD (p = 0.017) scores were significantly higher in the non-survivor group. Similarly, the DNI on the day of admission (p = 0.045), PT (p = 0.040), INR (p = 0.039) and D-dimer (p = 0.027)

Table 5 Comparisons between survivors and non-survivors among the patients with sepsis and SIRS

	Survivor group (n = 79)	Non-survivor group (n = 30)	p-value
Clinical characteristics			
Age, years	4.7 ± 5.0	3.5 ± 3.6	0.176
Male gender	41 (51.9)	19 (63.3)	0.284
Corticosteroids therapy	38 (48.1)	17 (56.7)	0.424
Positive blood culture	4 (5.1)	5 (16.7)	0.111
Positive urine culture	4 (5.3)	4 (14.3)	0.208
Mechanical ventilation	57 (72.2)	26 (86.7)	0.112
Length of ICU stay, days	14.5 ± 18.6	40.4 ± 42.9	0.003
ICU scoring systems			
PRISM III	7.1 ± 5.4	10.0 ± 9.0	0.119
PIM2	10.4 ± 17.1	31.9 ± 31.4	0.001
PELOD	7.3 ± 6.9	11.5 ± 10.1	0.017
Hematologic variables			
DNI, %	2.4 ± 3.3	5.6 ± 8.1	0.045
WBC, $10^3/\mu L$	15.7 ± 11.9	18.5 ± 11.2	0.283
ANC, /μL	11,502 ± 9,196	13,470 ± 9,414	0.324
Hb, g/dL	10.6 ± 2.1	10.3 ± 1.7	0.531
Platelets, $10^3/\mu L$	342.3 ± 210.5	364.4 ± 291.9	0.663
ESR, mm/hr	20.7 ± 22.3	24.4 ± 31.2	0.596
CRP, mg/L	29.8 ± 56.4	46.4 ± 67.3	0.211
Coagulation parameters			
PT, sec	12.9 ± 4.4	18.0 ± 12.5	0.040
INR	1.1 ± 0.3	1.5 ± 1.0	0.039
aPTT, sec	32.9 ± 9.6	37.5 ± 19.6	0.230
Fibrinogen, mg/dL	262.1 ± 145.3	267.2 ± 170.8	0.918
D-dimer, ng/mL	1,711 ± 3,538	6,129 ± 7,089	0.027
ATIII, %	79.2 ± 27.7	81.6 ± 45.9	0.848

ICU intensive care unit, *PRISM* pediatric risk of mortality, *PIM* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *DNI* delta neutrophil, *WBC* white blood cells, *ANC* absolute neutrophil count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PT* prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *ATIII* antithrombin III

Data are presented as the mean ± standard deviation or number of patients (percentage).

P-values are from the chi-square test or Student's t-test used to compare the difference between the survivor and non-survivor groups.

levels were higher in the non-survivor group. Likewise, when compared the the

DNI's time-course of 7 days after PICU admission between survivor and non-survivor groups, significant changes over time in both groups and differences of trends between two groups were not observed, but the overall differences of values between the two groups were significant ($p < 0.0001$) (Figure 5).

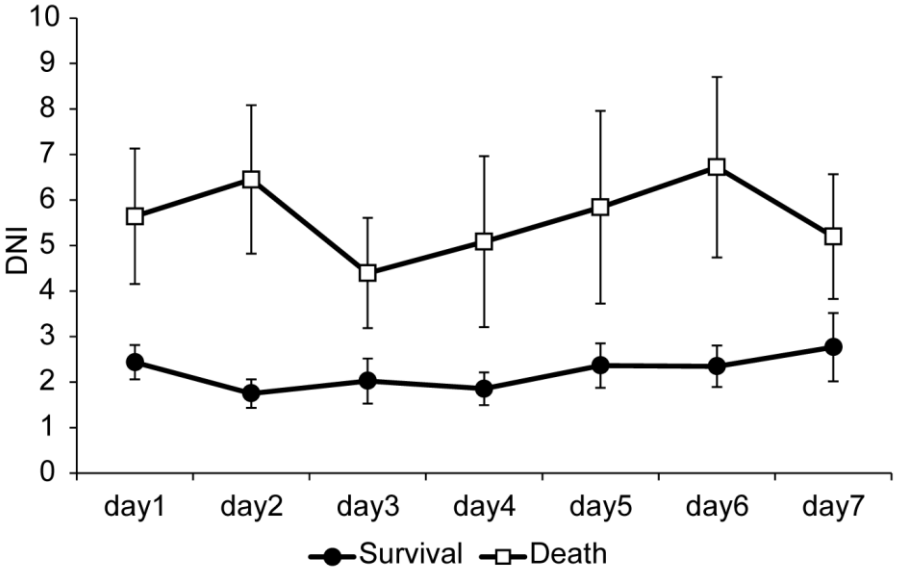

Fig. 5 Delta neutrophil index values (mean and standard error) in survivor (circle dotted line) and non-survivor (square dotted line) groups among patients with sepsis and SIRS over the first seven ICU days.

B. Comparisons of patients according to DNI level at ICU admission and the relationship between DNI and other parameters

Table 6 compares characteristics among the three patient subgroups based on DNI level at ICU admission among patients with sepsis and SIRS; DNI <5% ($n = 87$), DNI 5% to 10% ($n = 12$) and DNI >10% ($n = 10$). The proportion of survivors and patients who received mechanical ventilation were not significantly different between the three subgroups. The PIM2 ($p = 0.007$) and PELOD ($p = 0.011$) scores tended to be higher as DNI values increased. PT ($p = 0.018$) and INR ($p = 0.018$) levels were highest in the high DNI group. DNI

had a significant correlation with the three ICU scores (r = 0.224 for PRISM III, r = 0.296 for PIM2 and r = 0.277 for PELOD), as well as platelet count (r = –0.220), CRP (r = 0.318) and PT (r = 0.220). However, DNI was not correlated with WBC, ANC, hemoglobin, ESR, or aPTT.

Table 6 Comparisons of patients with sepsis and SIRS according to DNI level at ICU admission

	Low DNI (<5) (n = 87)	Intermediate DNI (5-10) (n = 12)	High DNI (>10) (n = 10)	p-value
Clinical characteristics				
Age, years	4.2 ± 4.6	3.8 ± 4.8	6.8 ± 5.0	0.234
Male gender	46 (52.9)	7 (58.3)	7 (70.0)	0.571
Survivors	66 (75.9)	9 (75.0)	4 (40.0)	0.054
Mechanical ventilation	63 (72.4)	10 (83.3)	10 (100)	0.126
ICU scoring systems				
PRISM III	7.3 ± 6.4	8.6 ± 6.3	12.4 ± 8.0	0.073
PIM2	13.0 ± 19.5	24.6 ± 30.0	35.4 ± 39.0	0.007
PELOD	7.6 ± 7.5	9.0 ± 7.5	15.6 ± 10.6	0.011
Hematologic variables				
WBC, 10^3/μL	15.4 ± 9.6	25.9 ± 19.7	15.0 ± 12.9	0.012
ANC, /μL	11,128 ± 8,052	19,544 ± 13,673	11,001 ± 9,775	0.011
Hb, g/dL	10.5 ± 1.8	10.7 ± 2.7	9.9 ± 2.1	0.639
Platelets, 10^3/μL	368.7 ± 241.3	307.2 ± 143.5	221.2 ± 232.0	0.138
ESR, mm/h	21.5 ± 25.0	8.1 ± 5.3	32.8 ± 29.0	0.184
CRP, mg/L	29.0 ± 55.8	40.2 ± 55.4	73.3 ± 84.4	0.083
Coagulation parameters				
PT, sec	13.7 ± 5.7	13.5 ± 2.6	21.1 ± 19.0	0.018
INR	1.1 ± 0.4	1.1 ± 0.2	1.8 ± 1.5	0.018
aPTT, sec	33.3 ± 12.5	37.8 ± 13.1	38.5 ± 19.9	0.353

ICU intensive care unit, *PRISM* pediatric risk of mortality, *PIM* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *WBC* white blood cells, *ANC* absolute neutrophil count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PT* prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time

Data are presented as the mean ± standard deviation or number of patients (percentage).

P-values are from the chi-square test or ANOVA test used to compare the difference between DNI groups.

C. Results of logistic regression analysis

When analyzed by univariate regression to determine predictive factors of mortality in the patients with sepsis and SIRS, the variables with a *p* -value <0.1 were length of ICU stay (OR=1.029; 95% CI, 1.012–1.047; *p* =0.001), PIM (OR=1.037; 95% CI, 1.016–1.057; *p* <0.0001), PELOD (OR=1.062; 95% CI, 1.009–1.118; *p* =0.021), DNI at ICU admission (OR=1.112; 95% CI, 1.023–1.208; *p* =0.012), PT (OR=1.102; 95% CI, 1.014–1.198; *p* =0.022) and INR (OR=3.173; 95% CI, 1.180–8.529; *p* =0.022). The results of multivariate logistic regression analysis of the variables that were significant on univariate analysis (length of ICU stay, PIM, PELOD, DNI at ICU admission and PT*)*, adjusting for age and gender, are shown in Table 7. Length of ICU stay (OR=1.038; 95% CI, 1.016–1.060; *p* =0.001), PIM (OR=1.037; 95% CI, 1.004–1.070; *p* =0.025) and PT (OR=1.108; 95% CI, 1.013–1.211; *p* =0.024) were the variables found to be statistically significant for predicting mortality on multivariate logistic regression analysis.

Table 7 Results of multivariate logistic regression analysis in the patients with sepsis and SIRS

Factors	OR	95% CI for OR	*P*-value
Length of ICU stay	1.038	1.016–1.060	0.001
PIM	1.037	1.004–1.070	0.025
PELOD	0.982	0.893–1.081	0.713
DNI	1.110	0.998 –1.235	0.055
PT	1.108	1.013–1.211	0.024

OR odds ratio, *CI* confidence intervals, *ICU* intensive care unit, *PIM* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *DNI* delta neutrophil index, *PT* prothrombin time

D. Comparisons between groups who were treated and were not with steroids

Table 8 shows comparisons between groups who were treated and were not with steroids among patients with sepsis and SIRS. In the non-survivor group of patients who received steroid therapy, the percentages of sepsis (*p* = 0.048) and positive blood cultures (*p* = 0.007) were higher. DNI values on day 2 (*p* = 0.034) and 7 (*p* = 0.017) were also significantly higher but other

Table 8 Comparisons between groups who were treated and were not treated with steroids among patients with sepsis and SIRS

	Steroid treated group (*n* = 55)			Steroid not-treated group (*n* = 54)		
	Survivor (*n* = 38)	Non-survivor (*n* = 17)	*p*-value	Survivor (*n* = 41)	Non-survivor (*n* = 13)	*p*-value
Clinical characteristics						
Age, years	4.5 ± 4.6	3.3 ± 3.1	0.342	4.9 ± 5.4	3.8 ± 4.2	0.507
Male gender	17 (44.7)	13 (76.5)	0.029	24 (58.5)	6 (46.2)	0.434
Sepsis	30 (78.9)	17 (100)	0.048	21 (51.2)	7 (53.8)	0.869
Positive blood culture	0 (0)	4 (23.5)	0.007	4 (9.8)	1 (7.7)	1.000
Positive urine culture	0 (0)	1 (6.2)	0.314	4 (10)	3 (25)	0.331
Mechanical ventilation	29 (76.3)	14 (82.4)	0.735	28 (68.3)	12 (92.3)	0.146
Length of ICU stay, days	13.8 ± 18.9	43.2 ± 42.3	0.013	15.1 ± 18.6	36..8 ± 45.1	0.116
ICU scoring systems						
PRISM III	6.4 ± 5.2	7.4 ± 10.0	0.690	7.9 ± 5.6	13.1 ± 6.4	0.005
PIM2	7.7 ± 14.3	24.8 ± 33.8	0.060	12.9 ± 19.3	41.3 ± 26.3	<0.0001
PELOD	6.6 ± 5.7	8.8 ± 10.1	0.398	8.0 ± 7.9	14.9 ± 9.2	0.012
DNI, %						
DNI–day 1	2.4 ± 3.9	5.1 ± 6.6	0.134	2.4 ± 2.7	6.2 ± 10.0	0.195
DNI–day 2	1.7 ± 3.1	6.5 ± 8.3	0.034	1.7 ± 2.2	6.2 ± 9.5	0.145
DNI–day 3	2.3 ± 4.9	5.0 ± 6.4	0.122	1.7 ± 2.7	3.3 ± 5.8	0.420
DNI–day 4	2.3 ± 3.6	6.5 ± 11.5	0.170	1.5 ± 1.8	2.6 ± 4.6	0.450
DNI–day 5	2.5 ± 4.5	8.3 ± 13.2	0.110	2.1 ± 2.8	1.8 ± 2.0	0.758
DNI–day 6	2.5 ± 3.5	8.4 ± 10.8	0.065	2.1 ± 2.8	3.6 ± 5.0	0.296
DNI–day 7	1.7 ± 2.4	5.8 ± 5.4	0.017	4.1 ± 6.7	4.0 ± 8.1	0.968
Hematologic variables						
WBC, $10^3/\mu L$	14.4 ± 10.2	18.6 ± 11.7	0.169	17.0 ± 13.2	18.3 ± 10.9	0.751
ANC, $10^3/\mu L$	10.5 ± 8.0	14.3 ± 9.1	0.164	12.3 ± 10.1	12.3 ± 9.9	0.995
Hb, g/dL	11.0 ± 1.9	10.5 ± 1.9	0.642	10.2 ± 2.2	10.0 ± 1.4	0.851
Platelets, $10^3/\mu L$	349 ± 227	398 ± 320	0.764	335 ± 196	320 ± 255	0.819
ESR, mm/hr	17.3 ± 16.4	25.8 ± 17.5	0.255	23.3 ± 25.9	23.5 ± 39.0	0.986
CRP, mg/L	28.4 ± 51.2	33.4 ± 55.5	0.754	31.1 ± 61.4	62.5 ± 78.8	0.149
Coagulation parameters						
PT, sec	12.1 ± 2.9	14.3 ± 5.6	0.143	13.7 ± 5.4	22.8 ± 17.1	0.085
INR	1.0 ± 0.2	1.2 ± 0.4	0.137	1.1 ± 0.4	1.9 ± 1.4	0.085
aPTT, sec	31.5 ± 9.5	31.7 ± 13.5	0.939	34.3 ± 9.7	45.1 ± 24.0	0.140

ICU intensive care unit, *PRISM* pediatric risk of mortality, *PIM* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *DNI* delta neutrophil, *WBC* white blood cells, *ANC* absolute neutrophil count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PT* prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time

Data are presented as the median (interquartile range) or number of patients (percentage).
P-values are from the the chi-square test or Student's t-test used to compare the difference between the survivor and non-survivor groups.

characteristics showed no significant difference. In patients who were not treated with steroids, there were no significant differences except that the 3 ICU scores were significantly higher in non-survivor group compared to survivor group.

IV. DISCUSSION

We retrospectively analyzed 149 children admitted to the PICU during a period of 19 months based on medical records. At ICU admission, the median DNI was significantly higher in the non-survivor group than in the survivor group. As admission DNI level increased, ICU scoring system values and the proportion of patients on mechanical ventilation increased. Additionally, the proportion of survivors decreased. The DNI at PICU admission was also significantly correlated with ICU scores, as well as WBC, hemoglobin, platelet count, CRP and aPTT. DNI at PICU admission was a significant factor to predict mortality on multivariate logistic regression analysis. The optimal cut-off value obtained by ROC curve analysis for predicting survival was 3.1%, and mortality was significantly higher in patients with DNI ≥3.1% than in patients with DNI <3.1%. The DNI remained significantly higher in the non-survivor group from day of admission to day seven compared to the survivor group. When analyzed only 109 patients who meet the criteria of sepsis or SIRS, DNI on day 6 only showed a statistically significant difference between sepsis and SIRS group and DNI on the day of admission was higher in the non-survivor group vs. survivor group. In addition, the overall differences of values between survivor and non-survivor groups were significant during all the observational period but DNI was not found to be predictive factor for mortality

in patients with sepsis and SIRS.

It is very challenging to identify patients with increased mortality risk early among critically ill children admitted to the PICU. The ideal marker of outcome in the PICU should be highly sensitive, specific, easily measurable, fast, inexpensive and correlate well with disease severity and prognosis. The DNI, which corresponds to the IG fraction in circulating blood, can be measured using an ADVIA-series automated cell analyzer. The DNI is an easily measurable parameter that is reported with the CBC count and a WBC differential. Thus, it has the advantage of no additional cost and being readily available. This study was performed to establish the clinical usefulness of the DNI by analyzing whether DNI predicts mortality and correlates with ICU scoring systems that reflect disease severity and other laboratory parameters in PICU patients.

In a previous study conducted in adult subjects by Nahm et al. [17] DNI was helpful in evaluating the clinical severity of patients with suspected sepsis. In another study by Park et al. [21] an increased DNI value at ICU admission was significantly associated with the presence of severe sepsis/septic shock and overt DIC in adult medical ICU patients clinically diagnosed with sepsis at the time of ICU admission. According to recent studies, DNI was an independent predictive factor of the 28-day mortality in adult patients with sepsis [31] and DNI at 72 h after bacteremia was useful in assessing the prognosis of adult patients with bacteremia [32]. In this study, initial DNI was a predictive factor for mortality in heterogeneous patients group but did not show the ability to distinguish between sepsis and SIRS and statistical significance on multiple regression analysis for mortality prediction in patients with sepsis and SIRS. This may be due to differences in the characteristics of the patients in accordance with the definition of sepsis, SIRS and severe sepsis/septic shock. In addition, it is because of the difficulties for an accurate diagnosis of sepsis in patients admitted to the PICU who have recently received antibiotic therapy and show

the progress of a complex disease in most cases.

In this study, the optimal cut-off value of DNI to predict mortality was 3.1%. In comparison, previous studies on circulating IG, which is reflected by DNI, proposed a cut-off value of 3% for determining the presence of sepsis [22,23]. In a report by Park et al., it was suggested that the optimal cut-off value of DNI was 6.5% to predict severe sepsis/septic shock, and if the DNI increased up to 4–6% or more, careful attention was required to detect possible concomitant DIC and/or severe sepsis/septic shock in patients with suspected sepsis [21]. The optimal cut-off value for neonatal sepsis mortality was 12% [25]. One reason that accounts for the difference between the cut-off value in previous studies and ours is that the presence of severe sepsis/septic shock was the primary outcome in a previous study, whereas survival status was our primary outcome. In addition, the newborn study only enrolled neonates with blood culture-proven infection.

In our study, the non-survivor group showed consistently higher DNI values than the survivor group during the first seven days of PICU admission. This trend has been reported in previous studies on other biomarkers. In one study, patients with a consistently high CRP level showed a poor outcome in the ICU [9]. There was also a report that the procalcitonin level of a sepsis group was significantly higher than that of a systemic inflammatory response syndrome (SIRS) group during the observed period [33]. Furthermore, the eosinophil count of the non-survivor group was significantly lower than that of survivors during seven continuous days of ICU admission [15]. The DNI level of the non-survivor group was significantly different from that of the survivor group, as it was consistently >3.1% on serial measurements taken over seven days. This difference was also seen in the patients with sepsis and SIRS. Therefore, aggressive intensive therapy as well as diagnostic decisions are needed in critically ill children when their DNI levels exceed 3% continuously, even if they do not have any symptoms and signs suggesting high-risk conditions such

as sepsis.

IG counts in the peripheral blood which is reflected by DNI may indicate various disease states such as bacterial sepsis, inflammation, trauma, cancer, steroid therapy or myeloproliferative diseases [22,34,35]. Therefore, this study is the first study to demonstrate that the DNI can be used as a prognostic marker in a heterogeneous population of critically ill pediatric patients, unlike previous studies that considered only patients with suspected or diagnosed sepsis and we suggest that DNI be considered a new indicator for predicting mortality in PICU patients. On the other hand, the main limitation of this study is that it was a retrospective review of medical records. Large-scale prospective studies will be helpful in elucidating the role of DNI that reflects disease severity and predicts mortality.

V. CONCLUSION

In conclusion, DNI is associated with disease severity and mortality rate, and day-to-day evaluation of DNI has the potential to serve as a prognostic marker in PICU patients. Accordingly, determining the DNI level at ICU admission and monitoring the subsequent trending of DNI can be helpful in deciding whether additional and more invasive diagnostic procedures are required or whether therapeutic interventions should be modified. Measurement of the DNI in PICU patients may add significant information to that provided by markers and scoring systems already in use for assessing disease severity and predicting mortality.

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< ABSTRACT(IN KOREAN)>

소아 중환자실에서 예후 인자로서의 Delta neutrophil index (DNI)

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목적: 중환자실에 입원한 환아들의 예후를 예측하는 것은 매우 중요하다. 중환자실에 입원하여 치료받는 환아들에 대하여 pediatric index of mortality 2 (PIM2), pediatric risk of mortality III (PRISM-III), pediatric logistic organ dysfunction (PELOD)와 같은 점수가 사망률을 예측하는 도구로 제시되고 있다. Delta neutrophil index (DNI)는 호중구과 호산구, 다형핵백혈구 백분율을 이용하여 만든 지표로서 패혈증의 진단 및 예후를 예측하는데 도움이 된다고 알려져 있다. 본 연구에서는 중환자실에 입원한 소아들의 예후를 예측하는데 있어서 DNI의 유용성을 알아보고자 하였다. 방법: 세브란스병원 소아 중환자실에 입원하여 치료한 총 149명의 환아를 대상으로 후향적으로 의무기록을 조사하여 분석하였다. 대상 환아들의 입실 당시 DNI와 CBC, CRP, PT, aPTT 및 PIM2, PRISM III, PELOD 점수, 그리고 생존 여부를 조사하였다. DNI는 자동혈구분석기인 ADVIA 2120 (Sienmens, Inc.)로 측정하였다. 결과: 총 149건의 중환자실 입원 사례 중 생존은 103건, 사망은 46건이었다. 생존군에서 DNI는 평균 2.0 (표준편차 3.1), 사망군에서는 7.8 (9.7)로 두 군간의 유의한 차이를 보였다 (p<0.0001). DNI가 5미만인 군(n=116), 5이상 10미만인 군(n=15), 그리고 10이상 군(n=18)으로 나누어 세 군간의 차이를 비교하였을 때 DNI 10이상 군에서 생존자의 비율(P<0.0001)이 유의하게 가장 낮게 나타났다. DNI와 다른 예후 예측 인자들과의 상관분석을 했을 때, PIM2, PRIM III, PELOD 점수와 백혈구, 혈색소, 혈소판, CRP 그리고 aPTT와는 유의한 상관관계를 보였다. 중환자실 입실당시 DNI는 다중회귀 분석에서 생존여부에 대하여 유의한 예측인자로 나타났으며 receiver operating characteristic (ROC) 곡선을 이용하였을 때 area under the curve (AUC)가 0.673 이었으며 절단값은 3.1%였다. 생존곡선상 DNI가 3.1%미만인 군에서 생존율이 더 유의하게 높았으며 (P<0.0001) ICU 입실 후 7일간 사망군에서 지속적으로 높은 값을 보였다 (P<0.0001). 패혈증과 전신성 염증 반응 증후군(systemic inflammartory response syndrome :SIRS)에 해당되는 109명의 환자들만을 대상으로 분석하였을 때 6일째 DNI 값만이 유의한 차이를 보였고 (p=0.006) 사망군에서 입실시 DNI값이 더 높았다(p=0.045). 결론: 소아 중환자실에서 입실 당시 DNI와 이후 변화는 환자의 생존 예후 예측에 유용한 지표로 생각된다.

핵심되는 말 : Delta neutrophil index • Pediatrics • Intensive care unit • Mortality