소아의 전신성염증반응증후군에서 백혈구와 혈소판 지표들의 예후 유용성

소아진단검사의학과
손 병 희

평가 목적

1. 소아의 전신성염증반응증후군과 패혈증 여부에 따른 백혈구와 혈소판 지표들의 변화 양상
2. 백혈구와 혈소판 지표들의 예후인자로서 유용성

전신성염증반응증후군 (systemic inflammatory response syndrome, SIRS)

감염, 외상, 화상, 혹은 급성 췌염 등 생체에 대한 여러 침습에 의해 발생한 전신성인 염증반응

단구(單球), 대식세포를 중심으로 한 면역담당세포 또는 염증세포에서 생산한 염증성 시토카인이 염증국소에서 혈중에 방출하여 고시토카인 혈증을 나타낸다.

체온, 맥박, 호흡수 및 백혈구수의 4항목 2항목이상의 이상소견이 있는 경우

1. 소아 SIRS 기준

1. 체온 : >38.5℃ or <36 ℃
2. 맥박 : >2SD above normal for age
3. 호흡수 : >2SD above normal for age
4. 백혈구수 : (↑ ↓) or >10% immature neutrophils

4항목 2항목이상의 이상소견이 있는 경우

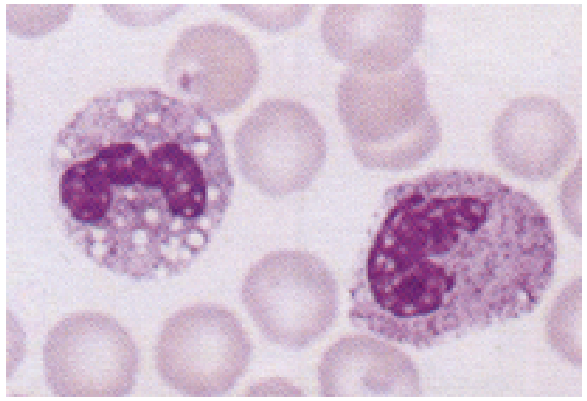
2. 소아 sepsis 기준 : SIRS에서 감염증이 확인된 경우

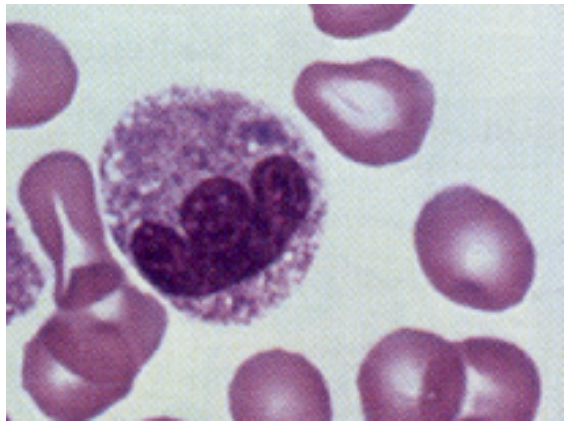
3. 예후 지표 : 입원 4주 이내 사망한 경우

SIRS에서 백혈구 활성화

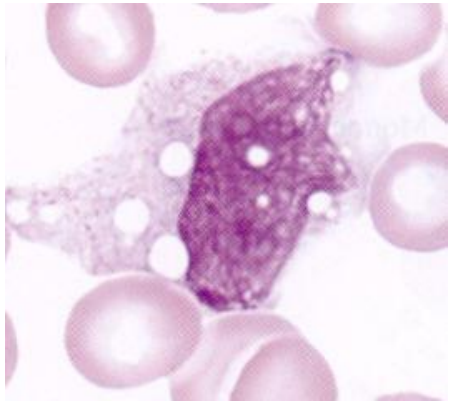
SIRS에서 염증성 싸이토카인 (IL-1, IL-6, TNF-alpha) 분비 증가

1. 호중구 활성 : toxic changes (granules, vacuoles, Döhle bodies)
   Left-shift (metamyleocyte, myelocyte, promyelocyte)





2. 단구 활성 : cytoplasmic vacuoles & granules, 위족



백혈구 형태 변이를 나타내는 CBC 지표

- Coulter LH 750 : 8000개 이상 백혈구 부피를 direct current impedance로 측정함

(1) Neutrophil volume distribution width (NDW)

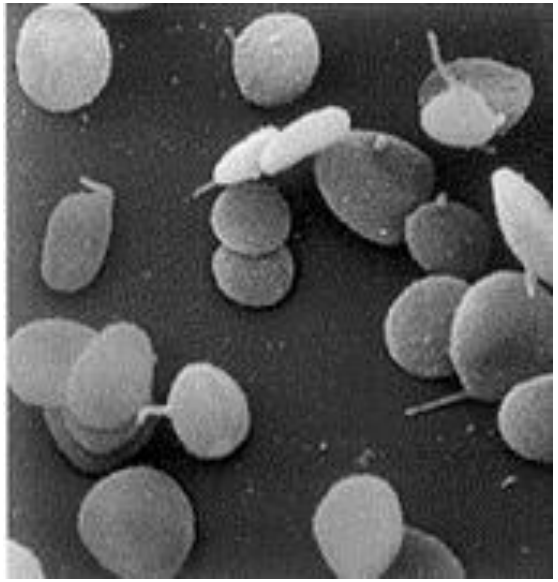
호중구 부피의 표준편차

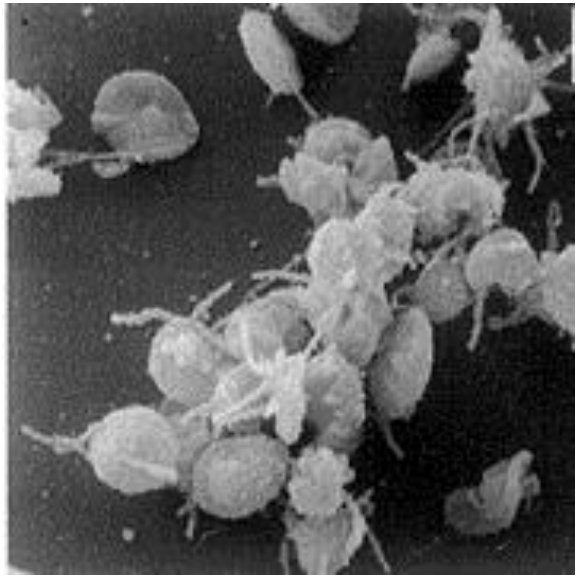
(2) Monocyte volume distribution width (MDW)

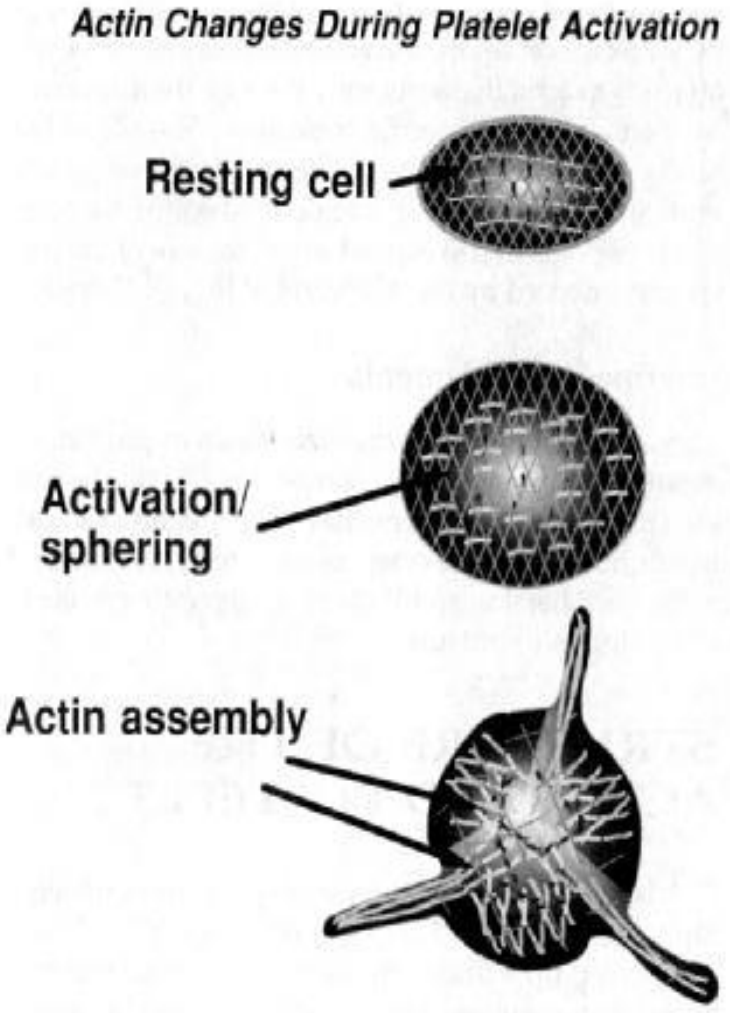
단구 부피의 표준편차

SIRS에서 혈소판 활성화

염증성 싸이토카인과 트롬빈 등에 의한 혈소판 활성화



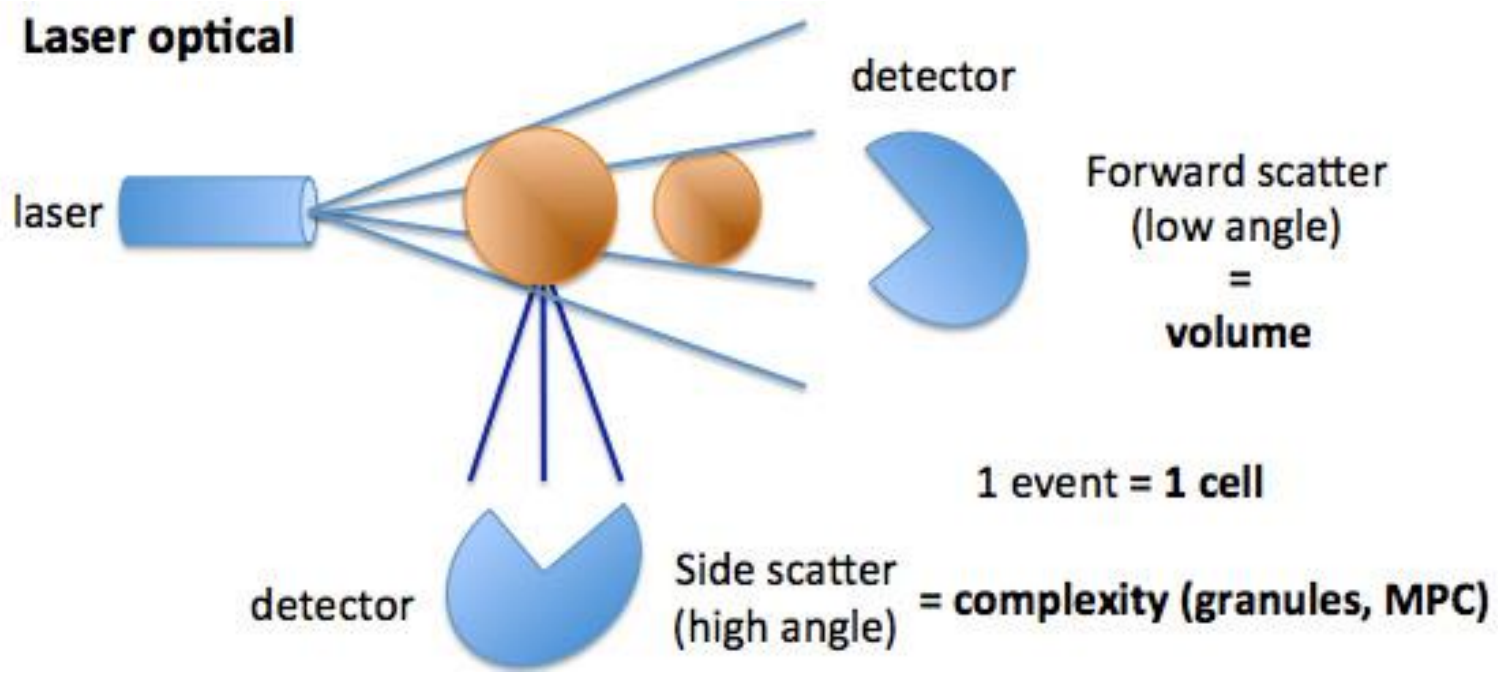


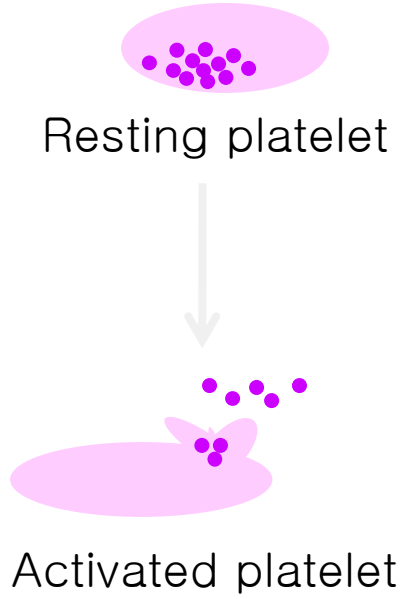


ADVIA2120i 혈소판 지표들

- mean platelet volume (MPV)
- platelet volume distribution width (PDW, variation in platelet size)
- platelet-crit (PCT, the percentage of blood volume occupied by platelets)
- mean platelet component concentration (MPC, platelet density)
- platelet component distribution width (PCDW, platelet shape variation)
- mean platelet dry mass (MPM)
- platelet dry mass distribution width (PMDW)
- large platelets(LPLT)

Mean platelet component (MPC) 측정 원리



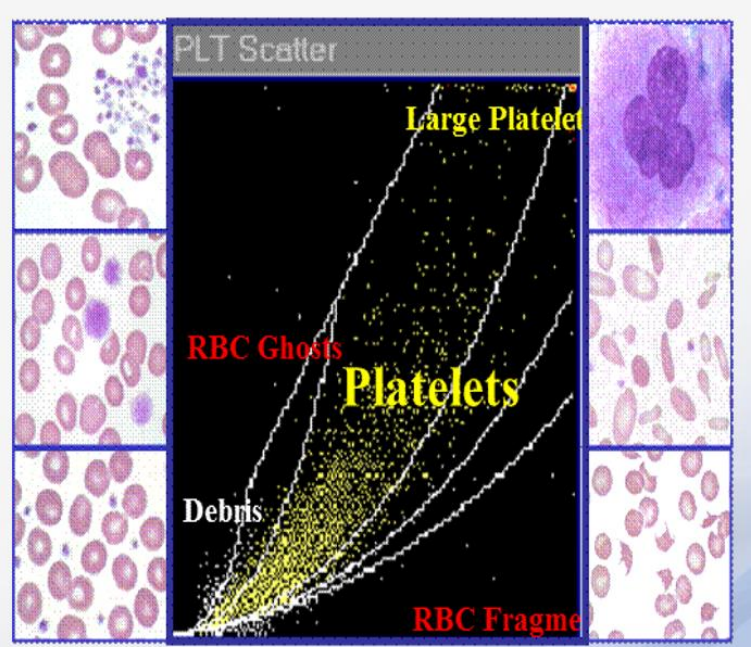


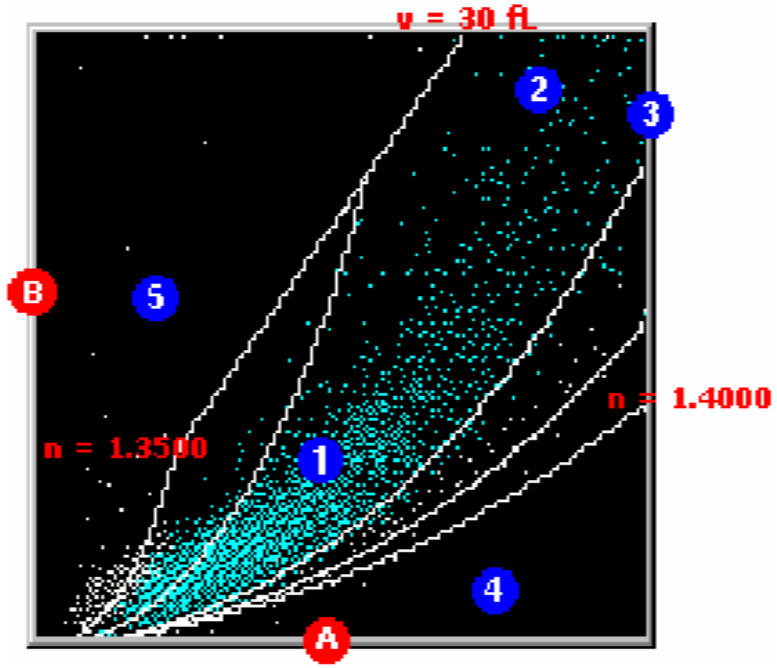
High angle detector: 혈소판 내부 과립 및 복잡성 측정

혈소판 활성화로 혈소판 과립 분비 → high angle detector 빛 양 감소 (MPC 감소)

Measurement- PLT Scatter Cytogram

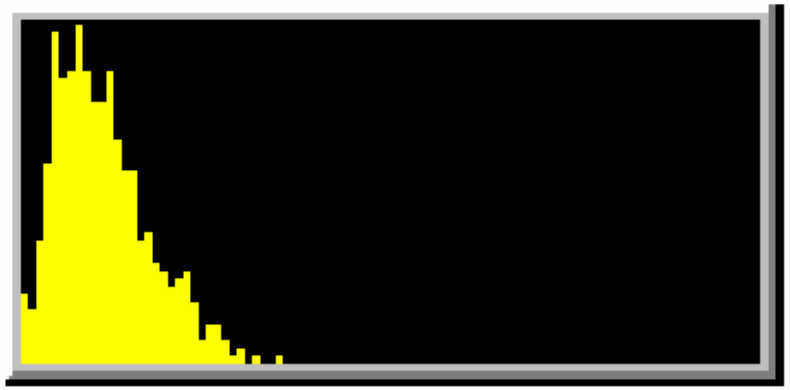
The PLT Scatter cytogram is the graphical representation of two light-scatter measurements: the high-angle (5° to 15°), high-gain light scatter is plotted on the x axis (A), and the low-angle (2° to 3°), low-gain light scatter is plotted on the y axis (B).





1. Platelets
2. Large platelets
3. Red blood cells
4. RBC fragments
5. RBC ghosts

<Platelet low angle histogram>



The Platelet VOL histogram of the two-dimensional PLT analysis shows the distribution of cells by volume. Volume data are obtained from the integrated analysis.

- MPV (mean platelet volume)

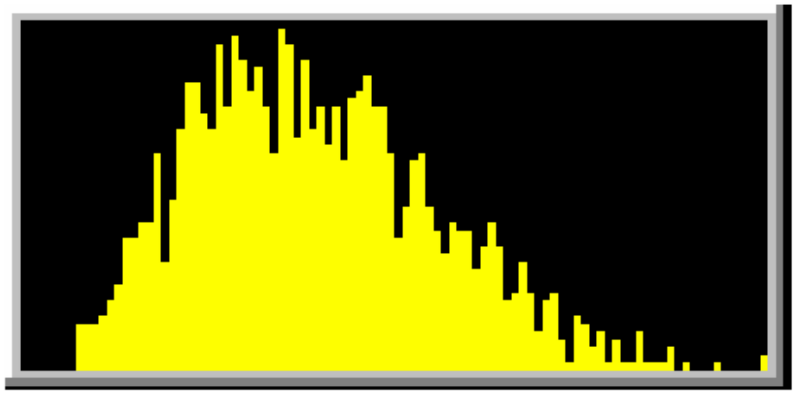
  = Mean of Platelet VOL histogram
- PDW (Platelet Volume Distribution Width)

  = 100 x (SD of Platelet VOL histogram ÷ MPV)
- PCT (Platelet Crit)

  = (PLT x MPV) ÷ 10,000
- Large PLT ($x10^9/l$)

  = Platelets with volumes greater than 20 fL

<Platelet high angle histogram>

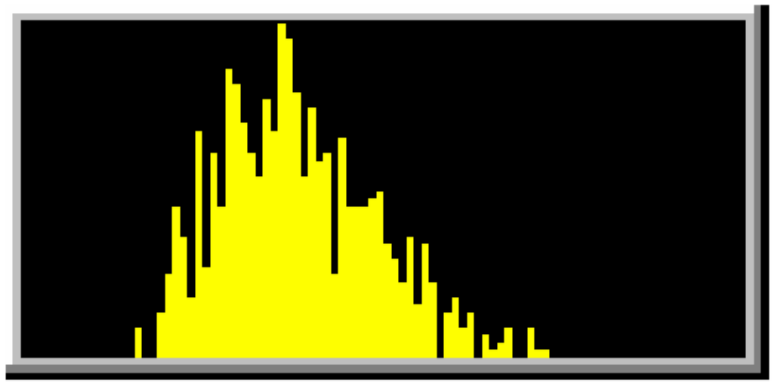


The Platelet X histogram is a 100-channel display of the high-angle (5° to 15°), high-gain light scatter measurements that corresponds to the x axis on the PLT Scatter cytogram.

- MPC (Mean Platelet Component Concentration)
  = Mean of Platelet PC histogram

- PCDW (Platelet Component Distribution Width)
  = SD of Platelet PC histogram

<Platelet PM histogram>

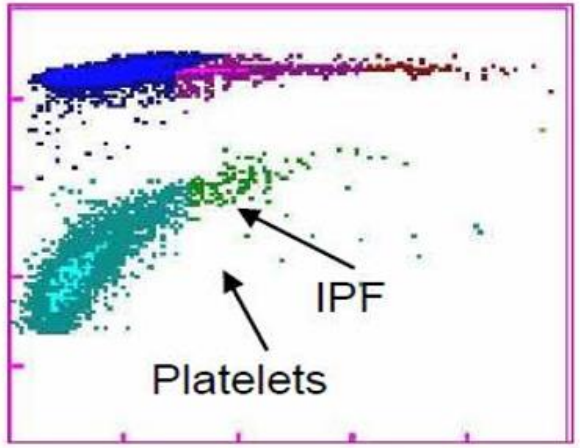


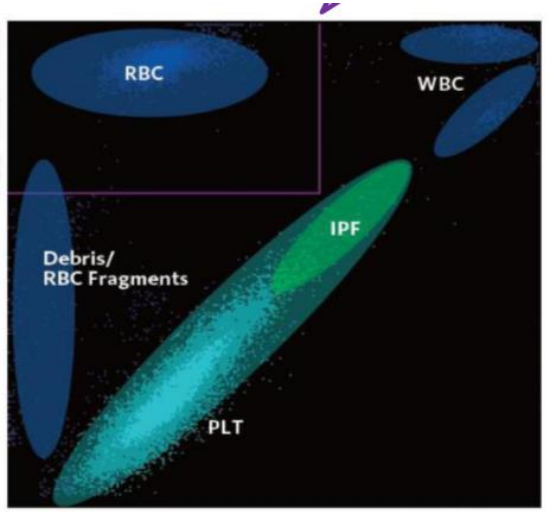
The Platelet PM histogram of the two-dimensional PLT analysis shows the distribution of platelets by the platelet dry mass (PM).

- MPM (Mean Platelet Dry Mass)
  = Mean of Platelet PM histogram

- PMDW (Platelet Dry Mass Distribution Width)
  = SD of Platelet PM histogram

IPF (immature platelet fraction)

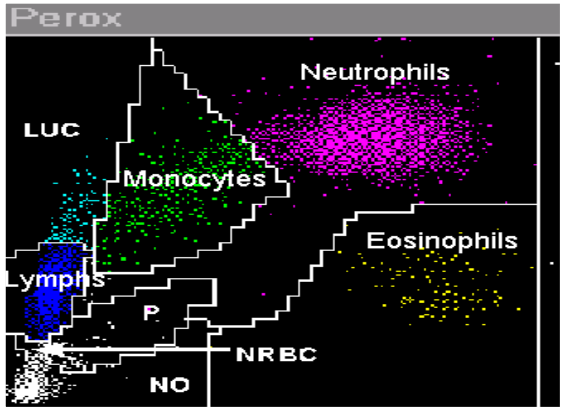




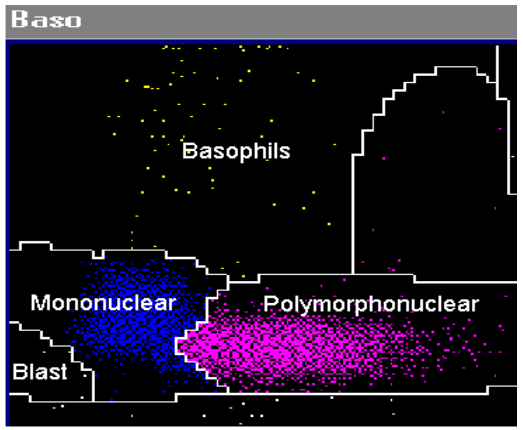
- 최근 골수에서 만들어져 말초로 분비된 혈소판
- 망상혈소판수
- 크기가 크고 세포질에 RNA 성분 높음
- fluorescent dyes 염색
- IPF % = $\frac{\text{immature platelets}}{\text{total number of platelets}}$

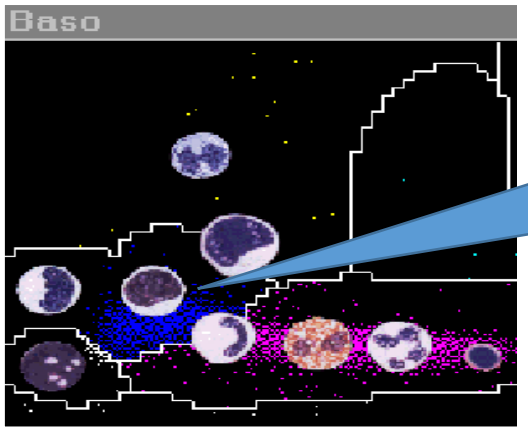
DNI (Delta Neutrophil Index)

Peroxidase channel



Basophile/Lobularity channel





미성숙 호중구 증가

⬇

Mononuclear cell로 측정됨

Delta Neutrophil =(Neu% + Eo%) – PMN %

방 법

1. 대상: 소아진단검사의학과로 의뢰된 CBC 결과 중에서 염증지표 CRP가 의뢰된 검체 232 개

2. 검사지표들

   (1) TBA-c16000 : hs-CRP

   (2) DxH 800 : NDW, MDW

   (3) ADVIA 2120i : DNI, PLT, MPV, PCT, PMDW

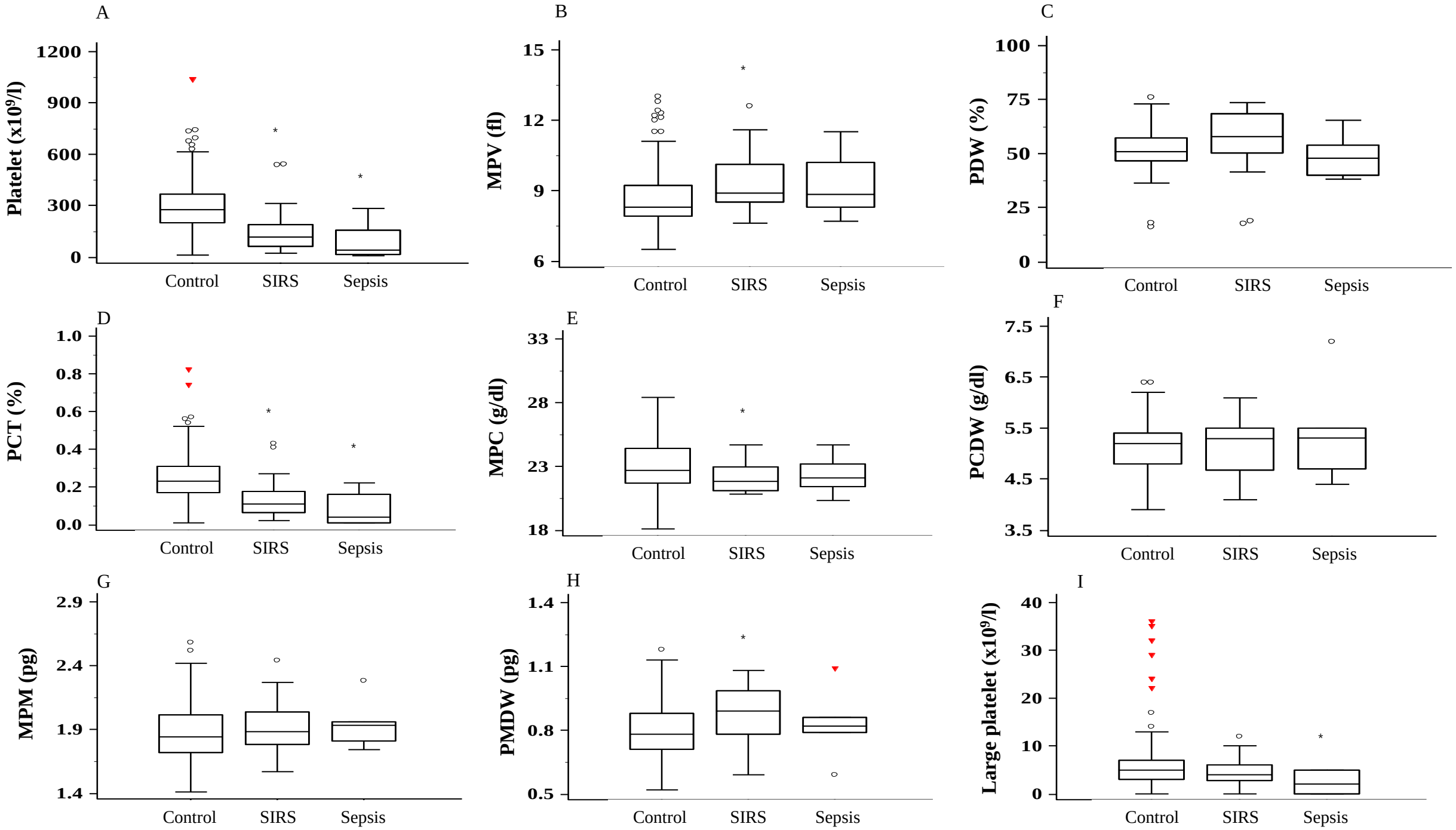
   (4) XE-2100 : IPF

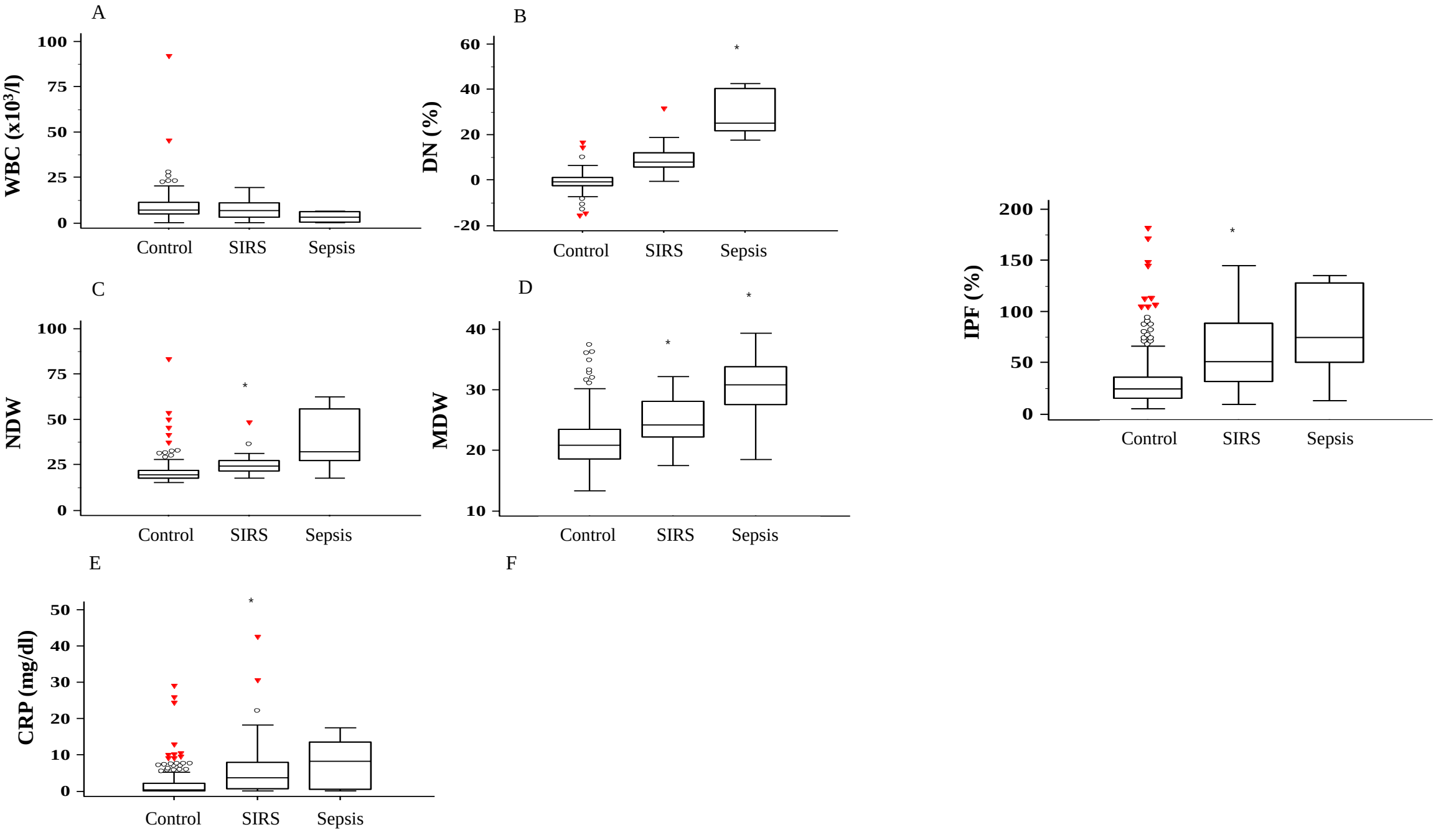
Baseline characteristics

	Control (n=201)	SIRS (n=25)	Sepsis (n=6)	P-value
Age, years, mean (SD)	7.2±5.9	7.9±7.1	10.8±5.6	0.305
Gender, n (%)				0.499
Male	121 (60.2)	16 (64.0)	6 (83.3)	
Female	80 (39.8)	9 (36.0)	1 (16.7)	
Clinical diagnosis, n (%)				0.736
Infection	73 (36.3)	6 (24.0)	1 (16.7)	
Malignancies	34 (16.9)	7 (28.0)	4 (66.7)	
Cardiac anomalies	31 (15.4)	6 (24)	1 (16.7)	
Hepatic failure	6 (3.0)	1(4.0)	0 (0.0)	
Other*	57 (28.4)	4 (16.0)	1 (16.7)	

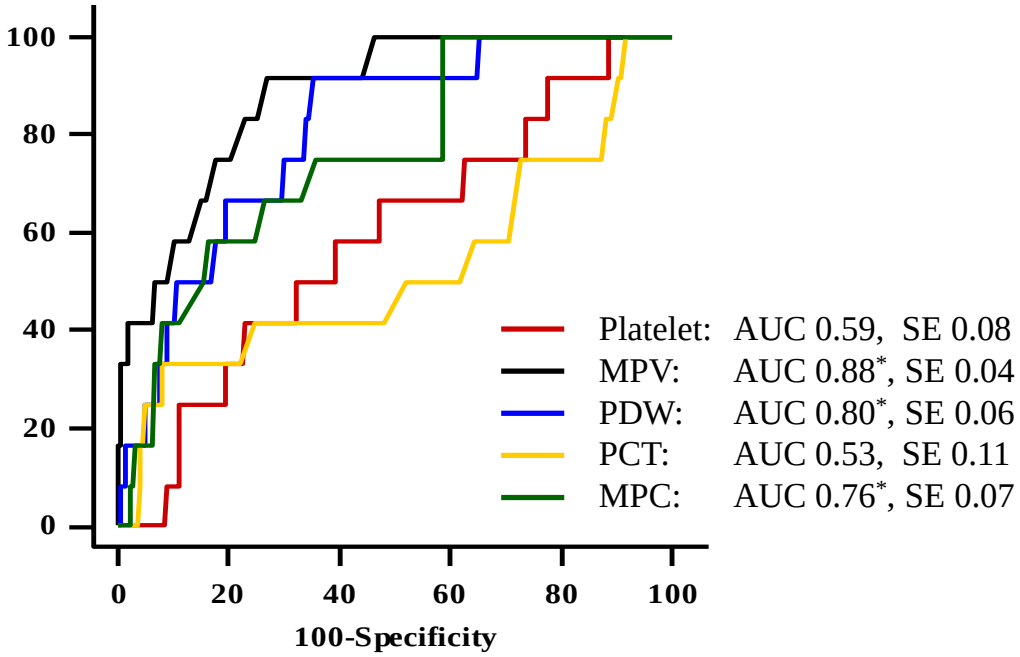
정상, SIRS 및 sepsis에서 지표변화

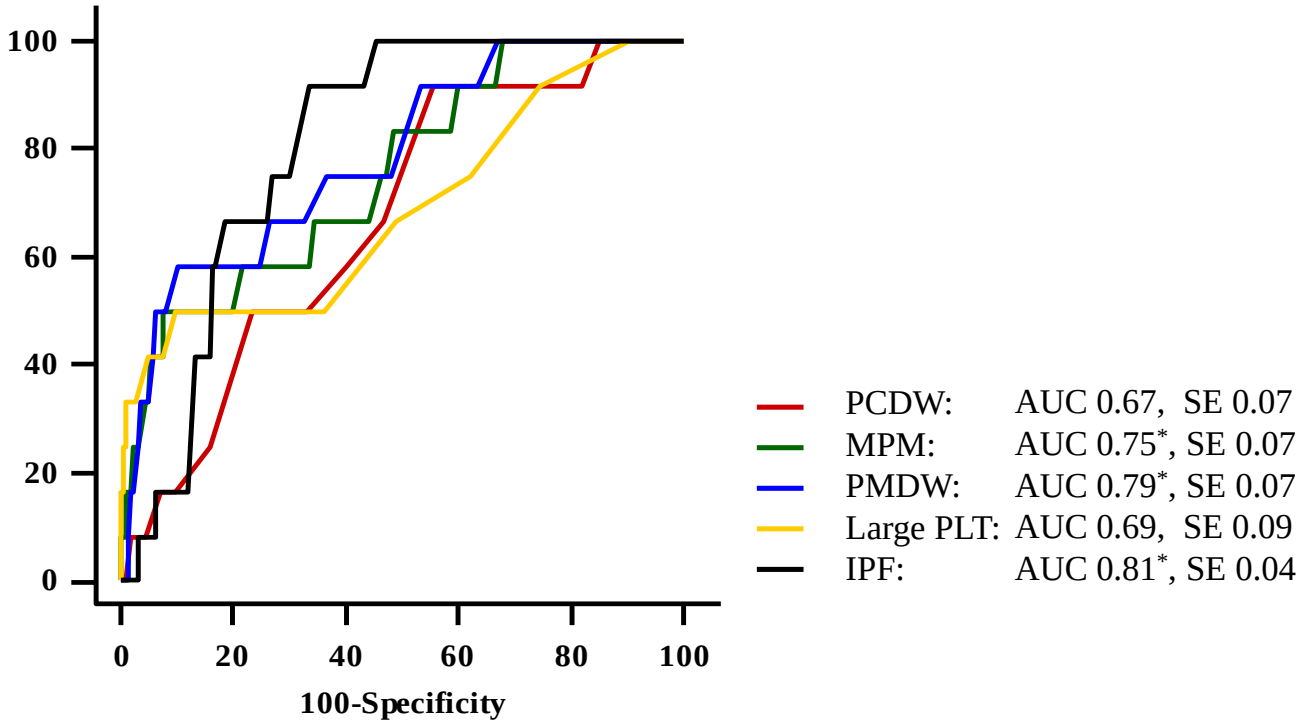
	Control (n=201)	SIRS (n=25)	Sepsis (n=6)	P-value
WBC parameters				
WBC ($x10^3$/l)	8.9 ± 8.2	7.5 ± 5.6	3.1 ± 3.2*†	0.156
DN (%)	-0.9 ± 3.6	9.3 ± 6.6*	28.7 ± 10.3*†	<0.001
NDW	21.1 ± 6.8	25.4 ± 6.5*	38.0 ± 17.5	<0.001
MDW	21.5 ± 4.2	25.1 ± 3.8*	30.1 ± 7.0*	<0.001
Platelet parameters				
Platelet ($x10^9$/l)	290.4 ± 151.1	158.5 ± 142.6*	90.0 ± 109.3*	<0.001
MPV (fl)	8.6 ± 1.2	9.3 ± 1.3*	9.2 ± 1.4	0.039
PDW (%)	51.8 ± 8.4	55.8 ± 14.8	48.9 ± 10.2	0.095
PCT (%)	0.24 ± 0.12	0.14 ± 0.11*	0.08 ± 0.09*	<0.001
MPC (g/dl)	22.9 ± 1.9	22.2 ± 1.1*	22.3 ± 1.5	0.087
PCDW (g/dl)	5.14 ± 0.48	5.18 ± 0.51	5.40 ± 0.98	0.428
MPM (pg)	1.88 ± 0.22	1.93 ± 0.20	1.94 ± 0.19	0.433
PMDW (pg)	0.80 ± 0.13	0.88 ± 0.14*	0.83 ± 0.16	0.026
Large platelet ($x10^9$/l)	5.77 ± 5.30	4.52 ± 2.80	2.3 ± 2.6*	0.149
IPF (%)	32.1 ± 28.7	59.4 ± 37.0*	79.2 ± 46.6	<0.001
CRP (mg/dl)	2.0 ± 3.9	7.4 ± 10.5*	8.0 ± 7.0	<0.001


A
Platelet (x10⁹/l)
1200
900
600
300
0
Control
SIRS
Sepsis
B
MPV (fl)
15
12
9
6
Control
SIRS
Sepsis
C
PDW (%)
100
75
50
25
0
Control
SIRS
Sepsis
D
PCT (%)
1.0
0.8
0.6
0.4
0.2
0.0
Control
SIRS
Sepsis
E
MPC (g/dl)
33
28
23
18
Control
SIRS
Sepsis
F
PCDW (g/dl)
7.5
6.5
5.5
4.5
3.5
Control
SIRS
Sepsis
G
MPM (pg)
2.9
2.4
1.9
1.4
Control
SIRS
Sepsis
H
PMDW (pg)
1.4
1.1
0.8
0.5
Control
SIRS
Sepsis
I
Large platelet (x10⁹/l)
40
30
20
10
0
Control
SIRS
Sepsis

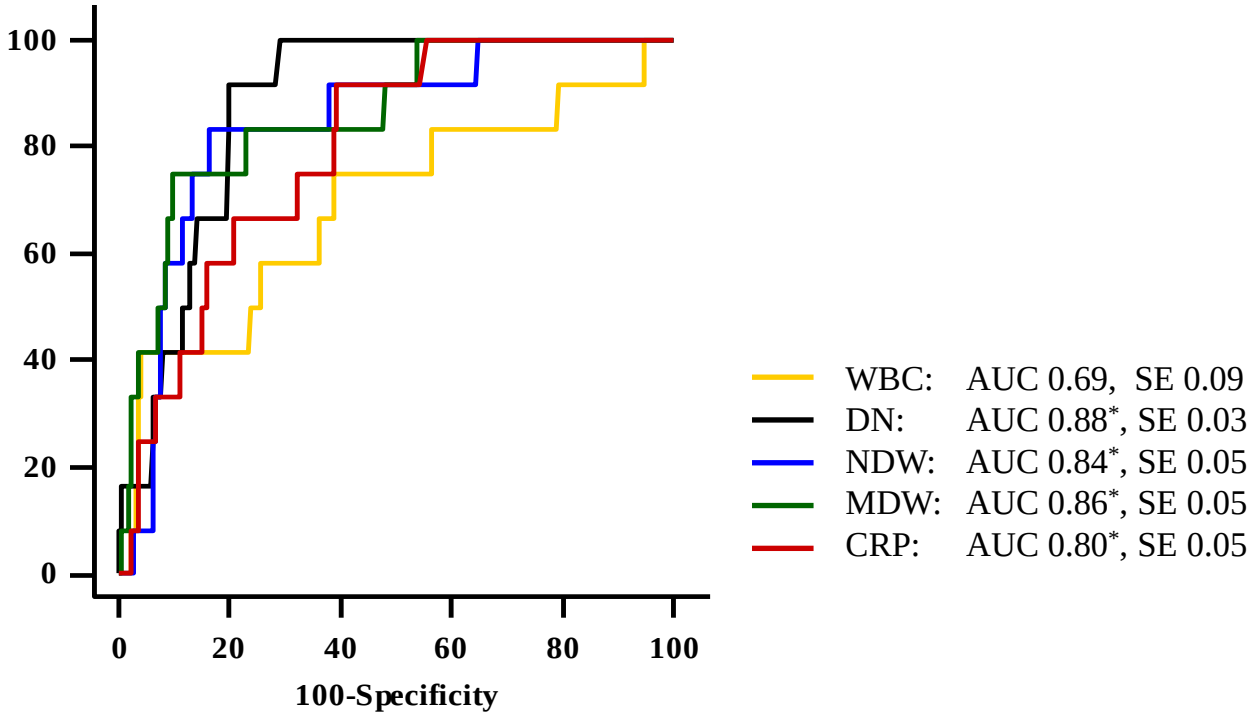

A
WBC (x10³/l)
100
75
50
25
0
Control
SIRS
Sepsis
B
DN (%)
60
40
20
0
-20
Control
SIRS
Sepsis
C
NDW
100
75
50
25
0
Control
SIRS
Sepsis
D
MDW
40
30
20
10
Control
SIRS
Sepsis
IPF (%)
200
150
100
50
0
Control
SIRS
Sepsis
E
CRP (mg/dl)
50
40
30
20
10
0
Control
SIRS
Sepsis
F

Receiver operating characteristic (ROC) - (1)





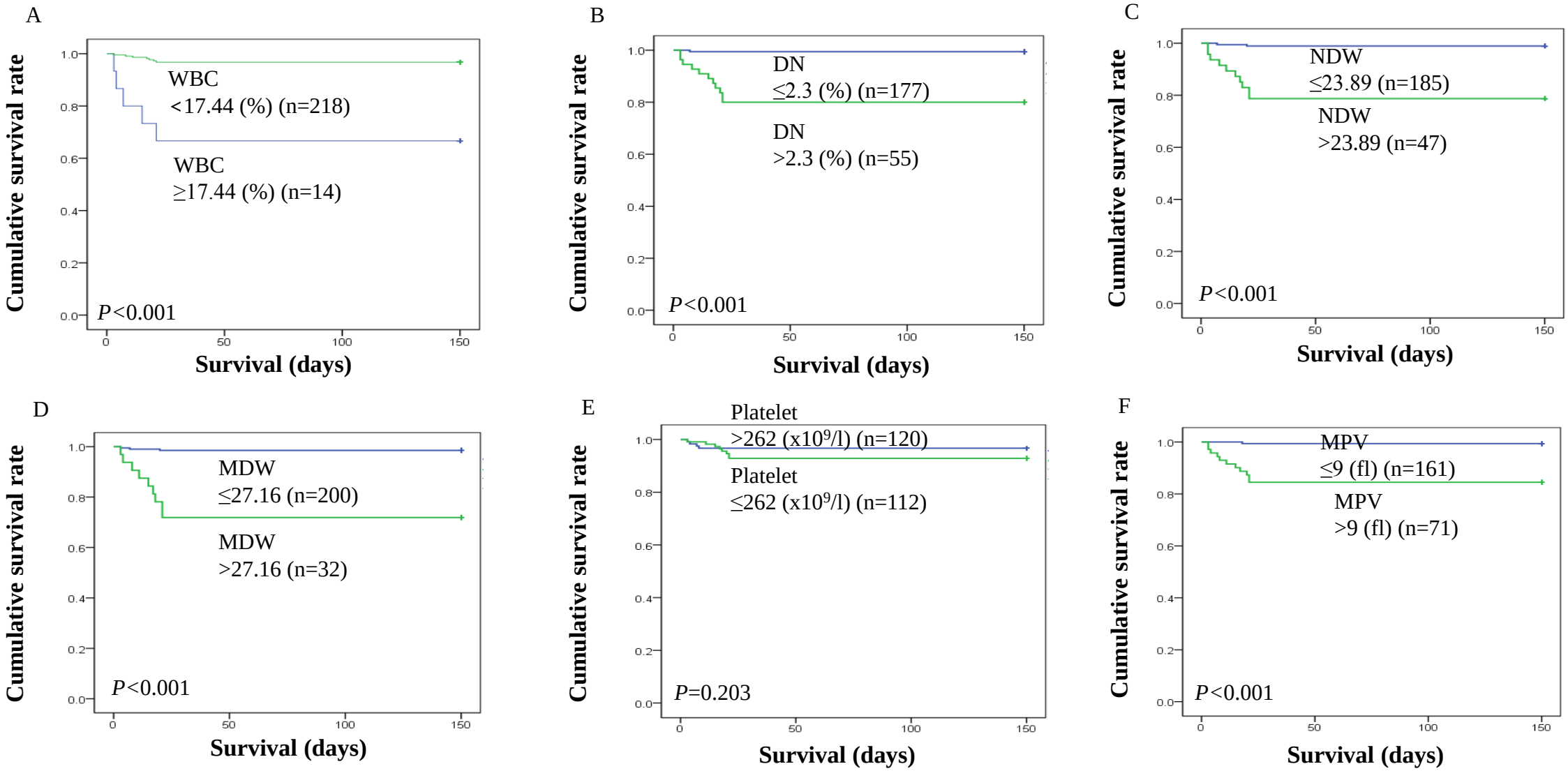
Receiver operating characteristic (ROC) - (2)



ROC 곡선을 이용한 지표들의 예후관련성

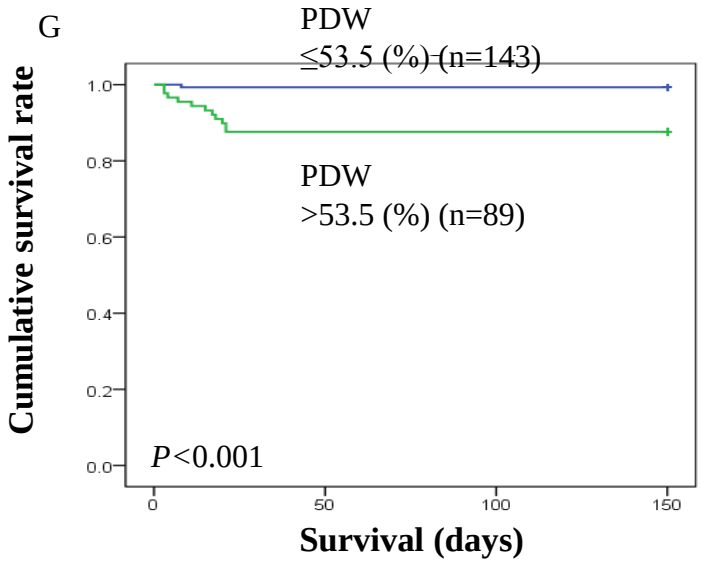
	AUC (95% CI)		Cut-off value	Sensitivity	Specificity
WBC parameters					
WBC ($x10^3$/l)	0.69	(0.52-0.86)	>17.44	41.7	95.9
DN (%)	0.88*	(0.82-0.93)	>2.3	91.7	80.0
NDW	0.84*	(0.74-0.94)	>23.89	83.3	83.2
MDW	0.86*	(0.76-0.96)	>27.16	75.0	90.0
Platelet parameters					
Platelet ($x10^9$/l)	0.59	(0.43-0.75)	≤ 262	66.7	52.7
MPV (fl)	0.88*	(0.80-0.96)	>9.0	91.7	72.7
PDW (%)	0.80*	(0.70-0.91)	>53.5	91.7	64.5
PCT (%)	0.53	(0.33-0.72)	>0.38	33.3	91.8
MPC (g/dl)	0.76*	(0.63-0.89)	≤ 21.2	58.3	83.6
PCDW (g/dl)	0.67	(0.53-0.81)	≤ 5.2	91.7	44.1
MPM (pg)	0.75*	(0.62-0.89)	> 2.16	50.0	92.3
PMDW (pg)	0.79*	(0.66-0.92)	> 0.98	58.3	89.5
Large platelet ($x10^9$/l)	0.69	(0.51-0.87)	> 9.0	50.0	90.0
IPF (%)	0.81*	(0.73-0.88)	>31.0	91.7	66.4
CRP (mg/dl)	0.80*	(0.70-0.90)	>0.94	91.7	60.9

Kaplan-meier 분석 (1)



Kaplan-meier 분석 (2)

G



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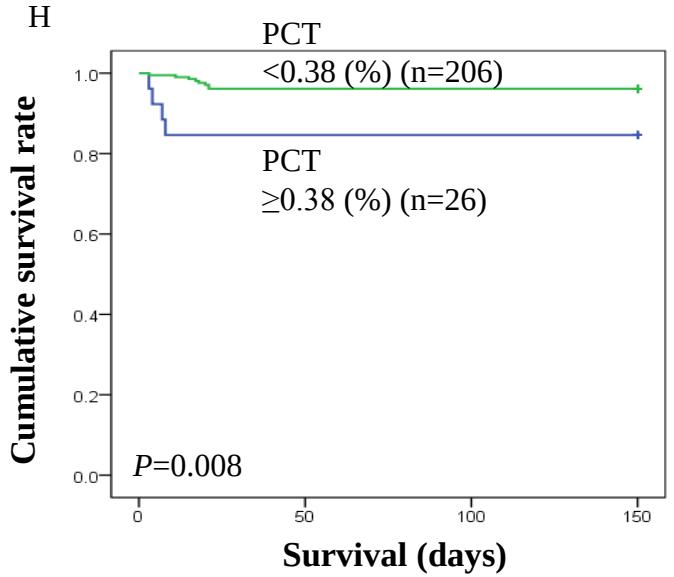

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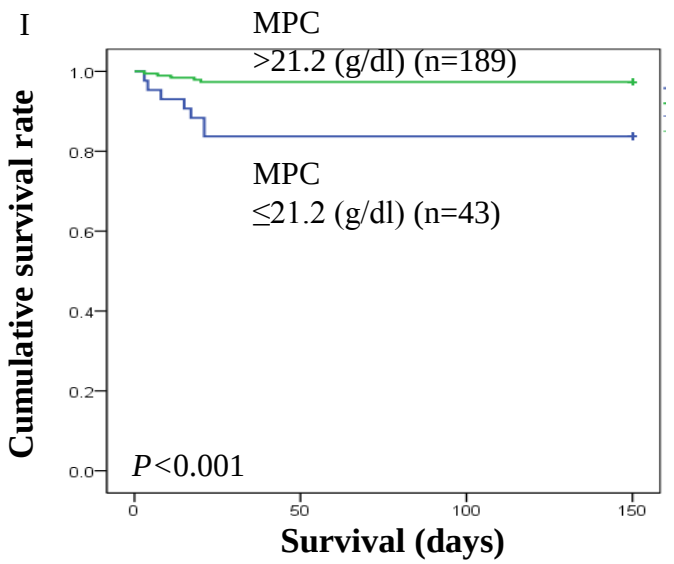

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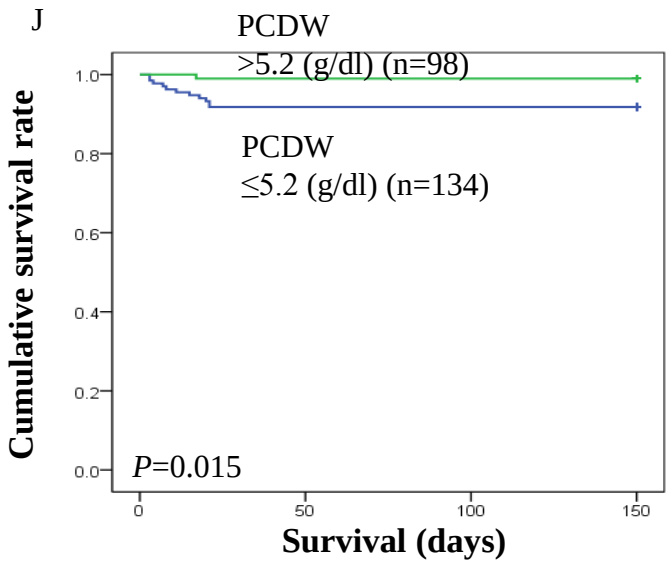
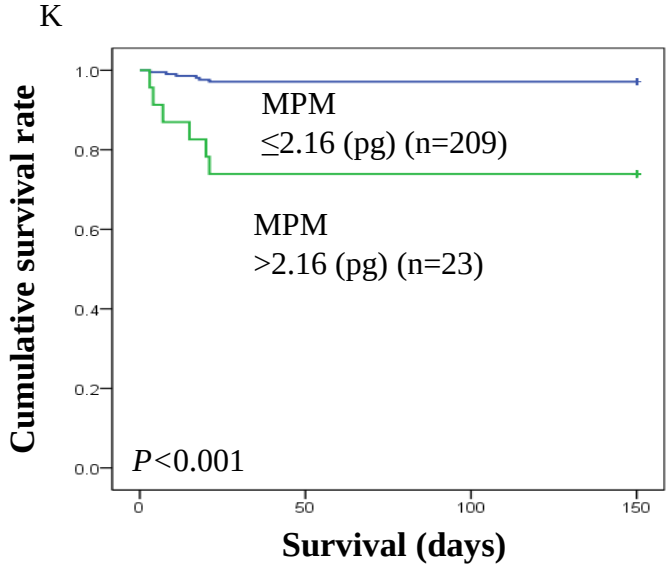
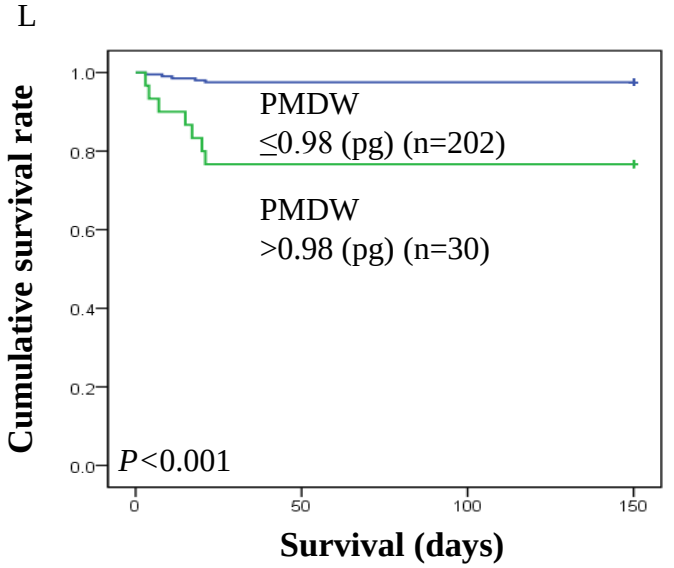


K

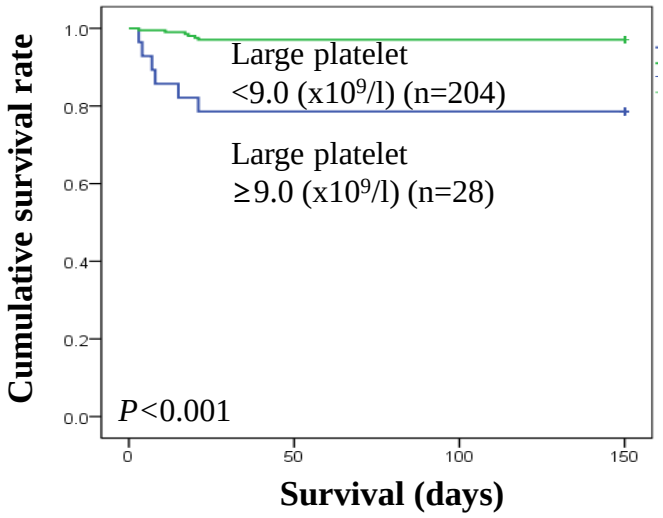


L

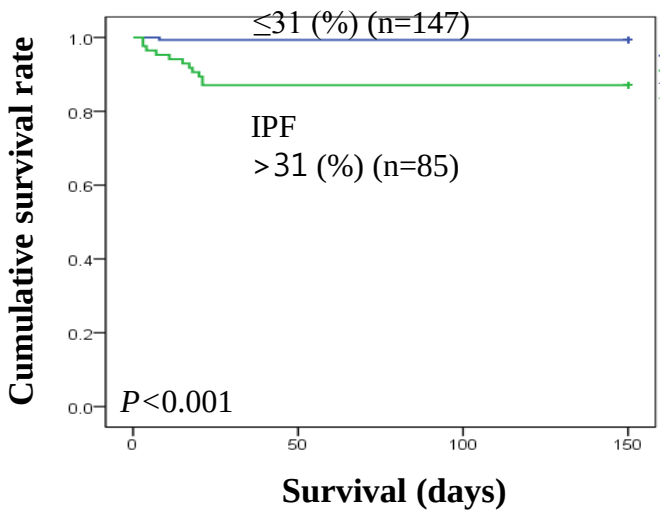


Kaplan-meier 분석 (3)

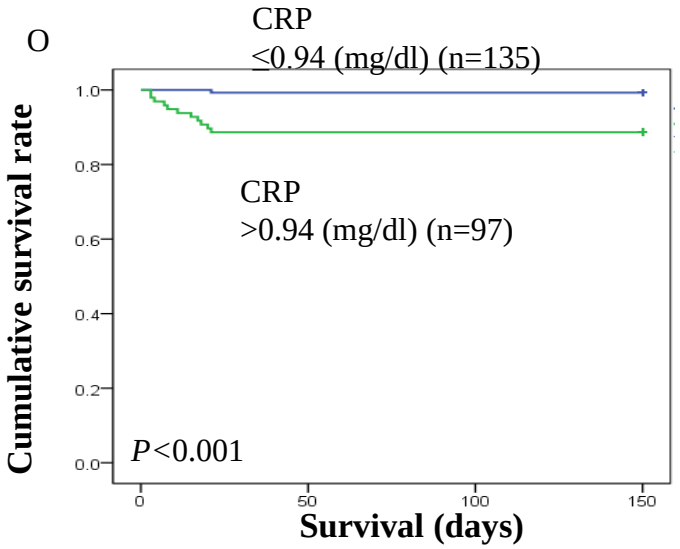
M



N



O



Cox 비례회귀분석을 통한 사망위험율

	HR	95% CI	*P* value
WBC parameters			
WBC (≥ 17.44 x10^3/l vs. < 17.44 x10^3/l)	9.12	2.81-29.57	<0.001
DN (≤ 2.3 % vs. > 2.3 %)	19.08	2.41-151.23	0.005
NDW (≤ 23.89 vs. > 23.89)	15.11	3.27-69.91	<0.001
MDW (≤ 27.16 vs. > 27.16)	1.30	1.16-1.47	<0.001
Platelet parameters			
Platelet (> 262 x10^9/l vs. ≤ 262 x10^9/l)	1.56	0.46-5.24	0.476
MPV (≤ 9 fl vs. > 9 fl)	13.93	1.71-113.48	0.014
PDW (≤ 53.5 % vs. > 53.5 %)	8.71	1.09-69.83	0.042
PCT (≥ 0.38 % vs. < 0.38 %)	0.48	0.14-1.60	0.232
MPC (≤ 21.2 g/dl vs. > 21.2 g/dl)	0.32	0.10-1.02	0.055
PCDW (≤ 5.2 g/dl vs. > 5.2 g/dl)	0.15	0.02-1.15	0.067
MPM (≤ 2.16 pg vs. > 2.16 pg)	3.23	0.98-10.64	0.054
PMDW (≤ 0.98 pg vs. > 0.98)	3.78	1.15-12.42	0.029
Large platelets (≥ 9.0 x10^9/l vs. <9.0 x10^9/l)	0.36	0.11-1.20	0.097
IPF (≤ 31 % vs. >31 %)	11.97	1.48-96.59	0.020
CRP (≤ 0.94 mg/dl vs. > 0.94 mg/dl)	6.84	0.85-55.13	0.071

결과 요약

1. 소아 SIRS와 sepsis에서 백혈구지표 DN, NDW, MDW가 정상 보다 유의하게 증가
2. 소아 SIRS와 sepsis에서 혈소판지표 중에서는 MPV, PCT, IPF가 유의하게 증가
3. 백혈구지표 중에 DN의 예후지표로서의 유용성이 가장 우수하였으며, NDW와 MDW도 유의한 예후지표이었음
4. 혈소판지표 중에 MPV가 가장 유용한 예후지표이며, PDW, PMDW, IPF도 유의한 예후지표이었음

결론

1. 소아의 전신염증반응증후군과 패혈증의 예후인자로서 백혈구 지표인 DN, NDW, MDW와 혈소판지표인 MPV, PDW, PMDW, IPF의 유용성을 확인하였음
2. 향후 이들 지표들의 예후인자로서 유용성이 활용될 수 있기를 기대함

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