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Dendritic cells in childhood sepsis☆

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Abstract
Purpose: Our aim was to investigate the level and the maturation status of dendritic cells (DCs) in pediatric patients with sepsis and its relation to prognosis.
Materials and methods: The study included 16 children with sepsis, 24 children with complicated sepsis, and 40 healthy control children. The patients were investigated within 24 hours of intensive care unit admission and after 28 days. Flow cytometric detection of DCs was done.
Results: Within 24 hours, the levels of both plasmoid DCs and monocytoid DCs and the expression of CD86 and CD83 on DCs were significantly lower in patients than in controls, and the difference was marked in patients with complicated sepsis. The amount of CD86 and CD83 per cell was significantly lower in patients with complicated sepsis. The baseline numbers of monocytoid DCs and plasmoid DCs were higher in the survival patients than in nonsurvival patients. In addition, the expression of CD86 and CD83 on the entire DCs was significantly higher in the survival patients with sepsis.
Conclusion: Sepsis is associated with reduced level of DCs and decreases their maturation. The estimation of DCs number and maturation state may be used as prognostic makers of sepsis.

1. Introduction

Sepsis refers to the disseminated inflammatory response elicited by microbial infections. It remains a current challenge. It is increasing in frequency, expensive to treat, and lethal, with an associated rate of death as high as 70%. There is growing evidence that sepsis develops when the appropriate initial host response to systemic infection becomes amplified and then unregulated, finally leading to the paralysis of the immune system [1]. Host defense against pathogenic microorganisms requires the coordinated actions of the innate and acquired immune system. However, dysregulation of the immune system occurs during severe sepsis, leading to either a rapid death caused by the development of multiorgan failure or an increase in complications caused by long-term immunosuppression [2-7]. Several defects in both innate and acquired immunity had been described in sepsis [6]. Apoptosis of B and T lymphocytes and reduced numbers of DCs were observed in patients with sepsis [8,9].

Dendritic cells (DCs) are the most potent antigen-presenting cells and play a key role in linking innate and adaptive host immune responses to microorganisms and the

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initiation of specific immune responses [10]. Dendritic cells serve 2 general functions in controlling T-cell immunity. The first is to process and present antigens to T cells, which is essential for T-cell activation and expansion. Second, DCs secrete cytokines that condition the extracellular milieu and determine the nature of the T-cell response [11]. Infectious microbes contact with the immature DCs and promote maturation, which is characterized by an increased capacity to present antigens and stimulate T cells and secretion of proinflammatory cytokines, which promote differentiation of type 1 T cells that efficiently clear the infectious agent [12]. Distinct subsets of circulating DCs can be identified in peripheral blood (PB), including myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) [13]. Although arising from common precursor cells in the bone marrow, mDCs and pDCs are phenotypically and functionally different [14]. Myeloid DCs secrete interleukin-12, which directly induces differentiation of type 1 T cells [12]. Plasmacytoid DCs secrete interferon-α, which is well known for its potent antiviral properties [15]. As a result of the pivotal role of DCs in immune activation, the modification of DC system during sepsis is becoming an area of active investigation [16].

The aim of this study was to investigate the level and the maturation status of DCs in pediatric patients with sepsis and its relation to prognosis, through flowcytometric analysis of PB DCs and their expression of CD83 and CD86.

2. Patients and method

The present study is a case-control prospective study conducted in the pediatric intensive care unit (ICU) of Children Hospital, Assiut University, during the period between June 2012 and December 2012. Forty children were included in this study and classified according to their diagnoses as follows: sepsis, which included 16 children (group 1), and complicated sepsis, which included 24 children (group 2). Forty healthy children with matchable age and sex were included in the study as a control group (group 3). An informed written consent was obtained from their guardians, and the study was approved by the Faculty of Medicine Ethic Committee for the Scientific Research Conduct. The patients were investigated within 24 hours of ICU admission (on admission) and after 28 days from admission and treatment.

Sepsis was characterized by confirmed infection (positive culture) or highly suspected infection (evidence of infectious focus) combined with 2 or more of the conditions considered for systemic inflammatory response syndrome, which are as follows: (*a*) (axillary) temperature higher than 37.5°C or lower than 36°C; (*b*) heart rate more than 160 beats/min in infants and more than 150 beats/min in children, or >2 SD above the reference values for age; (*c*) respiratory frequency greater than 60 movements/min in infant and greater than 50 movements/min in children, or >2 SD above the reference values for age; and (d) total leukocyte count more than 12 000 cells/mm^3, less than 4000 cells/mm^3, or more than 10% band forms [17]. Complicated sepsis included patients with severe sepsis and septic shock and was characterized as sepsis associated with organ dysfunction, hypoperfusion, or hypotension (systolic blood pressure <10th percentile for age), even after appropriate volume resuscitation, plus the presence of systemic perfusion disorders [18]. Sepsis-related Organ Failure (SOFA) score was calculated as an evaluation of the degree of severity of organ dysfunction/failure in 6 systems including respiratory, coagulation, liver, cardiovascular, central nervous, and renal systems. This evaluation represented by points ranged from 0 to 4 [19]. The Surviving Sepsis Protocol (international guidelines for management of severe sepsis and septic shock) was used in the treatment for patients [20]. The *nonsurvival* of patients was defined as death within 28 days after onset of sepsis. Seventeen patients died, 3 with sepsis and 14 with complicated sepsis. This study included children aged 1 month to 16 years presented by symptoms suggestive of sepsis, severe sepsis, or septic shock. Cases with systemic inflammatory response syndrome alone without criteria suggesting sepsis or complicated sepsis were excluded from this study.

The patients and controls were subjected to the following laboratory investigations: complete blood count (Celltac E automated hematology analyzer, Tokyo, Japan), blood culture, serum electrolytes (by AVL 9180 analyzer; Roche Diagnostics GmbH, Mannheim, Germany), blood urea and serum creatinine (Cobas Integra 400 Chemistry Analyzer; Roche Diagnostics GmbH), C-reactive protein (Atlas C-reactive Protein latex Reagent Kit; Atlas Medical, Cambridge, UK), and flow cytometric detection of DCs.

2.1. Flow cytometric detection of DCs numbers and phenotype

Dendritic cells in whole PB samples were enumerated using fluoroisothiocyanate (FITC)-conjugated monoclonal antibodies against lineage markers (includeing anti-CD3, CD14, and CD19), phycoerythrin (PE)-conjugated anti-CD123, PE-conjugated anti-CD11c, and peridinium-chlorophyll-protein (Per-CP)–conjugated anti–HLA-DR. All monoclonal antibodies were purchased from Becton Dickinson Biosciences, San Jose, Calif.

To determine DCs numbers, 100 μL of blood sample was stained with 10 μL of FITC-conjugated lineage-specific markers (CD3, CD14, and CD19), 10 μL of Per-CP–conjugated anti–HLA-DR, and 10 μL of PE-conjugated DCs markers (anti-CD11c or anti-CD123). To detect the expression of CD86 and CD83 on DCs, 100 μL of blood sample was stained with 10 μL of PE-conjugated lineage-specific markers (CD3, CD14, and CD19), 10 μL of Per-CP–conjugated anti–HLA-DR, and 10 μL FITC-conjugated CD86 or CD83. The tubes were incubated for 15 minutes at room temperature in the dark. Red blood cell lysis was done.

After one wash, the cells were resuspended in phosphate-buffered saline and analyzed by FACSCalibur flow cytometry with Cell Quest software (Becton Dickinson Biosciences). Fifteen thousand events were analyzed, and an isotype-matched negative control was used with each sample. The numbers of $CD11c^+$ (mDCs) and $CD123^+$ (pDCs) and the expression of CD86 and CD83 on the entire DCs population (HLA-DR+ lineage-specific−negative events) were detected by flow cytometry as shown in Fig. 1. CD86 and CD83 levels were recorded as a percentage of expression and as a geometric mean of fluorescence intensity (MFI).

2.2. Statistical analysis

Data analysis was done by Statistical Package for Social Sciences (SPSS, Chicago, Ill), version 16. All data were expressed as mean ± SD of the mean. Differences between the groups were examined for statistical significance using

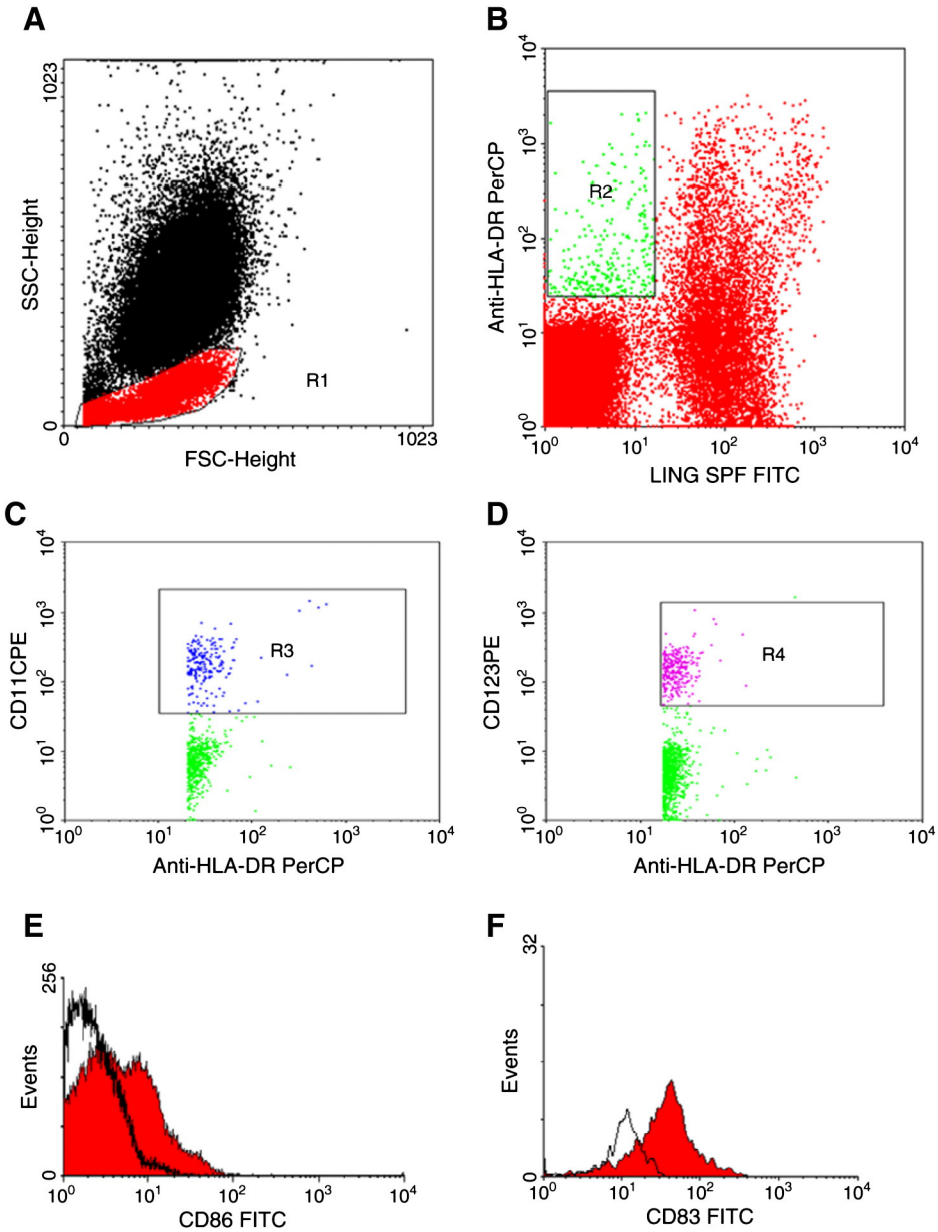

Fig. 1 Flow cytometric detection of DCs. A, Forward and side scatter histogram was used to define the lymphocyte and monocytes population (R1). B, R2 gate containing the entire DCs ($HLA\text{-}DR^+$ $lineage\text{-}specific^-$ populations) within the lymphocytes and monocytes population was selected, compared with the negative isotype control (not shown). C and D, Then, the percentage of mDCs ($HLA\text{-}DR^+$ $lineage\text{-}specific^-$ $CD11c^+$) (R3) and the pDCs ($HLA\text{-}DR^+$ $lineage\text{-}specific^-$ $CD123^+$) (R4) were determined. E and F, The geometric MFI of the expression of CD86 and CD83 on the entire DC population. The positivity was defined as fluorescence (red histogram) higher than that of the isotype control (open histogram).

Table 1 Baseline characteristics of septic patients and the controls on admission (within 24 hours of ICU admission)

	Group 1: patients with sepsis (16)	Group 2: patients with complicated sepsis (24)	Controls (30)	P^1	P^2	P^3
Age	3.75 ± 2.9	2.6 ± 2.5	3.06 ± 1.6			
SOFA score	10 ± 3.1	14.5 ± 2.3		.040		
Length of hospital stay	23.8 ± 5.2	27.8 ± 6.3		.124		
C-reactive protein	19 ± 15	45 ± 29	8 ± 4.6	.002	.003	.00
WBCS	21.6 ± 9	26.6 ± 12	6.5 ± 1.8	.143	.00	.00
Hemoglobin	8.2 ± 1.6	8.1 ± 1.7	11.7 ± 2.17	.530	.000	.000
Platelet count	276 ± 250	121 ± 64	216 ± 62	.031	.076	.000
Sodium	144 ± 10.5	152 ± 17.6	134.4 ± 6.4	.040	.02	.010
Potassium	4.46 ± .9	4.6 ± 1	4.2 ± .6	.500	.375	.061
Calcium	7.5 ± .9	7.6 ± 1	7.6 ± .9	.750	.750	.696
Urea	17.9 ± 14.5	20 ± 14.2	9.2 ± 2	.670	.021	.020
Creatinine	135 ± 88	149 ± 123	50 ± 26.3	.030	.000	.000

One-way ANOVA test. Data represented as means ± SD. $P \leq .05$ is significant.
P^1, group 1 vs group 2; P^2, group 1 vs controls; P^3, group 2 vs controls.

independent-sample *t* test and 1-way analysis of variance (ANOVA). Differences between patients at presentation and after 28 days of admission were examined for statistical significance using the paired *t* test. A *P* value of .05 or less denoted the presence of a statistically significant difference. Pearson correlation coefficient was used to examine the correlations among different studied parameters.

3. Results

Some demographic, clinical, and laboratory data of the patients and the controls were presented in Table 1. Regarding DC levels in the patients and controls within 24 hours of ICU admission, the levels of both pDCs and mDCs were significantly lower than those of the controls, and the difference was more marked in patients with complicated sepsis. The mDCs/pDCs ratio was not significantly different between the patients and the controls. The expression of costimulatory molecule, CD86, and maturation marker CD83 on the entire DCs (HLA-DR+ lineage-specific−negative events) was significantly lower in the patients than in the controls, and the difference was marked in patients with complicated sepsis. In addition, the amount of CD86 and CD83 per cell, represented by the MFI, was significantly lower in patients with complicated sepsis than in the controls. There was no significant difference in the expression of CD86 and CD83 on the entire DCs between the patients with sepsis and those with complicated sepsis (Table 2).

Comparing the survival and nonsurvival (who died within 28 days of onset of sepsis) septic patients, the baseline numbers (within 24 hours of admission) of mDCs and pDCs were higher in the survival than in nonsurvival patients. In addition, the expression of CD86 and CD83 on the entire DCs in nonsurvival patients with sepsis was significantly lower than that in the survival patients (Table 3). Sepsis-related Organ Failure score was higher in nonsurvival than in survival patients (11.90 ± 2.75 and 9.10 ± 2.84, $P < .015$). Also C-reactive protein level was higher in nonsurvival than in survival patients (54.60 ± 26.27 and 35.75 ± 21.26 mg/dL, $P = .043$).

After 28 days of ICU admission and treatment, the level of both mDCs and pDCs in septic patients was significantly increased than the level detected on admission, whereas the

Table 2 Frequencies of DCs and their expression of CD86 and CD83 in patients with sepsis and controls on admission (within 24 hours of ICU admission)

	Group 1: patients with sepsis (16)	Group 2: patients with complicated sepsis (24)	Controls (40)	P^1	P^2	P^3
mDCs %	0.31 ± 0.24	0.11 ± 0.09	1.4 ± 0.42	.015	.001	.001
pDCs %	0.27 ± 0.19	0.11 ± 0.16	1.03 ± 0.29	.002	.001	.000
mDCs/pDCs ratio	1.43 ± 0.29	1.42 ± 0.35	1.53 ± 0.27	.962	.431	.215
$CD86^+$ expression on the entire DCs %	72.91 ± 23.49	61.57 ± 20.62	85.36 ± 27.97	.724	.001	.002
MFI of $CD86^+$ on the entire DCs	107.46 ± 35.05	97.90 ± 24.85	156.03 ± 55.67	.882	.011	.001
$CD83^+$ expression on the entire DCs %	37.46 ± 13.45	28.00 ± 8.01	42.68 ± 13.99	.335	.001	.000
MFI of $CD83^+$ on the entire DCs	53.50 ± 19. 65	43.50 ± 28.57	75.45 ± 16.14	.457	.001	.001

One-way ANOVA test. Data represented as means ± SD. $P \leq .05$ is significant.
P^1, group 1 vs group 2; P^2, group 1 vs controls; P^3, group 2 vs controls.

Table 3 Baseline frequencies (within 24 hours of ICU admission) of DCs and their expression of CD86 and CD83 in survival and nonsurvival patients with sepsis

	Survivals (23)	Nonsurvivals (17)	*P*
mDCs %	0.32 ± 0.18	0.08 ± 0.06	.000
pDCs %	0.29 ± 0.22	0.07 ± 0.06	.000
$CD86^+$ expression on the entire DCs %	30.59 ± 11.46	19.44 ± 9.70	.014
MFI of $CD86^+$ on the entire DCs	115.07 ± 34.12	85.58 ± 24.75	.022
$CD83^+$ expression on the entire DCs %	20.48 ± 8.54	13.28 ± 3.40	.017
MFI of $CD83^+$ on the entire DCs	58.40 ± 23.13	36.85 ± 23.44	.023

Independent-sample *t* test. Data represented as means ± SEM. $P \leq .05$ is significant.

level was still lower than that of the controls. No significance difference in the expression of CD86 and CD83 before and after treatment (Table 4). Sepsis-related Organ Failure score improved from admission days to day 28 (11.50 ± 1.77 to 9.89 ± 2.38, $P = .015$). The mean level of C-reactive protein decreased from admission day to day 28 (37.50 ± 21.16 mg/dL to 26.10 ± 20.5 mg/dL, $P = .025$). There were negative correlations between both mDCs and pDCs with SOFA score, white blood cells (WBCs), urea, creatinine, and C-reactive protein (Table 5).

4. Discussion

Despite extensive use of broad-spectrum antibiotics, mechanical ventilation, improvement of nutritional support, and other supportive measures, the mortality rate in our ICU remains high. The mortality rate was 42.5% (17/40) among our studied patients with sepsis and complicated sepsis. This indicates that ICU admission remains associated with high mortality, particularly for patients with complicated sepsis (14/24). Previous studies indicated that the development of marked immune suppression in sepsis is more often associated with morbid outcome [8,21].

The decline of both mDCs and pDCs in our patients with sepsis and complicated sepsis may contribute to the suppression of the immune response and the impaired host capacity to respond to the microbial infection and may contribute to the development of sepsis. The increased migration of circulating DCs into peripheral sites of inflammation or the decreased repopulation of DCs from the bone marrow could explain this decrease of DCs. Our results are in agreement with that of Guisset et al [22], who reported reduced numbers of circulating DCs in their patients within 24 hours after onset of septic shock. Hotchkiss et al [9] observed a marked reduced number of DCs in the spleen of patients with sepsis. Efron and Moldawer [16] demonstrated depletion of DCs in murine lymph nodes during polymicrobial sepsis.

The partial improvement in the number of mDCs and pDCs in patients after 28 days compared with on admission may suggest that incomplete recovery of DCs occurred with the clinical improvement. Our results are in line with that of Poehlmann et al [23], who observed a profound reduction in peripheral mDC and pDC counts in septic patients at baseline that remained significantly decreased on day 28 compared with controls. Sepsis can be considered a race between the pathogens and the host immune response. Pathogens seek an advantage by incapacitating various aspects of host defenses. They induce the apoptotic depletion of immune effector cells [21]. Apoptosis may be responsible for the decline in the DCs population in PB of our septic patients. Riccardi et al [24] found a significant higher percentage of apoptotic DC cells in septic patients in comparison with healthy subjects, and at the clinical resolution of septic episode, patients still show significantly reduced mDCs number in comparison with healthy subjects.

Table 4 Frequencies of DCs and their expression of CD86 and CD83 in patients with sepsis on admission and after 28 days of admission and the controls

	Patients on admission (23)	Patients at follow-up (23)	Controls (40)	P^1	P^2	P^3
mDCs %	0.23 ± 0.23	0.93 ± 0.45	1.4 ± 0.42	.000	.001	.001
pDCs %	0.22 ± 0.33	0.61 ± 0.25	1.03 ± 0.29	.000	. 000	.000
mDCs/pDCs ratio	1.38 ± 0.29	1.47 ± 0.35	1.53 ± 0.27	.177	.395	.258
$CD86^+$expression on the entire DCs %	28.41 ± 9.11	41.06 ± 14.18	45.92 ± 26.37	.005	.000	.597
MFI of $CD86^+$ on the entire DCs	94.62 ± 15.28	135.69 ± 28.81	156.03 ± 55.67	.002	.001	.289
$CD83^+$expression on the entire DCs %	16.92 ± 3.1	20.74 ± 3.83	21.34 ± 6.99	.029	.045	.752
MFI of $CD83^+$ on the entire DCs	51.06 ± 13.75	71.86 ± 15.77	75.45 ± 16.14	.000	.001	.398

Data represented as means ± SD. $P \leq .05$ is significant.
P^1, patients vs controls (1-way ANOVA test); P^2, patients on admission vs follow-up (paired *t* test). P^3, follow-up vs controls (1-way ANOVA).

Table 5 Correlations between baseline DCs and some investigated parameters in septic patients

		SOFA score	WBCs	Urea	Creatinine	C-reactive protein
r	mDCs %	−0.582	−0.698	−0.516	−0.432	−0.682
P		.001	.001	.017	.016	.001
r	pDCs %	−0.613	−0.647	−0.625	−0.615	−0.516
P		.001	.001	.001	.001	.004

r indicates correlation coefficient.

The immature DCs capture and process foreign antigens and then differentiate into mature DCs. The mature DC is characterized by its expression of high levels of major histocompatibility complex II and costimulatory molecules such as CD40, CD80, and CD86 [25,26]. CD80 and CD86 stimulated via CD28 [27]. Any defect in this cascade will result in the failure of competent antigen presentation, which will impair the body's ability to clear a microbial challenge such as that seen with sepsis [28]. Surface CD83 expression is a hallmark of mature human DCs. The expression of CD83 by DCs is consistent with its reported functions in the regulation of antigen presentation [29]. Cell surface or immobilized CD83 has been shown to enhance $CD8^+$ T-cell activation [30].

The decreased expression of CD86 and CD83 observed in our complicated septic patients may be associated with the immune paralysis in these patients. Our results are consistent with the results of Riccardi et al [24], who reported that sorted DCs from septic patients showed reduced levels of CD83 and CD86 than the healthy controls. Nolan et al [27,31] reported that both humans and mice with sepsis exhibit a loss of CD86 on circulating monocytes. Newton et al [32] reported that the expression of CD86 was significantly decreased on peritoneal macrophages after the onset of sepsis.

The higher baseline numbers of mDCs and pDCs in the survival than in nonsurvival septic patients and the lower expression of CD86 and CD83 on the entire DCs in nonsurvival septic patients in this study may suggest that a proper DC count and function is essential for a successful outcome of sepsis. Both SOFA score and C-reactive protein were higher in nonsurvival than in survival septic patients, and they improved after 28 days. de Jong et al [33] found that nonsurvivors had greater disease severity, expressed by higher Simplified Acute Physiology Score II and SOFA score. Keshet et al [34] found that the high C-reactive protein was a marker of sepsis and that higher C-reactive protein was significantly associated with mortality. Also, Memiş et al [35] found that median C-reactive protein levels were significantly higher among the nonsurvival than among survival septic patients. Our findings were in accordance with that of de Jong et al, Keshet et al, and Memiş et al. The negative correlation of DCs with SOFA score, WBCs, urea, creatinine, and C-reactive protein may also suggest the importance of DCs in the estimation of prognosis of sepsis. Our results are in line with that of Guisset et al [36], who reported that the early low DC counts were correlated with disease severity as assessed by Simplified Acute Physiology score or SOFA score and predicted fatal outcome.

5. Conclusion

Sepsis is associated with a reduced level of DCs and decreases their maturation. The estimation of DCs number and maturation state may be used as prognostic makers of sepsis.

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