Cytokine 120 (2019) 22–27

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Interleukin-18 serum levels in sepsis: Correlation with disease severity and inflammatory markers

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ARTICLE INFO

Keywords:
Sepsis
Septic shock
Interleukin 18
Biomarker

ABSTRACT

Purpose: Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection and a syndrome shaped by pathogen and host factors with characteristic that evolve over time. The study was conducted to evaluate the prognostic and discriminative value of IL-18 assessment in comparison to PCT, CRP, WBC in early stage of sepsis and septic shock.

Methods: An observational and prospective study was conducted in the group of 40 ICU patients with diagnosis of sepsis or septic shock, serum PCT, IL-18, CRP and WBC measurements were performed on admission, and on the 2nd, 3rd and 5th therapy day. The level of IL-18 was determined with commercially available test according to manufacturer's protocol.

Results: There were no statistically significant differences in IL-18 levels in survivors vs non-survivors and in sepsis vs septic shock subgroups the IL-18 levels were statistically significant in the course of the study except for the 5th day.

Conclusion: The PCT, CRP and WBC levels revealed no significant differences between any analyzed subgroups in all time points during study. According to our results the IL-18 is a biomarker better differentiating sepsis and septic shock status than PCT, CRP and WBC but with no prognostic impact.

1. Introduction

Sepsis is the major health problem because of the high morbidity and mortality in the intensive care units (ICU) worldwide [1]. It is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection and a syndrome shaped by pathogen and host factors with characteristic that evolve over time [2]. The intensity and duration of the immune-inflammatory response is regulated by cytokines. Their excessive and uncontrolled release can lead to cell metabolism dysfunction, and organ failure, and ultimately death [3].

Cytokines include the interleukins (IL), interferons (IFN), chemokines. Among the interleukins is a group with a pro-inflammatory effect: TNF-α (tumor necrosis factor- α), IL-6 (interleukin 6), IL-12, IL-18 and anti-inflammatory (IL-4 and IL-10). One of the first defense cytokines is IL-18 that is implicated mainly in the generation of T-helper response [4].

Initially described as an IFN-γ-inducing factor (interferon-gamma-inducing factor), IL-18 is involved in Th1 (type 1 T helper) and NK

Abbreviations: NLRs, nucleotide-binding oligomerization domain-like receptors; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase activation and recruitment domain; MAP, mean arterial pressure; MODS, multiple organ dysfunction syndrome; MRSA, methicillin-resistant Staphylococcus aureus; G-CSF, granulocyte colony-stimulating factor; MIP-2, macrophage inflammatory protein; SAPS II, simplified acute physiology score; IL-17-producing γδ T cells, IL-17-producing gammadelta T cells

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https://doi.org/10.1016/j.cyto.2019.04.003
Received 17 November 2018; Received in revised form 11 March 2019; Accepted 5 April 2019
Available online 16 April 2019
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Table 1
Demographic and clinical characteristics of the critically ill patients in sepsis vs septic shock and survivors vs non-survivors subgroups.

	Sepsis (n = 17)	Septic shock (n = 23)	Survivors (n = 29)	Non-survivors (n = 11)
Age (years)[a]	64.8	64.6	62.9	69.3
Sex (female/male)[b]	9/8	15/8	16/13	8/3
APACHE II 1st day[a]	20.2 (11–29)	23.8 (11–40)	19.9 (11–40)	23.8 (13–32)
SOFA 1st day[a]	8.1 (3–17)	9.5 (4–14)	8.4 (3–17)	10.2 (5–14)
SOFA 5th day[a]	6.7 (1–15)	8.5 (0–15)	6.4 (0–15)	11.3 (7–15)
WBC [x10^3mm] 1st day[a]	13.4 (4.6–26.9)	18.0 (2–54)	14.8 (1.8–54.4)	19.2 (7.7–40.4)
WBC [$\times 10^3$ mm] 5th day[a]	13.2 (4.8–21.4)	15.5 (2–55)	13.9 (1.8–55.3)	16.1 (4.9–30.9)
CRP [mg/l] 1st day[a]	216.7 (29.2–455)	192.6 (4–536)	218.7 (29–535)	97.5 (3.8–155)
CRP [mg/l] 5th day[a]	131.1 (34.3–342)	114.8 (51–205)	125.9 (34.3–342)	110.7 (62.3–204.7)
PCT [μg/l] 1st day[a]	21.5 (0.7–153.5)	28.5 (1–134)	24.1 (0.65–153.49)	29.7 (0.2–134)
PCT [μg/l] 5th day[a]	3.6 (0.5–6.5)	16.9 (1–164)	15.4 (0.51–163.8)	7.1 (1.5–21.7)
Source of infection				
Abdominal[b]/SOFA[a]	9/ 9.2 (6–17)	21/ 9.4 (6–14)	20/ 9.0 (4–17)	10/ 10.2 (5–14)
Respiratory[b]/SOFA[a]	8/ 6.6 (3–11)	2/ 11.0 (10–12)	9/ 7.2 (3–12)	1/ 10 (10–11)
Pathogen[b]				
Gram-positive	5	5	9	1
Gram-negative	4	8	7	5
Mixed	1	6	5	2
Unknown	7	4	8	3

[a] Presented values are expressed as mean with range.
[b] Actual number of patients.

(natural killer) cell activation, but also in Th2, IL-17-producing γδ T cells (IL-17-producing gammadelta T cells) and macrophage activation [5].

IL-18 is classified to the IL-1 family of cytokines due to the structural and functional similarity to IL-1. Similarly to IL-1α and IL-33, precursor of IL-18 is released from cells undergoing apoptosis, probably as a result of neutrophil proteases (proteinase-3) activity [6].

IL-18 is also present as an integral membrane protein but requires caspase-1 for full activity in order to induce IFN-γ (interferon-gamma) [7]. Intracellular activation of caspase (caspase-1 or caspase-1 like enzymes) in antigen presenting cells is mediated through TLR (Toll-like receptor) or Fas signaling, respectively. Caspase-1 and the extracellular serine esterase, PR-3 (proteinase-3), induce activation of biologically active interleukin 18 (18 kDa) by cleavage of its precursor pro-IL-18 (24 kDa) [8]. The active form of IL-18 is released mainly from macrophages and dendritic cells, while an inactive precursor of IL-18 remains in the mesenchymal cells' intracellular compartments [9]. An increased expression of both the inactive and active form of IL-18 is observed in T and B cells, keratinocytes, adrenal cortex cells, chondrocytes, epithelial and Kupffer cells [10].

IL-18 binds to its specific receptor (IL-18Rα, also known as IL-1R7) forming a low affinity ligand chain. This is followed by recruitment of the IL-18Rβ chain. IL-18 then uses the same signaling pathway as IL-1 to activate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and induce inflammatory mediators such as adhesion molecules, chemokines and Fas ligand [5].

Its effect on the NK cells accelerates their maturation, the production of IL-1, TNF-α and IFN-γ and augments these cells cytotoxicity by inducing enhanced expression of perforins and FAS ligand (CD95L) [11]. Pathogens are robust activators of caspase-1 and IL-1β/IL-18 processing. Pathogens or PAMPs (pathogen associated molecular patterns) that gain access to the host cell cytosol can be sensed by resident NLRs (nucleotide-binding oligomerization domain-like receptors). NLRP3 can sense bacterial, viral, and fungal pathogens that enter the cytosol, most likely via virulence factors, PAMPs, or DAMPs (damage-associated molecular patterns) [12]. After being stimulated by diverse PAMPs and DAMPs, NLRP 3 recruits ASC (apoptosis-associated speck-like protein containing a CARD (caspase activation and recruitment domain)) and caspase-1, leading to activation of caspase-1, maturation and secretion of IL-1β and IL-18 [13]. Produced mainly by antigen-presenting cells, IL-18 is a pleiotropic factor involved in the regulation of both innate and acquired immune responses, playing a key role in autoimmune, inflammatory, and infectious diseases [14].

The activity of IL-18 is balanced by the presence of high affinity, naturally occurring IL-18 –binding protein. In humans, increased disease severity can be associated with imbalance of IL-18 to IL-18–BP. Neutralization of IL-18 by soluble receptors was compared with that of IL-18BP. At an equimolar concentration of IL-18BP to IL-18, inhibition of 90% of IL-18 activity was observed, whereas a 4-fold molar excess of the soluble IL-18Ra had no effect [15].

The aim of our study was to evaluate the usefulness of assessment of serum IL-18 in sepsis/septic shock diagnosing, and for differentiating survivors vs non-survivors in critically ill patients hospitalized in the Department of Anesthesiology and Intensive Therapy of Wroclaw Medical University, and establish the relationship with inflammatory biomarkers such as procalcitonin (PCT), C-reactive protein (CRP), white blood cells (WBC), and clinical scores APACHE (Acute Physiology and Chronic Health Evaluation) II and SOFA (Sequential Organ Failure Assessment).

2. Materials and Methods

2.1. Study population

This study was the observational and prospective where forty critically ill patients with sepsis or septic shock diagnosis, were enrolled within 24 h of entry into the ICU (Table 1). The critically ill patients were classified according to the criteria for sepsis or septic shock [2]. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and septic shock was identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP (mean arterial pressure) ≥ 65 mmHg and having a serum lactate level > 2 mmol/l despite adequate volume resuscitation [2].

The exclusion criteria were age below 18 years, pregnancy or terminal illness with a no chance for meaningful recovery.

All patients in the study received a standard treatment for sepsis or septic shock (mechanical ventilation, antimicrobial therapy, vasopressor therapy, fluid resuscitation). For all patients the following data were recorded: age, gender, source of infection on the admission, basic laboratory tests, CRP, PCT and WBC levels on admission, on the 2nd, 3rd and 5th study day. The clinical patients status was assessed with the APACHE II score [16] on admission to the ICU, and the extent of multiple organ failure was evaluated with SOFA [17] on admission, and

on the 2nd, 3 rd and 5th therapy day.

The study was conducted in the Department of Anesthesiology and Intensive Therapy of Wroclaw Medical University, Poland. The research was approved by the Medical Ethics Committee of Wroclaw Medical University and was performed in accordance with Helsinki Declaration of 1975, as revised in 1983. The informed consent was obtained from the patients or their legal representatives.

The control group included 30 healthy volunteers (14 female and 16 male) with mean age 62.5 and range (in years) 52–84, who were recruited from the Diagnostics Laboratory for Teaching and Research of Wroclaw Medical University.

2.2. Blood sampling and IL-18 assessment

Blood samples were drawn on the admission, on the 2nd, on the 3rd and 5th study day. The obtained serum was aliquoted and stored at −80 °C until analysis. The IL-18 levels in serum samples of septic patients and healthy volunteers were examined by means of the commercially available immunoenzymatic test (Human IL-18 Platinum ELISA, eBioscienceDx Diagnostics, Austria), according to the manufacturer's instruction. Samples were measured in duplicates and results were presented as ng/ml. The test sensitivity was 9.0 pg/ml.

2.3. Statistical analysis

All statistical analyses were performed with StatSoft. Inc. (2014). STATISTICA (data analysis software system), version 12.0. www.statsoft.com. The normality of the distribution was estimated by the Kolmogorov-Smirnov test. The data were analyzed with a nonparametric test (Mann-Whitney *U* test) to compare the two groups. A $P \leq$ value 0.05 was considered to be statistically significant. Correlation analysis with continuous data was conducted using Pearson's correlation test (r).

3. Results

The patients' status was assessed by APACHE II and SOFA scores. APACHE II score on the 1st day in survivors vs non-survivors was 19.9 and 23.8, respectively, and in sepsis vs septic shock subgroup was 20.2 and 23.8, respectively. In non-survivors and in septic shock subgroups the most common source of infection was abdominal (n = 10 and n = 21, respectively). The ICU mortality was 25%.

The mean IL-18 level in healthy volunteers group was 208 ng/l. The mean IL-18 level in septic patients whole cohort was 1274 ng/l (1st day), 1156 ng/l (2nd day), 1141 ng/l (3rd day), 1138 ng/l (5th day), respectively. These results were significantly different with $P < 0.001$ at all time points of the study.

There was a strong correlation between IL-18 and WBC in the septic shock non-survivors subgroup on the 1st day ($r = 0.85$, $P = 0.029$) and in septic shock survivors on the 2nd and 3rd day ($r_{2nd} = 0.82$, $P = 0.02$; $r_{3rd} = 0.98$, $P = 0.006$). In the septic shock survivors there was a strong negative correlation between IL-18 and CRP on all analyzed days except for the 3rd day ($r_{1st} = -0.84$, $P = 0.0039$; $r_{2nd} = -0.87$, $P = 0.049$; $r_{5th} = -0.98$, $P = 0.013$). There were no statistically significant differences in IL-18 level in survivors vs non-survivors (Table 2). In sepsis vs septic shock the IL-18 level was statistically significant in the course of the study except for the 5th day (Table 3). There were no statistically significant differences in IL-18 level in survivors vs non-survivors in patients with septic shock diagnosis (Table 4). There were statistically significant differences in IL-18 level except for the 5th day in sepsis vs septic shock survivors (Table 5). The SOFA score value was significantly different in survivors vs non-survivors for all analyzed days except for the 1st day and there were no statistically significant differences in SOFA score value in sepsis vs septic shock in the study except for 3rd day (Table 6). In the septic patients group the IL-18 level was higher in case of abdominal source of infection and significantly different in comparison to pulmonary source of infection at all time points during study (Table 7). There was no significant difference for PCT assessments in the same group of patients (Table 7). The CRP, PCT levels and WBC revealed no significant differences between any analyzed subgroups at all time points during study. There was no statistically significant difference of IL-18 levels in infections caused by Gram-positive vs Gram-negative pathogens at all time points during study (Table 8).

Table 2
Comparison of IL-18 levels in survivors vs non-survivors during the five study days.

	Survivors (n = 29)	Non-survivors (n = 11)	P value*
$IL\text{-}18_{1st\ day}$	846 (671–1372)	1147 (762–1629)	0.450
$IL\text{-}18_{2nd\ day}$	926 (486–1296)	1328 (804–1420)	0.228
$IL\text{-}18_{3rd\ day}$	818 (517–1461)	1082 (985–1611)	0.228
$IL\text{-}18_{5th\ day}$	836 (411–1553)	1096 (642–1888)	0.285

Data are presented as median values and interquartile range (IQR) (25th to 75th) percentiles. IL-18, interleukin 18.

* P value for difference between survivors and non-survivors. The concentration of IL-18 is expressed with ng/l.

Table 3
Comparison of IL-18 levels in sepsis vs septic shock during the five study days.

	Sepsis (n = 17)	Septic shock (n = 23)	P value*
$IL\text{-}18_{1st\ day}$	740 (599–993)	1218 (846–1775)	0.013
$IL\text{-}18_{2nd\ day}$	600 (448–945)	1328 (936–1686)	0.0002
$IL\text{-}18_{3rd\ day}$	577 (457–1109)	1143 (824–1581)	0.020
$IL\text{-}18_{5th\ day}$	473 (407–892)	1108 (690–1745)	0.070

Data are presented as median and interquartile range (IQR) (25th to 75th) percentiles. IL-18, interleukin 18;

* , P value for difference between sepsis and septic shock. The concentration of IL-18 is expressed with ng/l.

Table 4
Comparison of IL-18 levels for survivors included in sepsis vs septic shock during the five study days.

	Sepsis (n = 17)	Septic shock (n = 12)	P value*
$IL\text{-}18_{1st\ day}$	740 (599–993)	1364 (914–1914)	0.023
$IL\text{-}18_{2nd\ day}$	600 (448–945)	1481 (964–2271)	0.0007
$IL\text{-}18_{3rd\ day}$	577 (457–1109)	1310 (743–1551)	0.040
$IL\text{-}18_{5th\ day}$	473 (407–892)	1269 (724–1654)	0.236

Data are presented as median values and interquartile range (IQR) (25th to 75th) percentiles. IL-18, interleukin 18.

* P value for difference between survivors included in sepsis and septic shock. The concentration of IL-18 is expressed with ng/l.

Table 5
Comparison of IL-18 levels in survivors vs non-survivors with septic shock diagnosis during the five study days.

	Survivors (n = 12)	Non-survivors (n = 11)	P value*
$IL\text{-}18_{1st\ day}$	1364 (914–1914)	1147 (702–1629)	0.440
$IL\text{-}18_{2nd\ day}$	1481 (964–2271)	1328 (804–1420)	0.340
$IL\text{-}18_{3rd\ day}$	1310 (743–1551)	1082 (985–1611)	1.00
$IL\text{-}18_{5th\ day}$	1269 (724–1654)	1096 (642–1888)	1.00

Data are presented as median values and interquartile range (IQR) (25th to 75th) percentiles. IL-18, interleukin 18.

* P value for difference between survivors and non-survivors with septic shock diagnosis. The concentration of IL-18 is expressed with ng/l.

Table 6
SOFA score values in survivors vs non-survivors and in sepsis vs septic shock during five study days.

	Survivors (n = 29)	Non-survivors (n = 11)	P value*	Sepsis (n = 17)	Septic shock (n = 23)	P value*
$SOFA_{1st\ day}$	8.4 (3–17)	10.2 (5–14)	0.11	8.1 (3–17)	9.5 (4–14)	0.15
$SOFA_{2nd\ day}$	7.7 (2–16)	10.8 (5–14)	0.01	7.4 (2–16)	9.4 (2–14)	0.10
$SOFA_{3rd\ day}$	6.9 (1–13)	11.4 (6–15)	0.0004	6.4 (2–13)	9.5 (1–15)	0.01
$SOFA_{5th\ day}$	6.4 (0–15)	11.3 (7–15)	0.0007	6.7 (1–15)	8.5 (0–15)	0.18

Data are presented as median values and in the brackets as minimum and maximum values. SOFA, Sepsis-related Organ Failure Assessment.
* P value for difference between survivors and non-survivors, and between sepsis and septic shock.

Table 7
The levels of IL-18 and PCT in abdominal and pulmonary source of infection.

	Abdomen	Lungs	P value*
$IL\text{-}18_{1st\ day}$	1204 (747–1632)	736 (599–762)	0.020
$IL\text{-}18_{2nd\ day}$	1155 (804–1586)	542 (418–963)	0.006
$IL\text{-}18_{3rd\ day}$	1126 (793–1611)	530 (431–743)	0.005
$IL\text{-}18_{5th\ day}$	1037 (665–1754)	411 (407–443)	0.01
$PCT_{1st\ day}$	9.8 (4.2–32.2)	3.7 (1.2–34.3)	0.720
$PCT_{2nd\ day}$	8.0 (2.9–20.9)	13.0 (1.6–54)	0.930
$PCT_{3rd\ day}$	7.2 (3.6–17.7)	11.6 (2.1–21.1)	0.640
$PCT_{5th\ day}$	6.3 (1.8–7.5)	2.2 (0.5–5.7)	0.57

Data are presented as median values and interquartile range (IQR) (25th to 75th percentile). IL-18, interleukin 18; PCT, procalcitonin.
* P value for difference between abdominal and pulmonary source of infection. The concentrations of IL-18 and PCT are expressed with ng/l and μg/l, respectively.

Table 8
Comparison of IL-18 levels in Gram-positive and Gram-negative infections.

	Gram-positive (n = 10)	Gram-negative (n = 12)	P value*
$IL\text{-}18_{1st\ day}$	1106 (761–1372)	753 (598–1449)	0.28
$IL\text{-}18_{2nd\ day}$	945 (804–1119)	963 (397–1420)	0.53
$IL\text{-}18_{3rd\ day}$	841 (793–1322)	649 (434–1461)	0.28
$IL\text{-}18_{5th\ day}$	977 (889–1553)	859 (372–1745)	0.97

Data are presented as median values and interquartile range (IQR) (25th to 75th percentiles). IL-18, interleukin 18.
* P value for difference between Gram-positive and Gram-negative infections. The concentrations of IL-18 are expressed with ng/l.

3.1. IL-18 and ROC analysis in sepsis patients

In ROC curve of IL-18 analysis for sepsis diagnosis on the day of admission the cut-off value for IL-18 was 761 ng/l, and area under curve (AUC) was 0.729, sensitivity was 0.706, specificity was 0.826 (P = 0.006, PPV = 0.75, NPV = 0.79, Youden index = 0.532) (Fig. 1). On the 2nd therapy day the cut-off value was 762 ng/l, AUC was 0.872, sensitivity was 0.625, specificity was 0.905 (P = 0.00005, PPV = 0.83, NPV = 0.76, Youden index = 0.57 (Fig. 1). On the 3rd therapy day the cut-off value was 577 ng/l, AUC was 0.724, sensitivity was 0.53, specificity was 0.9 (P = 0.01, PPV = 0.81, NPV = 0.72, Youden index = 0.53 (Fig. 1). On the 5th therapy day the cut-off value was 503 ng/l, AUC was 0.72, sensitivity was 0.6, specificity was 0.94 (P = 0.07, PPV = 0.86, NPV = 0.8, Youden index = 0.54) (Fig. 1).

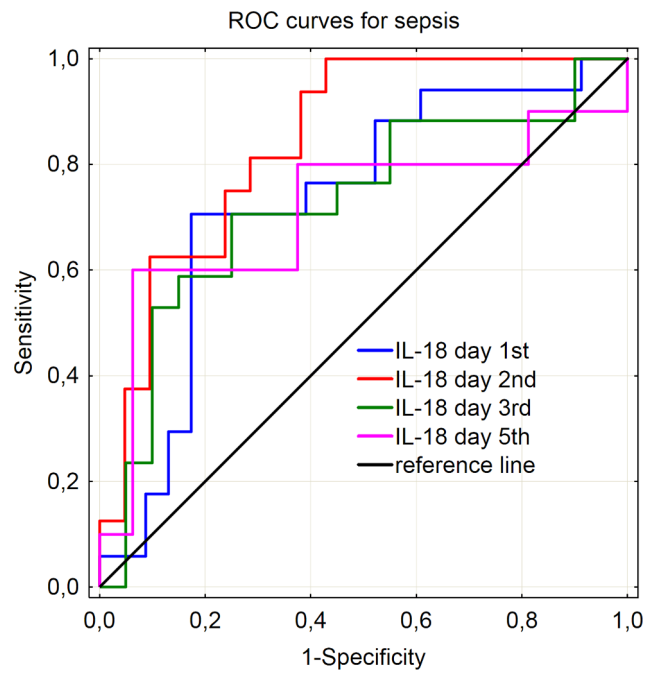

Fig. 1. ROC curve for IL-18 analysis for sepsis diagnosis. ROC, receiver operating curve; AUC, area under curve; IL-18, interleukin 18.

4. Discussion

According to newest definition sepsis results from an aberrant or dysregulated host response to infection and the presence of life-threatening organ dysfunction. IL-18 has been regarded to be an important factor in the pathophysiology of sepsis [18].

This study was performed in order to determine the prognostic and discriminative properties of IL-18 in critically ill patients. In the study, the level of IL-18 was significantly higher in septic patients cohort vs healthy volunteers at all study time points. Similarly, Feng et al. revealed in septic patients cohort analysis that serum levels of IL-18 and IL-6 were significantly higher in septic patients that in control healthy adults group [19]. IL-1β and IL-18 gene expression was upregulated in septic patients with more robust modulation in the non-surviving patients [20]. Oberholzer et al. revealed that septic patients who died and patients with septic shock exhibited higher levels of IL-18 than survivors and septic patients without shock [21]. This observation is coincident with our in term of IL-18 release range in septic shock vs sepsis group. In Garcia-Obregon analysis a significantly higher level of IL-18 was detected in the plasma from septic patients than in the plasma from the healthy volunteers [22].

IL-18 participates in innate immune reprogramming [23]. In animal model Philippart et al. demonstrated the importance of IL-18 in preventing alveolar macrophage endotoxin tolerance through studies of IL-18 mRNA expression in IL-18r −/− mice and injection of IL-18 in rag2 −/− and μ −/− mice. Authors concluded that at homeostasis in the lungs, constitutive expression of granulocyte–macrophage colony-stimulating factor, IL-18, IFN-γ and possibly IL-15 create microenvironment specific to the lungs that prevents alveolar macrophages from becoming tolerant to endotoxin [24]. Kinoshita et al. in animal model investigated the efficacy of IL-18 treatment in postburn MRSA (methicillin-resistant Staphylococcus aureus) infection. Alternate-day injections of IL-18 into burn-injured C57BL/6 mice significantly increased their survival after MRSA infection and after methicillin-sensitive *S. aureus* infection. IL-18 treatment increased/restored the serum TNF-α, IL-17, IL-23, G-CSF (granulocyte colony-stimulating factor), and MIP-2 (macrophage inflammatory protein) levels, as well as the neutrophil

count, after MRSA infection of burn-injured mice. It also improved impaired neutrophil functions, phagocytic activity, production of reactive oxygen species, and MRSA-killing activity. Neutrophils from IL-18-treated burn-injured mice were adoptively transferred into non-treated burn-injured mice 2 days after MRSA challenge, and survival of the recipient mice increased [25].

Grobmyer et al. revealed that the LPS (lipopolysaccharide) (1or 2 ng/kg) was insufficient to increase plasma IL-18 in healthy adults measured 3, 12, and 24 h following challenge. In contrast, in the first 96 h of admission to the surgical ICU, mean maximal serum IL-18 was elevated (1222 ± 259 ng/ml) in septic patients compared to healthy adults (191 ± 42 ng/ml, $P < 0.01$) [26]. In our study all patients with abdominal source of sepsis/ septic shock underwent different range of surgical interventions and presented significantly higher level of IL-18 than patients with pulmonary source of sepsis/ septic shock or healthy volunteers. This observation, in our opinion, should be explained by more advanced organ dysfunctions in abdominal sepsis/ septic shock. This fact is confirmed by higher SOFA score values observed in abdominal patients' subgroup independently of the analysis configuration.

In our study results we didn't reveal any significant difference between IL-18 release in Gram-positive vs Gram-negative pathogen infections. On the contrary Oberholzer in his analysis revealed that degree of IL-18 release is significantly higher in case of Gram-positive than in Gram-negative infections [21]. There was 50% of septic shock diagnosis in Gram-positive group in our study and 82% of septic shock diagnosis in Oberholzer's analogous group. Possibly this is one of the reasons responsible for these opposed results.

Esquerdo et al. evaluated expression of genes involved in inflammasome signaling pathways in septic patients, their interaction networks and the predicted functions modulated in survivors and non-survivors. Authors observed higher IL-18 and IL-1b expression at the gene level in the septic patients, and measured their plasma levels. IL-18 plasma levels were significantly higher in septic patients, but no significant differences were detected between the surviving (981.4 pg/ml; range: 363.6–3464.2 pg/ml) and non-surviving patients (936.0 pg/ml; range: 362.6–3097.6 pg/ml) [20]. These results are coincided with ours and revealed, that in sepsis/ septic shock at the gene level the outcome does not influence the IL-18 release. In our study IL-18 results in survivors vs non-survivors and in survivors vs non-survivors cohort with septic shock diagnosis confirmed that IL-18 level has no predictive impact independently of the analysis configuration. In contrast, Eidt et al. revealed in comparative IL-18 analysis in septic patients that mortality in study population was directly proportional to IL-18 plasma levels and that IL-18 was the only factor associated with the prediction of mortality [3]. According to Edit's results in severe sepsis and septic shock groups the measurements of IL-18 may increase the prediction power of a lethal outcome to 88.9% and 90% respectively [3]. In our study though the SOFA score values were significantly lower in survivors group, confirming less advanced MODS (multiple organ dysfunction syndrome), this fact was not reflected by significantly lower IL-18 level in survivors. Additionally the non-survivors group was a small group with very differentiated IL-18 levels. In our opinion these two factors are responsible for non-significant difference in IL-18 release between these two groups in our results.

Emmanuilidis et al. in analysis of systemic IL-18 and IL-12 release during postoperative sepsis demonstrated that serum IL-18 level was significantly increased in sepsis non-survivors compared with survivors at all time points of the study [27].

As we observed earlier there was no significant difference in CRP and WBC level in the course of the study. According to our results the CRP and WBC measurements present no diagnostic and prognostic values though being used as everyday septic patient's assessment [28]. The strong correlations between IL-18 and WBC and CRP in septic shock survivors subgroup revealed that IL-18 closely reflects the immuno-inflammatory process in case of well-controlled course of septic shock treatment.

The IL-18 level didn't correlate with APACHE II and SOFA score values as it was revealed in our results. Two studies enrolled patients with sepsis respectively septic shock and found genes associated with disturbed immune function already early in the course of the disease. Both studies compared patients with sepsis to healthy controls. Cazalis et al. found no correlation of the gene signature with SAPS II score (Simplified Acute Physiology Score), while Parnell et al. found a pronounced dysregulation of identified genes in non-surviving patients compared to survivors [29,30]. In our opinion this geno-immunological chaos was responsible for lack of correlations between IL-18 and WBC and CRP in non-survivors subgroup in our study and finally for no efficacy of the treatment.

5. Conclusion

Based on the revealed results we conclude that the IL-18 release has no prognostic impact in sepsis/septic shock, and IL-18 is a biomarker with diagnostic and discriminative properties better than PCT, CRP and WBC. Its extent of release is source dependent and IL-18 early assessment is a sepsis source indicative starting from the 1st ICU treatment day. This study has some limitations as it was conducted at a single center with relatively small population size. A large study is needed to validate our results.

Acknowledgements

This work was supported by Wroclaw Medical University (grant number 75 Pbmn).

Conflict of interest

We declare that all authors have no conflicts of interest.

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