ORIGINAL ARTICLE

# Interleukin-18 levels reflect the long-term prognosis of acute lung injury and acute respiratory distress syndrome

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**Abstract**

*Purpose*   The purpose of this study was to investigate the relationship between the blood levels of interleukin (IL)-18 measured in the early stage of acute respiratory failure and the prognosis for patient survival.

*Methods*   The study subjects were 38 patients with acute respiratory failure treated at our institution during the 4-year period from April 2004 to March 2008. The underlying clinical condition was defined as acute respiratory distress syndrome (ARDS; $n = 12$) or acute lung injury (ALI; $n = 26$). The serum levels of interleukin (IL)-18, IL-12, and tumor necrosis factor (TNF)-α were measured by enzyme-linked immunosorbent assays.

*Results*   The ARDS group showed significantly higher serum levels of IL-18, IL-12, and TNF-α even at an early stage after disease onset compared with the ALI group. A negative correlation was noted between the $PaO_2/FIO_2$ ratio (P/F ratio) and serum IL-18 level. Analysis of all 38 patients with ALI/ARDS revealed a 30-day mortality rate of 7.9 %, 60-day mortality rate of 15.8 %, and 90-day mortality rate of 18.4 %. The early-stage serum levels of IL-18, IL-12, and TNF-α were significantly higher in the non-survivors at 60 and 90 days, but not at 30 days, than in the corresponding survivors.

*Conclusion*   The present data demonstrate an inverse correlation between serum IL-18 level and the P/F ratio, suggesting the possible involvement of IL-18 in the pathogenesis of respiratory failure in patients with ALI/ARDS. Early-stage serum IL-18, IL-12, and TNF-α levels appear to reflect the >60-day prognosis in patients with ALI/ARDS.

**Keywords**   Interleukin 18 · Sepsis · ALI · ARDS · Prognosis

## Introduction

When mice preinjected with thermally killed *Propionibacterium acnes* cells are administered a small quantity of lipopolysaccharide (LPS), an interferon (IFN)-γ-inducing factor distinct from interleukin (IL)-12, named IL-18, is produced in the blood [1]. IL-18 is produced by macrophages, especially Kupffer cells in the liver [2]. It has been demonstrated that there is no microscopic evidence of liver tissue necrosis and no elevation of the serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase levels in mice injected with an anti-IL-18 antibody before LPS administration at 1 week after pretreatment with the killed *P. acnes* cells [3].

In a previous study, we demonstrated elevated serum IL-18 levels in patients with sepsis, with a significant correlation noted between serum IL-18 level and sepsis severity [4]. We also investigated serum IL-18 levels in patients with acute pancreatitis and found that the serum IL-18 level reflects acute pancreatitis severity and is correlated with the serum total bilirubin level in these patients [5]. Furthermore, we have investigated the possibility of important roles for IL-18 in the development of postoperative hepatic failure [6], dengue fever [7], multiple organ dysfunction syndrome (MODS) complicating sepsis [8], and fulminant hepatitis [9]. From these studies, we have inferred the

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possible involvement of IL-18 in the genesis of various serious disease states.

IL-18 was reported to be detectable in bronchoalveolar lavage (BAL) fluid at an early stage in pulmonary inflammatory disorders associated with increased lung vascular permeability [10]. From continuous investigation of the serum IL-18 levels in sepsis patients with endotoxemia, we have reported the possible involvement of IL-18 in the development of acute respiratory failure (ARF) [11, 12].

In this study, we investigated the serum levels of IL-18, IL-12, and tumor necrosis factor (TNF)-$\alpha$ in the early stage after disease onset in patients with ARF complicating sepsis (septic ARF) and examined the relationships between serum cytokine levels and survival prognosis of the patients.

## Materials and methods

This study was conducted after obtaining informed consent for participation from each patient or their family members, and with approval from the Ethics Committee of Iwate Medical University.

Diagnosis of sepsis was based on the criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [13]. For evaluation of lung oxygenation capacity, we determined the PaO$_2$/FIO$_2$ ratio (P/F ratio). Diagnoses of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) were made in accordance with the criteria of Bernard et al. [14]. Accordingly, in this study we diagnosed the condition as ALI when the P/F ratio was $\geq$200 but <300, and as ARDS when the P/F ratio was <200. The Acute Physiology and Chronic Health Evaluation score (APACHE II score) [15] and Sequential Organ Failure Assessment score (SOFA score) [16] were employed for grading the severity of the patients' clinical condition. The severity scoring was performed through consultation among multiple acute medicine specialists qualified as infection control doctors.

The subjects of this study were 38 tracheally intubated septic ALI/ARDS patients with APACHE II scores of $\geq$15 (22 men, 16 women) in whom blood sampling was feasible within about 3 h of the diagnosis of ALI/ARDS and who were seen during the 4-year period from April 2004 to March 2008.

Treatments for sepsis, septic shock, disseminated intravascular coagulation, etc. were in accordance with commonly prescribed therapeutic measures. For treatment of MODS, generally prescribed conventional therapies against the various pathophysiological abnormalities were undertaken as required. Respiratory management against ALI/ARDS was performed at a tidal volume of 8–10 ml/kg and a positive end-expiratory pressure of 5–12 cmH$_2$O. Sivelestat sodium hydrate was administered at 0.2 mg/kg/h during tracheal intubation and for 1–2 days after removal of the endotracheal tube, for a maximum duration of 14 days.

Immediately after blood sample collection, the serum was separated and stored in a freezer at −80 °C until analysis. IL-18 was measured by enzyme-linked immunosorbent assay (ELISA) (MBL, Nagoya, Japan). The determination limit of the assay was 12.5 pg/ml; normal range was $\leq$259.4 pg/ml. IL-12 was quantified by ELISA (Cosmo Bio, Tokyo, Japan) with a determination limit of 6 pg/ml. TNF-$\alpha$ was determined by ELISA (TFB, Tokyo, Japan) with a determination limit of 3 pg/ml.

Values are expressed as means ± SD. Wilcoxon's rank-sum test was used to analyze the data for comparisons of background characteristics or various factors between the survivor and non-survivor groups. Pearson's formula was used to test for correlations between P/F ratio and serum cytokine levels. The $\chi^2$ test was used for intergroup comparisons of mortality rates in the ALI group and the ARDS group. The log-rank test was used for survival curves. In all the tests, values of $p < 0.05$ were considered to denote significant differences.

## Results

A total of 12 septic ALI patients and 26 septic ARDS patients were enrolled. There was no significant difference in the male/female ratio between the two groups. However, P/F ratio, APACHE II score, SOFA score, and serum levels of IL-18, IL-12, and TNF-$\alpha$ were all significantly higher in the ARDS group than in the ALI group at the time of diagnosis of ALI/ARDS (Table 1).

At the time of diagnosis of ALI/ARDS, significant inverse correlations were noted between P/F ratio and serum levels of IL-18 ($r = -0.6021$, $p < 0.0001$), IL-12 ($r = -0.4924$, $p = 0.0017$), and TNF-$\alpha$ ($r = -0.6480$, $p < 0.0001$, respectively). Furthermore, there were significant positive correlations between serum levels of IL-18 and TNF-$\alpha$ ($r = 0.8040$, $p < 0.0001$), IL-18 and IL-12 ($r = 0.7768$, $p < 0.0001$), and IL-12 and TNF-$\alpha$ ($r = 0.6984$, $p < 0.0001$) at the time of diagnosis of ALI/ARDS.

No significant differences were observed between the ALI group and the ARDS group with respect to mortality rates at 30 days ($p = 0.31$), 60 days ($p = 0.37$), and 90 days ($p = 0.27$) (Table 2). The 90-day survival rates did not differ significantly between the ALI group and the ARDS group (Fig. 1).

Regarding 30-day prognosis, the non-survivor and survivor groups were compared with respect to P/F ratio,

**Table 1** Background characteristics of the acute lung injury (ALI) group and the acute respiratory distress syndrome (ARDS) group

| Factor | ALI ($n = 12$) | ARDS ($n = 26$) | $p$ value |
|---|---|---|---|
| Age (years) | $66 \pm 15$ | $67 \pm 18$ | 0.8854 |
| M/F | 7/5 | 14/12 | 0.7960 |
| P/F ratio | $240 \pm 33$ | $132 \pm 41$ | <0.0001 |
| APACHE II score | $25 \pm 8$ | $31 \pm 9$ | <0.0001 |
| SOFA score | $9 \pm 3$ | $13 \pm 5$ | 0.0024 |
| IL-18 (pg/ml) | $1,314 \pm 800$ | $2,467 \pm 1,880$ | 0.0120 |
| IL-12 (pg/ml) | $113 \pm 66$ | $181 \pm 119$ | 0.0178 |
| TNF-$\alpha$ (pg/ml) | $147 \pm 55$ | $242 \pm 122$ | 0.0022 |
| Peritonitis | 5 | 12 | |
| Soft tissue infection | 2 | 4 | |
| Pneumonia | 2 | 3 | |
| Biliary system | 1 | 2 | |
| Urinary tract | 1 | 3 | |
| Other | 1 | 2 | |

**Table 2** The 30-, 60- and 90-day mortality rates in the ALI group and the ARDS group

| Group | Mortality | | |
|---|---|---|---|
| | 30-day | 60-day | 90-day |
| ALI ($n = 12$) | 0 % (0/12) | 8.3 % (1/12) | 8.3 % (1/12) |
| ARDS ($n = 26$) | 11.5 % (3/26) | 19.2 % (5/26) | 23.1 % (6/26) |
| Total ($n = 38$) | 7.9 % (3/38) | 15.8 % (6/38) | 18.4 % (7/38) |
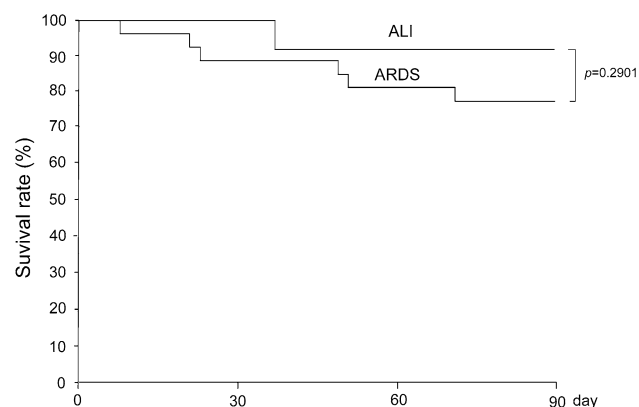


**Fig. 1** Survival curves of acute lung injury (ALI) group and the acute respiratory distress syndrome (ARDS) group

APACHE II score, SOFA score, and serum levels of IL-18, IL-12, and TNF-$\alpha$ at the time of diagnosis of ALI/ARDS. Comparisons revealed no significant intergroup differences in any of these variables (Table 3). When the prognosis was compared between 60-day survivors and non-

**Table 3** Comparison of various factors between the 30-day survivor and non-survivor groups

| Factor | Survived ($n = 35$) | Died ($n = 3$) | $p$ value |
|---|---|---|---|
| P/F ratio | $170 \pm 63$ | $112 \pm 48$ | 0.1881 |
| APACHE II score | $29 \pm 8$ | $45 \pm 11$ | 0.1218 |
| SOFA score | $11 \pm 4$ | $19 \pm 4$ | 0.0936 |
| IL-18 (pg/ml) | $1,781 \pm 1,106$ | $5,863 \pm 3,050$ | 0.1476 |
| IL-12 (pg/ml) | $160 \pm 108$ | $340 \pm 111$ | 0.1146 |
| TNF-$\alpha$ (pg/ml) | $145 \pm 97$ | $406 \pm 131$ | 0.1121 |

Values are expressed as mean $\pm$ SD

**Table 4** Comparison of various factors between the 60-day survivor and non-survivor groups

| Factor | Survived ($n = 32$) | Died ($n = 6$) | $p$ value |
|---|---|---|---|
| P/F ratio | $175 \pm 62$ | $118 \pm 55$ | 0.0581 |
| APACHE II score | $27 \pm 8$ | $43 \pm 8$ | 0.0041 |
| SOFA score | $11 \pm 4$ | $17 \pm 4$ | 0.0060 |
| IL-18 (pg/ml) | $1,649 \pm 1,056$ | $4,523 \pm 2,449$ | 0.0368 |
| IL-12 (pg/ml) | $146 \pm 102$ | $325 \pm 73$ | 0.0006 |
| TNF-$\alpha$ (pg/ml) | $182 \pm 80$ | $367 \pm 146$ | 0.0299 |

Values are expressed as mean $\pm$ SD

**Table 5** Comparison of various factors between the 90-day survivor and non-survivor groups

| Factor | Survived ($n = 31$) | Died ($n = 7$) | $p$ value |
|---|---|---|---|
| P/F ratio | $179 \pm 58$ | $109 \pm 56$ | 0.0161 |
| APACHE II score | $27 \pm 7$ | $42 \pm 7$ | 0.0006 |
| SOFA score | $10 \pm 4$ | $18 \pm 4$ | 0.0010 |
| IL-18 (pg/ml) | $1,534 \pm 846$ | $4,621 \pm 2,250$ | 0.0117 |
| IL-12 (pg/ml) | $147 \pm 103$ | $296 \pm 102$ | 0.0085 |
| TNF-$\alpha$ (pg/ml) | $176 \pm 72$ | $370 \pm 134$ | 0.0098 |

Values are expressed as mean $\pm$ SD

survivors, P/F ratio at the time of diagnosis of ALI/ARDS showed no significant intergroup difference, whereas APACHE II score, SOFA score, and serum levels of IL-18, IL-12, and TNF-$\alpha$ were all significantly higher in the non-survivor group than in the survivor group (Table 4). With regard to the 90-day prognosis, the P/F ratio, APACHE II score, SOFA score, and serum levels of IL-18, IL-12, and TNF-$\alpha$ at the time of diagnosis of ALI/ARDS were significantly higher in the non-survivor group than in the survivor group (Table 5).

The background characteristics of the seven patients who had died by day 90 are presented in Table 6. Four of these patients had MODS, and three died of underlying heart failure.

**Table 6** Background characteristics of the patients who died within 90 days

| Case | Age | Sex | APACHE II score | SOFA score | Day of death from onset of ALI/ARDS | Origin of disease | Cause of death |
|------|-----|-----|-----------------|------------|--------------------------------------|-------------------|----------------|
| 1 | 77 | M | 54 | 22 | 8 | Peritonitis | MODS |
| 2 | 86 | F | 33 | 14 | 21 | Peritonitis | HF |
| 3 | 83 | M | 49 | 21 | 23 | Pneumonia | HF |
| 4 | 74 | F | 39 | 13 | 37 | Peritonitis | MODS |
| 5 | 71 | M | 39 | 15 | 47 | Multiple trauma | HF |
| 6 | 65 | M | 42 | 19 | 51 | Peritonitis | MODS |
| 7 | 51 | M | 37 | 15 | 71 | Multiple trauma | MODS |

*HF* heart failure

## Discussion

Disorders that cause ARDS are widely diverse. Respiratory distress can occur in subjects suffering from excessive stress. It should be recognized that not only respiratory distress, but also ARDS, can develop as a manifestation of MODS in response to stress. Excessive biological responses evoked against various stresses have come to be combined under the new disease entity of systemic inflammatory response syndrome (SIRS) [13]. Hypercytokinemia is considered to be closely involved in the pathophysiology of SIRS. Under normal physiological conditions, the production of cytokines is under positive and negative regulation, so that abnormal production is usually kept under control. Once this regulation is disrupted, cytokines are produced in abnormal quantities and cause disease states such as ARDS. Among the cytokines, TNF-α has been demonstrated in several experimental models to cause pulmonary disorders, enhance the effects of other mediators, and exhibit preclotting activity involved in microthrombus formation in the lung [17, 18]. Both TNF-α and IL-1β not only increase neutrophil degranulation, reactive oxygen species production, and lysozyme release, but also cause increased synthesis of chemotactic factors for endothelial adhesion molecules, neutrophils, and monocytes [19]. It has been reported that soon after the onset of inflammation in the lung, pulmonary vascular permeability increases and IL-18 emerges in the BAL fluid [10]. There is a possibility that IL-18 may be involved in the development of respiratory failure in patients with sepsis and concurrent endotoxemia [11]. It is generally thought that IL-18 stimulates lymphocytic Fas ligand function and induces apoptosis of Fas-positive cells, whereas IFN-γ induced by IL-18 stimulates Fas antigen expression [19]. IL-18 does not stimulate IFN-γ production independently, and concurrent stimulation by IL-12 is essential. Strong synergism between IL-12 and IL-18 in the induction of IFN-γ production has been documented. As shown in studies reported to date, soluble Fas and IL-18 are considered to play important roles in sepsis and thereby in the pathogenesis of various disease states [4, 8].

The present data revealed the existence of a significant correlation between the P/F ratio and the serum IL-18 level in the early stage after onset of ALI/ARDS, indicating that more severe respiratory distress leads to higher serum IL-18 levels. It has been reported that IL-18 induces cytokines and chemokines, such as granulocyte macrophage colony-stimulating factor, TNF, and IL-8, but no detailed analyses were conducted to clarify whether IL-18 induces these mediators directly by acting upon the cells producing them or indirectly by inducing the production of other cytokines [20]. The present finding of correlations between serum TNF-α level and serum IL-12 level and between serum TNF-α level and serum IL-18 level suggests that each of these cytokines may mutually stimulate the production of another. In our previous report, we demonstrated that serum IL-18 level was significantly higher in patients with septic MODS than in patients with sepsis not complicated by MODS and also showed a correlation with SOFA score [21]. We further documented close relationships between serum IL-18 level and serum TNF-α, IL-6, and IL-8 levels. There is also a report suggesting that IL-18 and IL-12 act synergistically to produce lung injury [22].

The mortality rates of ALI and ARDS have been reported in other studies, such as The King County Lung Injury Project (KCLIP) [23] and Scandinavia [24] and Australia [25] studies. In the KCLIP study, mortality rates were 38.5 % for ALI and 41.1 % for ARDS. In the Scandinavia study, mortality rates were 41.4 % for ALI and 41.2 % for ARDS; and in the Australia study, mortality rates were 32 % for ALI and 34 % for ARDS. In these studies, the mortality of ARDS seemed to be almost the same as that of ALI or showed a tendency to be slightly higher. Because the mortality of ALI/ARDS varies with the type and seriousness of the primary illness (e.g., higher mortality of sepsis patients compared with external injury or pneumonia patients), Takeda et al. [26] recommended that ARDS should be classified into several subgroups to

limit the numbers of patients enrolled in randomized clinical trials. In our study, only septic ARF patients were enrolled. Nevertheless, the prognosis of ARDS showed a tendency to be slightly greater than that of ALI, although the difference was not significant. Our findings were consistent with the results of other studies including patients with not only sepsis but also other diseases [23–25]. It should be noted, however, that the common risk factor for ALI was severe sepsis (79 % of total) in the KCLIP study [23]. Furthermore, 73 % of patients with ALI/ARDS were reported to have sepsis in the SOAP databases [27]. Moreover, Doyle et al. [28] reported that sepsis was the most common clinical disorder associated with the development of ALI and that mortality in patients with sepsis associated with ALI was 72 %. However, the P/F ratio at the time of onset of ARDS did not affect the outcome [28]. In previous studies [23, 27, 28], sepsis was, at least in part, an important factor for mortality in ALI/ARDS, even when other diseases were included. Therefore, the prognosis of ALI may not differ significantly from that of ARDS, as found in our study as well as other studies. Subgroup classification may have an effect on mortality among diseases (e.g., sepsis versus external injury or pneumonia) rather than that between ALI and ARDS. Explanation of the prognosis between ALI and ARDS has not been completely clear. Further studies are required to clarify this point.

The present findings showed that the serum levels of TNF-α, IL-12, and IL-18 in the early stage after the onset of ALI/ARDS may serve as late-stage prognostic factors for survival on day 60 or day 90 after onset, and further suggested that the remote relationships of the levels of these cytokines with prognosis on day 30 after onset are likely to indicate that early death can be prevented by various counterbalancing factors, even if these cytokines act to cause early tissue damage.

For the present series of patients with ALI/ARDS showing an APACHE II score of 30, the overall 30-, 60-, and 90-day mortality rates were 7.9, 15.8, and 18.4 %, respectively. These mortality rates are remarkably lower than those reported in previous studies [14, 29–32], but they are considered to be reproducible because they are essentially comparable with previously obtained results at our institution, despite slight variations in the period [33]. It remains to be examined why such gratifying results were obtained at our institution. As a rule, we do not employ low tidal volumes during respiratory management at our institution, and if the P/F ratio shows only poor improvement, an infusion of methylprednisolone (41.7 mg/h) is administered for 48 h at the discretion of the attending physician. Wherever possible, we ensure that the patient is made to lie in the prone position for 30 min in both morning and afternoon every day. Furthermore, all patients receive sivelestat sodium hydrate,

which is currently only available in Japan. In contrast to the STRIVE study [34], we believe in the usefulness of sivelestat sodium hydrate [35]. No additional specific therapeutic measures other than conventional therapies for sepsis are undertaken at our institution. However, our therapeutic results seem to be directly linked to the early initiation of treatment at our institution via an integrated start-to-finish process from the initial therapeutic approach to surgery and intensive care management.

In conclusion, the present data suggest the possibility that effective control of IL-18 and other cytokines such as TNF-α and IL-12 in the early stage after onset of ALI/ARDS may contribute to improvement of the therapeutic results in these patients.

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