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# Cytokine profile of macrophage activation syndrome associated with Kawasaki disease

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ABSTRACT

The present study aimed to assess the kinetics of cytokine release and compare the accuracy of serum biomarkers for the diagnosis of macrophage activation syndrome (MAS) associated with Kawasaki disease (KD). Serum neopterin, interleukin (IL)-18, IL-6 and soluble tumour necrosis factor receptor type I (sTNFR-I) and sTNFR-II levels were determined using enzyme-linked immunosorbent assay in 78 patients with KD, including five with MAS. Results were compared to the clinical features of MAS. Serum neopterin, IL-18, sTNFR-II levels and sTNFR-II/I ratio were significantly elevated in KD patients with MAS compared to those in the acute phase. Receiver operating characteristic curve analysis revealed areas under the curve and cutoff values of neopterin, IL-18, sTNFR-II levels and sTNFR-II/I ratio were 0.9750/30.0 nmol/L, 0.9813/1165 ng/mL, 0.9969/16,600 pg/mL and 0.9875/4.475, respectively. Serum sTNFR-II levels correlated positively with disease activity. These findings indicate that overproduction of interferon (IFN)–γ and TNF-α reflected by increased serum levels of neopterin and sTNFR-II are closely associated with the pathogenesis of MAS associated with KD. Serum sTNFR-II levels might be a useful marker to diagnose the transition to MAS.

## 1. Introduction

Kawasaki disease (KD) is an acute febrile childhood illness seen worldwide in all populations and is characterised by fever, rash, conjunctivitis, changes in the oral mucosa and extremities and cervical lymphadenopathy [1]. KD is a vasculitis with a predilection for the coronary arteries, and approximately 20–25% of untreated patients experience coronary artery abnormalities, including aneurysms [2].

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of childhood systemic inflammatory disorders. It is clinically characterised by fever, hepatosplenomegaly, lymphadenopathy, profound depression of all three blood cell lines, deranged liver function, intravascular coagulation and central nervous system dysfunction. A characteristic feature is seen on bone marrow examination, which reveals, though not always, numerous morphologically benign macrophages exhibiting haemophagocytic activity. Among paediatric rheumatic diseases, MAS occurs most often in children with systemic juvenile idiopathic arthritis (s-JIA) and less commonly in children with KD [3–5].

Recent research has revealed that proinflammatory cytokines have an important role in the pathophysiology of KD. In particular, tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-8 and interferon (IFN)-γ have important roles in the pathogenesis of KD. Previous reports have shown that these serum cytokine levels increased during the active phase of KD [6–8]. Some reports have shown that serum TNF-α, IFN-γ and soluble IL-2 receptor levels were elevated in patients with KD having coronary artery lesions (CALs) compared to those without CALs [6,7]. These findings indicate that excessive activation of the immune system are related closely to the pathogenesis of KD including CALs development.

The hallmark of MAS is an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T lymphocytes and macrophages, which leads to marked hypercytokinemia. Previous reports revealed that CALs were frequently observed,

*Abbreviations:* MAS, macrophage activation syndrome; KD, kawasaki disease; IL, interleukin; sTNFR, soluble tumour necrosis factor receptor; IFN, interferon; TNF, tumour necrosis factor; CALs, coronary artery lesions; NK, natural killer

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especially in patients with KD associated with MAS [3,4]. These findings indicate that excessive production of proinflammatory cytokines might be closely associated with the development of MAS and CALs in patients with KD. However, the kinetics of cytokine release in patients with KD associated with MAS remains unknown.

MAS is a potentially fatal disease; therefore, timely and prompt diagnosis is essential to initiate life-saving treatment. However, it can be difficult to distinguish MAS from KD flares or sepsis like diseases. Differentiation of MAS from these conditions is essential to select timely and appropriate therapeutic interventions. However, to our knowledge, no definite clinical or laboratory parameter exists to establish MAS diagnosis.

To assess the kinetics of cytokine release and compare the accuracy of serum biomarkers for diagnosis of MAS, including neopterin, an interferon gamma (IFN-γ)-inducing sensitive marker of cell-mediated immunity demonstrating the T cell–macrophage interplay; IL-18, IL-6 and soluble TNF receptor type I (sTNFR-I) and sTNFR-II levels, whose levels correlate well with those of TNF-α and more stable in serum than TNF-α, we analysed these levels in patients with KD, including those with MAS, and compared them to the clinical features of KD and MAS.

## 2. Materials and methods

### 2.1. Patients and samples

Five KD patients with MAS and 62 KD patients without MAS were enrolled. Of five patients with MAS, serum samples were obtained in both acute phase of KD and MAS phases from two patients and only in the MAS phase from three. Therefore, we analysed 64 serum samples in the acute phase and 5 samples in the MAS phase. All serum samples in the acute phase were obtained at diagnosis of KD before administration of intravenous immunoglobulin. The clinical characteristics of KD patients in the acute and MAS phases are shown in Tables 1 and 2, respectively. KD was diagnosed based on classic clinical criteria [1]. MAS was diagnosed according to the guidelines proposed by Ravelli et al [9]. Internal vessel coronary artery diameters were assessed quantitatively by echocardiography. CALs were classified using the Z score system, and dilation was defined as Z score > 2.0. Serum was separated from cells, divided into aliquots, frozen and stored at −80 °C until use. The present study was approved by the institutional review board at Kanazawa University, and all specimens were used after informed consent was given.

**Table 1**
Clinical characteristics of 64 patients with Kawasaki disease in this study.

| | |
|---|---|
| Age (months) | 25.0 (1–125) |
| Sex (male/female) | 36/28 |
| *Clinical symptoms* | |
| Fever (%) | 64 (100%) |
| Conjunctivitis (%) | 48 (75.0%) |
| Rash (%) | 51 (79.7%) |
| Lymphadenopathy (%) | 42 (65.6%) |
| Changes of peripheral extremities (%) | 45 (70.3%) |
| Changes of oral cavity (%) | 51 (79.7%) |
| Coronary artery lesions (%) | 9 (14.1%) |
| *Laboratory findings* | |
| White blood cells counts (/mm$^3$) | 13,400 (4800–27100) |
| Platelet counts (/mm$^3$) | 345,500 (127000–631000) |
| CRP (mg/dl) | 8.9 (1.6–27.3) |
| AST (IU/l) | 34 (9–1533) |
| ALT (IU/l) | 22 (5–843) |
| Sodium (mEq/l) | 135 (130–145) |
| Total bilirubin (mg/dl) | 0.7 (0.0–5.4) |
| Total protein (g/dl) | 6.5 (4.7–8.5) |
| Albumin (g/dl) | 3.6 (2.6–4.5) |
| *Treatments* | |
| Aspirin only | 4 |
| IVIG | 39 (one time), 15 (two times), 5 (over three times) |
| Steroid | 5 |
| Urinastatin | 7 |
| Cyclosporine | 13 |
| Infliximab | 1 |

CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IVIG, intravenous immunoglobulin.

**Table 2**
Clinical characteristics of 5 patients with Kawasaki disease at the diagnosis of MAS.

| Patient | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Age (months) | 72 | 12 | 118 | 91 | 27 |
| Sex | F | M | M | M | F |
| The day of MAS diagnosis after KD onset | 15 | 24 | 10 | 3 | 6 |
| *Clinical manifestations* | | | | | |
| Fever | + | + | – | + | + |
| Rash | + | – | + | + | + |
| Conjunctivitis | – | – | – | + | + |
| Cervical lymphadenopathy | – | – | + | + | + |
| Changes of oral cavity | + | – | + | + | + |
| Changes of peripheral extremities | – | – | + | + | + |
| Coronary artery lesions | | | | | |
| CNS symptoms | – | – | + | – | + |
| bleeding | – | – | – | – | + |
| hepatomegaly | – | – | – | – | – |
| splenomegaly | – | – | – | – | – |
| laboratory findings | | | | | |
| ferritin (ng/ml) | 21,231 | 854 | 7688 | 11,556 | 2376 |
| Platelets (/mm$^3$) | 10.7 | 26.2 | 10.2 | 9.1 | 2.8 |
| CRP (mg/dl) | 4.6 | 0.4 | 0.6 | 3.18 | 20.3 |
| AST (IU/l) | 189 | 1152 | 111 | 129 | 335 |
| ALT (IU/l) | 130 | 643 | 42 | 45 | 174 |
| LDH (IU/l) | 981 | 1169 | 1190 | 1,368 | 2012 |
| Triglyceride (mg/dl) | 103 | 87 | 133 | 63 | 136 |
| Fibrinogen (mg/dl) | 179 | 179 | 113 | nd | 127 |
| FDP (μg/ml) | 559.4 | 49.9 | 38 | nd | 41.8 |
| FDP D dimer (μg/ml) | 277.5 | 24.4 | 26.2 | nd | nd |
| *Treatments* | | | | | |
| Aspirin | + | + | + | – | + |
| Urinastatin | – | + | + | – | – |
| Methylprednisolone | – | – | – | – | + |
| Dexamethasone | – | – | + | – | – |
| Doses of IVIG before MAS developed | 1 | 3 | 1 | 0 | 1 |

MAS, macrophage activation syndrome; KD, kawasaki disease; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; FDP, fibrin degradation product; IVIG, intravenous immunoglobulin.

### 2.2. Measurement of serum cytokine levels

Serum neopterin, IL-18, IL-6, sTNFR-I and sTNFR-II levels were measured using a commercial enzyme-linked immunosorbent assay according to the manufacturer's instructions (neopterin: IBL, Hamburg, Germany; IL-18: MBL, Nagoya, Japan; sTNFR-I, sTNFR-II, IL-6: R&D Systems, Inc., Minneapolis, MN, USA).

### 2.3. Statistical analysis

Inter-group comparisons were analysed using the Mann–Whitney *U* test. Correlations were expressed using the Spearman rank correlation coefficient. For the analysed measures, $P < 0.05$ was considered significant.

## 3. Results

### 3.1. Cytokine release in KD patients with MAS

Serum neopterin, IL-18, sTNFR-II, sTNFR-II/I, IL-6 and sTNFR-I

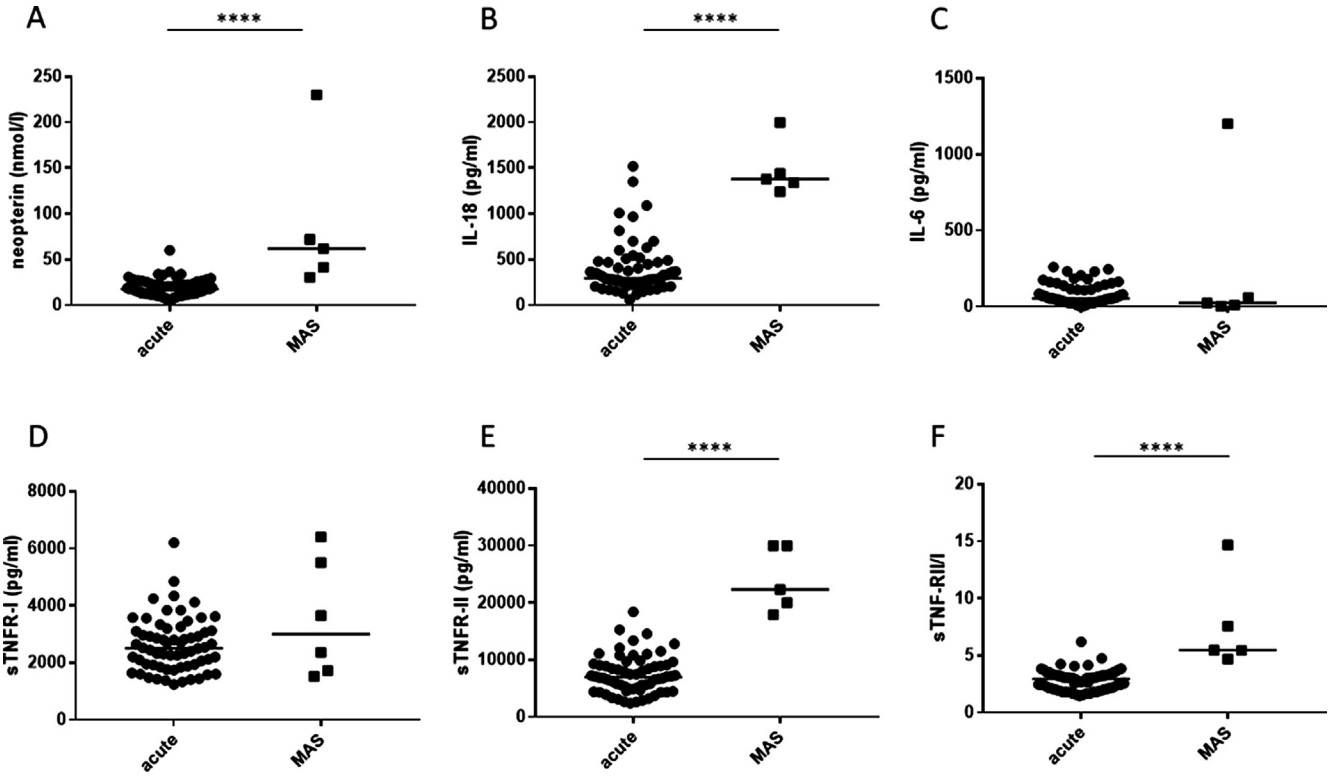


**Fig. 1.** Comparison between serum cytokine levels in acute phase of KD and MAS phase. Serum levels of (A) neopterin, (B) IL-18, (C) IL-6, (D) sTNFR-I, (E) sTNFR-II and (F) sTNFR-II/I are shown. Bars represent median values. Statistically significant differences between each patient group are shown as $^{****}P < 0.0001$.

levels in patients who had KD with MAS were not significantly different from those in the acute phase (median, 62.0 [range, 30.5–230.0] vs. 17.7 [5.0–60.0] nmol/L; 1380 [1240–2000] vs. 295 [60–1520] pg/mL; 22,300 [17,900–30,000] vs. 7000 [2430–18,400] pg/mL; 5.48 [4.69–14.67] vs. 2.95 [1.47–6.22] pg/mL; 24 [3–1200] vs. 54 [4–260] pg/mL and 3650 [1520–6400] vs. 2510 [1240–6200] pg/mL, respectively (Fig. 1A–F).

Because many inflammatory cytokines are associated with the pathogenesis of KD and MAS, we believe that monitoring the cytokine profile in combination with these cytokines might be more useful for evaluating disease activity. Consequently, we attempted to represent the cytokine profile with a radar chart (Fig. 2). Patients with MAS had more severe hypercytokinaemia during the MAS phase than those in the acute phase (Fig. 2). We compared serum sTNFR-II levels during the acute phase, before MAS development and at the time of MAS diagnosis, in two patients with MAS, whose sera were obtained in the acute and MAS phases. As shown in Supplementary Fig. 1, serum sTNFR-II levels were elevated during MAS compared to during the acute phase.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cyto.2019.03.001.

### 3.2. Comparison of serum biomarkers for the diagnosis of MAS complicating KD

As shown in Table 3, receiver operating characteristic (ROC) curve analysis revealed that cutoff values of serum neopterin, IL–18, sTNFR-II

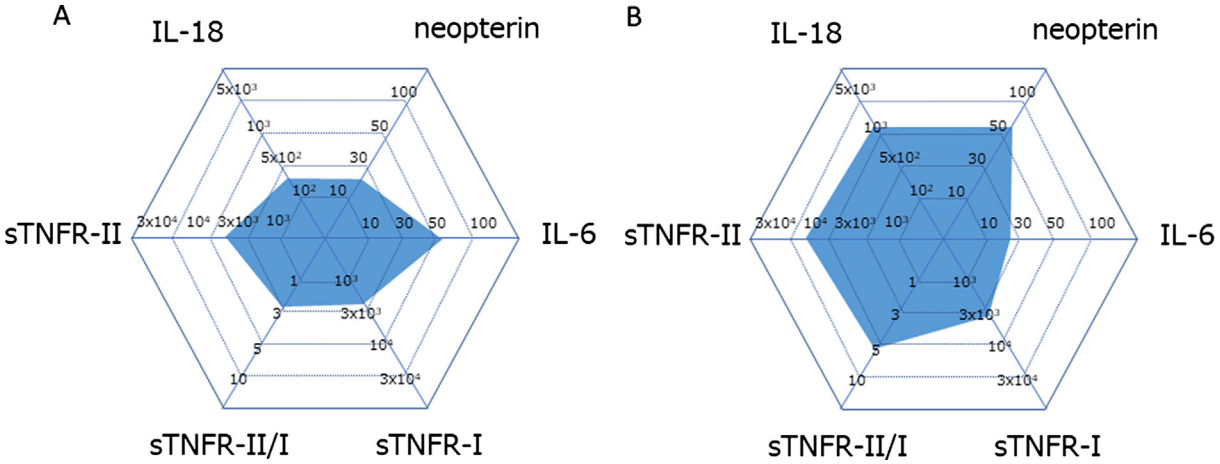


**Fig. 2.** Cytokine profiles with radar charts in KD patients in the acute phase of KD and MAS phase. Representative profiles of serum cytokines, including neopterin, IL-18, IL-6, sTNFR-I, sTNFR-II, and sTNFR-II/I are shown. (A) acute phase, (B) MAS phase. Median values of serum cytokine levels in acute phase (n = 64) and in MAS phase (n = 5) are shown.

**Table 3**
Receiver operating characteristic curve analysis of serum biomarkers for the diagnosis of MAS complicating KD.

| Biomarkers | Cut off values | Area under the ROC curve values |
|---|---|---|
| Neopterin | 30.0 | 0.9750 |
| IL-18 | 1165 | 0.9813 |
| sTNFRII | 16,600 | 0.9969 |
| sTNFR-II/I | 4.475 | 0.9875 |

levels and sTNFR-II/I ratio were 30.0 nmol/L, 1165 ng/mL, 16,600 pg/mL and 4.475, respectively. The area under the ROC curve values of neopterin, IL-18, sTNFR-II levels and sTNFR-II/I ratio were 0.9750, 0.9813, 0.9969 and 0.9875, respectively.

### *3.3. Correlation between serum sTNFR-II levels and measures of disease activity in patients with MAS associated with KD*

Levels of serum ferritin, aspartate aminotransferase (AST) and lactate dehydrogenase (LDH), platelets counts and C-reactive protein (CRP) are used clinically as indicators for disease activity in KD and MAS. Therefore, we assessed the correlation of sTNFR-II levels with these indicators. The sTNFR-II levels correlated positively with ferritin, AST, LDH (Fig. 3), whereas the sTNFR-II levels were not significantly correlated with platelets counts and CRP levels (Fig. 3).

## 4. Discussion

MAS is a relatively infrequent complication in paediatric rheumatic diseases. The estimated incidence of MAS associated with KD has been reported to be 1.1–1.9% [2–4]. MAS complications can occur in patients at a wide range of ages, with the peak at 1–2 years of age. However, previous reports have shown that approximately half of patients with MAS associated with KD were > 5 years old, suggesting that older age might be a predisposing factor for MAS development [2]. MAS can occur at any stage of KD. MAS is diagnosed before KD in 6% of cases, presents simultaneously in 21% and is diagnosed after KD diagnosis in 73% [2]. Four of five patients in the present study developed MAS after KD was diagnosed. MAS should be considered when KD recurs within the first month of the disease.

The hallmark of MAS includes uncontrolled and dysfunctional immune responses, involving continual activation and expansion of T lymphocytes and macrophages, which, in turn, lead to marked hypercytokinaemia. In the pathogenesis of MAS complicating s-JIA, IL-18 has important roles in the development of MAS [10,11]. IL-18 overproduction in s-JIA is associated with MAS development through natural killer (NK) cell dysfunction [12,13]. In our study, serum IL-18 levels in KD patients were significantly elevated in the MAS phase compared to the active phase of KD. However, those levels were not high compared to those in patients with MAS complicating s-JIA. Furthermore, NK cells from patient 3 were activated in response to recombinant IL-18 as well as healthy children (data not shown). These findings indicate that IL-18 might not be closely associated with MAS

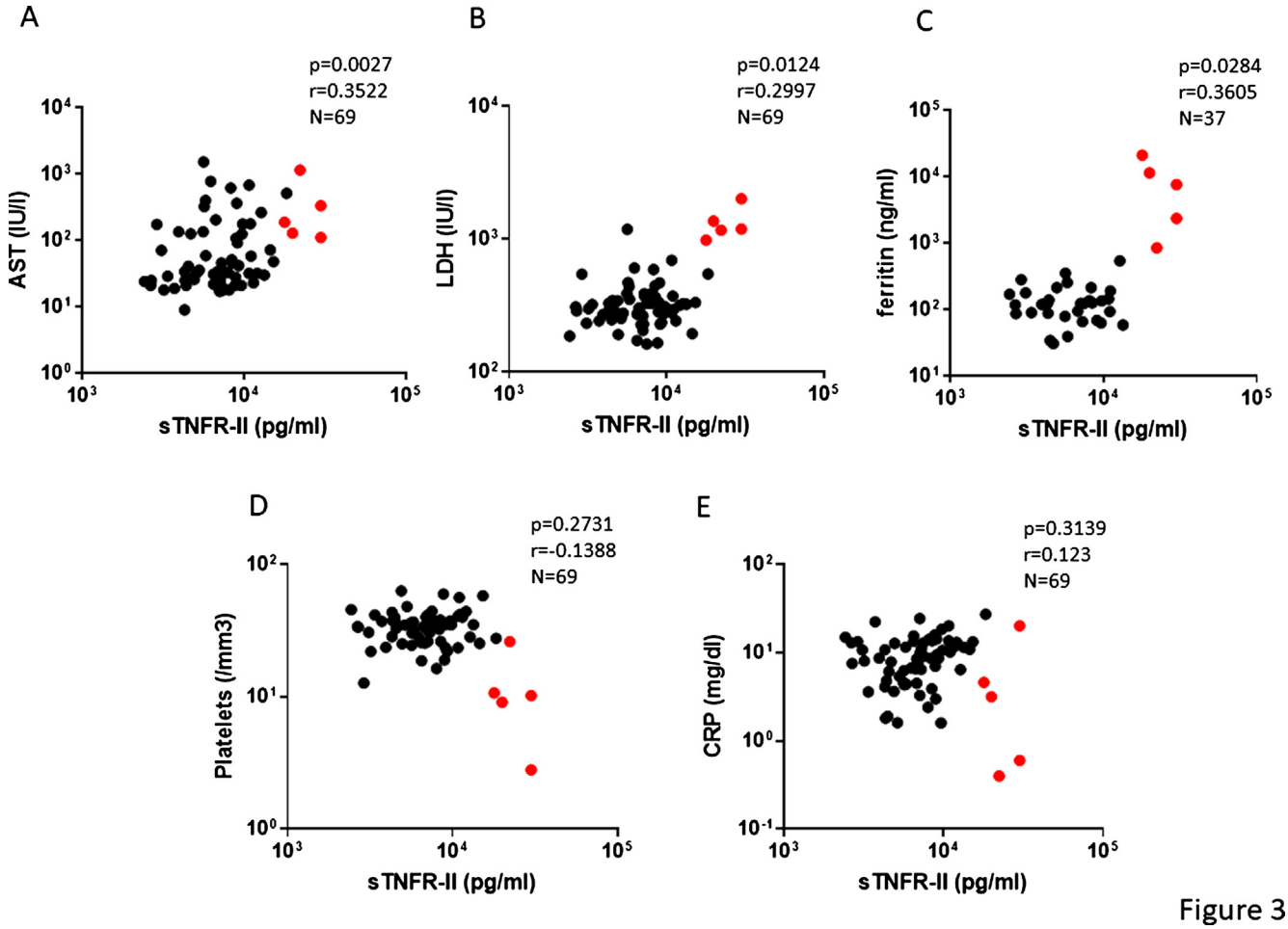


Figure 3

**Fig. 3.** Correlations between sTNFR-II and other measures of disease activity. Serum sTNFR-II levels were compared to other serum markers. (A) AST, (B) LDH, (C) ferritin, (D) Platelets, and (E) CRP. Red circles indicate serum sTNFR-II levels in patients with MAS. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

development in KD.

On the other hand, IFN-γ and TNF-α are key cytokines in the pathogenesis of MAS [14–16]. Recent reports have shown that serum levels of IFN-γ and IFN-γ-induced chemokines and sTNFR-II are markedly elevated in patients with MAS compared to those in patients with active-phase s-JIA without MAS [14,15]. In the present study, serum neopterin and sTNFR-II levels in KD patients were significantly elevated in the MAS phase compared to the active phase of KD. Neopterin is produced by activated monocytes/macrophages in response to IFN-γ [17]. Serum sTNFR-II levels correlate well with those of TNF-α [18]. From these findings, overproduction of IFN-γ and TNF-α might be closely associated with MAS development in KD, and it might be the common mechanism of MAS and haemophagocytic lymphohistiocytosis (HLH) development.

A proper diagnosis of MAS is essential to start appropriate therapeutic interventions and prevent unfavourable outcomes. However, it often is difficult to distinguish MAS from KD flares especially in the early stage of MAS. Differentiating MAS from these conditions is essential for timely selection of appropriate therapeutic interventions. However, to our knowledge, no definite clinical or laboratory parameter exists that can effectively diagnose MAS. We compared the accuracy of serum biomarkers, including neopterin, IL-6, IL-18, sTNFR-I, sTNFR-II and sTNFR-II/I, for the diagnosis of MAS complicating KD. ROC curve analysis revealed that serum sTNFR-II levels had the highest area under the ROC curve value, indicating that serum sTNFR-II levels are the most accurate biomarker for the diagnosis of MAS complicating KD.

MAS occurs most often in children with s-JIA. Therefore, it is crucial to distinguish MAS complicating KD and MAS complicating with s-JIA. However, the clinical features and laboratory parameters of patients with s-JIA and KD tend to overlap. This makes the clinical diagnosis of these conditions difficult, and at present, it is challenging for a pediatrician to diagnose patients accurately. Our observations in this study and previous studies revealed the comparison of serum cytokine profile in KD and s-JIA, in particular, serum IL-18 levels might be useful for the accurate diagnosis of KD or s-JIA [10,19]. On the other hand, MAS also occurs in other pediatric rheumatic diseases including systemic lupus erythematosus [20] and juvenile dermatomyositis [21]. Serum cytokine profile in MAS associated with these diseases has not been fully analyzed yet. Further studies to determine serum cytokine profiles in MAS associated with different backgrounds are desired to understand the pathogenesis of MAS and to develop the diagnostic tools.

We previously reported the clinical course of a patient with KD having MAS and CALs, whose elevated serum sTNFR-II level and sTNFR-II/I ratio were linked to CAL development [22]. Previous reports have revealed that CALs were observed frequently in KD patients with MAS [3,4]. These results indicate that MAS might be a risk factor for the development of CAL in KD. Furthermore, TNF-α-mediated inflammation might be critical in the pathogenesis of MAS as well as CAL development in KD. It might be important to suppress TNF-α-mediated inflammation as early as possible in the clinical setting of KD.

The limitation of this study is the small sample size. Further studies with a large cohort are essential to clarify the clinical significance of serum sTNFR-II levels as an indicator of disease activity and predictor of MAS development in KD.

Despite these limitations, we have been able to demonstrate that IFN-γ and TNF-α are closely associated with the pathogenesis of MAS associated with KD. Serum sTNFR-II levels might be a useful marker to diagnose the transition to MAS.

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## Financial disclosure

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## Conflict of interest

The authors have no conflicts of interest to disclose.

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