Rheumatol Int (2016) 36:1399–1405
DOI 10.1007/s00296-016-3546-8

Rheumatology INTERNATIONAL

EPIDEMIOLOGY OF RMD

Epidemiological study of adult-onset Still's disease using a Japanese administrative database

Nobuo Sakata[1] · Sayuri Shimizu[1] · Fumio Hirano[2] · Kiyohide Fushimi[1]

Received: 15 March 2016 / Accepted: 2 August 2016 / Published online: 9 August 2016

Abstract Adult-onset Still's disease (AOSD) is a rare disease, and large epidemiological studies of this disease are limited. Furthermore, it has been difficult to show the incidence and characteristics of severe AOSD complications due to the rarity of this disease. The aim of our study was to describe the demographics of AOSD and the incidence and characteristics of severe complications. Using a large Japanese administrative database, we identified hospitalized patients with AOSD and described the demographics. We also calculated the incidence of severe complications (i.e., macrophage activation syndrome [MAS] and disseminated intravascular coagulation [DIC]) and in-hospital mortality in AOSD patients, and then analyzed the age-controlled difference between men and women. We identified 513 patients with AOSD (mean age: 53.1 years; women 64.1 %). According to the age distribution, there was no distinct peak age. The thirties and the sixties were relatively large age groups. There were 76 patients of AOSD with MAS or DIC observed in this study. The incidence of severe complications was 14.8 %, 95 % CI [11.9, 18.2]. Women were more likely to have severe complications than men after controlling for age (odds ratio: 2.07; [1.14, 3.73]; $p = 0.014$). AOSD does not predominantly affect young adults in our study population. Elderly AOSD patients can be observed more than before due to global population aging. Severe complications are more likely to occur in women than in men.

Keywords Adult-onset Still's disease · Epidemiology · Macrophage activation syndrome · Population aging

Introduction

Adult-onset Still's disease (AOSD), first described in 1971 by Bywaters, is a systemic inflammatory disease with unknown etiology, which causes high-spiking fever, evanescent rash, arthralgia, and lymphadenopathy [1, 2]. The diagnosis of AOSD is based on a constellation of symptoms, and Yamaguchi's criteria are one of the most well-known diagnostic criteria [2, 3]. Most patients are treated with steroid therapy and sometimes with immunosuppressants. Recently, the efficacy of biological agents (i.e., IL-6 antagonists and TNF-α blockers) for AOSD has been supported in many studies [1, 4].

This disease is relatively benign and not usually fatal according to the existing literature [1, 5–8]. However, AOSD can cause macrophage activation syndrome (MAS) and disseminated intravascular coagulation (DIC), both of which can be life-threatening [1, 9–11]. However, AOSD is a rare disease (the incidence is estimated to be 0.16–0.4/100,000 persons) [1]. Therefore, there have not been many epidemiological studies conducted. Most of the existing studies were conducted with a small number of patients, which makes it difficult to determine the incidence and characteristics of severe complications and the mortality rate. Indeed, there is no robust evidence regarding the incidence of severe AOSD complications. AOSD affects young people, and sometimes life-threatening

✉ Kiyohide Fushimi
kfushimi.hci@tmd.ac.jp

[1] Department of Health Policy and Informatics, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

[2] Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

complications occur; therefore, it is significant to ascertain the likelihood of complications in the clinical course.

The purpose of this study was to describe the demographics and mortality of AOSD and the incidence and characteristics of severe complications using a large Japanese administrative database.

Methods

Data source

We used a large Japanese administrative database entitled "Diagnosis and Procedure Combination" (DPC). The DPC is a classification scheme consisting of 18 major diagnostic categories, 507 diagnostic groups, and 2658 case-mix groups used for reimbursement of hospitalization costs in the per-diem payment system. The DPC data contained information regarding the inpatients during their hospital stay, including age, sex, main diagnosis, comorbidity, complications, medication, treatment procedures, and their prior admission history [12, 13]. The DPC database also have the information on the death whether it was related to the main disease or not, which the physician judged and input the data in fatal cases.

We used data obtained between July 1, 2010, and March 31, 2012. In 2012, 1505 hospitals joined the DPC system, which covers 53.3 % of the hospital beds for acute inpatient care in Japan. Of these hospitals, 1058 hospitals were included in this study dataset. All collected data were anonymous and impossible to link with any other information that could identify patients; therefore, informed consent was not obtained from the patients. Prior approval by the ethics committee of Tokyo Medical and Dental University was obtained for this study.

Patient selection

We identified patients who were admitted with AOSD as their main disease (International Classification of Diseases (ICD)-10 code: M06.1) in the DPC database. MAS (D76.3) and DIC (D65) were defined as severe complications of AOSD; we included patients who were diagnosed with MAS or DIC as their main disease and recorded AOSD as comorbidity or complication. The patients who had both MAS and DIC were regarded as MAS patients. We selected the first admission of AOSD for each patient in the database.

To limit the AOSD patients to those who were actually examined and treated, we selected patients who underwent imaging exams (at least one of contrast-enhanced computed tomography scan (enhanced CT), MRI, and any scintigraphy) and blood cultures during their hospital stay. Also, we only selected patients who took prednisolone (PSL) $\geq$20 mg/day or 0.5 mg/kg/day, which is described as a moderate initial dose in previous studies [1], and who stayed in the hospital for $\geq$4 days. The doses of other administered corticosteroids were converted to the equivalent doses of PSL.

Exclusion

We excluded patients with uncertain diagnoses, described as "AOSD suspected," and those with exacerbation or recurrence, described as "AOSD exacerbation" or "AOSD recurrence," in the database. Yamaguchi's criteria require AOSD to be distinguished from other collagen diseases and malignancies (i.e., rheumatoid vasculitis and malignant lymphoma). Therefore, we excluded patients with the following disorders as comorbidities or complications: rheumatoid arthritis (M05.0–M05.9), polyarteritis nodosa (M30.0–30.8), vasculitis (M31.3–31.6), dermatomyositis (M33.0–33.9), progressive systemic sclerosis (M34.0–34.9), systemic lupus erythematosus (M32.0–32.9), other systemic connective tissue diseases (M35.0–35.9), and any malignancy (C00–97).

Statistical analysis

Descriptive statistics were represented as means (SD) for continuous variables and as frequencies and percentages for categorical variables. We calculated the incidence of the severe complications (i.e., MAS and DIC) and in-hospital mortality rate of AOSD patients with an exact 95 % CI. We also analyzed the incidence of severe complications and the mortality of men and women using univariate logistic regression analysis and then added the estimation of the odds ratio (OR) and 95 % CI by extended Mantel-Haenszel estimate for adjusted age. In the Mantel-Haenszel estimate, patients were categorized into the following four age groups: 16–34, 35–54, 55–74 and $\geq$75 years due to the scarcity of AOSD.

Patients with missing values where we used to analyze were excluded from the analysis. A two-sided p value $< .05$ was considered to be statistically significant. All statistical analyses were performed using STATA 13 (StataCorp LP, Texas, USA).

Results

During the two years and nine months period, we identified 513 patients with AOSD. The characteristics of the study participants are shown in Table 1. The mean (SD) age was 53.1 (19.6) years, and woman represented 64.1 %. The sex ratio was almost consistent throughout all age

Table 1 Characteristics of adult-onset Still's disease patients

	Total	Male	Female	OR [95 % CI]	*p* value
Number of patients	513	184	329		
Mean age, years	53.1 ± 19.6	48.3 ± 18.3	55.9 ± 19.7		
Severe complications (MAS or DIC)[†]	76 (MAS51, DIC25)	17	59	2.07 [1.14–3.73]	0.014*
Total deaths[‡]	28	7	21	1.72 [0.72–4.14]	0.218
AOSD-related deaths[‡]	16	5	11	1.24 [0.42–3.62]	0.696

AOSD adult-onset Still's disease; *DIC* disseminated intravascular coagulation; *MAS* macrophage activation syndrome

[†] Odds ratio and *p* value obtained using extended Mantel-Haenszel estimate between male and female adjusted for age groups

[‡] Odds ratio and *p* value obtained using univariate logistic regression analysis

* Indicates statistical significance

groups except for the group aged ≥75 years, which had more women than the other groups. The age distribution of patients with AOSD revealed no distinct peak age (Fig. 1). The thirties and the sixties were relatively large age groups.

Severe complications

We observed 76 AOSD patients with severe complications (MAS, $n = 51$; DIC, $n = 25$) in this study (14.8, 95 % CI [11.9, 18.2]; Table 2). Of these patients, 52 patients underwent bone marrow aspiration or biopsy (MAS, $n = 41$; DIC, $n = 11$). Regarding the mortality, 8 out of 51 patients with MAS and 4 out of 25 patients with DIC died (15.7 % and 16.0 %, respectively). Women were more likely to have severe complications than men even after controlling for age (OR, 2.07; 95 % CI [1.14, 3.73]; $p = 0.014$). There was no significant difference observed in the test of homogeneity of ORs among age groups ($p = 0.76$). The incidence of severe complications among age groups was also not significant ($p = 0.19$), even after separate analysis for men and women ($p = 0.41$ and $p = 0.60$, respectively). Patients with severe complications were more likely to die compared to patients without severe complications ($p < 0.001$).

In-hospital mortality

There were 28 in-hospital deaths observed in this study. Of these, 16 deaths were related to AOSD (3.1, 95 % CI [1.8, 5.0]) and 12 deaths were unrelated (Table 2). Mortality increased with age; only one death was reported in patients aged <35 years. Although the mortality in women was higher than in men, there was no statistical difference in mortality according to sex ($p = 0.22$).

Treatment

The drug combinations for AOSD patients during their first admission are listed in Table 3. In the present study, 336 patients were treated with corticosteroids as a single agent

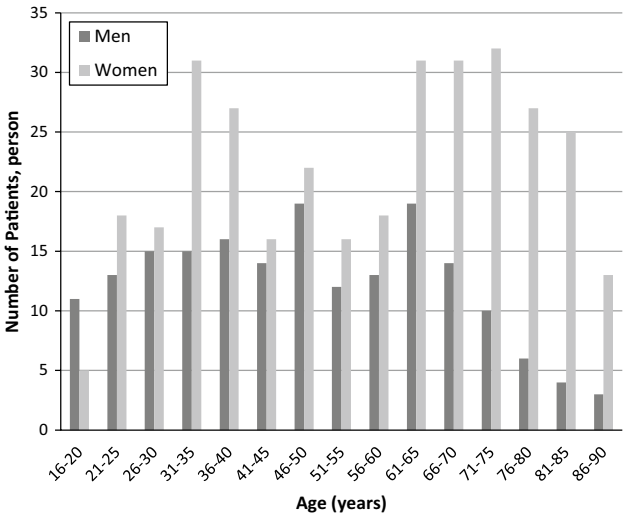

Fig. 1 Age distribution of adult-onset Still's disease patients

therapy. Cyclosporine (12.1 %) and methotrexate (7.2 %) were common choices for treatment with immunosuppressants. Biological agents were administered in 22 patients (4.3 %), though the use of any biological agents has not been officially approved for AOSD in Japan. Of these, the most-selected agent was tocilizumab ($n = 19$). 159 patients (31.0 %) were administered ≥500 mg/day of PSL, which was considered glucocorticoid pulse therapy.

Discussion

This epidemiological study of AOSD using Japan's nationwide administrative database provides three significant findings that were not shown in previous studies due to limitations in their sample sizes. First, there were many elderly AOSD patients in this study; about half of the patients were ≥55 years old and approximately 16 % were ≥75 years old. Second, the incidence and in-hospital mortality of MAS and DIC in AOSD patients were described in this

Table 2 Severe complications and in-hospital mortality

Age groups	Severe complications (MAS or DIC)	In-hospital mortality	
		Total deaths	AOSD-related deaths
16–34	15	1	1
35–54	24	5	3
55–74	19	7	5
≥75	18	15	7
Total	76	28	16
Incidence [95 % CI]	14.8 % [11.9–18.2]	5.5 % [3.7–7.8]	3.1 % [1.8–5.0]
p value*	0.192	<0.001	<0.001

AOSD adult-onset Still's disease; *DIC* disseminated intravascular coagulation; *MAS* macrophage activation syndrome

* *p* value obtained using the Chi-square test among age groups

Table 3 Treatment for adult-onset Still's disease

Therapy	Number of cases	(%)
GC only	336	(65.5)
GC + CyA	62	(12.1)
GC + MTX	37	(7.2)
GC + NSAIDs	33	(6.4)
GC + TCZ + others	19	(3.7)
GC + TAC	7	(1.4)
GC + MTX + TAC	6	(1.2)
GC + MTX + CyA	4	(0.8)
GC + TNF + others	3	(0.6)
Other therapy	6	(1.2)
(Pulse GC: PSL > 500 mg)	(159)	(31.0)

GC glucocorticoid; *CyA* cyclosporine; *MTX* methotrexate; *TAC* tacrolimus; *NSAIDs* non-steroidal anti-inflammatory drugs; *TCZ* tocilizumab; *TNF* TNF-α inhibitor; *PSL* prednisolone

study. Third, we revealed that women were more likely to have MAS and DIC as complications of AOSD.

Age distribution

AOSD has been observed to affect young adults characteristically, and those suffering from AOSD who are aged >60 years are rare [1, 4, 14, 15]. Contrary to previous studies, many elderly patients with AOSD were observed in our study. The mean age of patients in this study was older than in any previous study. The numerous elderly AOSD patients in our study could be explained by Japan's aging population.

In the most recent Japanese epidemiological study by Asanuma in 2014, published prior to the current research, the mean age at the onset of AOSD was reported to be 46 ± 19 years (Table 4), which was the second highest after our study [7]. The mean age at the onset in Asanuma's study

Table 4 Adult-onset Still's disease epidemiological studies

First author, year [Ref.]	Country	Number of cases	Female, *n* (%)	Mean or median age at onset	Population aged ≥65 years (% of total)[a]	Survey year
Present study	Japan	513	329 (64)	53	23.3	2010–2012
Kim 2014 [6]	Korea	82	60 (73)	34	7.9	1992–2012
Asanuma [7]	Japan	168	121 (72)	46	23.0	2010
Gerfaud-Valentin [1]	France	57	30 (53)	36	16.3	1998–2010
Chen 2012 [15]	China	61	32 (52)	30	7.4	1996–2010
Colina [18]	Italy	76	44 (58)	36	17.2	1985–2009
Franchini [22]	Italy	66	38 (58)	37	18.1	1991–2009
Zeng [20]	China	61	45 (74)	–	–	–
Pay 2006 [21]	Turkey	95	50 (53)	27	5.3	1995–2005
Wakai [16]	Japan	125	85 (68)	38	13.5	1993
Magadur-Joly [17]	France	62	32 (52)	36	13.5	1985–1991
Ohta [5]	Japan	90	60 (67)	32	11.2	1988

[a] Percentage at mid-year of survey period. Referred by OECD Health Statistics 2015

(2014) was higher than in Wakai's study (1997) or Ohta's study (1990), all of which were conducted the same way in Japan (46, 38 and 32 years, respectively; Table 4) [5, 7, 16]. Between the year of Asanuma's study and that of Ohta's study, the population aged ≥65 years in Japan had increased from 11.2 to 23.0 %. The mean ages and percentages of the population aged ≥65 years in other studies presented in Table 4 were also lower than in both the present study and Asanuma's study. Therefore, the higher mean age at the onset can be derived from the increased number of elderly AOSD patients due to population aging. The reason that the mean age in our study was higher than in Asanuma's study might be because the mean age of our study was not exactly the one at onset. The age in our study was the one as of first admission. Since we selected the patients under certain conditions as described above, they were likely to be at onset but still have the possibility of unrecorded recurrence.

We also inferred that the age distribution in our study could be derived from the composition of reference population because the age distribution seems to be compatible with Japan's demographic pyramid. Some prior studies reported the age distribution of AOSD, which was different in each study [17, 18]. It is likely that they were influenced by the reference population compositions.

Population aging in other countries is not as profound as in Japan; therefore, it is possible that elderly AOSD patients are not well-represented in research studies conducted in settings other than Japan. However, many countries are experiencing an increase in population aging, which could possibly lead to an increase in the number of elderly AOSD patients—similar to the situation in Japan.

Sex ratio

In our study, the number of women was 1.8 times that of men, which was consistent with prior Japanese, Korean, and Chinese studies [5–7, 16, 19, 20]. In some studies from other regions, it was also revealed that there are more women with AOSD than men, but not to the extent described in our study [18, 21–23]. There are only a few epidemiological research studies that indicate a male dominance in the number of AOSD patients; therefore, it is possible that AOSD is female dominant. However, greater female dominance based on sex ratios was likely to be observed in studies conducted in Asian countries compared to those in non-Asian countries [6, 7, 20]. Further research concerning ethnic differences between Asian and non-Asian countries is needed.

Severe complications and mortality

We demonstrated the incidence of MAS in AOSD patients (51/513, 9.9 %) based on the large samples with solid diagnosis procedure (bone marrow aspiration or biopsy) in most of the cases. The incidence in prior studies were 7.3–14.0 %, and our result was consistent [1, 6, 7]. Regarding the mortality of MAS in AOSD, there are few studies demonstrating that because of the rarity. In our study, the mortality of 51 patients with MAS was 15.7 %, but Lenert (2016) recently reported that all 7 of their AOSD patients with MAS survived in their retrospective research [24]. This could be due to the differences in hospital variations and treatments. While Lenert's research was conducted in a single tertiary hospital, our study included various hospitals all over Japan. Moreover, while 5 of 7 patients received anakinra (Interleukin-1 receptor antagonist) in Lenert's research, only one MAS patient received a biological agent in our study; this is because the use of biological agents for AOSD has not been officially approved in Japan. Future expansion of biological agent usage is expected to improve mortality in AOSD patients with severe complications.

While the incidence of DIC (4.9 %) in our research was close to Asanuma's report (6.3 %), other studies reported around 1–3 % [18, 23, 25]. This might be due to the diagnosis criteria of DIC. Regarding the diagnosis of DIC, the International Society for Thrombosis and Haemostasis (ISTH) published a scoring system for identifying overt DIC that is globally used. However, there are two other diagnosis criteria published by the Japanese Association for Acute Medicine and the Ministry of Health and Welfare that are more prevalent in Japan [26]. Since they have higher sensitivity and tend to be applied even for non-overt and non-sepsis DIC, DIC could be diagnosed more frequently in Japan. Thus, our research has the possibility of including a wider range of DIC patients than other countries' studies.

Regarding severe complications, female patients were twice as likely as male patients to have MAS or DIC in the present study. The mortality in women was also higher than in men. However, the mortality between men and women was not significantly different in the statistical test. This might be due to the lack of statistical power. Overall, we can infer that AOSD is a disease that is more likely to be severe in women than in men. This finding is supported by Lenert's study, which found that 6 out of 7 patients with MAS were female [24].

Limitations

There were some limitations in this study. First, while we selected patients who had AOSD as their main disease, as indicated by the ICD-10 code, the DPC database does not include clinical information regarding typical symptoms (i.e., arthritis, rash, and lymphadenopathy) or laboratory data (i.e., CRP and ferritin levels). Therefore, there is some possibility of the misdiagnosis or miscoding of the patients.

However, we screened AOSD patients by checking the use of diagnostic imaging examinations (enhanced CT, MRI, or scintigraphy), blood cultures, and the doses of PSL, and we also excluded suspected patients and patients with other collagen diseases and malignancies. The use of imaging exams suggests physicians' work-up for malignancy, such as lymphoma, and the blood cultures indicate physicians' work-up for bacterial infection. Corticosteroid therapy for AOSD implies that the physicians excluded infectious diseases and confirmed the diagnosis based on the criteria. As the diagnostic criteria of AOSD currently prevail, it is less likely that the physicians would not examine the typical symptoms in their diagnosing process. Furthermore, the variations and proportions of the therapy were similar to Asanuma's study, which was conducted based on clinical information and contained a more accurate diagnosis of AOSD compared to our study. The consistency of the treatment pattern in Asanuma's study supports the maintenance of diagnosis accuracy in the present study.

Second, since we selected the patients by implementation of diagnostic tests, dose of corticosteroid and length of hospital stay in the database, there is a selection bias due to these criteria. Therefore, the application of our findings is limited to the AOSD patients under the same condition.

Third, the DPC database could not trace admissions to different hospitals in each patient. Therefore, while we selected only the first admission cases in this study, there is still possibility that some of patients had previous history of admission for AOSD in other hospitals. Furthermore, we could not follow the clinical course in outpatient clinics after discharge because the database only provided in-hospital data during the study period. The post-discharge presence of cancer or other collagen diseases could not be also detected. Therefore, further research is necessary to evaluate the clinical courses according to sex and age groups.

Finally, the population of our study was mostly Japanese. Prior research conducted in non-Asian countries was not as female dominant, based on the sex ratio, as our study. Therefore, further research is needed to examine ethnic differences in AOSD patients.

Conclusion

AOSD does not predominantly affect young adults in our study population. Elderly AOSD patients can be observed more commonly due to population aging. We were also able to show that severe complications are more likely to occur in women than in men.

Funding This work was supported in-part by Grants-in-Aid for Research on Policy Planning and Evaluation (Ministry of Health, Labour and Welfare, Japan, H25-SEISAKU-SITEI-010 and H26-SEISAKU-SITEI-011).

Compliance with ethical standards

Conflict of interest All authors have declared no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent was not required.

References

1. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P (2014) Adult-onset Still's disease. Autoimmun Rev 13(7):708–722
2. Mahroum N, Mahagna H, Amital H (2014) Diagnosis and classification of adult Still's disease. J Autoimmun 48–49:34–37
3. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H et al (1992) Preliminary criteria for classification of adult Still's disease. J Rheumatol 19(3):424–430
4. Efthimiou P, Paik PK, Bielory L (2006) Diagnosis and management of adult onset Still's disease. Ann Rheum Dis 65(5):564–572
5. Ohta A, Yamaguchi M, Tsunematsu T, Kasukawa R, Mizushima H, Kashiwagi H et al (1990) Adult Still's disease: a multicenter survey of Japanese patients. J Rheumatol 17(8):1058–1063
6. Kim YJ, Koo BS, Kim YG, Lee CK, Yoo B (2014) Clinical features and prognosis in 82 patients with adult-onset Still's disease. Clin Exp Rheumatol 32(1):28–33
7. Asanuma YF, Mimura T, Tsuboi H, Noma H, Miyoshi F, Yamamoto K et al (2014) Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. Mod Rheumatol 7595:1–8
8. Evensen KJ, Nossent HC (2006) Epidemiology and outcome of adult-onset Still's disease in Northern Norway. Scand J Rheumatol 35(1):48–51
9. Efthimiou P, Kadavath S, Mehta B (2014) Life-threatening complications of adult-onset Still's disease. Clin Rheumatol 33(3):305–314
10. Hot A, Toh M-L, Coppéré B, Perard L, Madoux MHG, Mausservey C et al (2010) Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features and long-term outcome: a case-control study of 8 patients. Medicine (Baltimore) 89(1):37–46
11. Arlet J-B, Le THD, Marinho A, Amoura Z, Wechsler B, Papo T et al (2006) Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature. Ann Rheum Dis 65(12):1596–1601
12. Inoue T, Fushimi K (2013) Stroke care units versus general medical wards for acute management of stroke in Japan. Stroke 44(11):3142–3147
13. Kaneko T, Hirakawa K, Fushimi K (2014) Relationship between peri-operative outcomes and hospital surgical volume of total hip arthroplasty in Japan. Health Policy (New York) 117(1):48–53
14. Bagnari V, Colina M, Ciancio G, Govoni M, Trotta F (2010) Adult-onset Still's disease. Rheumatol Int 30:855–862
15. Chen PD, Yu SL, Chen S, Weng XH (2012) Retrospective study of 61 patients with adult-onset Still's disease admitted with fever of unknown origin in China. Clin Rheumatol 31:175–181

16. Wakai K, Ohta A, Tamakoshi A, Ohno Y, Kawamura T, Aoki R et al (1997) Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan. J Epidemiol 7(4):221–225
17. Magadur-Joly G, Billaud E, Barrier JH, Pennec YL, Masson C, Renou P et al (1995) Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis 54(7):587–590
18. Colina M, Zucchini W, Ciancio G, Orzincolo C, Trotta F, Govoni M (2011) The evolution of adult-onset Still disease: an observational and comparative study in a cohort of 76 Italian patients. Semin Arthritis Rheum 41(2):279–285
19. Kong X-D, Xu D, Zhang W, Zhao Y, Zeng X, Zhang F (2010) Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. Clin Rheumatol 29(9):1015–1019
20. Zeng T, Zou YQ, Wu MF, Yang CD (2009) Clinical features and prognosis of adult-onset still's disease: 61 Cases from China. J Rheumatol 36(5):1026–1031
21. Pay S, Türkçapar N, Kalyoncu M, Simşek I, Beyan E, Ertenli I et al (2006) A multicenter study of patients with adult-onset Still's disease compared with systemic juvenile idiopathic arthritis. Clin Rheumatol 25(5):639–644
22. Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, Sabbadini MG (2010) Adult onset Still's disease: clinical presentation in a large cohort of Italian patients. Clin Exp Rheumatol 28(1):41–48
23. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I et al (2014) Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. Medicine (Baltimore) 93(2):91–99
24. Lenert A, Yao Q (2016) Macrophage activation syndrome complicating adult onset Still's disease: a single center case series and comparison with literature. Semin Arthritis Rheum 45(6):711–716
25. Wouters JM, van de Putte LB (1986) Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases. Q J Med 61(235):1055–1065
26. Takemitsu T, Wada H, Hatada T, Ohmori Y, Ishikura K, Takeda T et al (2011) Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation. Thromb Haemost 105(1):40–44