Reumatizam 2022;69(2):90–102
https://doi.org/10.33004/reumatizam-69-2-2

PROEFSSIONAL PAPER STRUČNI RAD

CLINICAL PRESENTATION AND TREATMENT OF ADULT-ONSET STILL DISEASE – A SINGLE-CENTRE EXPERIENCE

KLINIČKA SLIKA I LIJEČENJE STILLOVE BOLESTI U ODRASLIH – ISKUSTVA JEDNOG CENTRA

Josip Tečer[1,*], Stela Hrkač[1,*], Antica Mihaličeк[1], Sara Tomašinec[1], Karla Lazibat[1], Majda Golob[1], Nikolina Ljubičić[1], Lea Šalamon[1], Jadranka Morović-Vergles[1], Joško Mitrović[1]

* both authors (the first and the second one) have equally contributed to this paper / oba autora (prvi i drugi) jednako su doprinijela radu

[1] Division of Clinical Imm unology, Allergology and Rheumatology, Department of Internal Medicine, School of Medicine and Faculty of Pharmacy and Biochemistry, University of Zagreb, University Hospital Dubrava, Zagreb / Zavod za kliničku imunologiju, alergologiju i reumatologiju Klinike za unutarnje bolesti Medicinskog i Farmaceutsko-biokemijskog fakulteta Sveučilišta u Zagrebu, Klinička bolnica Dubrava, Zagreb

Corresponding author / Adresa autora za dopisivanje:
Assisstant prof. Joško Mitrović, MD, PhD
Division of Clinical Immunology, Allergology and Rheumatology
/ Zavod za kliničku imunologiju, alergologiju i reumatologiju
Department of Internal Medicine, School of Medicine and Faculty of Pharmacy and Biochemistry, University of Zagreb
/ Klinika za unutarnje bolesti Medicinskog i Farmaceutsko-biokemijskog fakulteta Sveučilišta u Zagrebu
University Hospital Dubrava / Klinička bolnica Dubrava
Avenija Gojka Šuška 6
10000 Zagreb
Croatia / Hrvatska
E-mail / e-pošta: jmitrovi@kbd.hr

Received / Primljeno: 1st September 2022 / 1. 9. 2022.
Accepted / Prihvaćeno: 13th December 2022 / 13. 12. 2022.

Abstract

Introduction: Adult-onset Still disease (AOSD) is an autoinflammatory disease which most commonly occurs in adults over the age of 16, either with new onset or following earlier diagnosis of Systemic juvenile idiopathic arthritis. Due to nonspecific symptoms and a lack of specific laboratory-immunologic markers, it represents a diagnostic and treatment challenge. The aim of this retrospective observational study was to show a single-center experience in the diagnosis and treatment of AOSD. *Patients and methods:* This retrospective observational study included patients from the University hospital Dubrava Rheumatology and Clinical Immunology Outpatient Clinic who were diagnosed with AOSD and fulfilled the Yamaguchi classification criteria. The study included 14 patients (10 female (71.43%) and 4 male (28.57%). Information was acquired from available medical documentation – data about age, clinical presentation, laboratory parameters, treatment and outcomes were analyzed using methods of descriptive statistics. *Results:* The mean age at diagnosis was 44.7 years (range 19–64 y/o). Most common signs and symptoms at presentation were fever (92.7%), rash (85.7%), arthralgia (85.7%) and sore throat (71.4%). Levels of CRP were elevated in all, ferritin in 91,7% and ESR in 90% of patients. Two patients developed macrophage activation syndrome (MAS). Patients were most commonly treated with glucocorticoids (76.9%), methotrexate (46.2%) and NSAIDs (non-steroidal anti-inflammatory drugs) (7.14%) which led to disease remission in 84.6% of patients in the first year following initial diagnosis. *Conclusion:* Reported symptoms and laboratory findings in our group of patients with AOSD are in accordance with other similar studies. However, age at diagnosis was somewhat higher in our group which underlines the importance of AOSD as a part of differential diagnosis even in older age. It is important to keep potential life threatening complications, especially MAS, in mind when treating AOSD patients. Most common treatment of choice, glucocorticoids and methotrexate, led to initial disease remission in the majority of our patients.

Key words: adult-onset Still disease, fever, treatment, glucocorticoids, methotrexate, macrophage activation syndrome, Croatia

Sažetak

Uvod: Stillova bolest odrasle dobi (AOSD, engl. *adult onset Still disease*) autoinflamatorno je stanje koje se najčešće pojavljuje u odraslih iznad 16 godina, bilo kao novonastala bolest ili nakon ranije dijagnosticiranoga idiopatskog sistemskog juvenilnog artritisa. S obzirom na nespecifične simptome i nedostatak dijagnostičkog laboratorijsko-imunološkog markera, bolest predstavlja dijagnostički i terapijski izazov. Cilj ovog istraživanja bio je prikazati iskustvo jednog centra u dijagnosticiranju i liječenju AOSD-a. *Ispitanici i metode:* U ovo retrospektivno opservacijsko istraživanje uključeni su bolesnici Zavoda za kliničku imunologiju, alergologiju i reumatologiju KB Dubrava kojima je postavljena dijagnoza AOSD-a te su ispunjavali Yamaguchijeve kriterije (1992.). Ukupno je uključeno 14 bolesnika (10 žena i 4 muškarca). Podatci o dobi, kliničkoj slici, laboratorijskim nalazima, terapiji i ishodu liječenja prikupljeni su iz dostupne medicinske dokumentacije te su analizirani metodama deskriptivne statistike. *Rezultati:* Prosječna dob ispitanika pri postavljanju dijagnoze bila je 44,7 godina (raspon 19–64 god.). Najčešći simptomi pri dijagnozi bili su febrilitet u 92,9%, osip u 85,7%, artralgije u 85,7% te grlobolja u 71,4% ispitanika. Dvoje je bolesnika razvilo sindrom aktivacije makrofaga (MAS). Povišene vrijednosti CRP-a nađene su u svih bolesnika, feritina u 91,7% te sedimentacije eritrocita u 90% bolesnika. Bolesnici su najčešće bili liječeni glukokortikoidima (76,9%), metotreksatom (46,2%) i nesteroidnim protuupalnim lijekovima (NSAID, engl. *non-steroidal anti-inflammatory drugs*) (7,14%) što je dovelo do remisije unutar prve godine od postavljanja dijagnoze u 84,6% ispitanika. *Zaključak:* Simptomatologija i laboratorijski nalazi u našoj skupini bolesnika s AOSD-om u skladu su s drugim sličnim istraživanjima. S druge strane, dob pri postavljanju dijagnoze u našoj grupi nešto je viša, što upućuje na važnost AOSD-a kao dijela diferencijalne dijagnoze i u starijoj dobi. Uvijek je potreban oprez zbog mogućeg razvoja potencijalno životno ugrožavajućih komplikacija, poput MAS-a. Najčešći modaliteti liječenja bili su glukokortikoidi i metotreksat te je u većine bolesnika došlo do inicijalne remisije bolesti.

Ključne riječi: Stillova bolest odrasle dobi, vrućica, liječenje, glukokortikoidi, metotreksat, sindrom aktivacije makrofaga, Hrvatska

INTRODUCTION

Adult onset Still disease (AOSD) is a systemic, autoinflammatory disorder characterized by spiking fever, arthralgia and salmon-colored skin rash (1). The term AOSD was coined by Eric Bywaters in his research paper describing 14 adult patients with syndrome similar to systemic-onset juvenile idiopathic arthritis (sJIA) known as Still's disease (2).

There are no robust epidemiologic data for AOSD. It occurs worldwide, usually affecting young people (the median age of diagnosis is 36 years old) and its incidence has been estimated to 0.16 (per 100,000 persons) in France, 0.22 in Japan, and 0.4 in Norway (3–8).

The etiopathogenesis of AOSD is still not fully understood. It is thought that infectious factors can trigger a pathological immune response leading to disease manifestations, since there is similarity between AOSD and established infectious syndromes (e.g. abrupt onset, high fever, lymphadenopathy etc.) and many viruses and bacteria were isolated in patients with AOSD (3). AOSD is marked by activation of neutrophils and macrophages, parts of the innate immune system, while adaptive immunity seems to have a limited role (9–12). Inflammasome dysregulation, Il-1β and IL-17 seem to be in the center of AOSD pathogenesis (9,10,13–19).

AOSD can present in one of three main patterns: monophasic (usually lasts for a year with complete resolution of symptoms), intermittent (two or more disease flares with complete remission between episodes)

UVOD

Stillova bolest odrasle dobi (AOSD, engl. *adult onset Still disease*) sistemski je, autoinflamatorni poremećaj koji karakteriziraju vrućica, artralgija i kožni osip ružičaste boje lososa (1). Izraz AOSD skovao je Eric Bywaters u svom istraživačkom radu, u kojem je opisao 14 odraslih bolesnika sa sindromom sličnim sistemskom juvenilnom idiopatskom artritisu (sJIA, engl. *systemic juvenile idiopathic arthritis*), poznatom pod nazivom Stillova bolest (2).

Ne postoje čvrsti epidemiološki podatci za AOSD. Javlja se diljem svijeta, obično pogađa mlade ljude (srednja dob dijagnoze je 36 godina), a njegova učestalost procijenjena je na 0,16 (na 100.000 osoba) u Francuskoj, 0,22 u Japanu i 0,4 u Norveškoj (3–8).

Etiopatogeneza AOSD-a još uvijek nije u potpunosti razjašnjena. Smatra se da infektivni čimbenici mogu izazvati patološki imunološki odgovor koji dovodi do manifestacija bolesti, budući da postoji sličnost između AOSD-a i utvrđenih infektivnih sindroma (npr. nagli početak bolesti, visoka temperatura, limfadenopatija itd.) te su mnogi virusi i bakterije izolirani u bolesnika s AOSD-om (3). AOSD karakterizira aktivacija neutrofila i makrofaga, dijelova urođenoga imunološkog sustava, a izgleda da adaptivni imunitet ima ograničenu ulogu (9–12). Čini se da su disregulacija inflamasoma, Il-1β i IL-17 u središtu patogeneze AOSD-a (9,10,13–19).

AOSD se može pojaviti u jednom od tri glavna obrasca: monofazni (obično traje godinu dana s potpu-

and chronic (persistently active disease associated with destructive arthritis) (20). As previously stated, the most common symptoms of AOSD are fever, arthralgia, and skin rash. Fever usually precedes other symptoms and AOSD is often diagnosed while investigating patients with a diagnosis of fever of unknown origin (FUO) (3,21,22). Arthralgia typically involves the wrists, knees and ankles. Even though is initially mild and transient, it can involve into a chronic destructive polyarthritis (2,3,23). The rash is usually macular or maculopapular, salmon colored and occurs during fever spikes (21,24). Another characteristic presentation is sore throat, which often occurs as a first symptom (25). AOSD can also present with myalgia, lymphadenopathy, splenomegaly, hepatomegaly, pleurisy, pericarditis, weight loss and with other manifestations (3). One of the most dangerous and life-threatening complications of the inadequate control of inflammation in AOSD is macrophage activation syndrome (MAS). The incidence of MAS is reported to be as high as 23% among AOSD patients and it is linked with significantly lower survival rate (1,26–29). Laboratory work-up in AOSD patients typically shows leukocytosis with neutrophilia, elevated acute phase reactants like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), elevated liver enzymes and elevated ferritin with negative rheumatoid factor (RF) and negative antinuclear antibodies (ANA) (1). Elevated serum ferritin levels are a non-specific, but common finding in AOSD and could be used, in conjunction with other typical signs and symptoms, for AOSD diagnosis (1). Furthermore, Fautrel et al pointed to glycosylated ferritin (GF) as useful marker for AOSD diagnosis (3,30).

Several criteria sets were designed to aid in diagnosing AOSD. The Yamaguchi criteria have the highest sensitivity. They consist of four major and four minor criteria containing typical signs and symptoms but are limited by a long list of other conditions that need to be excluded (Table 1) (20,31). The Fautrel criteria are more specific but require measurement of glycosylated ferritin which is not widely available (20,32).

Most AOSD patients are treated with systemic glucocorticoids, however non-steroid anti-inflammatory drugs (NSAIDs) are also used, as well as conventional disease-modifying antirheumatic drugs (cDMARDs), most commonly methotrexate (MTX) (1). Biologics are used in patients refractory to glucocorticoids and cDMARDs. Evidence suggest that anti IL-1 agents (anakinra, canakinumab) have been more effective in AOSD with systemic features, while anti-TNFα agents have shown better results in AOSD patients with prominent articular symptoms and the anti IL-6 agent tocilizumab has shown effective in both features of AOSD (3,15,33–39).

Because of the variety of clinical presentations with non-specific symptoms and laboratory findings, AOSD

nim nestankom simptoma), intermitentni (dva ili više pogoršanja bolesti s potpunom remisijom između napada) i kronični (trajno aktivna bolest povezana s destruktivnim artritisom) (20). Kao što je prethodno navedeno, najčešći simptomi AOSD-a su vrućica, artralgija i kožni osip. Vrućica se obično javlja prije drugih simptoma i AOSD se često dijagnosticira tijekom obrade bolesnika s dijagnozom vrućice nepoznatog podrijetla (VNP) (3,21,22). Artralgija obično zahvaća zapešća, koljena i gležnjeve. Iako se u početku radi o blagom i prolaznom stanju, ono se može razviti u kronični destruktivni poliartritis (2,3,23). Osip je obično makularan ili makulopapulozan, ružičaste boje lososa i javlja se tijekom naglih skokova vrućice (21,24). Druga je karakteristična manifestacija grlobolja, koja se često javlja kao prvi simptom (25). AOSD se također može manifestirati mijalgijom, limfadenopatijom, splenomegalijom, hepatomegalijom, pleuritisom, perikarditisom, gubitkom težine i drugim manifestacijama (3). Jedna od najozbiljnijih komplikacija opasnih po život uslijed neadekvatne kontrole upale u sklopu AOSD-a jest sindrom aktivacije makrofaga (MAS). Istraživanja pokazuju da učestalost pojave MAS-a iznosi čak 23% u bolesnika s AOSD-om te da je povezana s iznimno niskom stopom preživljenja (1,26–29). Laboratorijski nalazi u bolesnika s AOSD-om obično pokazuju neutrofilnu leukocitozu, povišene reaktante akutne faze poput C-reaktivnog proteina (CRP) i sedimentacije eritrocita (SE), povišene jetrene enzime i povišen feritin s negativnim reumatoidnim faktorom (RF) i negativnim antinuklearnim protutijelima (ANA) (1). Povišene razine feritina u serumu nespecifičan su, ali čest nalaz kod AOSD-a i mogu se upotrebljavati, zajedno s drugim tipičnim znakovima i simptomima, za dijagnozu AOSD-a (1). Nadalje, Fautrel i suradnici istaknuli su bitnu ulogu glikoliziranog feritina (GF) kao korisnog markera za dijagnozu AOSD-a (3,30).

Osmišljeno je nekoliko skupova kriterija za pomoć u dijagnosticiranju AOSD-a. Yamaguchijevi kriteriji imaju najveću osjetljivost. Sastoje se od četiri glavna i četiri sporedna kriterija koji sadrže tipične znakove i simptome, ali su ograničeni dugim popisom drugih stanja koja se moraju isključiti (tablica 1) (20,31). Fautrelovi kriteriji su specifičniji, ali zahtijevaju mjerenje glikoziliranog feritina koji nije lako dostupan (20,32).

Većina bolesnika s AOSD-om liječi se sistemskim glukokortikoidima, međutim koriste se i nesteroidni protuupalni lijekovi (NSAR), kao i konvencionalni antireumatski lijekovi koji modificiraju tijek bolesti (engl. *conventional disease-modifying antirheumatic drugs*, cDMARD-ovi), najčešće metotreksat (MTX) (1). Biološki lijekovi upotrebljavaju se u bolesnika otpornih na glukokortikoide i cDMARD-ove. Dokazi upućuju na to da su anti-IL-1 lijekovi (anakinra, canakinumab) bili učinkovitiji u liječenju AOSD-a sa sistemskim zna-

Table 1 Yamaguchi criteria for Adult onset Still disease (AOSD)

Tablica 1. Yamaguchijevi kriteriji za Stillovu bolest odrasle dobi (AOSD)

Major criteria / Veliki kriteriji	Fever ≥ 39°C lasting for ≥1 week / Vrućica ≥ 39 °C trajanja ≥1 tjedan
	Arthralgias or arthritis lasting for ≥2 weeks / Artralgija ili artritis trajanja ≥2 tjedna
	Typical non-pruritic salmon colored skin rash / Tipični ne-pruritički osip boje lososa
	Leukocytosis (WBC ≥10 000/μL) with ≥80% of neutrophils / Leukocitoza ≥10 000/μL) s više od ≥80 % neutrofila
Minor criteria / Mali kriteriji	Sore throat / Grlobolja
	Lymphadenopathy / Limfadenopatija
	Splenomegaly or hepatomegaly / Splenomegalija ili hepatomegalija
	Abnormal liver function tests / Nenormalni testovi jetrene funkcije
	Negative tests for ANA and RF / Negativni testovi na RF i ANA
Exclusion criteria / Isključni kriteriji	Infections / Infekcije
	Malignancies / Malignomi
	Other rheumatic diseases / Druge reumatske bolesti

Legend/Legenda: WBC – White blood cells, ANA – antinuclear antibody, RF – Rheumatoid factor / WBC – leukociti, ANA – antinuklearna antitijela, RF – reumatoidni faktor

still remains a diagnosis of exclusion with malignancies and infections as the most important disorders to be ruled out. Even though diagnosis often has to be swift, it is important to remain open to change/adjustment of diagnosis depending on the disease course.

Furthermore, AOSD treatment also represents a challenge, since there are no widely accepted treatment guidelines. The goal of this study was to show a single-center experience in the diagnosis, treatment and outcomes of AOSD.

PATIENTS AND METHODS

This retrospective observational study included patients of the University hospital Dubrava Rheumatology and Clinical Immunology outpatient clinic who were diagnosed with AOSD from May 2005 to May 2022. In order to be included in this study, patients diagnosed with AOSD had to fulfil the Yamaguchi classification criteria, which consist of major, minor criteria and obligatory exclusion criteria; at least five criteria, of which two must be major, are required for diagnosis, i.e. classification (31). After applying said criteria, a total of 14 patients were included in the study. The study group included 10 female (71.43%) and 4 male (28.57%) patients. Data used in this study were obtained from available medical data about the

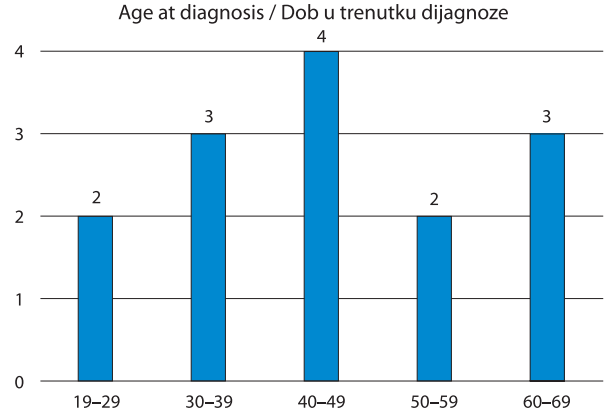


Figure 1 Bar chart showing the number of patients in each age group

Slika 1. Stupčasti grafikon s prikazom broja bolesnika po svakoj dobnoj skupini

čajkama, dok su anti-TNFα lijekovi pokazali bolje rezultate u bolesnika s AOSD-om s istaknutim zglobnim simptomima, a anti-IL-6 lijek tocilizumab pokazao se učinkovitim u objema značajkama AOSD-a (3,15,33–39).

Zbog raznolikosti kliničkih manifestacija s nespecifičnim simptomima i laboratorijskim nalazima, AOSD i dalje ostaje dijagnoza isključenja, s tim da su malignomi i infekcije najvažniji poremećaji koje treba isključiti. Iako dijagnoza često mora biti brza, važno je ostati otvoren za promjenu/prilagodbu dijagnoze ovisno o tijeku bolesti.

Nadalje, liječenje AOSD-a također predstavlja izazov, jer ne postoje široko prihvaćene smjernice za njegovo liječenje. Cilj ovog istraživanja bio je prikazati iskustvo jednog centra u dijagnosticiranju, liječenju i ishodima AOSD-a.

BOLESNICI I METODE

U ovo retrospektivno opservacijsko istraživanje uključeni su bolesnici Zavoda za kliničku imunologiju, alergologiju i reumatologiju KB Dubrava kojima je postavljena dijagnoza AOSD-a u razdoblju od svibnja 2005. do svibnja 2022. godine. Kako bi bili uključeni u ovo istraživanje, bolesnici s dijagnozom AOSD-a morali su ispunjavati Yamaguchijeve kriterije klasifikacije koji se sastoje od velikih, malih kriterija i obveznih isključnih kriterija. Za dijagnozu, odnosno klasifikaciju potrebno je najmanje pet kriterija, od kojih dva moraju biti velika (31). Nakon primjene navedenih kriterija u istraživanje je bilo uključeno ukupno 14 bolesnika. Skupinu ispitanika činilo je 10 žena (71,43%) i 4 muškarca (28,57%). Podatci korišteni u ovom istraživanju prikupljeni su iz dostupne medicinske dokumentacije bolesnika. Analizirano je mnoštvo parametara za svakog ispitanika, uključujući dob ispitanika pri postavljanju dijagnoze, znakove i simptome koji su se prezentirali tijekom početne dijagnoze i kon-

patients. A multitude of parameters was analyzed for each subject, including age at diagnosis, signs and symptoms exhibited during initial presentation and subsequent follow-up, laboratory findings at presentation, treatment received and outcomes. Outcomes were analyzed in the period of up to one year after initial diagnosis (due to varying intervals in follow-up examinations) and were classified as either "active disease" or "remission". Remission was defined as absence of significant self-reported symptoms in addition to absence of significant clinical findings upon examination which would require modification of treatment. Acquired data was analyzed using descriptive statistics methods.

RESULTS

Age at diagnosis

Patient's age at diagnosis ranged from 19 to 64 years, the mean age was 44.7 years. A variety of age groups, divided into decades for analysis, was represented in the patient group (Figure 1.). The age group between 40 and 49 years old was found to have the most patients. Notably, 64% of patients were diagnosed at an age above 40.

Signs and symptoms

A multitude of patient-reported, as well as clinically verified signs and symptoms, was analyzed and ranked by frequency (Figure 2.). Data analysis showed the four most common clinical manifestations in the subject group were: fever, characteristic rash, arthralgia and pharyngitis. The most common manifestation was fever, defined as a body temperature ≥ 39°C lasting 1 ≥ weeks, which was reported and/or verified in 92.9% of patients. The second most common clinical findings were characteristic (maculopapular nonpruritic salmon-pink) rash and arthralgia lasting 1 ≥ weeks, which were present in 85.7% of patients. Arthralgia was mostly symmetrical. Additionally, large joints were affected in all patients presenting with arthralgias, while small joints of the hands and feet were affected in approximately half of the patients (however only in addition to large joint affection). Sore throat was also among the most common symptoms, as it occurred in 71.4% of patients. It is worth noting that two patients (14.3%) developed MAS. All other signs and symptoms which occurred in the patients, ranked by their respective frequency, are shown in Figure 2.

Laboratory findings

Laboratory parameters of interest were analyzed in all patients. The number of leukocytes, levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, aspartate aminotransferase (AST), alatrolnih pregleda, laboratorijske nalaze pri dijagnozi, metode liječenja i ishode liječenja. Ishodi su analizirani u razdoblju do godinu dana nakon početne dijagnoze (zbog različitih intervala u kontrolnim pregledima) i klasificirani su ili kao „aktivna bolest" ili kao „remisija". Remisija je definirana kao odsutnost značajnih samoprijavljenih simptoma uz odsutnost značajnih kliničkih nalaza nakon pregleda koji bi zahtijevali modifikaciju liječenja. Dobiveni podatci analizirani su metodama deskriptivne statistike.

REZULTATI

Dob pri postavljanju dijagnoze

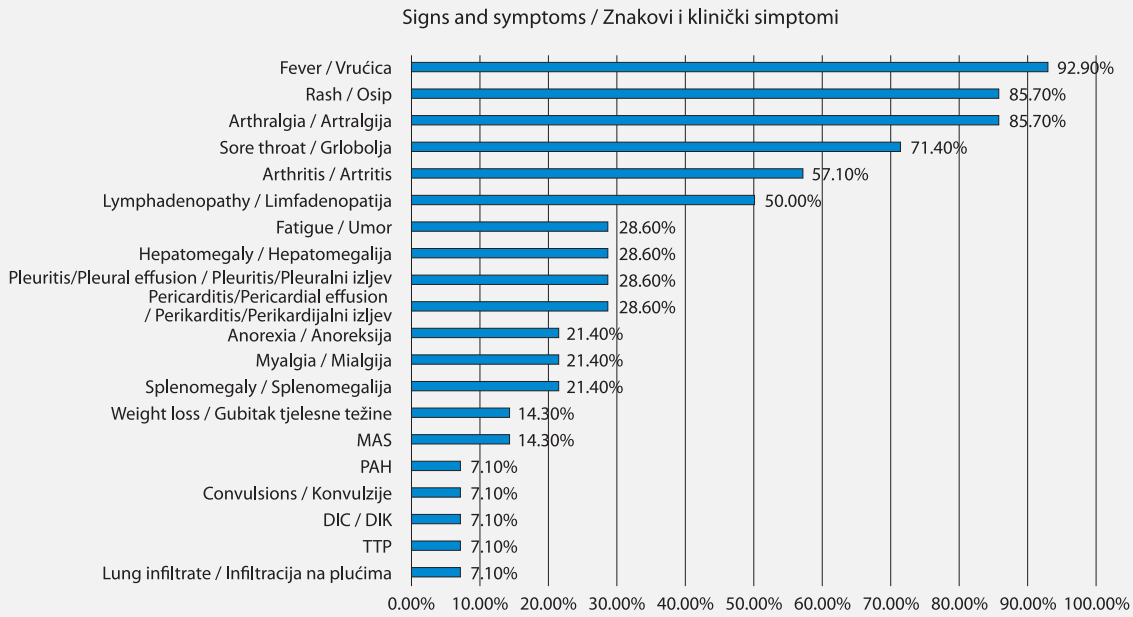
Dob bolesnika pri postavljanju dijagnoze bila je od 19 do 64 godine, a prosječna dob 44,7 godina. Različite dobne skupine, podijeljene u desetljeća za analizu, bile su zastupljene u skupini bolesnika (slika 1). Utvrđeno je da se najviše bolesnika nalazi u dobnoj skupini između 40 i 49 godina. Naime, kod 64% bolesnika dijagnoza je postavljena u dobi iznad 40 godina.

Znakovi i simptomi

Mnoštvo znakova i simptoma koje su prijavili bolesnici, kao i klinički potvrđenih znakova i simptoma, analizirano je i rangirano po učestalosti (slika 2). Analiza podataka pokazala je da su četiri najčešće kliničke manifestacije u skupini ispitanika: vrućica, karakterističan osip, artralgija i faringitis. Najčešća manifestacija bila je vrućica, definirana kao tjelesna temperatura ≥ 39 °C trajanja više od 1 ≥ tjedan, koja je prijavljena i/ili potvrđena u 92,9% bolesnika. Drugi najčešći klinički nalazi bili su karakteristični (makulopapulozni nepruritični, ružičasti [boje lososa]) osip i artralgija trajanja više od 1 ≥ tjedan, koji su bili prisutni u 85,7% bolesnika. Artralgija je uglavnom bila simetrična. Uz to, veliki zglobovi bili su zahvaćeni u svih bolesnika s artralgijama, dok su mali zglobovi šaka i stopala bili zahvaćeni u otprilike polovice bolesnika (ali samo uz zahvaćenost velikih zglobova). Grlobolja je također bila među najčešćim simptomima, jer se pojavila kod 71,4% bolesnika. Važno je napomenuti da se kod dva bolesnika (14,3%) razvio MAS. Svi ostali znakovi i simptomi koji su se javili kod bolesnika, poredani prema učestalosti, prikazani su na slici 2.

Laboratorijski nalazi

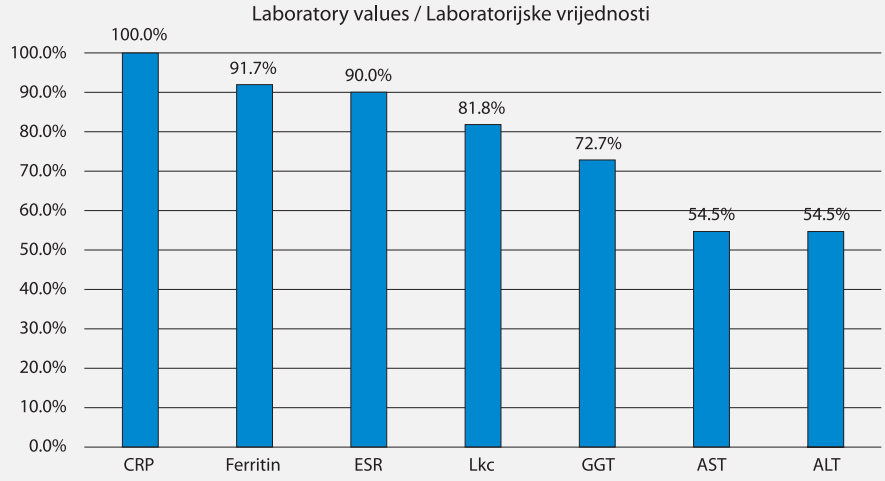
U svih bolesnika analizirani su laboratorijski parametri od interesa. Broj leukocita, razine C-reaktivnog proteina (CRP), brzina sedimentacije eritrocita (SE, to jest, ESR, engl. *erythrocyte sedimentation rate*), feritin, aspartat aminotransferaza (AST), alanin aminotransferaza (ALT) i gama-glutamil transferaza (GGT) procijenjeni su unutar ili izvan normalnog raspona, a procijenjena je i njihova apsolutna vrijednost (slika 3).



Legend / Legenda: MAS = macrophage activation syndrome / sindrom aktivacije makrofaga, PAH = pulmonary artery hypertension / plućna arterijska hipertenzija, DIC = disseminated intravascular coagulation / diseminirana intravaskularna koagulacija, TTP = thrombotic thrombocytopenic purpura / trombotična tromocitopenična purpura

Figure 2 Bar chart showing the percentage of patients presenting with specific signs/symptoms, ranked from the most to the least frequent

Slika 2. Stupčasti grafikon s prikazom postotka ispitanika koji su se prezentirali određenim kliničkim simptomima/znakovima, poredani po učestalosti od najčešćeg do najrjeđeg



Legend / Legenda: CRP = C-reactive protein / C-reaktivni protein, ESR = erythrocyte sedimentation rate / sedimentacija eritrocita, AST = aspartate aminotransferase / aspartat aminotransferaza, ALT = alanine aminotransferase / alanin aminotransferaza, GGT = gamma-glutamyl transferase / gama-glutamil transferaza

Figure 3 Bar chart showing the percentage of patients (Y-axis) with abnormal values of respective laboratory parameters

Slika 3. Stupčasti grafikon s prikazom postotka bolesnika (Y-os) s povišenim vrijednostima određenih laboratorijskih parametara

nine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) were evaluated for being either inside or outside of normal range and for their absolute value (Figure 3.). Analysis showed that all patients had abnormal (elevated) levels of CRP, followed by ferritin and ESR, which were elevated in 91.7% and 90% of patients. Leukocytosis was also present in the majority (81.8%) of patients, while elevated liver enzymes were found in more than half of the patients (Figure 3).

Analiza je pokazala da su svi bolesnici imali abnormalne (povišene) razine CRP-a, zatim feritina i ESR-a, koji su bili povišeni u 91,7% odnosno 90% bolesnika. Leukocitoza je također bila prisutna u većine (81,8%) bolesnika, dok su povišeni jetreni enzimi nađeni u više od polovice bolesnika (slika 3).

tients, respectively. Leukocytosis was also present in the majority (81.8%) of patients, while elevated liver enzymes were found in more than half (Figure 3.).

The two most commonly elevated laboratory values – CRP and ferritin were also analyzed for absolute value. We found they appeared in relatively large ranges – levels of CRP were found to have a range of 17.6mg/L – 538 mg/L (normal value < 5mg/L), with a mean value of 172.48mg/L and median of 143mg/L. The range of ferritin levels was 137μg/L – 33200μg/L (normal value 20–200μg/L), with a mean value of 5623.5μg/L and median of 2440μg/L. However, when two presumed data outliers (values of 11357 μg/L and 33200 μg/L) are excluded from analysis, the mean value of ferritin is 2276,1 μg/L.

Treatment and clinical outcomes

We analyzed treatment modalities which the patients received during the follow-up period of one year after initial diagnosis. The most commonly prescribed treatment in our patient group were high doses of glucocorticoids (30–99 mg of prednisone equivalent a day), which were used in 76.9% of patients (40). NSAIDs were used only in 7.14% of cases as first-line treatment. The most commonly chosen glucocorticoid-sparing agent was methotrexate (MTX), which was used to treat 46.2% of patients, while a biologic agent (anakinra) was used in one patient. Doses of MTX ranged from 10–25 mg per day, while anakinra was used in the standard dose of 100mg per day subcutaneously. In this particular case, anakinra was used as the patient had a treatment-resistant form of disease, control of which was dependent on high daily doses of glucocorticoids, while treatment with MTX had to be discontinued due to liver toxicity. Evaluation of clinical outcomes showed a vast majority of patients (84.6%) had achieved disease remission in the year following initial diagnosis, whereas the disease was deemed active in 15.4%. In the follow-up period, the disease course was monophasic in the majority of patients, while three patients presented with intermittent (relapsing) forms and one with a suspected chronic disease form. However, the disease was not fatal in any of the patients.

Rare manifestations

Among the numerous manifestations of AOSD, it is worth noting that two patients developed MAS. One of these patients presented with fever, arthralgia, generalized lymphadenopathy, erythematous macular rash, pancytopenia, liver disfunction and coagulopathy consistent with disseminated intravascular coagulation (DIC), hemophagocytosis was present in the bone marrow; while the likely trigger was a parvo B19 virus infection. The other MAS patient presented with fever,

Za dvije najčešće povišene laboratorijske vrijednosti – CRP i feritin također je analizirana apsolutna vrijednost. Otkrili smo da se pojavljuju u relativno velikim rasponima – utvrđeno je da razine CRP-a imaju raspon od 17,6 mg/L – 538 mg/L (normalna vrijednost < 5 mg/L), sa srednjom vrijednošću od 172,48 mg/L i medijanom od 143 mg /L. Raspon razina feritina bio je 137 μg/L – 33200 μg/L (normalna vrijednost 20–200 μg/L), sa srednjom vrijednošću od 5623,5 μg/L i medijanom od 2440 μg/L. Međutim, kada se dva pretpostavljena odstupanja podataka (vrijednosti od 11357 μg/L i 33200 μg/L) isključe iz analize, srednja vrijednost feritina iznosi 2276,1 μg/L.

Liječenje i klinički ishodi

Analizirali smo modalitete liječenja koje su bolesnici primili tijekom razdoblja praćenja od godinu dana nakon početne dijagnoze. Najčešće propisano liječenje u našoj skupini bolesnika bile su visoke doze glukokortikoida (30–99 mg ekvivalenta prednizona dnevno), koje su korištene u slučaju 76,9% bolesnika (40). Nesteroidni protuupalni lijekovi (NSAR) korišteni su samo u 7,14% slučajeva kao prva linija liječenja. Najčešće odabrani lijek za uštedu glukokortikoida bio je metotreksat (MTX) kojim je liječeno 46,2% bolesnika, dok je u jednog bolesnika korišten biološki lijek (anakinra). Doze MTX-a kretale su se od 10 do 25 mg dnevno, dok je anakinra korištena u standardnoj dozi od 100 mg dnevno supkutano. U ovom konkretnom slučaju korištena je anakinra jer je bolesnica imala oblik bolesti otporan na liječenje, čija je kontrola ovisila o visokim dnevnim dozama glukokortikoida, dok je liječenje MTX-om moralo biti prekinuto zbog toksičnog oštećenja jetre. Procjena kliničkih ishoda pokazala je da je velika većina bolesnika (84,6%) postigla remisiju bolesti u godini nakon početne dijagnoze, dok je bolest smatrana aktivnom u 15,4% slučajeva. U razdoblju praćenja tijek bolesti je u većine bolesnika bio monofazičan, dok su tri bolesnika imala intermitentni (relapsirajući) oblik bolesti, a kod jednog je bila prisutna sumnja na kronični oblik bolesti. Međutim, bolest nije bila smrtonosna ni kod jednog bolesnika.

Rijetke manifestacije

Među brojnim manifestacijama AOSD-a valja istaknuti da su dva bolesnika razvila MAS. Jedan od ovih bolesnika imao je vrućicu, artralgiju, generaliziranu limfadenopatiju, eritematozni makularni osip, pancitopeniju, disfunkciju jetre i koagulopatiju u skladu s diseminiranom intravaskularnom koagulacijom (DIK), hemofagocitoza je bila prisutna u koštanoj srži, dok je vjerojatni pokretač bila infekcija parvovirusom B19. Drugi bolesnik s MAS-om imao je vrućicu, pancitopeniju, artralgiju, koagulopatiju u skladu s DIK-om, izrazito povišene razine laktat dehidrogenaze (LDH) i osip

pancytopenia, arthralgia, coagulopathy consistent with DIC, markedly raised levels of lactate dehydrogenase (LDH) and a purpura-like rash; a preceding infection with Influenza type B was identified as a possible trigger. While presenting with MAS, both of the patients were treated with pulse doses of glucocorticoids (up to 250mg of prednisone equivalent during 3 days), with additions of either intravenous immunoglobulins or cyclosporin, as well as treatment of DIC with fresh frozen plasma and low molecular weight heparin. Both patients responded well to treatment, experienced rapid improvement and were discharged.

DISCUSSION

In our study, 10 out of 14 patients were female (71.43%) and 4 male (28.57%) which is similar to sex ratios reported by studies in Turkey (76,2% female patients) (41), in Japan (68%) (42) and China (72%) (43). On the other hand, other studies showed almost balanced sex ratios (3,4,44,45).

The mean age at disease onset in our study was 44,7 years with a range from 19 to 64 years. Balci et al. reported a similar mean age at disease onset of 44,5 years in the above mentioned Turkish cohort, while Evensen et al. in a Norwegian cohort and Hu et al. in a large Chinese cohort reported somewhat lower mean age at diagnosis of 33,8 and 37,7 years respectively (41,43,46). Similarly, Efthimiou et al. report mean age at diagnosis of approximately 38 years (range: 33.3–45.0) in their recently published systematic literature review of AOSD (1).

The diagnosis was made in patients of various age groups (defined as decades of life). However, it is worth noticing that most patients experienced disease onset between the ages of 40 and 49, while 64% of the patient group was diagnosed at an age above 40. This is different from data acquired in the systematic review of Efthimiou et al., which shows a peak of incidence between 16 and 35 years with 45–80% of diagnoses made at that age (1). However, similar to our results, Magadur-Joly et al. showed peak of incidence between the ages of 36 and 45 in their study (6). Furthermore, 3 patients (21%) in our cohort were diagnosed at an age above 60 years old. Although AOSD onset is not common at this age, several case studies consisted of 7–10% patients diagnosed at an age above 60 (1). This higher percentage of patients presenting at an age above 40 years old in our study shows the importance of suspecting AOSD in older patients presenting with fitting symptoms, even those above 60 years of age.

The most common symptom in our group was fever, which was reported in 92,9% of our patients. It was followed by arthralgia and rash, both found in 85,70% and sore throat found in 71,40% of patients. In the

nalik purpuri; prethodna infekcija gripom tipa B identificirana je kao mogući pokretač bolesti. Dok su imali MAS, oba su bolesnika liječena pulsnim dozama glukokortikoida (do 250 mg ekvivalenta prednizona tijekom tri dana), uz dodatke intravenskih imunoglobulina ili ciklosporina, a za liječenje DIK-a primjenjivali su se svježe smrznuta plazma i niskomolekularni heparin. Oba su bolesnika dobro reagirala na liječenje, stanje im se brzo poboljšalo i otpušteni su iz bolnice.

RASPRAVA

U našem istraživanju, od 14 bolesnika 10 su bile žene (71,43%), a 4 muškarca (28,57%), što je slično omjerima spolova iz istraživanja provedenih u Turskoj (76,2% bolesnika) (41), Japanu (68%) (42) i Kini (72%) (43). S druge strane, druga istraživanja pokazala su gotovo uravnotežene omjere spolova (3,4,44,45).

Prosječna dob na početku bolesti u našem istraživanju bila je 44,7 godina s rasponom od 19 do 64 godine. Balci i suradnici naveli su o sličnu prosječnu dob na početku bolesti od 44,5 godina u gore spomenutoj turskoj kohorti, dok su Evensen i suradnici u norveškoj kohorti i Hu i suradnici u velikoj kineskoj kohorti naveli nešto nižu prosječnu dob pri postavljanju dijagnoze, od 33,8 odnosno 37,7 godina (41,43,46). Slično tomu, u svojem nedavno objavljenom sustavnom pregledu literature za AOSD, Efthimiou i suradnici naveli su prosječnu dob pri postavljanju dijagnoze od približno 38 godina (raspon: 33,3–45,0) (1).

Dijagnoza je postavljena u bolesnika različitih dobnih skupina (definiranih kao različita desetljeća života). Međutim, bitno je primijetiti da je kod većine bolesnika bolest nastupila u dobi između 40 i 49 godina, dok je kod 64% bolesnika bolest dijagnosticirana u dobi iznad 40 godina. Ovo se razlikuje od podataka prikupljenih u sustavnom pregledu Efthimioua i suradnika, koji pokazuje vrhunac incidencije između 16 i 35 godina s 45–80% dijagnoza postavljenih u toj dobi (1). Međutim, slično našim rezultatima, u svojem istraživanju Magadur-Joly i suradnici pokazali su vrhunac incidencije u dobi između 36 i 45 godina (6). Nadalje, trojici bolesnika (21%) u našoj kohorti bolest je dijagnosticirana u dobi iznad 60 godina. Iako početak AOSD-a nije čest u ovoj dobi, nekoliko studija slučaja uključivalo je 7–10% bolesnika kojima je bolest dijagnosticirana u dobi iznad 60 godina (1). Ovaj veći postotak bolesnika kojima se bolest pojavila u dobi iznad 40 godina u našoj studiji pokazuje važnost sumnje na AOSD kod starijih bolesnika koji imaju odgovarajuće simptome, čak i onih starijih od 60 godina.

Najčešći simptom u našoj skupini bila je vrućica, koja je zabilježena u 92,9% naših bolesnika. Nakon nje, slijedili su artralgija i osip u 85,70% bolesnika, a grlobolja u 71,40% bolesnika. U gore spomenutom pregledu, Efthimiou i suradnici analizirali su znakove i simp-

above mentioned review, Efthimiou et al. analyzed signs and symptoms in the 6 largest case series published 5 years prior which showed the most common symptom was also fever, followed by arthralgia, which were reported in 91,3%–100% and 47,2%–94,9% of patients, respectively (1,43,45,47–50). In comparison to our study, typical rash and sore throat was reported in somewhat smaller percentages, 62,2–79,9% and 31,8–63,5% respectively (1,43,45,47–50). This data, in addition to studies which show that 3–20% of FUO in Europe is caused by AOSD, further underlines the importance of taking AOSD into account in differential diagnoses (3,21,22).

MAS, which is one of most common and most serious complications in AOSD, was diagnosed in two patients (14,30%) in our cohort. This is comparable to the frequency of MAS among AOSD patients of 12–17% reported by Gerfaud-Valentin et al. and up to 23,5% reported by Efthimiou et al. (1,38). None of the two patients in our study had fatal outcomes, which is in accordance to data that shows that MAS in AOSD seems to have better prognosis than MAS in other settings (3,51,52).

Other rare manifestations (pericardial effusion, DIC, PAH, TTP) found in our cohort were reported in literature as rare but serious complications of AOSD (1,53).

Our analysis of laboratory values in AOSD patients is generally in agreement with other, larger cohort studies. The Chinese multi-center study conducted by Hu et al. also reports elevated CRP, ferritin and ESR levels in over 90% of patients, ferritin being the most commonly elevated laboratory value (95.8%), while our results showed CRP to be the most common (in 100% of patients) (43). They also reported similar frequency of leukocytosis (85.6% compared to 81.8% in our study) and elevated liver function tests (61.6% compared to 54.5%) (43). Somewhat different results can be seen in a Japanese study by Asanuma et al., which reported elevated ESR in only 68.9% of patients and more frequent liver function test abnormalities (73.9%), however they showed comparable frequency of elevated CRP and ferritin (91.5% and 88.5%, respectively) (47). Analysis of absolute ranges and values of laboratory findings can be found in the aforementioned retrospective study of Balci et al., which reports considerably lower mean values of ferritin: 1475 μg/L, compared to our finding of 5623.5μg/L, as well as comparable mean values of CRP which were found to be 152 mg/L (172.48mg/L in our study) (41). This discrepancy in our initially reported ferritin levels might be the consequence of two presumed data outliers. When these were excluded from analysis, the mean value of ferritin dropped to 2276,1 μg/L, which is more comparable to that reported in the study of Balci et al. (41).

The treatment of AOSD remains as a challenge, mainly because of its complexity, rarity and incom-

tome u šest najvećih serija slučajeva objavljenih prije pet godina koji su pokazali da je najčešći simptom također bila vrućica, a zatim artralgija, koje su prijavljene u 91,3–100% i 47,2–94,9% bolesnika (1,43,45,47–50). U usporedbi s našim istraživanjem, tipični osip i grlobolja prijavljeni su u nešto manjem postotku, 62,2–79,9% i 31,8–63,5% (1,43,45,47–50). Ovi podatci, uz istraživanja koja pokazuju da je 3–20% slučajeva vrućice nepoznatog podrijetla (VNP) u Europi uzrokovano AOSD-om, dodatno naglašavaju važnost uzimanja u obzir AOSD-a u diferencijalnoj dijagnozi (3,21,22).

MAS, koji je jedna od najčešćih i najozbiljnijih komplikacija AOSD-a, dijagnosticiran je u slučaju dva bolesnika (14,30%) u našoj kohorti. To je usporedivo s učestalošću MAS-a među bolesnicima s AOS-om od 12–17% koju su u svojem istraživanju naveli Gerfaud-Valentin i suradnici i do 23,5% koje su u svojem istraživanju naveli Efthimiou i suradnici (1,38). Nijedan od dva bolesnika u našem istraživanju nije imao smrtni ishod, što je u skladu s podatcima koji pokazuju da se čini da MAS u AOSD-u ima bolju prognozu nego MAS u drugim bolestima (3,51,52).

Ostale rijetke manifestacije (perikardijalni izljev, DIK, PAH, TTP) nađene u našoj kohorti navedene su u literaturi kao rijetke, ali ozbiljne komplikacije AOSD-a (1,53).

Naša analiza laboratorijskih vrijednosti u bolesnika s AOSD-om općenito je u skladu s drugim, većim kohortnim studijama. Kineska multicentrična studija koju su proveli Hu i suradnici također navodi povišene razine CRP-a, feritina i ESR-a u više od 90% bolesnika, pri čemu je feritin najčešće povišena laboratorijska vrijednost (95,8%), dok su naši rezultati pokazali da je CRP najčešći (u 100% bolesnika) (43). Također su naveli sličnu učestalost leukocitoze (85,6% u usporedbi s 81,8% u našem istraživanju) i povišenih testova jetrene funkcije (61,6% u usporedbi s 54,5%) (43). Nešto drugačiji rezultati mogu se vidjeti u japanskoj studiji Asanuma i suradnika, koji su prijavili povišeni ESR u samo 68,9% bolesnika i češće abnormalnosti testova jetrene funkcije (73,9%), međutim pokazali su usporedivu učestalost povišenog CRP-a i feritina (91,5% u usporedbi s 88,5%) (47). Analiza apsolutnih raspona i vrijednosti laboratorijskih nalaza nalazi se u spomenutoj retrospektivnoj studiji Balcija i suradnika, koja navodi znatno niže srednje vrijednosti feritina: 1475 μg/L, u usporedbi s našim nalazom od 5623,5μg/L, kao i usporedive srednje vrijednosti CRP-a za koje je utvrđeno da iznose 152 mg/L (172,48 mg/L u našem istraživanju) (41). Ovo odstupanje u našim prvotno prijavljenim razinama feritina može biti posljedica dvaju pretpostavljenih odstupanja podataka. Kada su se oni isključili iz analize, srednja vrijednost feritina pala je na 2276,1 μg/L, što je više usporedivo s onom objavljenom u studiji Balcija i suradnika (41).

pletely understood pathophysiology, which result in the absence of internationally accepted treatment guidelines and a clear treat-to-target strategy (54). However, in the last 5 years some guidelines and reviews on treatment options have been published, e.g., from Italian and Japanese expert groups (55,56). In the existing literature, NSAIDs and GCs are generally considered the fist-line therapy for AOSD, followed by cDMARDs, which are to be used in steroid-dependent or refractory patients, while biologics have proven effective in those with active disease despite the above-mentioned treatment (35,54). In our subject group, the most common treatment choice were GCs (76.9%), followed by MTX (46.2%). This is in concurrence with the aforementioned reviews and guidelines, which state that GCs are effective in the amelioration of clinical symptoms in AOSD; Mimura et al. labelling it as a strong recommendation (57). Mimura et. al. also strongly recommended the use of MTX for its clinical efficacy and steroid-sparing effect (57), while Cavalli et al. report it to be (alongside cyclosporin) one of the most commonly used cDMARDs with efficacy in up to 80% of patients (56). NSAIDs are reported to be one of the first line treatments of AOSD but are, however, insufficient in patients with symptoms such as fever and polyarthritis, in which GCs are indicated (32,58). In the case of our cohort, a vast majority (92.9%) presented with fever, which is why NSAIDs were scarcely used and treatment choices in favor of GCs were made. IL-1 inhibitors, such as anakinra, are most frequently reported as treatment of choice among biologics, with largely favorable effects and have even shown superiority over DMARDs in a randomized multi-center study (4,45,59). Likely due to small sample size, we report only one patient in whom anakinra was used, however it is to be noted that remission was achieved in that patient. Moreover, it is worth noting that our subject group experienced largely favorable outcomes, as 84.6% have achieved disease remission in the year following initial diagnosis. The above-mentioned multi-center studies and case series also report similar treatment choices with largely favorable outcomes. Namely, Hu et al. report an almost equal remission rate of 84.4% using GCs, MTX and hydroxychloroquine (43). Similar reports can be found in the Turkish multi-center cohort study conducted by Kalyoncu et al., which found 83% of patients experienced remission after initial treatment with corticosteroids and MTX or other DMARDs (49). Asanuma et al. also showed favorable outcomes, as 88.4% of patients achieved remission (47).

CONCLUSION

In our single-center retrospective study in which we analysed characteristics of a group with AOSD patients, we have demonstrated results which are pre-

Liječenje AOSD-a ostaje izazov, uglavnom zbog svoje složenosti, rijetkosti i nedovoljno shvaćene patofiziologije, što rezultira nedostatkom međunarodno prihvaćenih smjernica za liječenje i jasne strategije za ciljano liječenje ove bolesti (engl. *treat-to-target*, T2T) (54). Međutim, u posljednjih pet godina objavljene su neke smjernice i osvrti o mogućnostima liječenja, primjerice oni talijanskih i japanskih stručnih skupina (55,56). U postojećoj literaturi, NSAR i GK općenito se smatraju prvom linijom liječenja za AOSD, nakon čega slijede cDMARD-ovi, koji se trebaju primjenjivati u bolesnika ovisnih o steroidima ili otpornih na steroide, dok su se biološki lijekovi pokazali učinkovitima u onih s aktivnom bolešću unatoč gore navedenim metodama liječenja (35,54). U našoj skupini ispitanika najčešći izbor liječenja bili su glukokortikoidi (GK) (76,9%), a zatim MTX (46,2%). Ovo je u skladu s prethodno navedenim pregledima literature i smjernicama, koje navode da su GK učinkoviti u ublažavanju kliničkih simptoma kod AOSD-a, a primjerice Mimura i suradnici iznimno ih preporučuju kao metodu liječenja (57). Mimura i suradnici također snažno preporučuju upotrebu MTX-a zbog njegove kliničke učinkovitosti i učinka uštede steroida (57), dok Cavalli i suradnici navode da je MTX (uz ciklosporin) jedan od najčešće korištenih cDMARD-ova s učinkovitošću u do 80% bolesnika (56). Navodi se da su NSAR-ovi jedni od prve linije liječenja AOSD-a, ali su, međutim, nedostatni u bolesnika sa simptomima kao što su vrućica i poliartritis, kod kojih su GK indicirani kao metoda liječenja (32,58). U slučaju naše kohorte velika većina bolesnika (92,9%) imala je povišenu tjelesnu temperaturu, zbog čega su nesteroidni protuupalni lijekovi (NSAR-ovi) rijetko korišteni te je izbor pao na liječenje glukokortikoidima (GK). Inhibitori IL-1, poput anakinre, najčešće se navode kao preferirana metoda liječenja što se tiče bioloških lijekova, s uglavnom povoljnim učincima, a čak su se pokazali učinkovitijima od DMARD-ova u rezultatima randomizirane multicentrične studije (4,45,59). Vjerojatno zbog male veličine uzorka, navodimo slučaj samo jednog bolesnika kod kojega je korištena anakinra, no valja napomenuti da je kod tog bolesnika postignuta remisija. Štoviše, bitno je napomenuti da je naša skupina ispitanika imala uglavnom povoljne ishode, budući da je kod 84,6% bolesnika postignuta remisija bolesti u razdoblju od godine dana nakon početne dijagnoze. Gore spomenute multicentrične studije i serije slučajeva također pokazuju slične metode liječenja s uglavnom povoljnim ishodima. U istraživanju koje su proveli Hu i suradnici navodi se gotovo jednaka stopa remisije od 84,4%, koja je postignuta primjenom GK-a, MTX-a i hidroksiklorokina (43). Slični rezultati mogu se pronaći u turskoj multicentričnoj kohortnoj studiji koju su proveli Kalyoncu i suradnici, a koja je otkrila da je 83% bolesnika postiglo remisiju nakon početnog liječenja korti-

dominantly in accordance with results of other, larger studies. However, older age at disease onset in our cohort points to importance of not leaving AOSD out of differential diagnosis in patients with characteristic symptoms, even in later decades of life. Life threatening complications of AOSD, especially MAS, should always be kept in mind in AOSD patients, as they have been consistently reported to appear in various cohorts, including the one described in this study. A number of abnormal laboratory findings, namely ferritin, CRP, ESR and leukocyte count, have shown to be present in the majority of our patients with AOSD, similar to existing studies. However, a highly specific and accurate biomarker to aid diagnosis is still lacking. Patient outcomes reported after using conventional treatment options and newer, biologic agents, are generally largely favorable, as a significant number of patients is reported to achieve remission. Internationally accepted treatment guidelines, based on randomized, controlled studies are yet to be established in order to improve patient outcomes and prevent fatal complications. A clear limitation of this study is a small sample size, which is why additional multicenter studies are needed to further evaluate the characteristics of AOSD patients in Croatia.

Acknowledgments

All authors have made substantial contributions to the conception and design of the study. SH, JT and AP have performed data acquisition and data interpretation. All authors have contributed to writing of the manuscript and have revised it. All authors have approved the final version of this manuscript and have agreed to be accountable for all aspects of the study.

Funding: For this work authors did not receive any funding.

Conflict of interest statement: The authors declare no conflict of interest.

kosteroidima i MTX-om ili drugim DMARD-ovima (49). U istraživanju koje su proveli Asanuma i suradnici također se navode povoljni rezultati, jer je 88,4% bolesnika postiglo remisiju (47).

ZAKLJUČAK

U našem retrospektivnom istraživanju jednog centra u kojoj smo analizirali karakteristike skupine bolesnika s AOSD-om, prikazali smo rezultate koji su pretežno u skladu s rezultatima drugih, većih istraživanja. Međutim, starija dob na početku bolesti u našoj kohorti ukazuje na važnost neisključivanja AOSD-a iz diferencijalne dijagnoze u bolesnika s karakterističnim simptomima, čak ni u kasnijim desetljećima života. Komplikacije AOSD-a opasne po život, posebno MAS, uvijek treba imati na umu kod bolesnika s AOSD-om, budući da je u istraživanjima dosljedno dokazano da se pojavljuju u različitim skupinama, uključujući onu opisanu u ovom istraživanju. Prisutnost brojnih abnormalnih laboratorijskih nalaza, feritina, CRP-a, ESR-a i broja leukocita primijećena je u većine naših bolesnika s AOSD-om, što je slično nalazima već postojećih istraživanja. Međutim, još uvijek nedostaje visoko specifičan i točan biomarker koji bi pomogao u dijagnozi. Ishodi bolesnika prijavljeni nakon korištenja konvencionalnih opcija liječenja i novijih, bioloških lijekova općenito su uglavnom povoljni, budući da je značajan broj bolesnika navodno postigao remisiju. Međunarodno prihvaćene smjernice za liječenje, temeljene na randomiziranim, kontroliranim studijama, tek treba uspostaviti kako bi se poboljšali ishodi za bolesnike i spriječile smrtonosne komplikacije. Jasno ograničenje ovog istraživanja jest mali uzorak ispitanika, zbog čega su potrebne dodatne multicentrične studije za daljnju evaluaciju karakteristika bolesnika s AOSD-om u Hrvatskoj.

Zahvala

Svi autori dali su značajan doprinos u pogledu koncepcije i plana studije. SH, JT i AP proveli su postupke prikupljanja podataka i interpretacije podataka. Svi su autori sudjelovali u pisanju rukopisa i revidirali ga. Svi su autori odobrili konačnu verziju ovog rukopisa i složili se da će biti odgovorni za sve aspekte studije.

Financiranje: Autori za ovaj rad nisu primili nikakva sredstva.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

REFERENCES / LITERATURA

1. Efthimiou P, Kontzias A, Hur P, Rodha K, Ramakrishna GS, Nakasato P. Adult-onset Still's disease in focus: Clinical manifestations, diagnosis, treatment, and unmet needs in the era of targeted therapies. Semin Arthritis Rheum. 2021;51(4):858–74.
2. Bywaters EGL. Still's disease in the adult. Ann Rheum Dis. 1971;30(2):121–33.
3. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev. 2014;13(7):708–22.
4. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I i sur. Adult-Onset Still Disease: Manifestations, Treatment, Outcome, and Prognostic Factors in 57 Patients. Medicine. 2014;93(2):91–99.
5. Sampalis JS, Esdaile JM, Medsger Jr. TA, Partridge AJ, Yeadon C, Senécal JL i sur. A controlled study of the long-term prognosis of adult Still's disease. Am J Med. 1995;98(4):384–8.
6. Magadur-Joly G, Billaud E, Barrier JH, Pennec YL, Masson C, Renou P i sur. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis. 1995;54(7):587–90.
7. Wakai K, Ohta A, Tamakoshi A, Ohno Y, Kawamura T, Aoki R i sur. Estimated Prevalence and Incidence of Adult Still's Disease: Findings by a Nationwide Epidemiological Survey in Japan. J Epidemiol. 1997;7(4):221–5.
8. Evensen KJ, Nossent HC. Epidemiology and outcome of adult-onset Still's disease in Northern Norway. Scand J Rheumatol. 2006;35(1):48–51.
9. Jamilloux Y, Gerfaud-Valentin M, Martinon F, Belot A, Henry T, Sève P. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. Immunol Res. 2015;61(1–2):53–62.
10. Choi JH, Suh CH, Lee YM, Suh YJ, Lee SK, Kim SS i sur. Serum cytokine profiles in patients with adult onset Still's disease. Br J Rheumatol. 2003;30(11):2422–7.
11. Komiya A, Matsui T, Nogi S, Iwata K, Futami H, Takaoka H i sur. Neutrophil CD64 is upregulated in patients with active adult-onset Still's disease. Scand J Rheumatol. 2012;41(2):156–8.
12. Matsui K, Tsuchida T, Hiroishi K, Tominaga K, Hayashi N, Hada T i sur. High serum level of macrophage-colony stimulating factor (M-CSF) in adult-onset Still's disease. Rheumatology (Oxford). 1999;38(5):477–8.
13. Rossi-Semerano L, Koné-Paut I. Is Still's disease an autoinflammatory syndrome? Int J Inflam. 2012;2012:480373.
14. Hayem F, Hayem G. Still's disease and the mitochondrion: The other face of an old friend? Med Hypotheses. 2012;79(2):136–7.
15. Lequerré T, Quartier P, Rosellini D, Alaoui F, de Bandt M, Mejjad O i sur. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: Preliminary experience in France. Ann Rheum Dis. 2008;67(3):302–8.
16. Giampietro C, Fautrel B. Anti-interleukin-1 agents in adult onset Still's disease Int J Inflam. 2012;2012:317820.
17. Rooney T, Murphy E, Benito M, Roux-Lombard P, FitzGerald O, Dayer JM i sur. Synovial tissue interleukin-18 expression and the response to treatment in patients with inflammatory arthritis. Ann Rheum Dis. 2004;63(11):1393–8.
18. Conigliaro P, Priori R, Bombardieri M, Alessandri C, Barone F, Pitzalis C i sur. Lymph node IL-18 expression in adult-onset Still's disease. Ann Rheum Dis. 2009;68(3):442–3.
19. Chen DY, Lan JL, Lin FJ, Hsieh TY. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. J Rheumatol. 2004;31(11):2189–98.
20. Alonso ER, Marques Alejandro Olivé. Adult-onset Still disease. U: Hochberg MC, izdavač. Rheumatology. 7. izd. Philadelphia: Elsevier, Inc.; 2019, str. 1437–44.
21. Crispín JC, Martínez-Baños D, Alcocer-Varela J. Adult-Onset Still Disease as the Cause of Fever of Unknown Origin. Medicine (Baltimore). 2005;84(6):331–7.
22. Zenone T. Fever of unknown origin in adults: Evaluation of 144 cases in a non-university hospital. Scand J Infect Dis. 2006;38(8):632–8.
23. Akritidis N, Papadopoulos A, Pappas G. Long-term follow-up of patients with adult-onset Still's disease. Scand J Rheumatol. 2006; 35(5):395–7.
24. Bagnari V, Colina M, Ciancio G, Govoni M, Trotta F. Adult-onset Still's disease. Rheumatol Int. 2010;30(7):855–62
25. Nguyen KH, Weisman MH. Severe sore throat as a presenting symptom of adult onset Still's disease: a case series and review of the literature. J Rheumatol. 1997;24(3):592–7.
26. Ruscitti P, Iacono D, Ciccia F, Emmi G, Cipriani P, Grembiale RD i sur. Macrophage activation syndrome in patients affected by adult-onset still disease: Analysis of survival rates and predictive factors in the Gruppo Italiano di Ricerca in reumatologia clinica e sperimentale cohort. J Rheumatol. 2018;45(6):864–872.
27. Wang R, Li T, Ye S, Tan W, Zhao C, Li Y i sur. Macrophage activation syndrome associated with adult-onset Still's disease: a multicenter retrospective analysis. Clin Rheumatol. 2020;39(8):2379–86.
28. Yang XP, Wang M, Li TF, Li W, Zhang L, Liu SY. Predictive factors and prognosis of macrophage activation syndrome associated with adult-onset Still's disease. Clin Exp Rheumatol. 2019;37 Supl 121(6):83–8.
29. Pannu AK, Singla V, Suri V, Kumar R, Mathur Y, Mohindra R i sur. Adult-onset Still's disease and fever of unknown origin in India. Clin Exp Med. 2022; 30:1–8
30. Fautrel B, le Moël G, Saint-Marcoux B, Taupin P, Vignes S, Rozenberg S i sur. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol. 2001;28(2):322–9.

31. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H i sur. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992;19(3):424–30.
32. Fautrel B. Adult-onset Still disease. Best Pract Res Clin Rheumatol. 2008;22(5):773–92.
33. Maria ATJ, Le Quellec A, Jorgensen C, Touitou I, Rivière S, Guilpain P. Adult onset Still's disease (AOSD) in the era of biologic therapies: Dichotomous view for cytokine and clinical expressions. Autoimmun Rev. 2014;13(11):1149–59.
34. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I i sur. Adult-Onset Still Disease: Manifestations, Treatment, Outcome, and Prognostic Factors in 57 Patients. Medicine (Baltimore). 2014;93(2):91–9.
35. Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, Sabbadini MG. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum. 2010;62(8):2530–5.
36. Gattorno M, Piccini A, Lasiglièl D, Tassi S, Brisca G, Carta S i sur. The pattern of response to anti–interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2008; 58(5):1505–15.
37. Pouchot J, Arlet JB. Biological treatment in adult-onset Still's disease. Best Pract Res Clin Rheumatol. 2012;26(4):477–87.
38. Jamilloux Y, Gerfaud-Valentin M, Henry T, Sève P. Treatment of adult-onset Still's disease: A review. Ther Clin Risk Manag. 2014;11: 33–43.
39. Lin YT, Wang CT, Gershwin ME, Chiang BL. The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. Autoimmun Rev. 2011;10(8):482–9.
40. Buttgereit F, Da Silva JAP, Boers M, Burmester GR, Cutolo M, Jacobs J i sur. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis. 2002;61(8):718–22.
41. Balci M, Pamuk O, Pamuk G, Uzundere F, Donmez S, Ali Balci M i sur. Epidemiology and outcome of adult-onset Still's disease in the Northwestern Thrace region in Turkey Epidemiology of adult-onset Still's disease in Turkey. Clin Exp Rheumatol. 2015;11: 818–23.
42. Wakai K, Ohta A, Tamakoshi A, Ohno Y, Kawamura T, Aoki R i sur. Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan. J Epidemiol. 1997;7(4):221–5.
43. Hu QY, Zeng T, Sun CY, Luo CN, Liu S, Ding TT i sur. Clinical features and current treatments of adult-onset Still's disease: a multicentre survey of 517 patients in China. Clin Exp Rheumatol. 2019;37 Supl 121(6):52–7.
44. Pouchout J, Sampalis JS, Beaudet F, Carette S, Décary F, Salusinky-Sternbach M i sur. Adult Still's Disease: Manifestations, Disease Course, and Outcome in 62 Patients. Medicine. 1991;70(2):118–36.
45. Sfriso P, Priori R, Valesini G, Rossi S, Montecucco CM, D'Ascanio A i sur. Adult-onset Still's disease: an Italian multicentre retrospective observational study of manifestations and treatments in 245 patients. Clin Rheumatol. 2016;35(7):1683–9.
46. Evensen KJ, Nossent HC. Epidemiology and outcome of adult-onset Still's disease in Northern Norway. Scand J Rheumatol. 2006; 35(1):48–51.
47. Asanuma YF, Mimura T, Tsuboi H, Noma H, Miyoshi F, Yamamoto K i sur. Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. Mod Rheumatol. 2015;25(3):393–400.
48. Nakamura H, Fujieda Y, Tarumi M, Kitakawa H, Hisada R, Nakagawa I i sur. Calcineurin inhibitors for adult-onset Still's disease: a multicentre retrospective cohort study. Clin Exp Rheumatol. 2020;38 Supl 127(5):11–6.
49. Kalyoncu U, Solmaz D, Emmungil H, Yazici A, Kasifoglu T, Kimyon G i sur. Response rate of initial conventional treatments, disease course, and related factors of patients with adult-onset Still's disease: Data from a large multicenter cohort. J Autoimmun. 2016;69: 59–63.
50. Zhang Y, Yang Y, Bai Y, Yang D, Xiong Y, Zeng X. Clinical characteristics and follow-up analysis of adult-onset Still's disease complicated by hemophagocytic lymphohistiocytosis. Clin Rheumatol. 2016;35(5):1145–51.
51. Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH i sur. Reactive hemophagocytic syndrome in adult systemic disease: Report of twenty-six cases and literature review. Arthritis Care Res (Hoboken). 2003;49(5):633–9.
52. Arlet JB, le Thi Huong D, Marinho A, Amoura Z, Wechsler B, Papo T i sur. Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature. Ann Rheum Dis. 2006;65(12):1596.
53. Efthimiou P, Kadavath S, Mehta B. Life-threatening complications of adult-onset Still's disease. Clin Rheumatol. 2014;33(3):305–14.
54. Macovei LA, Burlui A, Bratoiu I, Rezus C, Cardoneanu A, Richter P i sur. Adult-Onset Still's Disease-A Complex Disease, a Challenging Treatment. Int J Mol Sci. 2022;23(21):12810.
55. Mimura T, Kondo Y, Ohta A, Iwamoto M, Ota A, Okamoto N i sur. Evidence-based clinical practice guideline for adult Still's disease. Mod Rheumatol. 2018;28(5):736–57.
56. Cavalli G, Farina N, Campochiaro C, Baldissera E, Dagna L. Current treatment options and safety considerations when treating adult-onset Still's disease. Expert Opin Drug Saf. 2020;19(12):1549–58.
57. Mimura T, Kondo Y, Ohta A, Iwamoto M, Ota A, Okamoto N i sur. Evidence-based clinical practice guideline for adult Still's disease. Mod Rheumatol. 2018;28(5):736–57.
58. Cavalli G, Farina N, Campochiaro C, Baldissera E, Dagna L. Current treatment options and safety considerations when treating adult-onset Still's disease. Expert Opin Drug Saf. 2020;19(12):1549–58.
59. Nordström D, Knight A, Luukkainen R, van Vollenhoven R, Rantalaiho V, Kajalainen A i sur. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. J Rheumatol. 2012;39(10):2008–11.