failure (54.8%), arrhythmias (47.6%) and heart block (28.6%) were the most common presenting manifestations. 28.6% had isolated CS. 5 (11.9%) underwent endomyocardial biopsy and 2 of them (40%) had histopathologic evidence of CS. Mean left ventricular ejection fraction (LVEF) was 40.6 % on echocardiogram, and 29 patients (69%) had PPM/ICD placed for arrhythmia prevention. 35 (83.3%) underwent cardiac MRI, 37 (88.1%) cardiac PET scan and 23 (62.3%) had a follow up PET. 33 (78.6%) CS patients were treated with corticosteroids for a mean duration of 17.3 months. 21 of them were also treated with sDMARDs and 3 were subsequently switched to bDMARDs (Table 1). Mean prednisone dose at 12 months was 4.8mg, and 11 patients (33%) were tapered off corticosteroids.

**Conclusion:** In our sarcoid patient population, the prevalence of CS is 19.1%, which is higher than previously reported in the literature, suggesting CS may be underdiagnosed. There was a greater proportion of male patients in the CS population (54.8%) than the generalized sarcoidosis population (30%). This indicates that males with sarcoidosis may be more likely to have cardiac involvement. Patients treated with s/bDMARDs had a high response rate as reflected by clinical and imaging improvement. Steroid-sparing effect is suggested by the low prednisone dose at 12 months (Table 1). Methotrexate was the most commonly used DMARD (76.2%). Randomized clinical trials are needed to establish robust guidelines for the treatment of CS.

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## POS0217 ALL-CAUSE AND CAUSE SPECIFIC MORTALITY AMONG PATIENTS WITH BEHCET'S DISEASE VERSUS GENERAL POPULATION

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**Background:** Behcet's disease (BD) is a systemic vasculitis with multiorgan involvement.

**Objectives:** To compare the risk of all-cause and cause specific mortality among patients with BD compared to general population

**Methods:** Using the 2002-2017 Korea National Health Insurance database, we conducted a cohort study among BD patients compared to general population matched on age and sex at a 1:5 ratio. The primary outcome was death of any cause, and the secondary outcomes were cause-specific mortality for top 5 causes of death. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs), comparing BD patients versus general population.

**Results:** The PS-matched study cohort (mean age 42.1 years; 32.0% male) included 32288 BD patients and 161440 controls. During a mean follow-up of 9.6 years, 2214 deaths occurred. The HR [95%] for all-cause mortality was 10.6 [9.6-11.6]. The Top 5 causes of death derived from malignancy, cardiovascular disease, infection, respiratory disease, and injury: the HR [95%] for mortality from these causes were 8.5 [7.2-10.1], 10.8 [8.6-13.6], 14.6 [8.1-26.3], 12.0 [8.5-17.0], and 8.0 [5.0-13.0], respectively.

**Conclusion:** This population-based cohort study warns exceptionally heavy burden of the disease showing approximately 10 times higher mortality of BD patients compared to general population. In line with this, risk of cause specific mortality was also significantly higher among the BD patients, for 5 top causes of death.

**Disclosure of Interests:** None declared

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## POS0218 DECREASED MIR-122-5P IN NEUTROPHIL-DERIVED EXOSOMES ATTENUATED IMMUNOREGULATORY FUNCTION ON MACROPHAGES BY TARGETING IRF5 EXPRESSION IN BEHCET'S DISEASE

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**Background:** Behçet's disease (BD) is a chronic systemic vasculitis characterized by the overactivation of neutrophils and macrophages. Exosomes are membrane-derived vesicles that mediate intercellular communications and neutrophil-derived exosomes account for the major portion of serum exosomes in BD. However, the role of neutrophil-derived exosomes in BD remains unknown.

**Objectives:** 1) To investigate the production of exosomes by BD neutrophils; 2) To elucidate the regulation of macrophage by BD neutrophil-derived exosomes; 3) To explore the mechanism of immunoregulatory functions of BD neutrophil-derived exosomes.

**Methods:** BD and healthy control (HC) neutrophil-derived exosomes were extracted and quantified. Human monocyte-derived macrophages (HMDM) were stimulated with BD and HC neutrophil-derived exosomes, and TNF-α and IL-6 production were examined. Differently expressed miRNAs in BD neutrophil-derived exosomes were analyzed using miRNA sequencing. LPS-induced HMDM were treated with miRNA mimics or inhibitors, and TNF-α and IL-6 production were detected. miRNA was overexpressed in macrophages, and RNA sequencing was performed to analyze regulating pathways. Dual-luciferase assays were performed to confirm miRNA-mRNA interaction.

**Results:** BD neutrophils produced a significantly lower level of exosomes than HC ones. Both BD and HC neutrophil-derived exosomes suppressed TNF-α and IL-6 production by macrophages, but to a lesser extent by BD neutrophil-derived exosomes. Six downregulated miRNAs were presented in BD neutrophil-derived exosomes, including miR-122-5p. miR-122-5p mimics inhibited IL-6 and TNF-α production while miR-122-5p inhibitor promoted IL-6 and TNF-α production by HMDMs. Overexpression of miR-122-5p attenuated TLR4 and IFN-β signaling. miR-122-5p directly targeted 3'UTR of IRF5, the TF regulating TLR4 pathway and autocrine of IFN-β, and downregulated IRF5 expression confirmed by dual luciferase assay. Knocking down IRF5 dampened IL-6 and TNF-α production in HMDMs.

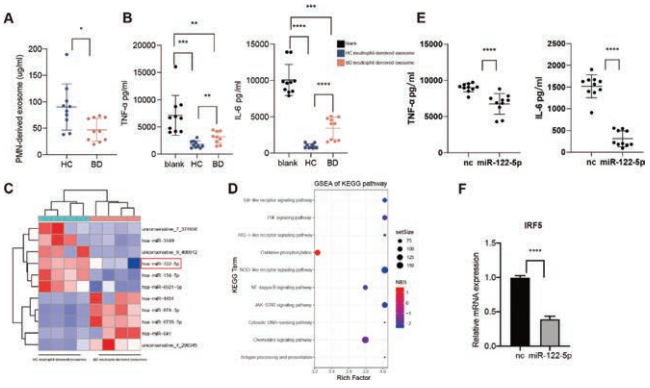


**Figure 1.** (A) Decreased production of BD neutrophil-derived exosomes. (B) Reduced suppression of macrophage activation by BD neutrophil-derived exosomes. (C) Differentially expressed miRNAs (downregulated) in BD neutrophil-derived exosomes. (D) miR-122-5p suppressed TLR4 and JAK-STAT signaling in HMDM. (E) miR-122-5p inhibited activation of HMDM. (F) miR-122-5p inhibited IRF5 expression in HMDM.

**Conclusion:** Our findings suggested the reduced production and immunoregulatory function of BD neutrophil-derived exosomes, mediated by lower levels of miR-122-5p in neutrophil-derived exosomes. Impaired BD neutrophil-derived exosomes might be implicated in the overactivation of macrophages in BD.

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## POS0219 EARLIER AND MORE AGGRESSIVE TREATMENT OF MAJOR ORGAN INVOLVEMENT WITH BIOLOGICS MAY PREVENT RELAPSES OR FURTHER NEW ORGAN INVOLVEMENT IN A SUBGROUP OF BEHÇET'S DISEASE PATIENTS

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**Background:** Conventional immunosuppressives (cIS) are the choice of treatment for major organ (ocular, vascular, central nervous (CNS) and gastrointestinal (GIS)) involvement to prevent relapses and organ damage in patients with Behcet's disease (BD).

**Objectives:** We aimed to investigate the rate of new major organ involvement in BD patients under cIS treatments during follow-up and to assess the characteristics and treatment protocols of these patients.

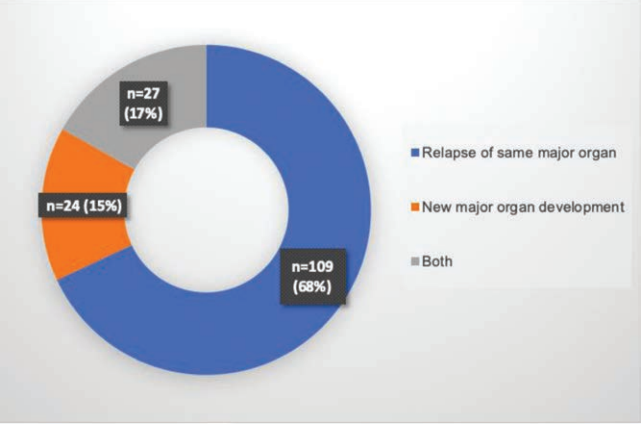
**Methods:** The files of 1114 patients diagnosed with BD and followed (1992-2019) in the Marmara University Behcet's Clinic were overviewed retrospectively. Patients with follow-up duration less than 6 months were excluded. A total of 806

patients, of whom 56% were male were included in the analysis. Demographic and clinical characteristics, follow-up and treatment data of the patients were recorded from files. Relapse of the same organ and/or new major organ development during the follow-up period of patients receiving cIS was defined as "event under cIS".

**Results:** Median age at diagnosis was 29 (10-65) years and median follow-up duration was 68 months (6-272). Genital ulcer, erythema nodosum and arthritis/arthralgia were more common in women, whereas papulopustular lesions, vascular and ocular involvement were more common in men (p<0.005 for all). Presence of major organ involvement was 56.9% (n=459) and the frequencies of vascular, ocular, CNS and GIS involvement were 29.8%, 33,5%, 9.7%, and 2%, respectively. At diagnosis 232 (50.5%) patients had major organ involvement, whereas it developed in 227 patients during a follow-up of median 3 years (0.5 - 32) after diagnosis. Major organ involvement developed earlier in males compared to females (median 2 years vs 4 years, p = 0.012). In patients with a first-degree relative history of BD, major organ involvement also developed earlier, however without reaching significance (median 1 year vs 3 years) (p= 0,066). 440 patients had follow-up data under cISs with the follow-up duration of median 65.5 months (6-272). Main reason for cISs use was major organ involvement (86.8%), less frequent reasons were mucocutaneous disease (9.3%) and joint involvement (3.8%). An event under ISs (mainly relapses) occurred in 160 (36.4%) patients with median 23 months after cISs initiation. Majority of events (68%) were relapses of the same major organ (Figure 1). The most commonly used cIS agent was azathioprine (87%). Among patients having an event under cISs, 91% of the relapses and 75% of new major organ involvement developed under azathioprine treatment. In patients with an event under cISs, treatment mostly switched to other ISs such as cyclophosphamide, interferon-alpha, and high dose corticosteroids. In 22% of patients, azathioprine was switched to tumor necrosis factor (TNF) inhibitors.

**Conclusion:** In our study, major organ involvement developed in 57% of the 806 BD patients. We observed that disease course was more severe under cIS treatment in male patients diagnosed at a younger age and with the history of familial BD. In one third (36%) of the patients under cIS treatment, a relapse or a new major organ involvement developed despite the cISs use, mainly under azathioprine. TNF-inhibitor use was approved for BD treatment within the last decade in Turkey. Therefore, azathioprine was switched to a TNF inhibitor in only 22%. Our results suggest that earlier and more aggresive treatment of major organ involvement with biologics may be an option in young male patients especially with the history of familial BD, who had the highest risk for severe disease course.

**Figure 1: Distribution of events under immunosuppressive treatments.**

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POS0220

## LONG-TERM SAFETY AND EFFECTIVENESS OF CANAKINUMAB IN CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES – 36-MONTH DATA FROM THE RELIANCE REGISTRY

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**Background:** The cryopyrin-associated periodic fever syndromes (CAPS) are hereditary monogenic autoinflammatory diseases with severe systemic and organ inflammation due to increased production of Interleukin-1β (IL-1β). The subcutaneously administered monoclonal antibody canakinumab (CAN) effectively inhibits IL-1β and results in rapid remission of CAPS symptoms in clinical trials as well as in real-life.

**Objectives:** The RELIANCE registry is designed to explore long-term safety and effectiveness of CAN under routine clinical practice conditions in pediatric (≥2 years) and adult patients with CAPS, including Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA).

**Methods:** This prospective, non-interventional, observational study with a 3-year follow-up enrolls patients in Germany with clinically confirmed diagnoses of CAPS routinely receiving CAN. In 6-monthly visits, clinical data, physician assessments and patient-reported outcomes are evaluated starting at baseline.

**Results:** 98 CAPS patients (52% female; 15 [15%] NOMID/CINCA subtypes) were enrolled by December 2021 (Table 1). At baseline, median age was 20 years and median duration of prior CAN treatment was 6 years. At the 36 months visit, 74% of patients reached disease remission by physicians´ assessment along with increasing rates of absent disease activity (patient's assessment, median 2.0 at baseline and 0.0 month 36). In addition, patients reported low levels of fatigue (absent to mild/moderate: 87% at baseline and 95% at month 36). At baseline, CAPS impaired social life in 47% of patients (37% at month 36) and 33% (23% at month 36) reported days off from school/work. Lab parameters were within normal limits. Remission and disease control were sustained as evaluated parameters remained stable or even decreased over time.

**Table 1. Patient and physician assessment of clinical CAPS disease activity and laboratory markers over time.**

| | Baseline | 12 months | 36 months |
|---|---|---|---|
| Number of patients, N | 98 | 72 | 40 |
| Number (%) of patients in disease remission (physician assessment) | 64 (68) | 48 (70) | 28 (74) |
| Patient's assessment of current disease activity; 0–10, median (min; max) | 2.0 (0; 7) | 2.0 (0; 7) | 0.0 (0; 6) |
| Patient's assessment of current fatigue; 0–10, median (min; max) | 3.0 (0; 9) | 2.0 (0; 8) | 1.0 (0; 8) |
| Number (%) of patients without impairment of social life by the disease | 34 (53) | 35 (65.0) | 17 (63) |
| CRP (mg/dl) I SAA (mg/dl); median | 0.1 I 0.3 | 0.1 I 0.5 | 0.1 I 0.3 |
| Number (%) of patients with disease-related symptoms | prior to inclusion into the study I at baseline | 12 months | 36 months |
| Fever | 75 (80) I 14 (15) | 19 (28) | 4 (11) |
| Fatigue | 84 (89) I 49 (52) | 36 (52) | 17 (46) |
| Conjunctivitis/Uveitis | 63 (67) I 27 (29) | 21 (30) | 7 (19) |
| Headache | 68 (72) I 30 (32) | 30 (43) | 9 (24) |
| Arthralgia/arthritis | 80 (85) I 32 (34) | 30 (43) | 14 (38) |
| Impairment of hearing | 35 (37) I 23 (25) | 18 (26) | 11 (30) |
| Trigger (cold, stress, infections, vaccinations, hormones) | 71 (76) I 32 (34) | 21 (30) | 3 (8) |
| **SAE** | **Number of events** | **Incidence rate* per 100 patient years** | |
| All types of SAE I SADR | 63 I 28# | 25.98 I 11.55 | |

CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; n. a., not annotated; SAA, serum amyloid A; SADR, serious adverse drug reaction; SAE, serious adverse event*Incidence rate = number of events * 36,525 / sum of observation days (=88,558)#Abdominal pain, Alport's syndrome, appendicitis, arthralgia, blister, cardiovascular disorder, chest pain, circulatory collapse, dehydration, diplopia, dyspnoea, erythema, febrile convulsion, gastroenteritis, glomerulonephritis, haemophilus test positive, myalgia, oedema, pneumonia, premature delivery, skin discoloration, tonsillectomy, tonsillitis bacterial, tonsillitis streptococcal, vision blurred (all N=1 event), pyrexia (3 events)