UNIVERSITÀ DI SIENA 1240

Dipartimento di Scienze Mediche, Chirurgiche e Neuroscienze

**Dottorato in Genetica, Oncologia e Medicina Clinica**

36° Ciclo
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# Ocular manifestations in juvenile Behçet's Disease: a registry-based analysis

Settore scientifico disciplinare: MED/16, MED/38

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2023/24

Università degli Studi di Siena
Dottorato in Genetica, Oncologia e Medicina Clinica
36° Ciclo

*Data dell'esame finale*
20/12/2023

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## Synopsis

Ocular inflammation represents one of the three cardinal manifestations of Behçet's disease (BD) along with recurrent oral and genital ulceration. The presence of uveitis, retinal vasculitis and related ocular complications is responsible for morbidity, damage accrual and disability. The disease is relatively uncommon in the pediatric age, accounting for 15-20% of all cases. This study aims to characterize ocular manifestations of BD in the pediatric age through an in-depth analysis of data from a large international cohort, the AIDA Network Behçet's disease registry.

This is a registry-based observational prospective analysis. All subjects with juvenile (j)BD enrolled in the registry showing ocular inflammatory manifestations before the age of 18 years were included.

The study cohort included 27 children (66.7% males). The mean (SD) age at onset was 11.9 (3.9) years. The median (IQR) age at the onset of ocular manifestations was 14.2 (4.7) years. Ocular manifestations were present at onset in 20 subjects (74.1%). There was an inverse correlation between age at BD onset and delay of ocular involvement (Pearson's r= -0.43, $p$=0.02). The HLA-B51 haplotype was present in 14 subjects (51.9%).

Ocular inflammation manifested bilaterally in 18 children (66.7%), affecting a total of 45 eyes. Uveitis was found in 39 eyes (86.7%), retinal vasculitis in 17 (37.8%), retinitis in 6 (13.3%), retrobulbar optic neuritis in 2 (4.4%), and papillitis in 1 (2.2%). Uveitis was classified anatomically as anterior in 11.1%, posterior in 40.0%, or panuveitis in 40.0% of eyes. Median age at ocular involvement was higher in children with posterior uveitis than in those with anterior uveitis or panuveitis ($p$=0.04; Dunn's post-hoc: $p$=0.02 for panuveitis and $p$=0.09 for anterior uveitis). Posterior uveitis was observed in 53.3% of males and 18.2% of females ($p$=0.04), anterior uveitis showed a tendency towards female sex (27.3% versus 6.7%, $p$=0.07).

Ocular complications occurred in 23 eyes (51.1%), the most frequent being cataract (28.9% of eyes), macular edema (20.0%) and posterior synechiae (15.6%). Patients with complications had lower age at ocular involvement

($p$<0.01), higher number of relapses ($p$=0.02) and more prolonged treatment with systemic corticosteroids (CS) ($p$=0.02). The presence of complications was associated with structural changes in the anterior or posterior segment ($p$<0.01).

The mean (SD) central macular thickness measured by optical coherent tomography at the enrolment and at the last follow-up were 302.2 (58.4) and 293.3 (78.2) μm, respectively. Fundus fluorescein angiography identified pathological signs in 12/19 procedures (63.2%), with a mean (SD) ASUWOG score of 17.9 (15.5).

Patients were treated with systemic CS in 20 out of 27 cases (74.1%), with a mean (SD) higher dosage of prednisone of 0.5 (0.3) mg/kg/day and a median (IQR) treatment duration of 17.0 (23.5) months. Azathioprine (44.4%), cyclosporin A (33.3%), methotrexate (22.2%), adalimumab (63.0%) and infliximab (25.9%) were the most common therapeutic choices.

At the end of the follow-up, a median (IQR) BODI score of 1.5 (3.3) was calculated; it inversely correlated with the age at ocular involvement (Spearman's r=-0.5681, $p$<0.01) and it was higher in children with bilateral ocular disease ($p$=0.02). In addition, signs of ocular damage were documented in 33 eyes (73.3%). As for the visual prognosis, a median (IQR) BCVA of 1.0 (0.5) was measured and blindness occurred in 7 eyes (15.6%) of 6 children. According to multivariate regression analysis, the presence of HLA-B51 may significantly predict a reduction of -0.3 of the BCVA at the last follow-up ($p$=0.01). Also, the BCVA at the initial evaluation (OR 0.59; $p$<0.01) and the presence of posterior synechiae (OR 1.62; $p$=0.01) were independent predictors of unilateral or bilateral blindness.

This research offers an exhaustive overview of ocular manifestations related to BD in children, drawing from an international registry cohort. Considering the rarity of this condition and the specific focus of the study, this in-depth analysis contributes significant insights to current literature, which may be leveraged for potentially shaping clinical approaches and inspiring future research.

**SUMMARY**

# 1. Introduction

## 1.1 Overview of Behçet's disease

Behçet's Disease (BD) is a rare condition initially described in 1937 by Hulusi Behçet, an eminent Turkish dermatologist (1). This persistent, recurrent, multisystem disorder involves both the innate and adaptive immune systems in its pathogenesis. Notably, recent classifications position BD at the intersection of autoimmune and autoinflammatory conditions (2).

While the precise etiology remains undetermined, it is apparent that external agents, whether bacterial or viral, can trigger cytokine or cell-mediated reactions via immunopathological pathways (3). A significant correlation exists with the human leukocyte antigen (HLA)-B51, suggesting a manifestation of the disease in those with a genetic predisposition (4). Also, additional genes have been identified that potentially hold a pivotal role in the pathogenesis of BD (5).

From a clinical perspective, BD predominantly exhibits recurrent inflammatory symptoms impacting the skin, mucosae, ocular structures, joints, vessels, the central nervous system (CNS), and, to a more limited degree, the peripheral nervous system (PNS). Distinctive characteristics of BD include recurrent oral and/or genital ulcerations and ocular manifestations such as posterior uveitis, panuveitis, and retinal vasculitis. Dermatological presentations like pseudofolliculitis and erythema nodosum are also observed (6,7). There exists a pronounced variability in the disease's manifestation among diverse BD patient cohorts, ranging from mild isolated mucocutaneous involvement to severe complications, inclusive of blindness, gastrointestinal perforation, disabling neurological affections, deep venous thrombosis, and arterial aneurysmal lesions susceptible to rupture (8).

### 1.1.1 Epidemiology

BD is found globally, although its highest prevalence follows the geographical area of the ancient "Silk Road," stretching from Mediterranean basin countries to the Far East. The disease is most prevalent in Iran (68 cases per 100000

inhabitants), Japan (10-15 cases per 100000 inhabitants), and Turkey (42 cases per 100000 inhabitants). Moving westward, the prevalence is lower (2 cases per 100000 inhabitants in Germany, between 2.5 and 15.9 cases per 100000 inhabitants in Italy) (9-11). In terms of incidence, the male-to-female ratio widely varies depending on the geographical areas examined. The condition often manifests more severely in males (9).

### 1.1.2 Pathogenesis

The pathogenesis of BD remains not fully elucidated. The prevailing hypothesis points to an aberrant immune response triggered by environmental and/or auto-antigens in genetically predisposed individuals. It has long been suggested that this hyper-response of the immune system underlies predisposing genetic factors. The increased frequency of BD along the ancient "Silk Road", familial aggregation, and the strong association with genes both inside and outside the region encoding the major histocompatibility complex (MHC) are the most significant clues supporting the intricate interplay between genetic and environmental factors in the disease's etiology (12–15).

The role of various environmental factors, especially infectious agents or the microbiota, may be pivotal in triggering inflammation mediated by the innate immune system and sustained by adaptive immune responses (14,16,17). It has been proposed that a high load of microorganisms colonizing the oral mucosa and molecular mimicry between microbial epitopes and autoantigens, such as those exposed by human heat shock proteins (HSPs), elicit immune responses and clones of autoreactive T cells. The presence of epitopes overlapping those of HSPs can be perceived as a danger signal, inducing direct activation of the innate immune system via Toll-like Receptor (TLR)-4, increasing the expression of adhesion molecules on endothelial cells. HSP-mediated activation of antigen-presenting cells (TLR-4/CD14) leads to the release of inflammatory cytokines from both the innate and adaptive immune systems (18,19).

The role of alterations in the salivary and intestinal microbiome has also been explored. The alteration of the microbiome in BD patients consists of a decrease in short-chain fatty acids, such as butyrate and propionate, compared to healthy individuals; this results in a reduction of the response of regulatory T cells (Treg) and the development of autoreactive T cells (20,21). Nevertheless, there is a general consensus that infectious agents and/or microbiome alterations are not directly responsible for the disease. Indeed, they may play a role in the disease's pathogenesis by triggering innate immunity and/or causing immune system dysfunctions in genetically predisposed individuals. In a meta-analysis comprising 78 studies, the frequency of HLA-B5/B51 in BD patients was 55-63%. Carriers of HLA B5/B51 had a 5.78 times higher likelihood of developing BD compared to those without this antigen (22). Although the significance of the HLA-B51 gene is well-known, BD can also be diagnosed in those who do not carry this haplotype. Even for HLA-B51, the frequency varies depending on the populations. The role of the HLA-B region in genetic susceptibility to the disease has been estimated to be around 12-19% (23). Genome-wide association studies (GWAS) conducted in recent years have confirmed that the HLA-B51 antigen is the most potent independent genetic susceptibility factor for the development of BD. Furthermore, the presence of new non-HLA susceptibility genes has been identified, including the endoplasmic reticulum aminopeptidase (ERAP)1, the interleukin IL-23 receptor (IL23R), the IL-23R/IL-12RB2 complex, IL-10, STAT, interferon (IFN)γR1 (24–31).
The identification of the epistatic interaction between the polymorphism of ERAP1 and HLA-B51 is one of the most significant advances in understanding the complex genetic and immunological pathogenesis of the disease. ERAP1 polymorphism is a significant genetic susceptibility factor frequently detected in GWAS studies. ERAP1 encodes an enzyme, amino peptidase, which is essential for processing peptides bound to class I MHC. This enzyme cleaves the N-terminal end of peptides derived from the proteasome to the appropriate length for the pocket that hosts the antigen to be presented by class I MHC molecules (32). The ERAP1 haplotypes p.Arg725Gln and

p.Asp575Asn were found to be associated with reduced peptide cleavage activity. This, in turn, results in an alteration of the peptides that bind to class I MHC, forming longer peptides (nonamers) which are less affine to the HLA-B51 presentation pocket (32–34). It is interesting to note that the peptides exposed by HLA-B51 are characterized by the presence of proline (Pro2) or alanine (Ala2) as anchor residues in position 2. A loss of function of ERAP-1 results in an increase in the formation of Ala2 and non-Ala2/Pro2 peptides exposed by HLA-B51, at the expense of Pro2 peptides, which are present in lower concentrations. This seems to induce an increase in the activation of Natural Killer (NK) cells with facilitation of the pro-inflammatory NK-1 subtype and an altered response of γδ T lymphocytes hyperproducing IL-4 and IFNγ (35). The epistatic interaction between these two polymorphic variants of ERAP1 and HLA was found only in HLA-B51 carriers (27,36,37). **Figure 1** schematically illustrates the mechanisms related to this interaction and the alterations resulting from reduced affinity between HLA-B51 and peptides (38).

Epistatic interactions between HLA-B51 and ERAP-1 variants in antigen-presenting cells alter T cell homeostasis. In particular, Treg cells are suppressed as a result of hypersecretion of IL-21, while Th1 pathways are activated, especially by IL-12-secreting NK-1 (a process possibly facilitated by IL-12R polymorphisms); there is also activation of Th17 as a result of hypersecretion of IL-23, possibly facilitated by IL-23R polymorphisms. Th17 cells are primarily involved in the production of pro-inflammatory cytokines IL-17A, IL-17F, IL-22. The pro-inflammatory picture is facilitated by the decrease in anti-inflammatory cytokines IL-10 and IL-35 as a result of Treg cell suppression. The association with HLA-B51 and the increased response to IL-17 play a key role in neutrophil activity (14,39,40). This, in the initial phase of inflammation, leads to hyperactivation of neutrophils and an intense neutrophilic infiltrate in the affected tissues. This is accompanied by an increase in serum levels of neutrophil-activating cytokines, mainly tumor necrosis factor (TNF)α, IL-1β, and IL-8 (40). A central consequence of this hyperstimulation of neutrophils is also the activation of neutrophil

extracellular traps (NET)osis, a bactericidal mechanism consisting of extracellular degranulation of nuclear chromatin together with antibacterial proteins from cytoplasmic granules. While NETosis is a programmed cell death mechanism activated in the presence of tissue damage and with protective purposes against microbial agents, a deficit in NET clearance is closely implicated in the development of autoimmune diseases as a result of prolonged extracellular exposure of intracellular antigens (41). Ultimately, various components of both the innate and acquired immune system are activated in BD patients, supporting the reclassification of BD as a condition halfway between autoimmune and autoinflammatory forms (2). **Figures 2a and 2b** schematically illustrate the complex components of the innate and acquired immune system involved in the pathogenesis of BD (38).

### 1.1.3 Clinical features

From a clinical perspective, BD is characterized by phases of exacerbation and asymptomatic or pauci-symptomatic intercritical periods. Classically, BD presents with a triad of oral aphthosis, genital aphthosis, and uveitis.

*Cardinal Manifestations*

- **Recurrent oral aphthosis**, observed at least three times per year, is the most common manifestation of the disease and has the highest diagnostic sensitivity. Aphthosis can appear anywhere on the non-keratinized mucosa. However, the most common sites are the lateral surfaces of the tongue and the inner part of the lips (42,43). They can vary in size and number, presenting as herpetiform aphthae, minor aphthae, and major aphthae, in increasing order of size, from 2-3 mm to more than 1 cm (44).
- **Recurrent genital ulcers** are less frequent than oral ones but are extremely specific for diagnostic purposes. In male patients, the scrotum is the most frequently affected site, while involvement of the penis is rarer. In females, the most commonly affected areas are the major and minor labia (42).

- **Ocular involvement** typically occurs in the second to fourth year from the onset of the disease. However, oculo-Behçet may also represent the initial manifestation of the disease; this is found in approximately 10-20% of cases. The average age at which ocular symptoms manifest, according to a study conducted on 1465 cases in 25 centers, is 27.4±10 years (9). The frequency of oculo-Behçet is higher among patients carrying the HLA-B51 haplotype, but no association has been found with severity (45). Although oculo-Behçet includes numerous entities that are relatively rare in BD, such as keratoconjunctivitis, conjunctival ulcers, keratitis, episcleritis, scleritis, ocular inflammation with involvement of the lacrimal glands, corneal neovascularization, and paralysis of the extraocular muscles, the most common event is undoubtedly represented by uveitis (9). This vision-threatening progressive condition can impact specific sections or the entire uveal tract. Notably, up to 25% of patients might experience vision loss within a decade, after which the progression of the disease generally stabilizes (46,47). Hence, effective management within this timeframe is pivotal to mitigate both the direct ocular impacts of Behçet's uveitis and its equally severe complications (48–50). Uveitis may occur as posterior uveitis and panuveitis, but also with retinal vasculitis and papillitis. Anterior uveitis is less common, but not rare. In their study, Tugal-Tutkun et al. observed anterior uveitis in 11% of cases, posterior uveitis in 28.8%, and panuveitis in 60.2% out of a cohort of 880 patients (1567 eyes). Intermediate uveitis, typified by isolated vitritis without anterior or posterior involvement, was more commonly associated with early-onset BD (49–51). However, the 2021 Standardization of Uveitis Nomenclature (SUN) classification criteria do not consider isolated vitritis for diagnosis but in conjunction with anterior, posterior, or panuveitis (52). Concurrent vitritis with posterior segment involvement is prevalent, often being so pronounced that it conceals the fundus view. In patients with BD, uveitis is not granulomatous, and ocular inflammatory attacks are generally

characterized by an acute relapsing course; individual episodes, although associated with intense activation of the inflammatory process, are self-limiting (9). Anterior uveitis is characterized by ocular pain, photophobia, tearing, ocular hyperemia, but the most typical feature is a shifting hypopyon,due to the gravitational dislocation of the sediment into another position upon postural change or head tilting test. This finding has been described in 5-32% of patients, and its frequency may be even higher if the patient is evaluated at the onset of the acute episode. If the hypopyon is observed only with gonioscopy (an examination that explores the iridocorneal angle), it is referred to as angular hypopyon. Another sign of anterior chamber involvement is ciliary injection, which is an expression of iridocyclitis. Diffuse vitritis is a common sign of ocular involvement in BD and is commonly associated with the presence of retinal perivasculitis, which mainly affects the retinal veins and is therefore called periphlebitis. Occlusive retinal periphlebitis is often associated with retinal hemorrhages as a result of neoangiogenic phenomena. In more severe cases, periphlebitis can cause occlusion of the retinal veins, deformation or atrophy of the iris, formation of epiretinal membranes, retinal ischemia, macular degeneration with changes in the pigmented epithelium, and optic atrophy. Capillaritis, visible only with fluorescein angiography, is also quite common. Necrotizing retinitis, recognized in 32-53% of cases, is another form of posterior uveitis. Superficial infiltrates disappear without scarring, while larger infiltrates can leave scars. During the ophthalmological examination, potential structural complications that can compromise visual acuity must be ruled out, such as increased intraocular pressure (a consequence of trabecular occlusion by inflammatory cells, or the result of posterior synechiae capable of occluding the pupil hole, or anterior synechiae that occlude the corneal angle); cataract (either as a consequence of intraocular inflammation or secondary to the systemic or topical use of glucocorticoids); macular edema (9). In particular, secondary glaucoma

is reported in 10.9% of patients with BD, half of which consists of steroid-induced open-angle glaucoma (53). Cataract is another common complication in patients with ocular involvement associated with BD and represents the most common cause of surgery in patients affected by ocular inflammatory involvement (54). In cases of isolated involvement of the posterior segment of the eye, atrophy of the retina and optic nerve represent the most common structural complications; they are associated with the presence of inadequately treated macular edema. In some cases, neoangiogenic processes can also be observed in the iris, as well as in the retina and/or optic disc. Neoangiogenesis is a common cause of intravitreal hemorrhages and tractional retinal detachment. In extreme cases, in the absence of adequate treatment, bulbar phthisis can be observed, which requires enucleation (9).

*Additional manifestations*

- **Skin manifestations** primarily fall into three categories: erythema nodosum, papular lesions, and acneiform lesions/ pseudofolliculitis. Pseudofolliculitis is an expression of a skin vasculitis that manifests with the presence of sterile pustules on an edematous-erythematous or purpuric base; in some patients, the lesion may develop around a hair follicle. The pubic area and the lower limbs are the most affected sites. Erythema nodosum is the second most common skin lesion in BD after pseudofolliculitis and results from a nonspecific panniculitis manifested as multiple painful subcutaneous nodules, of a reddish-purple color, more frequent on the lower limbs. Suppurative panniculitis, skin ulcers and pyoderma gangrenosum are other possible, but uncommon, skin manifestations in BD (55).
- Subjects affected by BD often present with joint pain in the absence of clear signs of **arthritis**. When arthritis does occur, the most commonly affected joints are the knees, ankles, wrists, and elbows, typically manifesting as mono-oligoarthritis. In BD patients, joint involvement is rarely associated with erosion and joint deformity (56,57).

- **Vascular manifestations** can affect both venous and arterial systems and are more commonly observed in males. Superficial thrombophlebitis and deep vein thrombosis together affect up to 40% of BD patients, especially in the lower limbs. However, atypical thromboses involving the caval districts, suprahepatic veins (Budd-Chiari syndrome), portal circulation, cerebral venous sinuses, and right cardiac chambers are not uncommon. Although thrombosis is fairly common, thromboembolic events are rare due to the high adherence of thrombotic formations to the vessel walls (58,59). The potential involvement of the arterial tree is a distinctive feature of BD and is generally characterized by aneurysmal lesions in peripheral and/or visceral arteries. The pulmonary arteries represent the district with the highest morbidity and mortality rates (59-61).
- **Cardiac involvement** is rare. However, cases of myocarditis, pericarditis, endomyocardial fibrosis, and coronary vasculitis have been reported. Acute coronary syndromes in the context of BD are not exceptional as a result of aneurysmal formations and thrombosis of the coronary arteries, arterial spasm, dissection, or even arteritis (62,63).
- **CNS involvement** (neuro-Behçet) often has a profoundly negative impact in terms of disability and quality of life (64). Neuro-Behçet can be categorized into parenchymal and non-parenchymal involvement, respectively accounting for (80% and 20% of neuro-Behçet cases) (64). Specifically, parenchymal forms may affect the cerebral hemispheres causing encephalopathy, hemiparesis, sensory deficits, seizures, cognitive dysfunctions, and aphasia. Brainstem involvement can lead to ophthalmoparesis and pyramidal and cerebellar deficits; lesions affecting the spinal cord can manifest with movement disorders and sphincter dysfunctions. On the other hand, cerebral venous thrombosis and intracranial aneurysms are the main manifestations of non-parenchymal CNS involvement (65). Peripheral neuropathy is a rare manifestation of BD (66).

- **Gastrointestinal manifestations** are associated with high morbidity and mortality and thus warrant special diagnostic and therapeutic attention. On average, gastrointestinal disturbances manifest between 4.5 and 6 years from the onset of the disease (67). Vasculitic and/or inflammatory lesions of the gastrointestinal tract can be observed at any site, but the ileocecal tract is the most frequently affected region (67,68). However, all other segments of the digestive system can be involved, including the esophagus, stomach, duodenum, colon, and rectum, while hepatobiliary and/or pancreatic involvement is rare (69,70). Gastrointestinal involvement typically presents with abdominal pain, diarrhea, and hematochezia, caused by mucosal ulcerations. Fistulas, intestinal stenosis, perforations, and massive hemorrhages can complicate the inflammatory bowel involvement and may require surgical intervention due to their particularly negative impact on the patient's prognosis (68).

### 1.1.4 Diagnosis and classification

There are no specific tests for the diagnosis of BD since specific biomarkers for the disease have not been identified to date. Therefore, the diagnosis is made on a clinical basis, based on the fulfilment of sets of diagnostic/ classification criteria. There are several sets of criteria, among which the most commonly used worldwide are the International Study Group criteria (ISGC) and the International Criteria for Behçet's Disease (ICBD) (6,7), illustrated in **Table 1**.

Table 1

| **ISGC**<br>**Mandatory criterion + ≥2 other criteria** | **ICBD**<br>**≥4 points** |
|---|---|
| Recurrent oral aphthosis (mandatory) | **2-point criteria** |
| Recurrent genital aphthosis | Oral aphthosis |
| Ocular or retinal inflammatory manifestations | Genital aphthosis |

| | |
|---|---|
| Skin manifestations (papulo-pustular lesions, erythema nodosum) | Inflammatory eye lesions |
| Positive pathergy test | **1-point criteria** |
| | Skin lesions |
| | Neurological involvement |
| | Vascular manifestations |
| | Positive pathergy test |

In addition to these criteria designed for an adult patient population, the PEDiatric Behçet's Disease (PEDBD) group also proposed a set of classification criteria for BD with onset in pediatric age (71) (**Table 2**).

Table 2

| **PEDBD criteria**<br>**(All items score 1 point)**<br>**≥3 points** |
|---|
| Recurrent oral aphthosis (minimum 3 attacks/year) |
| Genital aphthosis or ulcerations (typically resulting in scars) |
| Skin involvement (necrotizing folliculitis, acneiform lesions, erythema nodosum) |
| Eye involvement (panuveitis, posterior uveitis, anterior uveitis, intermediate uveitis, retinal vasculitis) |
| Neurological involvement (excluding headache not caused by intracranial hypertension) |
| ascular involvement (venous thrombosis, arterial thrombosis, arterial aneurysms) |

As for the diagnosis of BD-associated uveitis, in 2020, Tugal-Tutkun and colleagues proposed a diagnostic algorithm based on distinct ocular features (**Figure 3**). Their methodology encompassed four phases: gathering expert opinions on BD ocular features, retrospective clinical data analysis, prospective clinical data collection, and the creation of a diagnostic algorithm (72). The most indicative variables included superficial retinal infiltrates, retinal nerve fiber layer (RNFL) defects, angiographic evidence of occlusive retinal vasculitis and widespread retinal capillary leakage, in patients with

vitritis, given the absence of granulomatous anterior uveitis or choroiditis. The team hypothesized that these combined ocular indications, rather than individual lesions, would be more identifiable. Thus, the presence of all these signs in a patient would suggest a 92% probability of a BD-associated uveitis diagnosis (72). However, this diagnostic strategy requires further validation through broader, multicentric research and larger clinical samples.

### 1.1.5 Prognosis

Mortality mainly depends on complications arising from neurological involvement and major vessel involvement and is higher in male patients (73). Specifically, pulmonary artery aneurysms are the most frequent cause of death, followed by CNS diseases, Budd-Chiari syndrome, and obstruction of the vena cava. Among the causes of death, suicidal ideation should not be overlooked, which generally affects patients with more severe forms. The standardized mortality rate decreases significantly as the years of the disease progress, confirming that the impact of the pathology is greater in the first years following onset, both in terms of morbidity and mortality (73). Recently, the Behçet's Syndrome Overall Damage Index (BODI) was developed, a clinimetric tool aimed at assessing organ damage in patients with BD (74). It consists of 4 general domains that identify 46 dichotomous items (presence/absence) grouped into 9 areas of organ involvement. Each item and each sub-item is scored 1 point, and the total score can range from 0 to 46. The presence of organ damage must persist for at least six months to be included in the score, regardless of whether it is directly attributable to BD. The BODI provides a cumulative score and therefore cannot decrease during the patient's history.

### 1.1.6 Therapeutic aspects

The natural history of BD varies based on multiple demographic and clinical factors. Among these, particular attention should be paid to the patient's age and gender, the age at the onset of the disease, and the type of organ involvement. Considering these elements, the therapeutic strategy should be

based on the specific characteristics of the patient. In this regard, young male patients generally have a more severe course, especially if accompanied by an early onset of the disease. Joint and mucocutaneous involvement can significantly compromise the quality of life, but it does not lead to permanent damage and does not endanger the patient's life. On the contrary, major organ involvement (gastrointestinal, vascular, and neurological) can be life-threatening or significantly impact the patient's social function. If patients are not adequately treated, eye involvement can lead to blindness in 50% of cases, nervous system involvement can lead to permanent neurological deficits, while gastrointestinal involvement may cause perforation and require extensive resections. Finally, at the vascular level, the risk of aneurysmal perforations and thrombosis is high.
The initial therapy for the treatment of aphthosis and acneiform lesions is represented by topical drugs. Corticosteroids (CS) are useful in managing mucocutaneous and joint involvement. Nevertheless, EULAR (European League Against Rheumatism) recommends their administration at high doses in cases of potentially fatal major organ involvement or in cases of compromised visual function (75).

*The use of conventional Disease Modifying Anti-Rheumatic Drugs (cDMARDs)*
cDMARDs represent the essential therapeutic choice for managing the various clinical manifestations of MB. The primary goal of these immunosuppressive agents is to control the activity and severity of the disease while reducing the daily dose of CS. Specifically, colchicine is the first-line drug in the treatment of mucocutaneous and joint involvement; azathioprine (AZA) has shown benefits on mucocutaneous, ocular, and neurological components. Cyclosporine A (CsA) has also proven effective in controlling eye involvement, but prolonged administration can lead to renal and CNS side effects. Cyclophosphamide (CYC), combined with CS, is the first-choice cDMARD for the treatment of uncomplicated pulmonary artery aneurysms, in cases of vena cava thrombosis or Budd-Chiari syndrome. Another indication is given by parenchymal neurological involvement. CsA represents an alternative to AZA

in cases of deep and superficial venous thrombosis. It can also be used as maintenance therapy in cases of vasculo-Behçet with potentially fatal manifestations, after discontinuation of cyclophosphamide. Moreover, CsA is used as a second-line cDMARD in patients with ocular inflammation refractory to first-line therapy. On the contrary, CsA should be avoided in patients with signs of neurological involvement due to its reported neurotoxic activity. The immunomodulatory agent thalidomide (TLD) is currently recommended in patients with severe mucocutaneous or intestinal involvement or in patients refractory to the aforementioned approaches (75).

*The use of TNFα inhibitors*

According to EULAR guidelines, TNFα inhibitors should be used in patients with significant joint, mucocutaneous, neurological, ocular, and intestinal involvement resistant to conventional therapy (75). To date, most evidence on the role of anti-TNFα agents comes from studies on patients with BD with ocular, vascular, and neurological involvement. Infliximab (IFX) and adalimumab (ADA) are the main TNFα inhibitor agents used for the treatment of BD (82–87); however, in recent case reports and case series, the monoclonal antibodies golimumab (GOL) and certolizumab Pegol (CZP) have proven to be equally effective in patients with BD with diversified organ involvement (76-84).

*Other biological agents*

The anti-IL-1 biological agents anakinra (ANA) and canakinumab (CAN) have been mainly tested, but not exclusively, in patients with ocular involvement, in whom a satisfactory efficacy was observed in controlling uveitis and retinal vasculitis. The clinical efficacy of anti-IL-1 therapy persists despite the discontinuation of concomitant cDMARDs and the reduction of the daily glucocorticoid dosage (85-88). On the other hand, in a recent randomized, controlled, double-blind phase 3 clinical trial, the humanized recombinant anti-IL-1β antibody gevokizumab was found not to be superior to placebo in controlling uveitis relapses in patients with BD. However, the failure of the

study was attributed to the trial design rather than the inefficacy of the biological agent, as the severity of uveitis relapses and the frequency of macular edema were shown to be significantly reduced despite the decrease in corticosteroid dosage; concurrently, visual acuity was preserved, demonstrating gevokizumab's ability to prevent further structural damage (89).

The anti-IL-6 biotechnological agent tocilizumab (TCZ) has recently been proposed as a therapeutic alternative in patients with refractory neurological involvement; however, patients treated with TCZ experienced a flare-up of mucocutaneous manifestations, as a consequence of the loss of IL-6 protective action on the teguments (90,91).

### 1.1.7 Remarks about the pediatric disease

Even though the peak incidence is between the second and fourth decades of life, BD can manifest in 15-20% of patients before the age of 16, and exceptionally even in the neonatal period (92-96). When BD manifestations start in young age, sometimes a "pediatric" BD and a juvenile-onset BD are distinguished (93). In the first case, the classification criteria for BD are met before the age of 16; on the other hand, in juvenile-onset BD, some symptoms of the disease are observed before the age of 16, but the classification criteria are only met in adulthood, when the picture is enriched with further manifestations (93,97-99).

In pediatric subjects, genetic aspects and family history seem to have a greater weight, while in subjects over 30 years, the development of the disease might be more influenced by exposure over time to various environmental factors (44,100-102). In the study by Konè-Paut et al., a difference emerged in the percentage of familial cases between children (15%) and adults (2%) (103). Treudler et al., comparing a group of subjects with juvenile-onset BD to one made up of subjects with onset in later age, found 23% of familial cases in the former and only 8% in the latter (104). Furthermore, in familial cases, the age of BD diagnosis is lower compared to non-familial ones (105).

Several factors contribute to the variability of the frequency of jBD reported in different scientific studies. Firstly, the heterogeneity of inclusion criteria, which sometimes identify pediatric BD, sometimes juvenile-onset BD, and which are based on different sets of classification criteria or in some studies on expert opinion (6,7,93,96,98,99,101,103,106-112). Moreover, the more specific symptoms of the disease may appear late, hindering the early formulation of a definitive diagnosis (92,97). Lastly, epidemiological factors also play a role, as already mentioned before [10-12,113,114]. In particular, BD has a marked predilection for geographical areas located along the so-called "silk road", and this is reflected in a greater number of studies on the disease in the eastern and Mediterranean regions (104,114,115).
Geographical differences reflect environmental and genetic characteristics and influence the prevalence and expression of the disease (114,116). In addition to this, belonging to certain ethnic groups seems to play a crucial role in the frequency of different manifestations of the disease, as observed for example by Butbul et al. in Turkish and Israeli populations or by Konè-Paut et al. among European and non-European patients (71,117-119). Moreover, Mahr et al. found a higher prevalence of BD in non-Europeans compared to Europeans, particularly 34.6 per 100000 inhabitants in North Africans, 17.5 in Asians, and 2.4 in Europeans (117).
Studies conducted in the pediatric population do not agree on the distribution of BD between the sexes: there are cohorts in which a slight prevalence in boys, or girls, is evident, likely related to geographical variability and the number of subjects analyzed (71,94,96,98,99,103,107,112,120-125). From Kim et al.'s analysis, it emerged that the overall prevalence of the disease in the pediatric population favored females; however, stratifying the population concerning the fulfilment of the 2003 criteria of the Japanese Behçet's Disease Research Committee (126), a higher frequency of complete diagnosis cases in males emerged (110,126). Cattalini et al. emphasize that, although in general autoimmune diseases affect females more, in childhood this difference is less relevant, particularly in pediatric BD, in which no differences between the sexes seem to emerge (127).

Typically in juvenile BD, symptoms manifest gradually over the years (92). It is common for the syndrome to start with a limited set of symptoms and only develop in subsequent ages, allowing diagnosis within 16 years or later in adulthood (98,99,104,116). The average age of onset varies between 4 and 15 years, depending on the cohort examined (94,99,107,110,112,119,123, 128-130). According to Nanthapisal et al., it is around 4.87 years of age (128). In the study by Konè-Paut et al., it is around 7.83 years (71). Kim et al. report it at 10.9 years, similar to the 10.5 years at onset regarding the report by Shahram et al. (107,110). Higher ages of onset have been recorded in studies on the Turkish population (101,102,122). On the other hand, the average diagnostic delay when symptoms develop before the age of 16 is about 3 years in the larger pediatric cohorts, while it is about double in the study by Konè-Paut et al. and apparently different when comparing German and Turkish patients (71,112,114,121-123,131).

As in the adult counterpart, the disease presentation is heterogeneous, potentially involving the skin and mucous membranes, the visual, gastrointestinal, musculoskeletal, vascular, and nervous systems (94). Among the most frequent and earliest manifestations is the appearance of oral ulcers, circular lesions with a defined edge, which can be located on the tip of the tongue, on the lips, on the palate, and on the malar mucosa (92,94,98,99,101,102,118,132). It has been observed that the mucocutaneous picture in BD tends to attenuate over time with less severe and less frequent inflammatory attacks as age advances; however, this usually does not happen for oral aphthosis, which shows a more persistent course (12,133). Furthermore, the time interval between the appearance of the first and second clinical manifestation is longer than that between the second and subsequent ones, so recurrent oral aphthosis can be the only clinical manifestation of the disease for a long time (110).

In the context of mucosal involvement, genital ulcers can be detected on the scrotum and penis in boys, on the vulva in girls, and are usually painful (93,103,123). Their finding is more common in females, but it is still the second most frequent pediatric manifestation after oral lesions

(102,103,110,124,129,134). Their appearance is associated with older age of onset in the pediatric cohort studied by Krause et al.; moreover, Konè-Paut et al. also found that they are less frequent in prepubertal age (98,103). Potential other lesions can manifest in the perianal region (93,103,123).
Skin involvement includes a wide variety of manifestations, such as pseudofolliculitis, papulopustular lesions, erythema nodosum, acneiform lesions, and skin ulcers (135). Çirkinoğlu et al. reported that these manifestations are particularly found in the limbs, chest and dorsum (122). This arrangement helps in the differential diagnosis of acneiform lesions compared to common acne, common in adolescence (44,92). BD-associated pseudofolliculitis, unlike common folliculitis, is more frequently popular then pustular, can regress spontaneously, and does not respond to antibiotic therapy (110). As for the pathergy test, in childhood it is not regularly performed and, moreover, the procedure is not homogeneous among studies; in any case, a positivity range of 14.5-80% is reported, whose reliability appears limited (92,94,97,98,102,103,119,128).
Ocular inflammation usually develops in the form of uveitis (anterior, posterior, or panuveitis) and retinal vasculitis, and is more commonly found after the age of 10 (120). Furthermore, it seems that the type of ocular involvement varies in relation to the child's age. In fact, if this appears before the age of 10, anterior uveitis is more frequently observed, while later panuveitis can be observed (120). Other possible findings are papilledema, conjunctivitis, and keratitis (124). More often there is involvement of both eyes, especially in European subjects according to what was reported by Konè-Paut et al. (71,120,136). It has been observed by some authors that, in adults, ocular and cutaneous involvement plays a more significant role, unlike in children where musculoskeletal and gastrointestinal involvement is more commonly found (94,135). A low frequency of ocular involvement in childhood has been observed in several studies (110,121,137). Uveitis, in particular, seems to be less represented in children, although the literature is not unanimous on this point (71,138,139).

In children, the most common gastrointestinal symptoms are nonspecific, such as diarrhea and abdominal pain (94). However, more severe manifestations are also possible, such as bloody mucous diarrhea, vomiting, intestinal perforation, and ulcers located in the terminal ileum, colon, and anal region (94,111,129).

Regarding vascular involvement, as for adults, BD may affect vessels of different calibers, especially on the venous side, with thrombosis, for example, of the vena cava, Budd-Chiari syndrome, and thrombophlebitis, but also on the arterial side, with thrombosis and aneurysms (93,140,141).

Forms of neuro-Behçet are more frequently attributed to CNS involvement, with parenchymal or non-parenchymal involvement (65,142). They include a wide variety of conditions: meningoencephalitis, pyramidal syndrome, benign intracranial hypertension, venous sinus thrombosis, cerebellar signs, and nonspecific psychiatric disorders. The spinal cord is rarely involved (143).

Headache is the most common symptom (144). With this regard, Tekin et al. studied a monocentric cohort of 72 subjects of Turkish origin: in 15.3% of these, neurological involvement was found, and in 24.6% of cases, headache was reported (111). Metreau-Vastel et al. identified neurological involvement in 12 out of 40 children with BD; of these, 3 presented neurological symptoms as the first clinical manifestation (140). On the contrary, other studies report the first neurological symptoms between 2 and 5 years from the first manifestation of BD (145). Furthermore, both in the study by Mora et al. and in that by Metreau-Vastel et al., neurological manifestations were more frequently of a non-parenchymal type, especially cerebral vessel thrombosis (140,142). Uluduz et al. highlighted a male predominance in the pediatric neuro-Behçet population, with a male-to-female ratio of 5.5:1 (146).

It is important to emphasize that, throughout the pediatric literature, the definition of signs and symptoms related to BD is not uniform (94). For example, Karincaoglu et al. recorded organ involvement only if confirmed by laboratory, histological, or instrumental/ imaging investigations, while Hung et al. and Krause et al. also considered nonspecific symptoms (e.g., abdominal pain) (98,99,130).

Juvenile BD is a chronic-relapsing disease, with flare-up phases alternating with remission periods (110,118). Based on what has been seen so far, the diagnosis of jBD may be difficult as it is based only on clinical aspects that can be nonspecific and appear a long distance from each other; the lack of specific tests or biomarkers further complicates the diagnostic process (71,128). In addition to the criteria designed for the adult patient population (the aforementioned ISGC and ICBD), the PEDBD group has also proposed a set of classification criteria for BD onset in pediatric age (6,7,71) (see section 1.1.4). The specificity and sensitivity of these three sets of criteria vary depending on the cohort. In the cohort of patients studied by Kurt et al., the specificity of each group of criteria was 100%, while the ICBD were the most sensitive, as in the study by Nanthapisal et al. (128,147). The review by Batu et al. highlights how the expert opinion cannot be replaced with any set of criteria, because, due to the heterogeneous phenotypic combinations, regional variability, and age-related variability, neither the sensitivity nor the specificity of the criteria reach 100%, unless there are pathognomonic signs (71,97,107,112). Kurt et al. also confirmed the expert opinion as the gold standard, however emphasizing that the PEDBD criteria have a lower sensitivity compared to the other two more commonly used sets, which can only be increased by also including the pathergy test among the diagnostic procedures (147). In contrast to these observations, the PEDBD group, in drafting the criteria for pediatric BD, had not found a significant improvement in the performance of the same by including the pathergy test among the items (71).

An early diagnosis of BD would allow for timely therapy that may prevent or limit the onset of irreversible complications (128,135). The main ones to identify are complications resulting from the involvement of CNS, large vessels and ocular involvement, which are capable to lead to disability and loss of vision (103). In pediatric age, the involvement of the visual apparatus significantly affects the prognosis (103,110). Confirming this, the study by Tugal-Tutkun et al. and that by Pivetti et al. highlight cataracts, optic atrophy, retinal detachment, and maculopathy as the main complications (138,148).

According to Gallizzi et al., in addition to altered visual function, neurological involvement, such as the development of encephalopathy, affects morbidity and disability (103,112). The primary cause of mortality, however, is found in the cardiovascular manifestations of the disease (71). Overall, the frequency of severe complications (defined as death, blindness, meningoencephalitis, hemoptysis, intestinal perforation, severe arthritis) was found to be lower in patients with juvenile-onset BD compared to those with adult onset (104,149).

Therapeutic strategies vary according to the clinical manifestations of each patient, the presence of comorbidities, the preference of the family and the availability of drugs in different geographical regions. **Figure 4** summarizes the results of a recent metanalysis by Batu et al. nicely depicting how different therapeutic choices are declined according to the patient's specific phenotype in the real clinical practice (150). There are currently no guidelines for the treatment of BD in pediatric age; however, the French recommendations published in 2021 include considerations specifically applicable to pediatric age (151). Similarly to what is expected for adults, therapy should aim to achieve and maintain remission of the inflammatory process over time, control symptoms, improve the patient's quality of life, and prevent the development of complications and damage (93). To these general objectives are added, in pediatric age, those of ensuring normal growth, neuro-psychomotor and pubertal development, and preventing the disease from interfering with normal social life and school learning (151).

In this sense, the long-term use of CS is particularly discouraged due to their side effects: if administered chronically at a dosage greater than 0.3 mg of prednisone per kg, they are usually responsible for delayed growth and pubertal development, iatrogenic Cushing's syndrome, and organ complications (151). The use of oral or intravenous CS is therefore indicated only for limited periods of time, in order to control acute symptoms at the ocular, gastrointestinal, neurological, and vascular levels, or for particularly severe mucocutaneous manifestations. In addition, topical CS formulations

are used as first-line therapy in cases of anterior uveitis and persistent oral or genital ulcers (151).

Colchicine, at a dosage of 1-2 mg per day, is considered the first-line treatment for mucocutaneous and joint involvement, both by the 2018 EULAR recommendations and the French ones (75,151). Other possible therapeutic options include cDMARDs and bDMARDs, either alone or in combinations (97,112,151,152).

In particular, AZA (2 mg/kg/day) is indicated, either alone or in combination therapies, for the treatment of mucocutaneous lesions refractory to first-line therapy, in anterior uveitis (if recurrent or in young subjects), in mild-moderate posterior uveitis, in mild-moderate neurological involvement, in recurrent deep vein thrombosis, in mild peripheral aneurysms, and finally as a steady-state therapy in case of gastrointestinal involvement (151). CYC is recommended, due to its side effects, only in severe forms of cerebral and vascular parenchymal involvement, both venous and arterial (151). CsA is useful in controlling uveitis, reducing the use of CS, as an alternative to AZA, but should be avoided in cases of CNS manifestations (75,151). Mesalazine, on the other hand, is used to control mild gastrointestinal manifestations (151).

Biological drugs, in particular anti-TNFα either alone or more often in combination therapies, are indicated in refractory mucocutaneous lesions, in gastrointestinal involvement, and in severe ocular manifestations, in the latter case as an alternative to IFNα. In particular, the use of IFX is preferable in the most severe neurological and vascular manifestations. In general, therefore, biological immunosuppressive therapy is recommended in the presence of negative prognostic factors and in complex cases characterized by a higher risk of complications and recurrent clinical manifestations (75,97,151).

The recommendations also suggest the use of other molecules, such as apremilast, which is included in the small molecules group, the conventional immunosuppressant TLD, or the biological drug ustekinumab in case of severe mucocutaneous lesions (151).

## 1.2 Ophthalmology benchmarks in uveitis

In the following sections, some basic concepts in immuno-ophthalmology and technical aspects concerning the instrumental evaluation of eyes affected by uveitis will be explained to provide a concise guide for the experimental part.

### 1.2.1 Anatomical classification of uveitis

The uvea consists of three distinct segments, each with highly specialized specific functions: the iris, the ciliary body, and the choroid. Their exact anatomical location is shown in **Figure 5A**, taken from Sève et al (153). These structures, which are richly vascularized and abundant in immunocompetent elements, are capable to react to various pathogenic agents, resulting in different types of uveitis: exudative, plastic, and granulomatous inflammations. Isolated uveitis is actually rare, and the inflammatory process often also affects adjacent structures such as the corneal endothelium, vitreous, sclera, retina, and optic nerve.

Based on the anatomical location of the inflammation, a classification has been proposed that also aims to have practical implications from a diagnostic and prognostic perspective. The anatomical classification should be understood in terms of structures directly involved in the inflammatory process rather than based on secondary structural complications.

Starting from these premises, uveitis can be distinguished into anterior, intermediate, posterior, or diffuse (panuveitis) (154).

Anterior uveitis refers to an inflammatory involvement of the anterior chamber and vitreous, but with a more pronounced involvement of the anterior chamber than what can be described in the case of intermediate uveitis. Anterior uveitis includes iritis, iridocyclitis (concomitant inflammation of the anterior part of the vitreous), and anterior cyclitis.

The term intermediate uveitis should be used in that subset of patients where the vitreous body represents the main site of inflammation. The concurrent identification of peripheral vascular exudation (sheathing) or macular edema does not change the classification. The term pars planitis, on the other hand, should only be used in cases where intermediate uveitis manifests with

snowball or snowbank exudates in the absence of systemic infectious or autoimmune diseases, i.e., in idiopathic forms. Intermediate uveitis/pars planitis includes the terms posterior cyclitis and hyalitis.
The term posterior uveitis should be used in cases with predominant inflammation affecting the retina or choroid. Posterior uveitis includes focal, multifocal, or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis, and neuroretinitis.
The term panuveitis should be reserved for situations where there is no predominant site of inflammation, but it is possible to identify inflammation indistinctly in the anterior chamber, vitreous, and retina and/or choroid (in the latter case retinitis, choroiditis, or retinal vasculitis). For the definition of panuveitis, structural complications such as macular edema and neovascularization phenomena should not be considered.
As for the term retinal vasculitis, some clarifications need to be added. In particular, a retinal vascular occlusion in the absence of signs of inflammation should not be classified among retinal vasculitis. On the contrary, according to the current guidelines of the SUN working group, in order to speak of retinal vasculitis, it is necessary to identify the presence of perivascular exudate or the finding of occlusion on the fluorescein angiography examination (154).

### 1.2.2 Symptoms and signs of uveitis

The information provided by the following semeiological chapter is summarized from the work by Pivetti-Pezzi P. 1996 (155).

#### Anterior uveitis

Symptoms

Anterior uveitis is characterized by the presence of deep pain, due to the irritation of the ciliary nerves, photophobia, tearing, and blurred vision. In severe cases, there is persistent blepharospasm, while in milder forms, the disturbance only arises in the presence of illumination. The visual impairment ranges from mild to severe. In acute anterior uveitis, it is mainly linked to corneal changes and clouding of the aqueous humor and vitreous. In

recurrent and chronic forms, visual deficits may be more related to lens and vitreous opacities, proliferative epipupillary changes, papillary and macular edema, which are complications of long-standing anterior inflammation.

Signs

The signs characterizing anterior uveitis include congestion, perikeratic reaction, corneal endothelial precipitates, tyndall effect, cellular exudation in the anterior chamber, miosis, pupillary irregularities due to posterior synechiae, and intraocular hypotension.

- **Corneal endothelial precipitates**. They are aggregates of inflammatory cells in the aqueous humor and deposited on the corneal endothelial surface.
- **Tyndall effect**. The aqueous humor is normally clear and optically empty upon biomicroscopic examination. In anterior uveitis, however, vascular exudation of proteins, fibrin, and inflammatory cells impairs its transparency. In particular, the increase in protein content is responsible for the tyndall phenomenon and indicates the presence or persistence of the inflammatory process in the anterior chamber. The tyndall phenomenon is an assessment of the particulate present in the anterior chamber perceivable when a light beam passes through. The tyndall, in accordance with the SUN indications, is quantified on a scale ranging from 0 to 4+ based on the amount of protein present in the anterior chamber (154).

| **Tyndall** | **Characteristics** |
|---|---|
| 0 | Absent |
| 1+ | Mild |
| 2+ | Moderate (iris and lens visible in detail) |
| 3+ | Marked (iris and lens blurred) |
| 4+ | Abundant fibrin or plastic aqueous humor |

- **Cellular exudation in the anterior chamber**. The presence of inflammatory cells is always indicative of inflammation, and their quantity varies with the severity and stage of disease activity. It is

possible to quantify the presence of cells in the anterior chamber. In this case, too, quantification ranges from 0 to 4+ (154).

| Grade | Number of cells per field (1 mm x 1 mm at the slit lamp) |
|---|---|
| 0 | <1 |
| 0.5+ | 1-5 |
| 1+ | 6-15 |
| 2+ | 16-25 |
| 3+ | 26-50 |
| 4+ | >50 |

- **Hypopyon**. An extremely intense inflammatory reaction can induce such cellularity in the anterior chamber that, due to gravity, cells precipitate at the bottom, forming a white-yellowish level. The type of cells that form this level depends on the pathology in question and, in BD, it is mainly formed by polymorphonuclear cells.
- **Iris synechiae**. Synechiae are adhesions between the iris and adjacent structures determined by the deposition of fibrin and pigments subsequently subjected to organization by inflammatory cells and iris fibroblasts. They are distinguished into posterior and anterior. Posterior synechiae are established between the iris and the anterior capsule of the lens. They tend to form especially in forms characterized by high tyndall and in acute and subacute recurrent forms. Posterior synechiae can also significantly deform the pupillary aperture, sometimes giving it a flower appearance. If the synechia is arranged in a circular peripupillary manner, complete pupillary occlusion (pupillary block) can occur. Anterior synechiae lay between the iris and angular structures when predisposing events happen to bring the iris closer to the cornea. The formation of anterior synechiae is more common in chronic anterior uveitis.
- **Pupillary Occlusion and Iris Atrophy**. Pupillary occlusion is often linked to the presence of an epipupillary inflammatory membrane or

the presence of organized posterior synechiae in uveitis characterized by a high exudative component. Iris atrophy is the result of recurrent chronic uveitis that causes degenerative phenomena both at the stromal level and in the posterior pigmented epithelium.

- **Lens changes**. Lens changes during anterior uveitis include precipitates, pigmented deposits, and opacities. Changes in lens transparency are partly caused by the toxic action of inflammatory molecules on the lens and partly by the degeneration induced by the formation of posterior synechiae, which cause liquefaction of the superficial fibers of the capsule. The evolution towards cataract is a relatively frequent complication of recurrent and chronic anterior uveitis.
- **Vitreal changes**. Iridocyclitis is distinguished from iritis by the presence of cellularity and opacity in the retrolental space and anterior vitreous, caused by inflammatory involvement of the ciliary body (cyclitis). Vitreous opacities are associated with the presence of cell clusters, exudates, fibrin, and collagen residues that, based on distribution and morphological and kinetic characteristics, can be classified as anterior, posterior, diffuse, filiform, powdery, fixed, and mobile. The classification of vitreous opacity is between 0 and 4+ according to Nussenblatt et al in 1985 (156).

| **Vitreous opacity grading** | **Morphological characteristics** |
|---|---|
| 0 | Good examination of all the details of the posterior pole |
| Traces (±) | Striations and reflection of retinal nerve fibers not visible |
| 1+ | Good visualization of retinal vessels and optic disc |
| 2+ | Good visualization of the optic disc, but not the retinal vessels |
| 3+ | The optic disc is visible, but the edges are blurred; retinal vessels are poorly defined |
| 4+ | The optic disc is completely obscured |

In recurrent or chronic forms, the vitreous undergoes degenerative phenomena with rupture of the collagen mesh and retraction; vitreous

detachment is almost constant in anterior uveitis lasting over time. The collapsed vitreous forms areas of thickening and opacity that, together with cellular infiltrates, determine the characteristic "snowball" exudates, more typical of intermediate and posterior uveitis. These are visible as large, mobile exudates, mainly found in the vitreous periphery.

- **Changes in intraocular pressure**. Anterior uveitis, and in particular iridocyclitis, is characterized by a reduction in intraocular pressure due to reduced production of aqueous humor by the inflamed ciliary body. Generally, the tone returns to normal values as soon as the inflammatory process ceases. In chronic forms, however, hypotonia may persist, and in this case, it is linked to degeneration of the ciliary body that can result in atrophy of the eyeball. In some cases, however, acute uveitis may be associated with hypertension due to obstruction of Schlemm's canal and the iridocorneal angle secondary to the deposition of the protein and cellular material that characterizes the inflammatory process in the outflow pathways.

**Intermediate uveitis**

Symptoms

The symptoms of intermediate uveitis are mild, mainly characterized by floaters and transient blurring, while pain, congestion, and photophobia are absent.

Signs

Objective signs are found in the periphery of the ocular fundus. Inflammatory signs can be observed in the anterior chamber but with faint tyndall (maximum 1+) and some corneal endothelial precipitates essentially related to a "spill over" phenomenon (migration of cells into the anterior chamber).

- **Vitreal Changes**. In the anterior vitreous, it is possible to find inflammatory cells, pigment, and protein exudation that aggregate to form the "snowball" exudates, or "ant egg" exudates. These can come together to create layers that adhere to the pars plana of the choroid,

resulting in a pale preretinal layer (snow banks) from which glove-finger extensions can project into the vitreous. These membranes can organize into more or less tractional structures or even be the subject of neovascularization and therefore cause intraretinal hemorrhages. A constant in intermediate uveitis is the posterior detachment of the vitreous with or without vitreal collapse.

- **Retinal Changes**. Segmental peripheral vasculitis associated with preretinal vitreal exudates is common. The venules are mainly affected, showing periphlebitis and, more rarely, retinal vasculitis. Vasculitis remains mostly confined to the retinal periphery, but it can spread to the posterior pole. Periphlebitis is identified on ophthalmoscopic examination as a segmental sheathing of granular or moniliform appearance. In such cases, the ocular evaluation should include retinal fluorescein angiography and indocyanine green angiography, while optical coherence tomography (OCT) can identify and quantify a possible macular edema.

**Posterior uveitis/ uveoretinitis**

Uveoretinitis can be distinguished into focal, disseminated, and diffuse forms. Focal (and multifocal) forms are characterized by inflamed tissue easily distinguishable from the surrounding healthy tissue. When active, the focus appears raised, with blurred edges, of a whitish-yellowish or grayish color, sometimes surrounded by hemorrhage or periphlebitis. When the focus is inactive, the lesion flattens and results in a whitish scar surrounded by a hyperpigmented border. Uveoretinitis is disseminated when the inflammatory foci are numerous, concentrated in a quadrant or identifiable throughout the posterior pole. In diffuse forms, it is difficult to identify healthy areas among the numerous inflammatory foci. Overall, the lesions give the posterior pole an edematous, gray-yellowish, opaque appearance.

Symptoms

Symptoms are mainly characterized by visual impairment. Myodesopsias indicate vitreous exudation and, therefore, the spread of inflammation to the

vitreous humor. Photopsias (flashes of light) are instead related to the irritating stimulus that inflammation exerts on photoreceptors at the periphery of the lesions. Metamorphopsias (distorted images) are caused by retinal edema; in particular, micropsias are most often typical of macular edema and are generally associated with macropsias. Scotomas, positive in the acute phase, become negative in advanced stages. Not very relevant in the case of peripheral involvement, scotomas can also become very important, even leading to loss of central vision in the case of macular involvement. Visual blurring is extremely variable, ranging from mild, moderate, intermittent, constant, reversible, and irreversible, depending on the degree of secondary vitreous exudation and the location of choroido-retinal inflammation.

Signs

- **Vitreal alterations**. Characteristic of posterior uveitis is cellular exudation in the posterior vitreous. The exudation can take on the characteristics of snowball opacities, diffuse or localized, small or large. The intensity of vitreous opacity can be classified according to Nussenblatt et al. (156).
- **Retinitis/retinochoroiditis**. Characteristic are edema and exudation in the retinal layers. On ophthalmoscopy, the retina appears swollen, whitish, without reflections, with hemorrhages and exudates in the superficial layers. In the initial phases, the inflammatory process can be so intense as to create the "lighthouse in the fog" effect, or the identification of a whitish cottony patch secondary to intense vitreous exudation. In the area affected by retinitis, it is possible to distinguish perivascular lesions possibly associated with perilesional hemorrhages that take on a bright red color if the most superficial retinal layers are involved. The inflammatory process inevitably spreads to the underlying choroid, crossing the pigmented retinal epithelium.
- **Choroiditis/choroido-retinitis**. Choroiditis foci appear as pale, whitish-yellowish or grayish patches, with poorly defined blurred edges, over which the retinal vessels run normally. The intravitreal cell reaction is absent, at least until the inflammatory involvement of the

retina. Secondary retinal involvement is almost inevitable; at this point, the retina appears thickened, without reflections, but generally without signs of vasculitis or retinal necrosis. In diffuse choroiditis, subretinal exudation can be so intense as to cause an exudative retinal detachment. The scarring processes cause choroidal atrophy and proliferation of the pigmented retinal epithelium. This results in an appearance of whitish patches with sharp and pigmented edges with variable amounts of peri- and endo-lesional pigment.

- **Retinal vasculitis**. Retinal vasculitis is a frequent manifestation in the course of posterior uveitis and panuveitis, both as a consequence of choroido-retinal inflammation and possibly of the systemic pathology underlying uveitis, as in the case of BD. Inflammation can affect both arteries and veins, with peri- and endovasculitis phenomena. Periphlebitic venous involvement is the most frequently encountered. Characteristic of any vasculitis are the sheathing and cellular infiltration of the vessel walls. In the case of periphlebitis, on ophthalmic examination, the vein appears bordered by a double whitish striation, parallel to its wall and of variable extension, from segmental to diffuse. In segmental forms, the vessel takes on a granular or moniliform appearance, while in diffuse forms a certain degree of perivascular edema is possible. With the regression of the vasculitic process, there are also alterations in the vascular caliber with segmental constrictions or partial occlusions. Complications are related to alterations and occlusions of venous flow that cause retinal and vitreous hemorrhages, neovascularization, and therefore proliferative retinitis. In most cases, periphlebitic alterations start at the retinal periphery and then extend to the posterior pole. Periarteritis appears on objective examination with the same signs as periphlebitis, but phenomena of vascular obstruction with secondary edema and areas of retinal infarcts are much more frequent, visible as "cotton wool spots", ischemic areas, and neovascular formation. The evolution of retinal vasculitis inevitably

involves the posterior pole with macular, papillary, optic nerve edema, and, in the final stages, optic nerve atrophy.

**Panuveitis**

The symptomatology and semeiology of panuveitis is characterized by the overlap of multiple manifestations typical of both anterior and posterior uveitis, with a prevalence of one over the other depending on the specific etiology. From a clinical point of view, it is characterized by the presence of pain, chemosis, eyelid edema, marked conjunctival congestion, and reduction of vision up to the complete loss of light perception. Moreover, the association with retinal vasculitis and papillary involvement is frequent. From a semeiological point of view, panuveitis is characterized by the patterns already encountered in the course of involvement of anterior, intermediate, and posterior uveitis, as the various ocular segments are simultaneously present and more or less severe based on the extent of inflammation and which ocular segment is most involved.

### 1.2.3 Complications of uveitis

The following are the most common and feared uveitic complications. Some of them are secondary to specific inflammation of a particular ocular district, such as band keratopathy affecting patients with chronic persistent anterior uveitis; however, most complications can be found in all forms of uveitis, regardless of the anatomical segment involved by uveal inflammation (157).

- **Band keratopathy**. Typical of all chronic and persistent anterior uveitis, the alterations begin from the ends of the horizontal corneal meridian with non-homogeneous white-grayish opacities that slowly progress towards the center until they merge and form a band that crosses the cornea with a whitish and uneven appearance (158).
- **Complicated cataract**. Cataract is a common complication of all forms of uveitis and is a consequence of both chronic inflammation and local or systemic CS therapy. Lens opacities primarily affect the central and posterior parts (posterior subcapsular cataract), more sensitive to

inflammation, but subsequently, the anterior cortical part is also affected (total cataract). Early central lens involvement causes visual impairment from the outset, especially for near vision and when exposed to intense light sources (159).

- **Secondary glaucoma**. Secondary glaucoma is found in about 6% of endogenous uveitis, especially in anterior uveitis and in patients with panuveitis and marked anterior involvement, regardless of etiology, and more markedly in cases of severe inflammatory involvement. It can recognize several causes: papillary occlusion due to the formation of pupillary membranes or posterior synechiae; angular blockage due to the deposition of cellular and protein deposits at the iridocorneal angle; and trabecular blockage due to scar degeneration of the outflow pathways. In addition, iatrogenic glaucoma from CS is not uncommon (160).
- **Macular edema**. Macular edema can be found in all types of long-standing uveitis, especially if associated with an intense vitreal inflammatory reaction. Prolonged intraretinal edema can result in cystic degeneration and macular hole with permanent loss of central vision. Macular edema is the most common cause of impaired vision in patients with uveitis and impact negatively on prognosis (161,162). The diagnosis is made using OCT, which has become the gold standard for evaluating macular thickness. Fluorescein angiography and indocyanine green angiography are further useful methods for studying the macula, especially to exclude concomitant retinal vasculitis or choroidal neovascularization (162).
- **Retinal detachment**. Retinal detachment is a late complication of uveal inflammations. It can be secondary to vitreous contraction, retraction of cyclitic membranes, but also to intense retinal exudation. More common in intermediate uveitis and panuveitis, it can also be found in patients with anterior uveitis.
- **Intravitreal hemorrhages**. The development of vitreal strands in correspondence with organized preretinal exudates can facilitate vitreo-

retinal hemorrhages and retinoschisis.

- **Bulbar Atrophy**. In severe chronic uveitis, the persistent inflammation of the ciliary body causes such degeneration that it alters its function in qualitative, but also quantitative terms. This results in ocular hypotonia and progressive shrinkage due to reduced aqueous humor formation. Over time, fatty degeneration and ossification phenomena can also materialize. Irreversible hypotonia is generally below 6 mmHg.

### 1.2.4 Instrumental exams

For BD cases, particularly those affecting the posterior segment, ocular imaging is frequently necessary. At present, multimodal imaging is extensively used not just for diagnosing this condition, but also for evaluating disease activity, defining its extent, and tracking the response to treatment (163).

The findings of slit-lamp evaluation and fundus oculi examination, considered as first-line exams, have already been discussed in the previous chapter. Among the additional instrumental examinations, **fundus fluorescein angiography (FFA)** continues to be the primary investigative tool for diagnosing and monitoring the characteristic occlusive vasculitis or active vasculitis observed in BD posterior uveitis (164). Ozdal and colleagues found that the most frequent FFA findings in ocular BD were vasculitis in 38% of eyes, optic disc swelling in 14.8%, and macular swelling in 11.3% (165). The most distinguishing FFA sign in BD uveitis is a "fern-like capillary leakage" indicating disease activity, with the leakage typically spanning more than three quadrants of the retina (166). In a study involving 23 eyes with silent ocular BD, FFA imaging identified uveitic activity in 52.1% of the eyes examined, implying that inflammation remains radiologically active even when clinical symptoms are absent and suggesting that the ongoing treatment might be insufficient (167).

**Indocyanine green angiography (ICGA)**, specifically visualizing the choroidal circulation, allows the identification of choroidal inflammatory

processes with greater sensitivity compared to FFA. This examination is particularly useful in identifying subretinal neovascularization and multifocal choroiditis. Although BD is a systemic vasculitis, the inflammation and vasculitis are predominantly observed in the retina, leaving the choroidal vessels unaffected. Therefore, ICGA can be employed to distinguish BD from other conditions that primarily impact the choroid. However, ICGA doesn't offer any unique or definitive diagnostic markers specifically for BD (166,167).

In eyes with suitable optical media, **OCT** may provide information on the presence, extent, and characterization of posterior vitreal, retinal, or choroidal lesions. The routine execution of OCT is gaining an increasingly central role in clinical practice thanks to the reliability and non-invasiveness of the examination (168). It offers the possibility to examine macular complications, with cystoid macular edema being the most common one that requires close monitoring (163). The combination of OCT with angiography (angio-OCT) is useful as a complementary examination in the study of the macula, but it does not provide information about the involvement of the retinal periphery (169).

## 2. Aims and endpoints of the study

The general aim of this study is to characterize ocular involvement of BD in the pediatric age by analyzing data from a large international cohort, the AIDA Network Behçet's disease registry.
In this regard, the following objectives (O) and respective endpoints (E) have been addressed:

**O1:** to provide a comprehensive understanding of the occurrence, progression, and demographic distribution of ocular manifestations in jBD.

**E1.1:** frequency of ocular manifestations in the total jBD subjects

**E1.2:** demographic analysis

- gender and ethnicity distribution of the subjects with ocular manifestations onset in the pediatric age

**E1.3:** age-related analysis

- age distribution at the onset of ocular manifestations
- comparison between the age distributions of jBD onset and ocular involvement onset
- gender-based comparison of age distributions

**E1.4:** timing and progression of ocular manifestations

- % of subjects with ocular manifestations present since the onset of jBD
- time delay between jBD onset and the appearance of ocular manifestations
- correlation between age at jBD onset and delay of ocular involvement

**E1.5:** follow-up analysis

- duration of follow-up for subjects with ocular manifestations
- age distribution at the last recorded visit

**O2:** to explore the relationship between specific genetic markers and jBD-associated ocular manifestations.

**E2.1:** frequency of HLA-B51 haplotype

**E2.2:** comparison of specific characteristics based on HLA-B51 status

- age distribution at the time of ocular involvement
- delay of ocular involvement
- distribution of the number of ocular relapses

- anatomical classification of uveitis and presence of retinal vasculitis
- proportion of subjects using different therapies
- duration of systemic CS therapy
- Best Corrected Visual Acuity (BCVA) at the last follow-up
- proportion of eyes with visual impairment/ blindness, at the last follow-up
- distribution of BODI score at the last follow-up

**E2.3:** frequency of HLA-B27 haplotype and narrative description of specific clinical pictures

**E2.4:** proportion of subjects with familial jBD and narrative description of specific clinical pictures

**O3:** to describe the relationship between ocular manifestations and other systemic manifestations of jBD, with a focus on gender differences and age at disease onset in relation to specific clinical manifestations.

**E3.1:** frequency of major and minor organ manifestations in association with ocular disease

**E3.2:** frequency of single clinical manifestations

**E3.3:** gender-based stratification of clinical manifestations

**E3.4:** age distribution in relation to clinical manifestations

**O4:** to provide a comprehensive clinical analysis of jBD-associated ocular disease, including potential association with systemic manifestations, genetic markers, age and gender.

**E4.1:** distribution of ocular manifestations

- proportion of children with unilateral vs. bilateral ocular inflammation
- frequency of various ocular manifestations: uveitis, retinal vasculitis, retinitis, retrobulbar optic neuritis, and papilledema

**E4.2:** uveitis analysis

- distribution based on anatomical classification
- age distribution according to uveitis classification
- gender differences in uveitis anatomical patterns
- distribution of the number of ocular disease relapses across uveitis classes
- relationship between uveitis classes and systemic manifestations of jBD

**E4.3:** details of retinal vasculitis

- classification as arteritic and/or phlebitic
- association of retinal vasculitis with different classes of uveitis
- association of retinal vasculitis with the HLA-B51 haplotype

**E4.4:** visual acuity at the time of registry enrollment

- distribution of BCVA at the time of registry enrollment
- distribution of BCVA based on factors like sex, age at disease onset, HLA-B51 presence, uveitis classes, and ethnic origin

**O5:** to describe ocular complications in jBD, their frequency, and their association with visual acuity, disease progression, treatment patterns, and damage changes in the eye.

**E5.1:** frequency and types of ocular complications

- proportion of eyes with ocular complications
- frequency of various ocular complications
- description of less frequent complications

**E5.2:** potential association of the presence of ocular complications with other demographic, clinical and therapeutic variables

**E5.3:** potential association of complications with ocular damage

**O6:** to explore the findings of instrumental exams performed in children with ocular-jBD.

**E6.1:** fundus oculi examination

- proportion of normal vs. abnormal findings
- frequency of specific pathologic findings
- distribution of fundus abnormality across different anatomical classes of uveitis

**E6.2:** macular OCT examination

- proportion of normal vs. abnormal findings
- frequency of specific pathologic findings
- distribution of the value of central macular thickness (CMT) at the enrollment and last follow-up

**E6.3:** slit lamp evaluation

- frequency of active inflammation in the anterior chamber, fine keratic precipitates, vitreous inflammation, and grading of vitreous haze

**E6.4:** fundus fluorescein angiography

- proportion of positive vs. negative results
- distribution of the fluorescein angiographic score
- frequency of specific angiographic signs detected

**E6.4:** narrative description of the findings of other instrumental examinations

**O7:** to detail the treatments used in jBD patients with ocular manifestations and their associations with demographic and clinical parameters.

**E7.1:** systemic CS usage

- proportion of children treated with systemic CS
- frequency of oral and intravenous route administration
- distribution of the higher dosage of prednisone used
- distribution of the duration of CS therapy
- description of specific cases where local CS injections were used

**E7.2:** usage of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, cDMARDs, and bDMARDs

**E7.3:** comparison of drug usage according to demographic and clinical variables

- presence of major organ manifestations other than ocular
- gender, ethnic origin, and age at the onset of ocular involvement
- anatomical classes of uveitis
- presence of retinal vasculitis

**O8:** to describe the prognosis of children with jBD ocular involvement and identify risk factors associated and possibly predictive of disease outcomes such as BD overall damage, ocular damage, and visual prognosis.

**E8.1:** global prognosis evaluation

- distribution of BODI score at the end of the follow-up
- distribution of BODI score at the end of the follow-up according to demographic, clinical and therapeutic variables
- potential correlation between BODI score at the end of the follow-up and relevant demographic, clinical and therapeutic variables

**E8.2:** ocular damage assessment

- proportion of children with permanent changes in the anterior or posterior

ocular segments

- potential association between the presence of permanent changes in the anterior or posterior ocular segments and demographic, clinical or therapeutic variables
- potential correlation between the development of permanent changes in the anterior or posterior ocular segments and relevant demographic, clinical and therapeutic variables

**E8.3:** assessment of visual prognosis, including blindness

- distribution of BCVA at the end of the follow-up
- potential association between BCVA at the end of the follow-up and demographic, clinical or therapeutic variables
- potential correlation between BCVA at the end of the follow-up and relevant demographic, clinical and therapeutic variables.

# 3. Methods

## 3.1 Study design, inclusion criteria and data collection

This is an observational prospective registry-based study.

Data were retrieved from the AIDA Network Behçet's disease registry (ClinicalTrials.gov ID NCT05200715), resulting from the collaboration of 57 reference centers for BD at the international level.

The data was locked on September 29th, 2023 (**Figure 6**). Records were then filtered based on the following inclusion criteria:

• diagnosis of BD as per the ISG, ICBD, or PEDBD criteria (6,7,71)

• initial BD manifestations observed before the age of 18 years

• ocular inflammatory manifestations confirmed by an ophthalmologist to be related to BD

• BD ocular involvement observed before the age of 18 years.

The following variables were retrieved from the registry for the purpose of this study: patient ID, data access group, ethnic origin, sex, age, HLA-B asset, familial BD, presence of ocular involvement at BD onset, laterality of ocular involvement, ISG/ICBD/PEDBD criteria fulfilment, presence of oral aphthosis, genital aphthosis, skin involvement, type of skin manifestation, arthralgia, arthritis, myalgia, myositis, endoscopic gastrointestinal findings, neurological involvement, CNS involvement, type of CNS manifestation, PNS involvement, vascular involvement, type of vascular manifestation, cardiovascular involvement, headache, lymph node enlargement, splenomegaly, hepatomegaly, pleuritis, orchitis, epididymitis, fever of unknown origin, number of ocular relapses, type of ocular involvement, anatomical classification of uveitis, type of retinal vasculitis, BCVA, SUN uveitis pattern, fundus examination, macular OCT, fundus fluorescein angiography, bulbar ultrasound, orbital magnetic resonance imaging (MRI), anterior chamber inflammation, fine keratic precipitates, vitreal inflammation, systemic CS, route of CS administration, highest prednisone dosage, duration of CS treatment, peribulbar/intravitreal CS, NSAIDs, AZA, colchicine, CsA,

hydroxychloroquine (HCQ), methotrexate (MTX), mycophenolate mofetil (MMF), sulfasalazine/mesalazine, CYC, TCZ, ADA, IFX, etanercept (ETN), CZP, GOL, ANA, CAN, IFN, complications, BODI_damage to the anterior segment, BODI_damage to the posterior segment, BODI_visual impairment, BODI_blindness, BODI_cataract, total BODI score. Variables recorded in the registry at different timepoints were retrieved multiple times. In addition, attributes about eyes were extracted separately for the right and the left side. The data were then organized into two distinct datasets. In one dataset, variables were tailored to individual patients, while in the other, they were tailored to affected eyes. This separation ensured clarity for statistical analysis of both patient-specific and eye-specific data.

### 3.2 The AIDA Network Behçet's disease registry and its collaborative framework status

The AIDA Network Behçet's disease registry was developed as a specific action of the AIDA Network program (https://aidanetwork.org/en/). Established in 2019, the program aims to move beyond the isolation of reference centers for rare autoinflammatory diseases and autoimmune ocular diseases, facilitating the collection and exchange of clinical data, conduction of multicenter studies and dissemination of scientific knowledge at an international level.

The registry management function and high-level decision making are responsibility of the AIDA Network program governance, chaired by the principal investigator of the AIDA promoter center. The list of investigator centers participating in the AIDA Network Behçet's disease registry is available in the **Annex** section.

The registry is hosted by a virtual server in the platform of the Laboratory of Bioengineering of the University of Siena, which is located in the Data Center of the Azienda Ospedaliero-Universitaria Senese at the Santa Maria alle Scotte hospital in Siena (Italy). The registry service is based on REDCap (Research

Electronic Data Capture, https://projectredcap.org) a secure web application designed to support data capture for research studies.

Inspired by the FAIR guiding principles for scientific data management and stewardship, the AIDA Network Behçet's disease registry is included in the European Rare Disease Registry Infrastructure directory (ERDRI.dor, available at https://eu-rd-platform.jrc.ec.europa.eu/erdridor/home) and is committed to promote the interoperability with the other European Reference Network (ERN) RITA registries and potentially with the other ERNs.

### 3.3 Operative definitions

When describing BD clinical phenotype, ocular disease, neurologic manifestations (excluding isolate headache), vascular thrombosis/aneurisms, and gastrointestinal lesions confirmed by endoscopic exam were classified as major organ involvement. All other BD features were classified as minor organ involvement.

The anatomical classification of uveitis, the ocular inflammation grading system and the definition of ocular relapses were attributed by the treating ophthalmologist as per the Standardization of Uveitis Nomenclature (SUN) criteria (153). The grading of vitreous haze was assigned according to Nussenblatt et al (156). The presence of cataract was defined as per the Lens Opacities Classification System III (LOCS III) (170).

The findings of FFA were objectively assessed using the Angiography Scoring for Uveitis Working Group (ASUWOG) fluorescein angiographic score, as developed by Tugal-Tutkun et al., a semiquantitative dual fluorescein angiography scoring system for uveitis intended to assist in the follow-up of disease progression and monitoring response to treatment (possible range 0 – 40) (171).

The optical coherence tomography (OCT) parameters were evaluated by the operator against the reference values of the specific population and instrument employed (Zeiss, Heidelberg Engineering or Topcon models).

Visual acuity, expressed as BCVA decimals, was measured using age-appropriate Snellen charts. For a quick reference on BCVA interpretation, see **Table 3**.

Table 3

| SNELLEN (FEET) | DECIMAL FRACTION | DECIMALS | SNELLEN (METRIC) | logMAR | ICD-9-CM RANGES |
|---|---|---|---|---|---|
| 20/2000 | 1/100 | **0.01** | 6/600 | +2.0 | Near-Blindness |
| 20/1600 | 1/80 | **0.0125** | 6/480 | 1.9 | |
| 20/1250 | 1/63 | **0.016** | 6/380 | 1.8 | |
| 20/1000 | 1/50 | **0.02** | 6/300 | 1.7 | Profound Low Vision |
| 20/800 | 1/40 | **0.025** | 6/240 | 1.6 | |
| 20/260 | 1.5/50 | **0.03** | 6/192 | 1.5 | |
| 20/500 | 2/50 | **0.04** | 6/152 | 1.4 | |
| 20/400 | 1/20 | **0.05** | 6/120 | 1.3 | Severe Low Vision |
| 20/320 | 1.26/20 | **0.063** | 6/96 | 1.2 | |
| 20/250 | 1.6/20 | **0.08** | 6/76 | 1.1 | |
| 20/200 | 1/10 | **0.10** | 6/60 | 1.0 | |
| 20/160 | 1.25/10 | **0.125** | 6/48 | 0.9 | Moderate Low Vision |
| 20/125 | 1.6/10 | **0.16** | 6/38 | 0.8 | |
| 20/100 | 2/10 | **0.20** | 6/30 | 0.7 | |
| 20/80 | 2.5/10 | **0.25** | 6/24 | 0.6 | |
| 20/66.67 | 3/10 | **0.30** | 6/20 | 0.52 | Near Normal Vision Range |
| 20/63 | 3.2/10 | **0.32** | 6.4/20 | 0.5 | |
| 20/50 | 4/10 | **0.40** | 6/15 | 0.4 | |
| 20/40 | 5/10 | **0.50** | 6/12 | 0.3 | |
| 20/33.33 | 6/10 | **0.60** | 6/10 | 0.22 | |
| 20/32 | 6.3/10 | **0.63** | 6.3/10 | 0.2 | |
| 20/28.57 | 7/10 | **0.70** | 6/8.57 | 0.15 | |
| 20/25 | 8/10 | **0.80** | 6/7.5 | 0.1 | Range of Normal Vision |
| 20/22.22 | 9/10 | **0.90** | 6/6.67 | 0.05 | |
| 20/20 | 10/10 | **1.00** | 6/6 | 0.0 | |
| 20/18 | 11/10 | **1.1** | 6/5.5 | -0.04 | |
| 20/16.6 | 12/10 | **1.2** | 6/5 | -0.08 | |
| 20/16 | 12.5/10 | **1.25** | 6/5 | -0.1 | |
| 20/12.5 | 16/10 | **1.60** | 6/3.75 | -0.2 | |
| 20/10 | 20/10 | **2.00** | 6/3 | -0.3 | |

Corticosteroid dosages were converted to their prednisone equivalent and expressed in mg/kg/day. The most recent body weight recorded before therapy initiation was used for this calculation.

The total BODI score was used to assess the global damage associated with BD, according to Piga et al. (74). In addition, the oculo-specific items of the BODI were used to assess ocular damage. Those items are defined as follows:

- anterior segment changes: any changes documented by an ophthalmologist (e.g., synechiae, seclusion or occlusion pupillae);
- posterior segment changes: any changes documented by an ophthalmologist (e.g., vitreal haze, narrowing of retinal veins/arteries, retinal pigmentary changes, accumulation of pigment in macula, optic atrophy);
- visual impairment: a drop ≥3/10 in visual acuity for any cause (excluding refractive deficit and cataract) or visual field alteration due to retinal, macular involvement or glaucoma documented by an ophthalmologist;
- blindness: BCVA less than 6/60 (1/10) or central visual field equal or less than 10°, documented by an ophthalmologist;
- cataract: any cataract documented on ophthalmoscopy.

### 3.4 Statistical methods

Data were analyzed using the Jupyter Notebook via EDINA's Noteable platform, a cloud-based application providing access to coding environments (https://noteable.io) (172). Descriptive statistics included counts and frequencies for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) along with ranges for continuous variables. Shapiro-Wilk test was used to assess the normality distribution of data. Associations between categorical variables were analyzed using contingency tables with the Chi-Square test with Yates continuity correction. Differences in continuous data between independent groups were compared by the Mann-Whitney U test (2 groups) or Kruskal-Wallis H test with Dunn's post-hoc test (more than 2 groups). Differences in continuous data between paired groups were compared by the paired-samples T-test. Relationships between continuous variables were evaluated using Pearson's correlation for

normally distributed data and Spearman's correlation for non-normally distributed data. Univariate regression analysis was employed to predict outcomes, while multivariate regression analysis, utilizing multiple predictor variables simultaneously, was used to understand their combined effect on the outcome. For missing data, mode and median imputation were used, and results of the analysis conducted with and without imputation were provided. The threshold for statistical significance was set to $p<0.05$ and all p-values were two-sided.

### 3.5 Regulatory considerations

The study protocol adheres to the principles outlined in the Helsinki Declaration.

The AIDA Network Behçet's disease registry complies with the principles and rules of ELSI (ethical, legal, and social issues), including international and local data protection regulations. The registry conforms to the General Data Protection Regulation (GDPR) ensuring compliance with legal requirements regarding the processing of personal data.

For eligibility in the registry, patients (or their parents/legal guardians) must provide written consent. Patients receive from the investigator appropriate information about registry objectives, the type of information collected, how data will be used, the governance and data access rules for third parties and how to withdraw consent at any time.

The protocol of the AIDA Network Behçet's disease registry was approved by the Ethics Committee of Siena University Hospital on June 24, 2019 (Ref. 14951), with subsequent amendments, and by the Ethics Committees of all the participating investigator centers.

### 3.6 Role of the candidate

In the context of the current research and the preparatory work that enabled this study, the candidate has contributed to several key areas, which include:

- registry preparation, with specific reference to the pediatric aspects of

the diseases covered;

- registry development, with specific reference to modules collecting patient-reported information in the pediatric and adult age groups;
- training of the investigators;
- study design and coordination;
- data collection for the patients treated at Siena University Hospital;
- data extraction and cleaning;
- statistical analysis;
- literature review and interpretation of the results;
- production of graphic materials;
- writing of the elaborate;
- communication and dissemination activities;
- funding activities to support the registry maintenance;
- cooperation with patients' advocate associations.

# 4. Results

## 4.1 Demographic data

By the data lock on September 29th, 2023, 1000 subjects affected by BD were included in the AIDA Network Behçet's Disease registry. Among them, 212 (21.2%) were considered jBD, with disease onset observed before the age of 18 years. Ocular manifestations of the disease were described in 93 subjects (43.9% of jBD) at different timepoints during the disease history. By stratifying the subjects based on the age of onset of ocular manifestations, we identified 27 subjects whose symptoms began before the age of 18. Those patients were included in the final dataset for the study. They had been enrolled in the registry from 14 investigator sites specialized in pediatric rheumatology (2 centers, 3 patients enrolled), internal medicine (6 centers, 8 patients), rheumatology (5 centers, 13 patients), and ophthalmology (1 center, 3 patients). The list of enrolling centers can be found in the **Annex** section.

The study group included 18 males (66.7%) and 9 females (33.3%). Regarding the ethnic origin of the study population, 20 participants (74.1%) were Caucasian, 5 were Arab (18.5%), 1 was Asian (3.7%), and 1 was Hispanic (3.7%).

The mean age at the onset of BD was 11.9 years (SD 3.9, range 4.0 – 17.7 years). The median age at the onset of ocular manifestations of the disease was 14.2 years (IQR 4.7, range 4.3 – 17.7 years). There was a statistically significant difference between the distributions of the age at BD onset and the age at ocular involvement ($p$=0.01) (**Figure 7a**). Males and females had similar ages at disease onset ($p$=0.77).

Ocular manifestations were present since the onset of BD in 20 subjects (74.1%), developed later during the course of the disease in 7 (25.9%), with a median delay of 0.0 (IQR 10.8) months (range 0.0 – 132.0). There was a negative correlation between the age at BD onset and the delay of ocular involvement with moderate strength (Pearson's r= -0.43, $p$=0.02) (**Figure 7b**). The median duration of ocular disease was 7.5 years (IQR 12.0, range

0.1 – 29.0 years), with a mean patient age at the last recorded visit of 23.2 years (SD 8.5, range 8.9 – 42.8 years).

### 4.2 Genetic data

Twenty-two out of 27 children (81.5%) were tested for possible genetic mutations related to a BD-like clinical phenotype, all resulting negative.

The HLA-B51 haplotype was present in 14 subjects (51.9%), absent in 8 (29.6%), and unknown in 5 (18.5%). The characteristics of the subjects in relation to the presence or absence of HLA-B51 are shown in **Table 4**.

Table 4

| | **HLA-B51 +** | **HLA-B51-** | ***p*** |
|---|---|---|---|
| **Age at ocular involvement** years, mean (SD) | 12.2 (4.3) | 14.0 (2.4) | 0.29 |
| **Delay of ocular involvement** years, median (IQR) | 0.0 (0.4) | 0.1 (0.5) | 0.67 |
| **N. ocular relapses** median (IQR) | 1.0 (5.0) | 0.5 (2.8) | 0.17 |
| **Anterior uveitis** eyes n. (%) | 4/24 (16.7) | 1/13 (7.7) | 0.86 |
| **Intermediate uveitis** eyes n. (%) | 0/24 (0.0) | 1/13 (7.7) | 0.72 |
| **Posterior uveitis** eyes n. (%) | 8/24 (33.3) | 6/13 (46.2) | 0.53 |
| **Panuveitis** eyes n. (%) | 10/24 (41.7) | 4/13 (30.8) | 0.90 |
| **Retinic vasculitis** eyes n. (%) | 9/24 (37.5) | 4/13 (30.8) | 0.96 |
| **Use of systemic CS** patients n. (%) | 12/14 (85.7) | 4/8 (50.0) | 0.19 |
| **Duration of CS therapy** months, median (IQR) | 16.5 (22.8) | 9.0 (14.0) | 0.45 |
| **BCVA at the last follow-up visit** median (IQR) | 1.0 (0.5) | 1.0 (0.0) | **0.03** |
| **Visual impairment** eyes n. (%) | 13/24 (54.2) | 3/13 (23.1) | 0.14 |
| **Blindness** eyes n. (%) | 3/24 (12.5) | 0/13 (0.0) | 0.48 |
| **BODI total** median (IQR) | 2.5 (3.0) | 0.0 (0.0) | 0.08 |

The anatomical classification of uveitis was similar for subjects with and without the HLA-B51 haplotype. The presence of HLA-B51 was associated with a higher frequency of TNFα inhibitor drug use (13/14 in the HLA-B51+ group, 4/8 in the HLA-B51- group, with $p$=0.02, which lost significance when applying continuity correction ($p$=0.08). In the HLA-B51+ group, the BCVA value at the last follow-up visit was lower than in the HLA-B51- group ($p$=0.05 calculated on native data; $p$=0.03 after missing data imputation). Also, at the last visit, ocular damage in the anterior and posterior segment, cataract, visual impairment and blindness (defined according to the BODI items description) were more frequent in subjects carrying HLA-B51 than in those without it, although statistical significance threshold was not reached. The HLA-B27 haplotype was present in 1 subject (3.7%), absent in 11 (44.7%), and unknown in 15 (55.6%). The HLA-B27+ subject was a Caucasian male who, from the age of 15.1 years, presented with a clinical picture characterized by major oral aphthae and recurrent scrotal ulcers, low-grade fever, arthralgia, myalgia, laterocervical lymphadenitis, posterior uveitis, and retinal vasculitis; the boy had 20 bilateral ocular relapses over 11 years of follow-up, leading to the development of macular edema, papillitis, cataract, posterior synechiae, pupillary seclusion, micro-vasculitis of the arterioles supplying the optic nerve, ghost vessels, exudative retinal detachment, and bilateral blindness.

One girl had a familial form of BD, also diagnosed in her sister. This patient was a carrier of both the HLA-B51 haplotype and the HLA-Bw4 haplotype with isoleucine at aminoacidic position 80 (HLA-Bw4-80I). On the other hand, the NGS panel for monogenic autoinflammatory diseases was negative, including genes associated with BD-like pictures. The clinical picture, which began at 14.1 years of age, was characterized by high fever, recurrent bipolar aphthosis (minor oral aphthae, ulcers of the labia majora and vaginal mucosa), panuveitis, and retinal vasculitis in the right eye and anterior uveitis in the left eye, headache, and arthralgia. During the course of the disease, she developed macular epiretinal membranes in the right eye and drusen at

the posterior pole. The BCVA at the last recorded ophthalmic visit was 1 in both eyes.
Of note, familial cases of jBD were overall reported in 21 out of 212 children from the registry (9.9%).

## 4.3 Clinical data

### 4.3.1 Systemic disease

Behçet's Disease manifested with ocular involvement in all subjects included in the study. In addition, there were other major organ manifestations (gastrointestinal with lesions documented by endoscopy, vascular or involving the central nervous system, excluding isolated headache) in 4/27 subjects (14.8%), while 23/27 (85.2%) had only minor manifestations of Behçet's disease (mucocutaneous, musculoskeletal, headache, reticuloendothelial and serosal involvement, fever) in association with ocular disease. The frequency of the various clinical manifestations of BD in the study cohort is shown in **Figure 8**. Stratifying by gender, skin lesions (pseudofolliculitis, erythema nodosum) were more frequent in males (75.0%) than in females (22.2%) in a statistically significant manner ($p$=0.03). On the other hand, headache was reported more frequently in females (77.8%) than in males (12.5%), with $p$=0.01. Regarding the mean age at the onset of BD, this was significantly higher in patients with recurrent genital ulcers (15.1±1.7 years) compared to those who did not manifest them (10.2±3.8 years), with $p$<0.01. Conversely, children with arthritis or fever had an earlier onset compared to those without these clinical manifestations ($p$=0.03 according to arthritis; $p$=0.02 according to fever) (**Figure 9**).

### 4.3.2 Ocular disease

During the course of the disease, ocular inflammation manifested unilaterally in 9/27 children (33.3%) and bilaterally in 18/27 (66.7%), affecting a total of 45 eyes. Uveitis was found in 39 eyes (86.7%), retinal vasculitis in 17

(37.8%), retinitis in 6 (13.3%), retrobulbar optic neuritis in 2 (4.4%), and papillitis in 1 (2.2%).

Regarding uveitis, it was classified anatomically as anterior in 5 eyes (11.1%), posterior in 18 (40.0%), and panuveitis in 18 (40.0%). Median age at BD onset was higher in subjects with posterior uveitis than in those with panuveitis or anterior uveitis ($p$=0.01; Dunn's post-hoc: $p$=0.01 for panuveitis and $p$=0.01 for anterior uveitis); median age at ocular involvement was higher in children with posterior uveitis than in those with anterior uveitis or panuveitis ($p$=0.04; Dunn's post-hoc: $p$=0.02 for panuveitis and $p$=0.09 for anterior uveitis) (**Figure 10**). Posterior uveitis was observed in 53.3% of males and 18.2% of females ($p$=0.04), anterior uveitis showed a tendency towards female sex (27.3% versus 6.7%, $p$=0.07), while panuveitis was represented in similar percentages of males (40.0%) and females (54.5%, $p$=0.41) (**Figure 11**)

There were no statistically significant associations between the anatomical classes of uveitis and the presence of any systemic manifestations of BD, including oral ulcers, genital ulcers, myalgia, gastrointestinal endoscopic lesions, neurological manifestations, vascular manifestations, headache, lymph nodes enlargement, fever and skin lesions ($p$>0.05). Arthralgia accompanied anterior uveitis in 83.3% of cases, panuveitis in 64.7% and posterior uveitis in 27.8% ($p$=0.02); arthritis accompanied anterior uveitis in 33.3% of cases, panuveitis in 23.5% and posterior uveitis in 0.0% ($p$=0.05). Retinal vasculitis was described as arteritic in 1 eye (2.2%) and as both arteritic and phlebitic in 4 eyes (8.9%), while the data was missing for the remaining 12 eyes. Retinal vasculitis was observed in association with posterior uveitis or panuveitis. Its frequency was similar in subjects with and without the HLA-B51 haplotype ($p$=0.96).

The mean (SD) BCVA measured at the time of enrolment in the registry was 0.78 (0.42), range 0.0 – 2.0. The distribution of BCVA at the time of enrolment was similar according to the sex ($p$=0.84), age at disease onset ($p$=0.30), presence of HLA-B51 ($p$=0.16), different anatomical classes of uveitis ($p$=0.80) and ethnic origin ($p$=0.11).

During follow-up, children had an average of 6.2 relapses of ocular disease (SD 14.7, range 0-80). The mean number of relapses was similar across the anatomical classes of uveitis ($p$=0.23, **Figure 12**).

### 4.3.3 Complications

Ocular complications occurred in 23 eyes (51.1%). The most frequent complications are listed in **Table 5**.

Table 5

| **Complications** | **Frequency (eyes)** |
|---|---|
| Cataract | 13 (28.9%) |
| Macular edema | 9 (20.0%) |
| Posterior synechiae | 7 (15.6%) |
| Macular epiretinal membrane | 3 (6.7%) |
| Band keratopathy | 3 (6.7%) |
| Pupillary seclusion | 3 (6.7%) |
| Glaucoma (2 open-angle; 1 angle-closure) | 3 (6.7%) |
| Ghost vessels | 3 (6.7%) |
| Steroid-induced ocular hypertension | 2 (4.4%) |
| Exudative retinal detachment | 2 (4.4%) |
| Posterior vitreous detachment | 2 (4.4%) |
| Retinal ischemia | 2 (4.4%) |
| Retinal edema | 2 (4.4%) |
| Macular thinning | 2 (4.4%) |
| Others | 3 (6.7%) |

As for less frequent complications, overall included as "Other" in the table, the following findings were reported in addition to the previous ones: 1 eye with panuveitis and retinal vasculitis developed 360° iris synechiae and iris atrophy; 1 eye with posterior uveitis, retinitis and retinal vasculitis developed retinal pigment epithelial alterations, retinal fibrosis, neovascularization of disc, chorioretinal scars, vitreomacular traction, vitreous hemorrhage, macular atrophy, subretinal fibrosis, retinal tears, rhegmatogeus retinal detachment

and chorioretinal atrophy; 1 eye with panuveitis, retinitis and retinal vasculitis had also macular ischemia.

Subjects with ocular complications had lower median BCVA at the enrolment in the registry than subjects without complications: median (IQR) 0.8 (0.6) versus 1.0 (0.1) ($p$=0.11).

In the group with ocular complications, the patient had lower age at the onset of ocular manifestations [mean (SD) 10.8 (3.9) years vs. 14.9 (2.2) years, $p$<0.01], higher number of ocular relapses over time [median (IQR) 2.0 (14.0) vs. 1.0 (1.0), $p$=0.02] and more prolonged treatment with systemic CS [median (IQR) 30.0 (55.0) months vs. 9.0 (10.0) months, $p$=0.02] (**Figure 13a**). The duration of the ocular disease was similar between patients with or without ocular complications ($p$>0.05).

Ocular complications were associated with the use of bDMARDs ($p$=0.02), TNF$\alpha$ inhibitors ($p$=0.02) and ADA ($p$=0.03) with moderate strength (Cramér's V=0.34). After correcting for the association of major organ involvement other than ocular, the different use of bDMARDs and TNF$\alpha$ inhibitors between subjects with and without complications was statistically significant only in the absence of further major organ involvement ($p$<0.01) (**Figure 13b**).

The presence of ocular complications was associated with the finding of damage changes in the anterior or posterior segment (p<0.01) with high strength (Cramér's V=0.62).

### 4.4 Instrumental data

- Data about the findings of the **fundus oculi** examination were available for 35 procedures. The examination was normal in 17/35 eyes (48.6%) and abnormal in 18 (51.4%). The following findings were reported in pathologic fundus exams: macular edema in 9 eyes (25.7%), sheathing of the arteries in 4 (11.4%), retinal edema in 4 (11.4%), sheathing of the veins in 4 (11.4%), microvasculitis of the arterioles supplying the optic nerve in 3 (8.6%), white pearl-like precipitates on the surface of the inferior peripheral retina or posterior

hyaloidal face in 3 (8.6%), dry macula in 3 (8.6%), posterior vitreous detachment in 2 (5.7%), retinal vasculitis (**Figure 14**) in 2 (5.7%), posterior pole drusen in 2 (5.7%), papillitis in 2 (5.7%), exudative retinal detachment in 2 (5.7%), and others (acute periphlebitis, full-thickness necrotizing retinitis, venous and capillary dilatation with engorgement, branch retinal artery occlusion, synechiae, patchy perivascular sheathing with inflammatory whitish-yellow exudates surrounding retinal hemorrhages, superficial retinal infiltrates, branch retinal vein occlusion) in 1 eye (2.9%). The inhomogeneous frequency of fundus abnormality across different anatomical classes of uveitis is shown in **Figure 15**.

- Data about the findings of the **macular OCT** examination were available for 17 procedures (37.8%). The examination was normal in 13/17 eyes (76.5%) and abnormal in 4 (23.5%). The following findings were reported in pathologic macular OCT exams: diffuse intraretinal fluid (**Figure 16a**) in 3 eyes (17.6%), intraretinal cysts in 2 eyes (11.8%), spongy edema in 2 eyes (11.8%), tractional epiretinal membrane (**Figure 16b**) in 1 eye (5.9%). The mean (SD) CMT at the enrolment in the registry (measured in 10 eyes) was 302.2 (58.4) micron (range 239 – 404). The mean (SD) CMT at the last follow-up available (measured in 9 eyes) was 293.3 (78.2) micron (range 180 – 404).
- The following findings at the **slit lamp evaluation** were reported: active inflammation in the anterior chamber was found in 6/19 exams (31.6%); fine keratic precipitates were found in 2/9 exams (22.2%); vitreous inflammation was found in 7/18 exams (38.9%); vitreous haze was graded in 7 eyes according to Nussemblatt grading system as grade I in 5 eyes, grade II in 1 eye, grade IV in 1 eye.
- Data about the findings of **fundus fluorescein angiography** were available for 7 eyes undergoing 19 procedures. The exam identified signs of posterior uveitis and/or retinal vasculitis in 12/19 procedures (63.2%) while it resulted negative in 7 (36.8%). When applying the

ASUWOG fluorescein angiographic scoring system on the earliest procedures performed for the 7 eyes, the mean (SD) total score was 17.9 (15.5) (range 0 – 37). Considering all the procedures performed over time, the following angiographic signs were detected (**Figure 17**): optic disc hyperfluorescence at 5-10 min in 8 eyes (41.2%) (leakage at the optic disc with blurring of margin in 5 eyes; partial staining of the disc with distinct margins in 1 eye; normal staining of the scleral rim in 2 eyes), macular edema at 10 min in 11 eyes (57.9%) (faint hyperfluorescence in 2 eyes; incomplete ring of leakage in 3 eyes; complete ring of leakage in 2 eyes; pooling of dye in cystic spaces in 4 eyes), retinal vascular staining/leakage in posterior pole arcades at 5-10 min in 8 eyes (42.1%) (diffuse in 6 eyes; more extended or multifocal but limited area in 2 eyes), retinal vascular staining/leakage in periphery at 5-10 min in 7 eyes (36.8%) (one quadrant in 1 eye; two quadrants in 1 eye; three quadrants in 2 eyes; four quadrants in 3 eyes), capillary leakage in the posterior pole at 5-10 min in 6 eyes (31.6%) (diffuse in 5 eyes; limited in 1 eye), capillary leakage in periphery at 5-10 min in 6 eyes (31.6%) (diffuse in two quadrants in 1 eye; diffuse in three quadrants in 1 eye; diffuse in four quadrants in 4 eyes), retinal capillary nonperfusion in 4 eyes (21.1%) (macular in 1 eye; posterior pole three quadrants in 2 eyes; posterior pole four quadrants in 1 eye), neovascularization in 2 eyes (10.5%) (optic disc in 1 eye; elsewhere multiple in 1 eye), pinpoint leaks in 6 eyes (31.6%) (extensive in 6 eyes), and retinal staining/pooling at 5-10 min in 4 eyes (21.1%) (extensive in 3 eyes; limited in 1 eye).

- **Indocyanine green angiography** was not performed in any patients.
- **OCT-angiography** was performed in 4 eyes, resulting in a normal picture.
- **Bulbar ultrasound** was performed in 4 eyes, resulting in pathologic findings in all cases: vitreous turbidity in 3 eyes and retinal detachment in 1.

### 4.5 Therapeutic data

Children affected by BD-associated ocular inflammation were treated with systemic CS in 20/27 cases (74.1%) by oral (17/20, 85%) or both oral and intravenous (3/20, 15%) route. The mean (SD) higher dosage of prednisone employed was 0.5 (0.3) mg/kg/day, range 0.1 – 1.0. The median (IQR) duration of CS therapy was 17.0 (23.5) months, range 1.0 – 137.0. The use of systemic CS was more frequent in children with posterior uveitis (82.4%) or panuveitis (76.8%) than anterior uveitis (50.0%), but the threshold of statistical significance was not reached (p=0.27).

A patient received bilateral subconjunctival injections of prednisone and unilateral peribulbar injections of prednisolone. He was affected by bilateral posterior uveitis complicated with bilateral macular edema, papillitis and microvasculitis of the arterioles supplying the optic nerve in one eye and exudative retinal detachment in the other one. In addition, another girl affected by posterior uveitis with microvasculitis of the arterioles supplying the optic nerve received peribulbar injection of CS in one eye.

**Table 6** visualizes the frequency of use of systemic CS, NSAIDs, colchicine, cDMARDs, and bDMARDs in children with ocular involvement. Data are presented after stratification by the concomitant presence/absence of further major organ manifestations, namely neurological, vascular or gastrointestinal inflammation. The difference between the two groups was not significant according to the Chi-Squared test.

Table 6

| **Molecules or drug classes** | **All children N. (%)** | **Major organ involvement N. (%)** | **Minor features N. (%)** | ***p*** |
|---|---|---|---|---|
| Systemic CS | 20/27 (74.1) | 3/4 (75.0) | 17/23 (73.9) | 1.00 |
| Colchicine | 9/27 (33.3) | 3/4 (75.0) | 6/23 (26.1) | 0.18 |
| NSAIDs | 4/27 (14.8) | 1/4 (25.0) | 3/23 (13.0) | 1.00 |
| cDMARDs | 22/27 (81.5) | 4/4 (100.0) | 18/23 (78.3) | 0.73 |
| AZA | 12/27 (44.4) | 3/4 (75.0) | 9/23 (39.1) | 0.43 |
| CsA | 9/27 (33.3) | 2/4 (50.0) | 7/23 (30.4) | 0.85 |

| | | | | |
|---|---|---|---|---|
| MTX | 6/27 (22.2) | 1/4 (25.0) | 5/23 (21.7) | 1.00 |
| HCQ | 2/27 (7.4) | 1/4 (25.0) | 1/23 (4.3) | 0.67 |
| MMF | 2/27 (7.4) | 1/4 (25.0) | 1/23 (4.3) | 0.67 |
| IFN | 2/27 (7.4) | 0/4 (0.0) | 2/23 (8.7) | 1.00 |
| TLD | 1/27 (3.7) | 0/4 (0.0) | 1/23 (4.3) | 1.00 |
| bDMARDs | 21/27 (77.8) | 3/4 (75.0) | 18/23 (78.3) | 1.00 |
| ADA | 17/27 (63.0) | 2/4 (50.0) | 15/23 (65.2) | 0.98 |
| IFX | 7/27 (25.9) | 1/4 (25.0) | 6/23 (26.1) | 1.00 |
| ETN | 2/27 (7.4) | 1/4 (25.0) | 1/23 (4.3) | 0.67 |
| CZP | 2/27 (7.4) | 1/4 (25.0) | 1/23 (4.3) | 0.67 |
| GOL | 2/27 (7.4) | 1/4 (25.0) | 1/23 (4.3) | 0.67 |
| ANA | 1/27 (3.7) | 1/4 (25.0) | 0/23 (0.0) | 0.31 |
| CAN | 2/27 (7.4) | 1/4 (25.0) | 1/23 (4.3) | 0.67 |

After stratification by the concomitant presence/absence of further major organ manifestations at disease onset, sex, ethnic origin or age at the onset of ocular involvement, the differences in the use of each drug were not statistically significant ($p$>0.05 for all of them). The frequency of employment of each drug was similar according to anatomical patterns of uveitis, except for methotrexate (MTX) which was more frequently used for anterior uveitis (60.0%) than posterior uveitis (5.6%) or panuveitis (33.3%) ($p$=0.02). MTX was prescribed as a combination therapy with IFX in 1 child or ADA in 2 children, as a monotherapy in 3 children. There were no statistically significant associations between the presence of retinal vasculitis and the use of any specific drug classes or single molecules.

### 4.6 Prognostic data

When assessing the global prognosis of jBD in our cohort, a median (IQR) BODI score of 1.5 (3.3) (range 0 – 5) was calculated at the end of the follow-up, with a median disease duration of 7.5 (IQR 12.0) years [0.1 – 29.0]. According to linear correlation analysis, the total BODI score at the end of the follow-up was inversely correlated to the age at onset of ocular involvement (Spearman's r=-0.5681, $p$<0.01) (**Figure 18a**). Also, the total BODI score at

the end of the follow-up was higher in case of bilateral ocular disease than unilateral ($p$=0.02) (**Figure 18b**).

At the end of the follow-up, ocular damage according to the oculo-specific BODI items was observed in 33/45 eyes (73.3%). Changes in the anterior segment were reported in 17 eyes (37.8%), changes in the posterior segment in 22 (48.9%), cataract in 13 (28.9%), visual impairment in 22 (48.9%) and blindness in 7 eyes (15.6%).

- The age at onset of BD-associated ocular inflammation was lower in the group of children who developed permanent changes in the anterior segment during the disease course ($p$=0.01) (**Figure 19**). A statistically significant association was found between the presence of ocular complications and the development of permanent changes in the anterior segment ($p$<0.01). After running logistic regression analysis including age at onset of ocular inflammation and presence of ocular complications, only the latest was a significant predictor of the development of permanent changes in the anterior segment with statistical significance (Coefficient=2.48, OR=11.9, $p$=0.04).
- The age at the last follow-up visit was lower in the group of children who developed permanent changes in the posterior segment during the disease course ($p$=0.02). A statistically significant association was found between the presence of ocular complications and the development of permanent changes in the posterior segment ($p$<0.01). After running logistic regression analysis including age at the last follow-up visit and presence of ocular complications, only the latest was a significant predictor of the development of permanent changes in the posterior segment with statistical significance (Coefficient=2.69, OR=14.7, $p$<0.01).

When assessing the visual prognosis of the cohort, a median (IQR) BCVA of 1.0 (0.5)(range 0.0 – 2.0) was measured at the end of the follow-up. After median imputation of missing data, the BCVA at the end of the follow-up was found to be lower in the presence of HLA-B51 ($p$=0.03), abnormal fundus

oculi examination ($p$=0.05), macular edema ($p$<0.01), cataract ($p$=0.05) and posterior synechiae ($p$<0.01) (**Figure 20**). After running the multivariate regression analysis, the following results were achieved:

| **Variable** | **Coefficient** | **Standard Error** | **t-value** | **P-value** |
|---|---|---|---|---|
| **Intercept (const)** | 1.2754 | 0.108 | 11.787 | < 0.001 |
| Fundus_Pathologic | -0.2095 | 0.110 | -1.903 | 0.064 |
| Macular edema_Yes | -0.1216 | 0.148 | -0.821 | 0.417 |
| Cataract_Yes | -0.1570 | 0.120 | -1.312 | 0.197 |
| Posterior synechiae_Yes | -0.2732 | 0.160 | -1.704 | 0.096 |
| HLA-B51_Yes | -0.2649 | 0.101 | -2.618 | **0.013** |

confirming that the presence of HLA-B51 may significantly predict a reduction of -0.3 of the BCVA at the last follow-up, assuming that the other variables analyzed remain constant.

Blindness, defined as BCVA<1/10 or central visual field ≤10°, was reported in 7 eyes (unilateral in 5 children, bilateral in 1). Children who eventually experienced unilateral or bilateral blindness had a lower median BCVA at the initial evaluation recorded in the registry, compared to those who did not develop blindness ($p$<0.01). In addition, unilateral or bilateral blindness was associated with the presence of abnormal fundus examination ($p$=0.03), macular edema ($p$=0.04) and posterior synechiae ($p$=0.01). Multivariate regression analysis including BCVA at the initial evaluation, macular edema, HLA-B51, sex, CS treatment duration, disease duration and posterior synechiae showed that BCVA at the initial evaluation (OR 0.59) and posterior synechiae (OR 1.62) were independent predictors of blindness.

| **Variable** | **Coefficient** | **Std. Error** | **t-value** | **p-value** |
|---|---|---|---|---|
| Constant | 0.5651 | 0.2970 | 1.9030 | 0.0723 |
| Sex_Male | 0.0456 | 0.1283 | 0.3557 | 0.7260 |
| BCVA_enrol | -0.5291 | 0.1462 | -3.6188 | 0.0018 |
| Cs_treatment_duration_m | -0.0005 | 0.0013 | -0.3766 | 0.7106 |
| Ocular_FUP | 0.0045 | 0.0087 | 0.5238 | 0.6065 |
| HLA-B51_Yes | -0.1212 | 0.0999 | -1.2135 | 0.2398 |

| | | | | |
|---|---|---|---|---|
| Macular edema_Yes | -0.1003 | 0.1552 | -0.6463 | 0.5258 |
| Posterior synechiae_Yes | 0.4837 | 0.1711 | 2.8272 | 0.0108 |

## 5. Discussion

This study aimed to provide a comprehensive characterization of ocular manifestations in children affected by BD by addressing demographic aspects, clinical observations (including systemic associations), instrumental findings, therapeutic solutions and prognostic factors for unfavorable outcomes.
The decision to enroll all subjects with disease onset during pediatric years, without making a distinction between 'pediatric-BD' and 'juvenile-onset BD', stems from the author's hypothesis that the pathogenetic basis of the disease is the same in both pediatric and adult populations. This hypothesis still recognizes age-related differences, such as variations in clinical presentation, overall and organ-specific outcomes, and treatment strategies. However, it's crucial to approach the existing literature with caution, since inconsistencies in disease definitions and the effects of disease duration can potentially skew interpretations, leading to misleading or inaccurate conclusions (149,173).
With these premises, jBD accounted for 21.2% of records in the AIDA Network Behçet's disease registry and ocular manifestations were observed in 43.9% of the jBD cohort anytime during the disease history. The prevalence is consistent with that resulting from a metanalysis conducted by Turk et al, where the overall frequency of ocular involvement in jBD was 45% [34-56%], similar to that of adult BD (174). We may reasonably conclude that ocular disease is a frequent manifestation of jBD, although there are contrasting data in the literature, including a large Turkish study where ocular manifestations were found in 27.3% of jBD (121,135).
Understanding the timing of appearance of ocular symptoms may inform our clinical practice and assist in defining a potential ophthalmological screening schedule for children with BD. With this regard, this study provides some interesting insights. The ocular symptoms typically manifested around the age of 14 years, with a potential range from 4 to 18 years. Similar mean ages at

ocular involvement were reported by Citirik et al. and Friling et al., while in the PEDBD cohort a lower age was reported (10.9 years) (71,175,176). Although for most children in our study ocular inflammation was among the initial signs of the disease, there was still a highly significant difference in the age distribution between the development of ocular symptom and the onset of BD, with the latter occurring around 11 years. Furthermore, there was an inverse relationship between the delay in ocular symptoms and the age at which BD began. Notably, the percentage of children showing ocular inflammation since disease onset was similar between our cohort and the cohort recently described by Ostrovsky et al., confirming to be around 70% of ocular BD cases (177). Taken collectively, these observations may imply that adolescents might exhibit ocular inflammation at (or soon after) the onset of the disease while, in contrast, for younger children, the earlier the onset of BD, the more prolonged the anticipated delay in ocular manifestations. This hypothesis is consistent with the findings in a historical cohort of children from Turkey, where only 8 out of 62 (12.9%) with ocular-BD were younger than 10 years (120).

In this study, a distinct male prevalence was observed among children with ocular BD. As discussed in section 1.1.7, the precise male/female ratio in jBD remains undefined, and a hypothesis suggesting a gender-neutral balance in children has been put forth, mirroring findings in other immune-mediated diseases (127). However, given the remarkable heterogeneity of this condition, it is plausible that specific symptom clusters could exhibit varying gender preferences. This was confirmed by a cluster analysis in 225 children, that identified five clusters, among which the ocular and the vascular ones had male preference and the mucocutaneous one had female preference (178). Also, Shahram et al., in their description of one of the most extensive cohorts of jBD, observed a higher incidence of ocular inflammation in males, and similar findings were reported in the PEDBD cohort (71,107).

As expected from the literature, the HLA-B51 haplotype was a significant genetic marker in our study cohort, with over half of the subjects carrying it. This haplotype appears to correlate with certain clinical features. However,

due to our limited sample size, many of these associations remain uncertain. In our group, individuals with HLA-B51+ were more prone to early ocular inflammation and experienced more relapses. They also underwent more prolonged systemic CS treatment and received anti-TNF therapy more often. Compared to HLA-B51- subjects, those with HLA-B51+ had a higher likelihood of visual impairment, permanent changes in both the anterior and posterior segments of the eye, unilateral or bilateral blindness, and overall disease-related damage. When coming to actual statistical significancy, only visual acuity at the last follow-up visit was affected by the presence of HLA-B51. This result was confirmed also by multiple regression analysis showing that the presence of HLA-B51 might independently predict a reduction of -0.3 of the BCVA. HLA-B51 was confirmed as the principal genetic predisposing factor by GWAS. A positive test increases the risk of developing BD by 5.79-fold and confers a higher probability of ocular involvement, with a correlation becoming stronger towards the East along the silk road (22,23,179,180). However, the prognostic value of this allele has not been established yet. According to a monocentric study conducted by our research group on adult BD patients, HLA-B51 may be a predictor of long-term structural complications and poor visual outcome (181). Similar findings were reported by other studies: Zouboulis et al. showed that, in patients with a non-vascular phenotype at onset (recurrent oral aphthosis, genital ulcers or articular involvement), HLA-B51 positivity is a negative prognostic marker (182); according to Kang et al., HLA-B51 could be associated with near total blindness in patients with posterior uveitis (183). On the contrary, visual acuity was not influenced by the presence of HLA-B51 in a Korean cohort (184).

We also identified two patients with further predisposing genotypes. One of them, a girl with a moderate clinical phenotype, carried the HLA-Bw4 with isoleucine at amino-acid position 80 (HLA-Bw4-80I) along with HLA-B51. In previous studies, the HLA-Bw4-80I was identified in HLA-B51- BD patients from Germany and Turkey. These patients had a 2.4-fold and 2.2-fold increased risk of developing the disease, respectively, when compared to

healthy individuals (185). The authors hypothesized that HLA-Bw4-80I could play a role in pathogenesis of the disease through the control of NK-/T-cell interactions with myeloid cells via ligation with KIR3DL allotypes, a polymorphic locus coding for NK cell regulatory molecules (185).
The other patient carried the HLA-B27 allele and his clinical picture was extremely severe, ending in multiple ocular complications and bilateral blindness. Mc Gonagle et al. suggested that BD, psoriasis, psoriatic arthritis and spondyloarthropathies likely have a common immuno-pathogenetic foundation, show clinical similarities and are linked with MHC class I alleles, including HLA-B51, HLA-B5, HLA-B27, and HLA-C0602 (186). However, the strength of these associations varies among the diseases. As for the role of HLA-B27 as a predisposing factor for BD, it was assessed by a metanalysis of 3939 cases and 6077 controls, indicating that the risk of HLA-B27 for BD progression is overall increased by a factor of 1.55, but important differences exist according to geographical areas (187). Furthermore, interaction between HLA-B alleles with other MHC and non-MCH genes, including HLA-B27, may influence the penetration and expressivity of the disease in general and its organ-specific manifestations. According to the analysis from Bettencourt et al., HLA-B27 may be a negative prognostic marker for disease severity, which could apply to our patient (188). Interestingly, HLA-B27 positivity resulted a good prognostic factor in ocular BD according to another study, suggesting a complex influence of this allele in the disease course (189).
The analysis of associated symptoms of BD split the cohort into two subsets according to the concomitant presence of further major organ manifestations. In the majority of children, ocular inflammation was associated only with minor manifestations of the disease. Neurological and vascular manifestations were observed in two patients each and gastrointestinal lesions only in one patient. These findings align with the distribution of clinical symptoms among pediatric clusters identified by Demir et al. In their study, the majority of patients with eye symptoms were categorized in the ocular-only group, while a lesser number were placed in the vascular-neurological group (178).

Moving to the ocular manifestations recorded in the 45 affected eyes, we found that uveitis was far the most common, affecting 86.7% of them, with two-thirds having bilateral inflammation. The anatomical classification of uveitis revealed that posterior uveitis and panuveitis were the most common forms (40% each), while anterior uveitis was reported only in a minority of cases. Bilateral posterior uveitis was recognized as the most common type of uveitis in jBD by the metanalysis conducted by Turk et al (174). Interestingly, factors like age at disease onset and gender appeared to impact the type of uveitis observed. Males and those who experienced a later disease onset (around the age of 14) were more likely to have posterior uveitis. Conversely, anterior uveitis was predominantly observed in those with an early systemic onset (around the age of 9), and consequently a longer delay before the appearance of ocular symptoms. The association of posterior uveitis with male sex was already reported in the PEDBD and the Iranian cohorts (71,107). Similarly, Sungur et al. observed a greater prevalence of anterior uveitis in children under the age of 10 compared to older pediatric age groups, with anterior uveitis being the predominant type in the younger group (120). Moreover, it's noteworthy that the distribution of anterior, posterior, and panuveitis in further jBD cohorts seems to align with this age- and gender-related trend (112,174). Nonetheless, these initial observations warrant further investigation with a more numerous sample size. Retinal vasculitis was the second most frequent ocular manifestation, reported in 37.8% of children, along with posterior uveitis or panuveitis. The prevalence was similar to that reported by Shahram et al. in the Iranian jBD cohort (107); it was lower in the Italian cohort (6.4%), which is reasonable given the high prevalence of anterior uveitis as discussed above (112); on the contrary, it was remarkably higher in the Israel series published by Ostrovsky et al. where non-occlusive retinal vasculitis was observed in 79.5% of cases, in parallel with the high prevalence of posterior uveitis or panuveitis detailed in that cohort (176). Differently from what was observed by Shahram et al., the frequency of retinal vasculitis was not influenced by sex (107).

In jBD, typical findings at the ophthalmological examination encompass shifting hypopyon, vitritis, retinal vasculitis, and retinitis. However, based on comprehensive imaging studies involving both adults and children with BD, it's crucial to closely monitor alterations in the thickness and structure of the choroidal and retinal layers. Balbaba et al. observed an increased subfoveal choroidal thickness in jBD patients with ocular involvement, a finding already known from adult studies (190,191). Also, they described two children with atrophic maculae and associated decrease in CMT (190). Since the choroid is a vascular layer, variations in its thickness can serve as a reliable indicator to assess the response to inflammation. On the other hand, a reduction was noted also in patients with long-standing disease, potentially due to choroidal fibrosis (192). In the study by Coskun et al., patients with identified macular atrophy exhibited a reduced mean CMT. This atrophy was attributed to retinal ischemia from repeated, unresponsive ocular flare-ups and also to a possible effect of subfoveal choroidal atrophy (192). Unfortunately, due to numerous missing entries in our data collection, we could only offer a descriptive overview of the available instrumental findings. The paucity of in-depth instrumental data might be attributed to the limited representation of ophthalmology units among the centers participating in the study. Indeed, most records were entered by rheumatologists, pediatricians and internal medicine specialists who relayed ophthalmological data indirectly. Another potential reason could be that children are subjected to instrumental exams primarily during the acute phase of the disease to prevent unwarranted medical interventions. However, this hypothesis seems less likely given that the recorded instrumental data frequently showed normal results for OCT, fundus examination, and FFA, confirming that, also in a pediatric context, instrumental exams are deemed a crucial component of disease monitoring. In detail, macular OCT exams revealed several alterations, including diffuse intraretinal fluid, intraretinal cysts, spongy edema and tractional epiretinal membranes, and showed a slight reduction of mean CMT from the enrolment in the registry up to the last follow-up available. Considering the follow-up duration around seven years and the concomitant improvement in median

BCVA, this latter observation aligns more with a physiological reduction of the macular thickness during growth or a positive therapeutic outcome, rather than being attributed to macular pathologic alterations.

We adopted the ASUWOG scoring system for a standardized description of FFA findings available for a small subset jBD children, an approach not seen in any previously published series to the best of our knowledge. The mean ASUWOG score at the first assessment available was 17.9 (15.5) (possible range from 0 to 40), representing a moderate extent and severity of retinal inflammation, with macular edema, retinal vascular staining or leakage in posterior pole arcades and optic disc hyperfluorescence being the most frequent findings, followed closely by peripheral retinal vascular staining or leakage. On the contrary, retinal neovascularization and retinal nonperfusion were rarely recorded. In the series published by Ostrovsky et al., retinal vascular occlusion was observed in 20.5% of cases, with peripheral occlusions accounting for two thirds of them (176).

Our findings indicate that a substantial portion of the morbidity associated with ocular jBD arises from its complications. Indeed, the presence of complications in general and, in detail, macular edema, cataract, and/or posterior synechiae were identified as risk factors linked to a reduced final BCVA. Also, complications were significantly associated with the development of permanent changes in the anterior or posterior segment of the eye. In our cohort, over half of the affected eyes exhibited complications, with these three conditions being the most prevalent, followed by a plethora of less common findings of various degree of severity. The prevalence of cataract was estimated around 15% in all children affected by jBD by the metanalysis conducted by Turk et al., and optic atrophy was the second most common ocular complication (around 8%) (174). In the series described by Sungur et al. stratifying patients according to the age at jBD onset, the primary complications identified were cataract, glaucoma and maculopathy; while there were no significant differences in the incidences of cataract and maculopathy across the age groups, secondary glaucoma was notably more prevalent in the late-adolescence group compared to the pre- and mid-

adolescence groups; additionally, the occurrence of band keratopathy was significantly higher in the pre-adolescence group compared to the others, being anterior uveitis more frequently identified before the age of 10 in this cohort (120). In other cohorts with varying prevalence of anatomical involvement of the uveal tract, they observed a different prevalence of the aforementioned complications, as well as additional ones such as epiretinal membrane, retinal atrophy, vitreous hemorrhage, and retinal detachment (177). As expected, we observed that individuals with frequent ocular relapses and prolonged systemic CS treatment exhibited more complications, potentially caused by the recurrent inflammatory insult and side effects of steroid therapy. Interestingly, children who experienced ocular symptoms at an early age faced a higher incidence of complications, regardless of the actual disease duration when complications were documented. With this regard, in the study by Sungur et al, no significant differences were observed among pediatric age groups (<10, 11-15 and 16-20 years) in the incidences of cataract and maculopathy; secondary glaucoma was markedly more frequent in the older group, and band keratopathy in the younger one (120). It warrants further validation with a more extensive cohort analysis, especially considering its potential significance in identifying patients who may benefit from more regular ophthalmological assessments.

Moving to the therapeutic information, our data underscores the complexity of treating BD-associated ocular inflammation in children. A wide range of molecules, including CS and both conventional and biologic immunosuppressors, were employed to manage the disease. A substantial proportion of children (74.1%) received systemic CS treatment, primarily via oral administration. Considering the relatively short duration of the ocular disease (median 7.5 years), this trend is less likely due to historical practices. Instead, it indicates that systemic CS continues to be a cornerstone in the current management of ocular jBD. We noticed a preference for the usage of low-to-moderate dosages of systemic CS (median 0.5 mg/kg/day of prednisone) for a long treatment period (median 17 months). Our findings align with several prior studies that confirm the ordinary use of systemic CS in

40-100% of children with ocular jBD (120,150,176,178). This is despite the well-recognized association of systemic CS with the development of cataracts and ocular hypertension, as well as its significant systemic side effects. Among the conventional DMARDs, AZA, CsA, and MTX were administered in 39%, 30%, and 22% of cases, respectively, with other agents being seldom prescribed. While AZA and CsA are recommended for ocular jBD by the EULAR and the French recommendations, the use of MTX is not encouraged as a monotherapy (75,151). Nevertheless, in the clinical practice it is often prescribed along with monoclonal TNFα inhibitors to minimize the risk of secondary failure due to anti-drug antibodies development, a practice derived from their use if other diseases. However, in our cohort, MTX was prescribed as a combination therapy only in half cases. Moreover, it was more commonly used for anterior uveitis than for posterior or panuveitis. Considering the prevalence of anterior uveitis in younger children in this study, as previously discussed, another potential explanation could be pediatricians' familiarity with MTX, derived from its application in juvenile idiopathic arthritis-associated uveitis. In fact, in the series by Ostrovsky et al., MTX was predominantly used by patients with juvenile-onset, while AZA was the preferred drug for young adults and the elderly, despite the fact that anterior uveitis was primarily observed in the elderly (176). Finally, the possibility of a physician’s personal preference or that other BD manifestations, such as arthritis, known to appear early during the disease course, may have driven the therapeutic choice cannot be excluded.

Regarding bDMARDs, the monoclonal TNFα inhibitor ADA was remarkably favored, followed by IFX. The use of other molecules inhibiting TNFα or leveraging different mechanisms of action was anecdotal. The preference for monoclonal TNFα inhibitors over ETN in jBD is supported by the international treatment recommendations (75,151). It has to be acknowledged that the only randomized controlled trial on TNFα inhibitor use in BD was conducted with ETN in 2005, which found ETN effective in suppressing mucocutaneous lesions in BD (193). Nevertheless, the preference for ADA and IFX relies on data from recent metanalyses and mirrors studies on other inflammatory

diseases, which suggest a superiority of monoclonal anti-TNFα agents over ETN for ocular manifestations (150,194-198).

Finally, in our cohort, nor the presence of major organ involvement neither any specific systemic manifestations independently influenced therapeutic decisions. On the contrary, the use of bDMARDs, and specifically TNFα inhibitors and ADA, was significantly associated with the detection of ocular complications, although our data didn't allow to investigate further the temporal relationship between the occurrence of each complication and the start of treatments. Nevertheless, it seems reasonable to infer that, in clinical decision-making, ocular manifestations are prioritized by physicians when formulating therapeutic strategies, as already observed by Batu et al (150).

While comprehensive long-term prospective studies on jBD prognosis are lacking, ocular complications appear to be the predominant disability factor. However, vascular, neurological, and intestinal manifestations also play a significant role in elevating morbidity and mortality (94). In this study, the severity of jBD-associated damage was evaluated through the total BODI score at the last follow-up visit resulting in a low-to-intermediate severity (median BODI of 1.5, ranging from 0 to 5 in our patients). Although there are no clear cut-offs to define the severity of damage according to the BODI score, damage accrual over time was defined by the authors themselves as an increase of at least one point in the BODI score (199). In our cohort, the BODI score at the last follow-up visit inversely correlated with the age at onset of ocular inflammation (but not with the age at onset of the systemic disease), and it was higher in children with bilateral ocular involvement. These observations indirectly hint at the significant impact of ocular disease on the overall prognosis in children. However, from a wider viewpoint, the influence of disease onset age on general prognosis remains unclear, given the inhomogeneous findings across studies, which could also be influenced by the disease relapsing-remitting course (101,104,149,174,200,201).

Regarding the oculo-specific items of the BODI, over 70% of eyes showed some degree of ocular damage by the end of the follow-up, with specific damages including, in descending order of frequency, visual impairment,

changes in the posterior or anterior segment, cataract and unilateral or bilateral blindness. Children with an earlier onset of BD-associated ocular inflammation were more likely to develop permanent changes in both the anterior and the posterior segment, possibly as a consequence of multiple flare-ups, complications, prolonged CS therapy or a more severe clinical phenotype. In addition, a lower BCVA at the last follow-up visit was associated with the presence of HLA-B51, abnormal macular edema, cataract and posterior synechiae, but regression analysis confirmed only HLA-B51 as an independent predictor of BCVA reduction, as previously discussed. Unilateral or bilateral blindness affected 22% of children (15% of eyes). Children who eventually became blind in at least one eye already had a reduced BCVA at the first assessment available in the registry, indicating an aggressive ocular disease, similarly to what has been observed by Ostrovsky et al (176). In addition, we observed an association between unilateral or bilateral blindness and the presence of macular edema and posterior synechiae. In a Japanese series of ocular jBD patients presented by Kitaichi et al., the percentage of blindness was notably lower at 7.4% of children, and the visual prognosis was significantly better compared to the adult series detailed in the same study (202). Irreversible BCVA less than 0.1 was found in 10% and 6.1% of affected eyes according to Kramer et al. and Ostrovsky et al., respectively (176,203). In the PEDBD cohort, a severe ocular prognosis was described for 12.3% of all jBD patients whose BCVA was less than 0.1 but only 1.4% of all jBD children had permanent blindness (71).

This study provides a thorough description of BD-associated ocular manifestations in the pediatric age based on an international registry cohort. Given the rarity of the syndrome and the specific focus of the research, such a comprehensive analysis adds valuable information to the existing literature, which may be leveraged to potentially guide clinical practice and future research. The duration of the follow-up was long enough to detect ocular complications and allow prognostic evaluations. Also, the use of objective measures, like the BODI for disease-related damage and the ASUWOG score to describe FFA findings, reduces the potential for bias and enhances the

replicability of the findings. On the other hand, we acknowledge a number of limitations which may potentially have influenced our findings. The study cohort was relatively small with imbalanced ethnicities (mostly Caucasic and, to a lesser extent, Arab), potentially limiting the generalizability of our findings to the broader population of children with ocular jBD. Potential recall bias, missing data and inexact correspondence between the retrospective and prospective sheets of the registry may have affected the accuracy and completeness of the records. Regrettably, reliable information about growth and pubertal development were lacking. To overcome the issue of missing data, imputation was needed for a small number of analyses, potentially reducing the accuracy of the results. For prognostic and therapeutic outcomes, including a control group of children with jBD but without ocular involvement would have enhanced the robustness of our findings, although a direct comparison between subjects with and without ocular inflammation was not the primary objective of this study. Also, the exclusion of jBD patients who developed ocular inflammation in adulthood precluded the opportunity to complete the entire spectrum of ocular manifestations in jBD within the current research. Some of these limitations may be addressed in future studies based on the AIDA Network BD Registry.

In conclusion, we conducted a thorough analysis of all children and adolescents with ocular jBD registered in the AIDA Behçet's disease registry. For most of them, ocular disease was the driving manifestation of jBD, evident in both their clinical phenotype—with few having other major organ involvement—and in their therapeutic management. While about 40% of children with jBD may incur in ocular inflammation at some point in their life, for only 13% it may happen before 18, explaining the inconsistency of the prevalence of ocular jBD in the literature. Age and sex seem to be important players in the game, but their role has still to be elucidated. Based on our findings, male adolescents appear to develop posterior uveitis either at or shortly after the onset of the disease. In contrast, anterior uveitis is more common in those who experience systemic symptoms before the age of 10. However, for this group, ocular inflammation typically manifests about three

years later. In the light of these observations, it may be beneficial to implement routine ophthalmological screenings for pediatric patients with BD, especially during mid- to late-adolescence. Establishing a functional partnership between the pediatric rheumatologist and the ophthalmologist could enhance early detection and management of ocular manifestations. In this view, we introduced objective measures of the ophthalmological findings by standardizing the description of OCT and FFA results and constituents of ocular damage, which is uncommonly found in the literature on jBD. Regrettably, the therapeutic management of ocular jBD still heavily rely on CS and a current trend to use low-to-moderate oral dosages for extended treatment courses was intercepted. Considering the wide array of therapeutic choices available, encompassing both conventional and biologic DMARDs, and in alignment with recent treatment guidelines, this approach should be strongly discouraged. Instead, a preference for short-term, moderate-to-high CS courses during acute disease phases is recommended. Chronic use of low-to-moderate doses of CS is known to result in delayed growth and pubertal development, the onset of iatrogenic Cushing's syndrome, and various organ complications. Notably, some of these ocular complications have been identified as determinants of visual prognosis in both this study and numerous other published cohorts. Robust research is necessary to endorse the use of more targeted therapies able to allow steroid sparing while preventing disease relapses, as a high number of relapses is the primary contributor to the development of ocular complications and permanent structural changes. Also, some of our findings converge on the possible existence of a subgroup of children with early onset BD and pronounced genetic background, who might face a worse global and ocular prognosis. However, due to the limited sample size and variable alignment with prior studies, more in-depth investigations are essential to understand the role of age and genetics while considering potential internal and external confounders.

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## 7. Graphic material

**Figure 1** [Ref. 38]

ERAP1-HLA-B51 interaction in BD. Variants with reduced ERAP-1 activity would lead to the formation of peptides with lower affinity for HLA-B51, as a result of the increase in less affine nonamers and Ala2 peptides at the expense of Pro2 peptides. This is due to the reduced cleavage activity of antigens by the proteasome. HLA-B51 has a lower affinity for longer peptides, such as nonamers, and a reduced affinity for Ala2 peptides. Peptides with lower affinity can adversely affect antigen presentation, thereby causing increased activation of NK cells and altered activation of T cells.

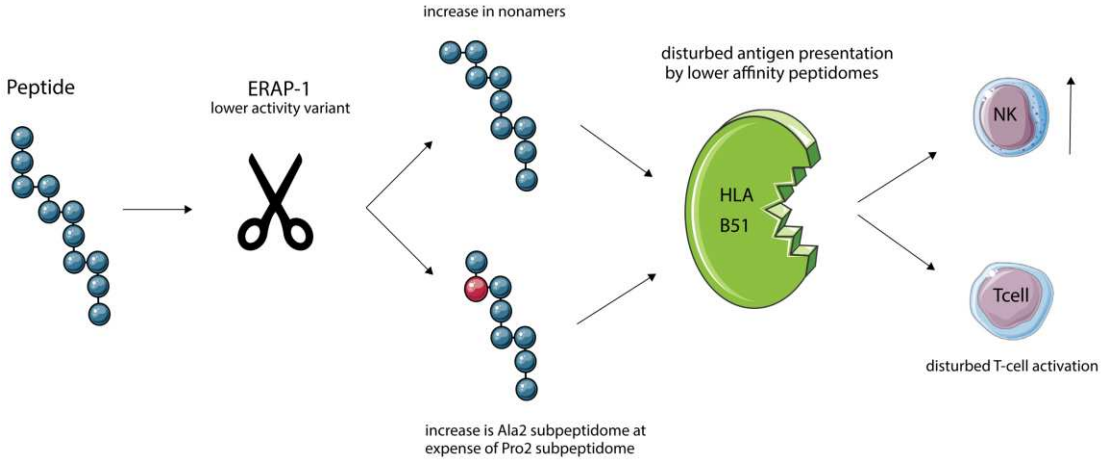
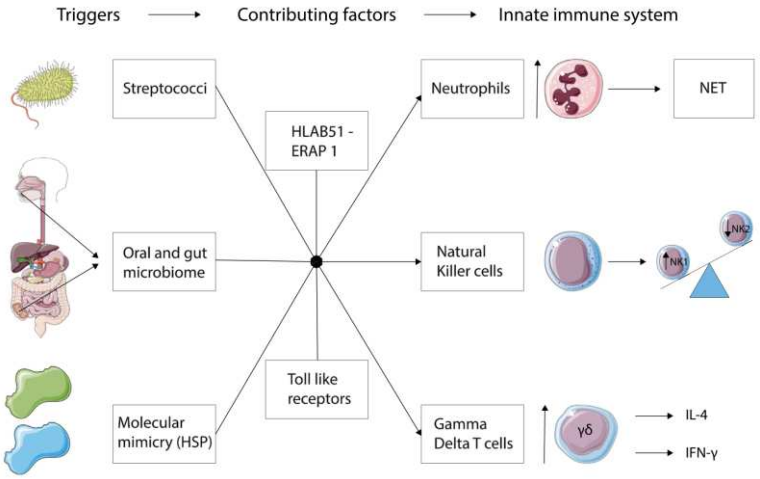


**Figure 2** [Ref. 38]
**a)** Innate immune system in the pathogenesis of BD. Potential triggering factors, such as oral and intestinal microbiome, or molecular mimicry, activate the innate immune system. The increased expression and activity of TLRs, along with potential alterations in antigen presentation due to MHC-I and ERAP-1 polymorphisms, are factors capable of initiating inflammation. Once activated, neutrophils release the NET. NK cells are skewed towards pro-inflammatory NK-1 subpopulations, and there is an upsurge in γδ T cells, which produce IL-4 and IFN-γ.




**b)** Adaptive immune system in the pathogenesis of BD. Th1 cells are increased and activated in response to the stimulus of NK-1 cells, likely influenced by polymorphisms of the IL-12R. Th1 cells produce pro-inflammatory factors such as IFN-γ, TNF-α, and IL-12. The expansion of Th17 cells is driven by elevated levels of IL-23, possibly also influenced by polymorphisms of the IL-23R. Th17 cells produce pro-inflammatory cytokines like IL-17A, IL-17F, and IL-22. There is a decline in T reg, leading to a reduction in anti-inflammatory cytokines IL-10 and IL-35. The decrease in T reg is a consequence of the action of IL-21 secreting cells.

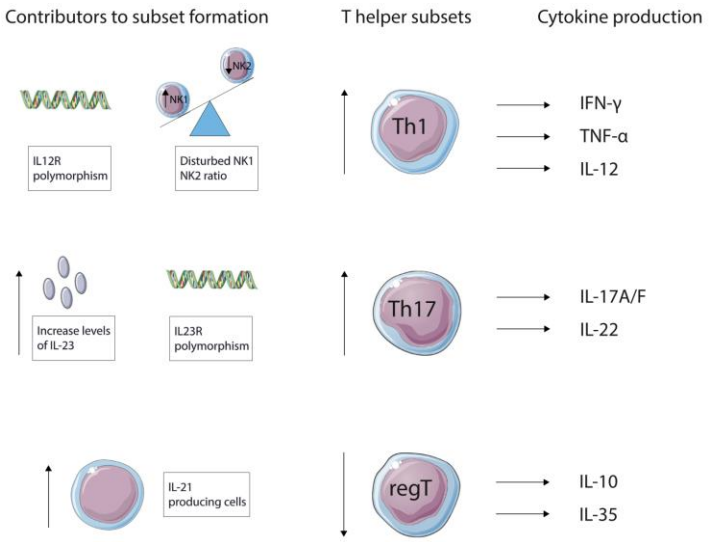


**Figure 3** [Ref. 72]

Diagnostic algorithm based on distinct ocular features for the diagnosis of BD-associated uveitis proposed by Tugal-Tutkun and colleagues.

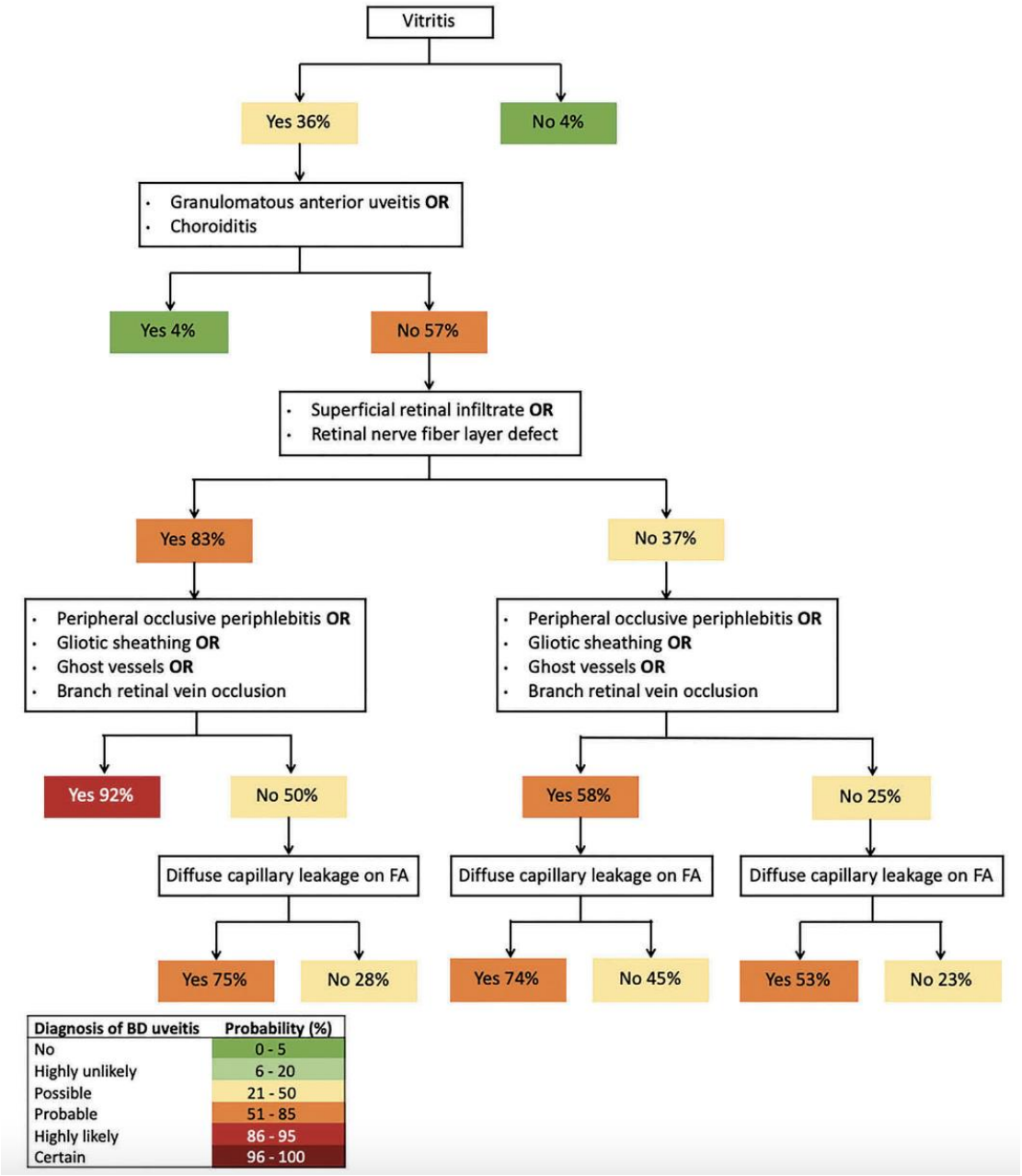


**Figure 4** [Ref. 150]

Chord diagram showing the use of different therapies according to the patient's phenotype in a real-life setting, as resulting from a recent metanalysis by Batu et al.

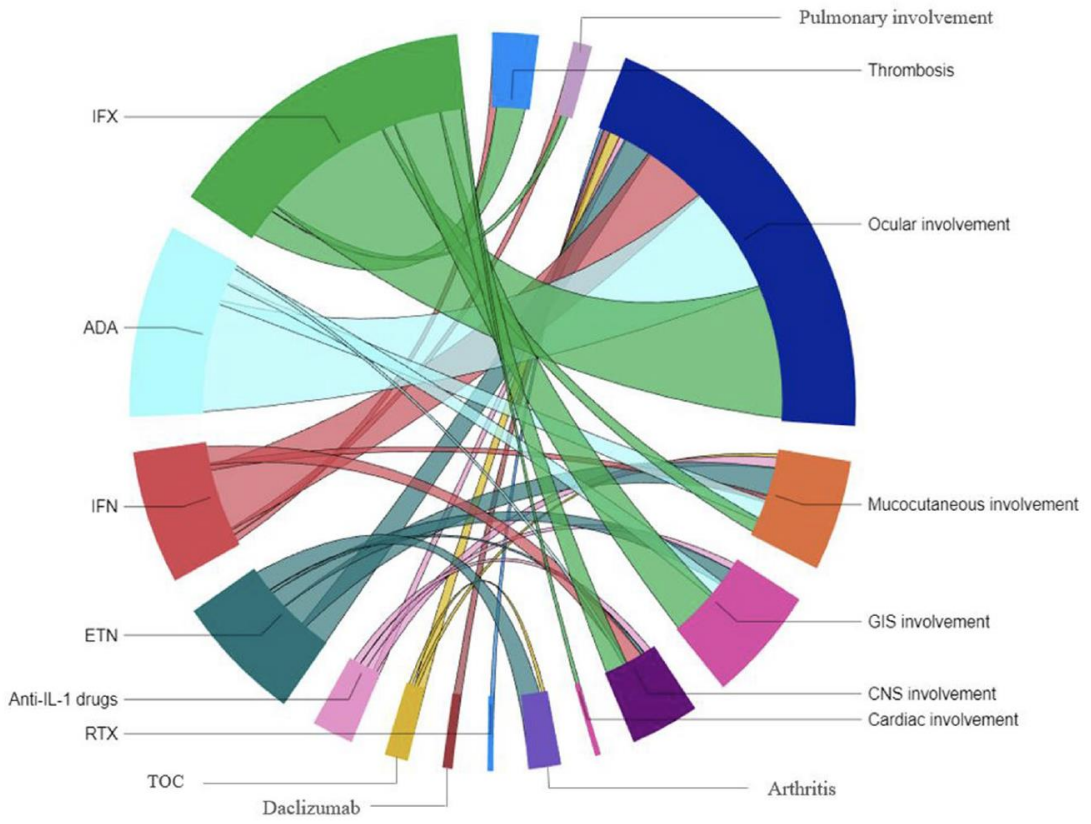


**Figure 5** [Ref. 153]

Graphical representation of the localization of the inflammatory process in cases of anterior uveitis (**A**), intermediate uveitis (**B**), posterior uveitis (**C**), and panuveitis (**D**) according to the criteria proposed by the SUN working group. Figure 5A also shows a schematic representation of the anatomy of the eye. The figure is taken from Sève P et al.

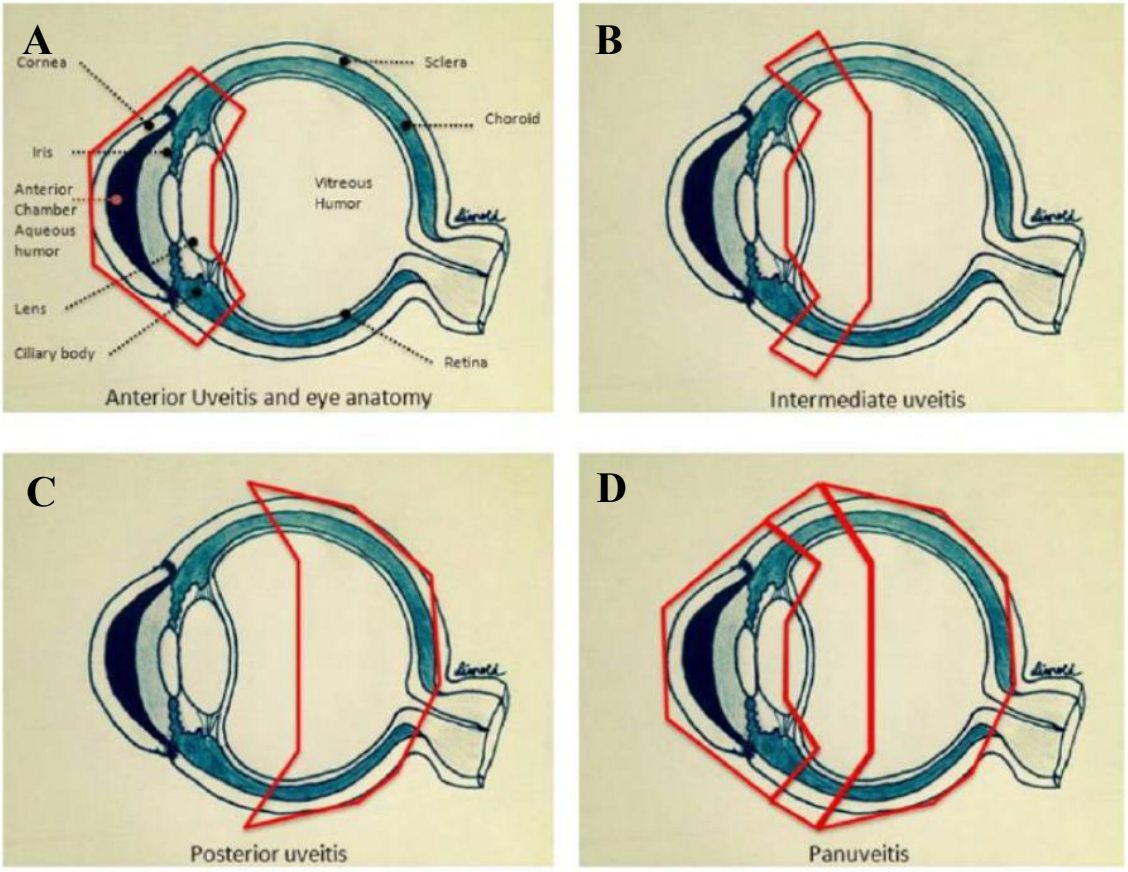


**Figure 6**

A diagram illustrating the patient selection process for the study as of the data lock on September 29th, 2023.

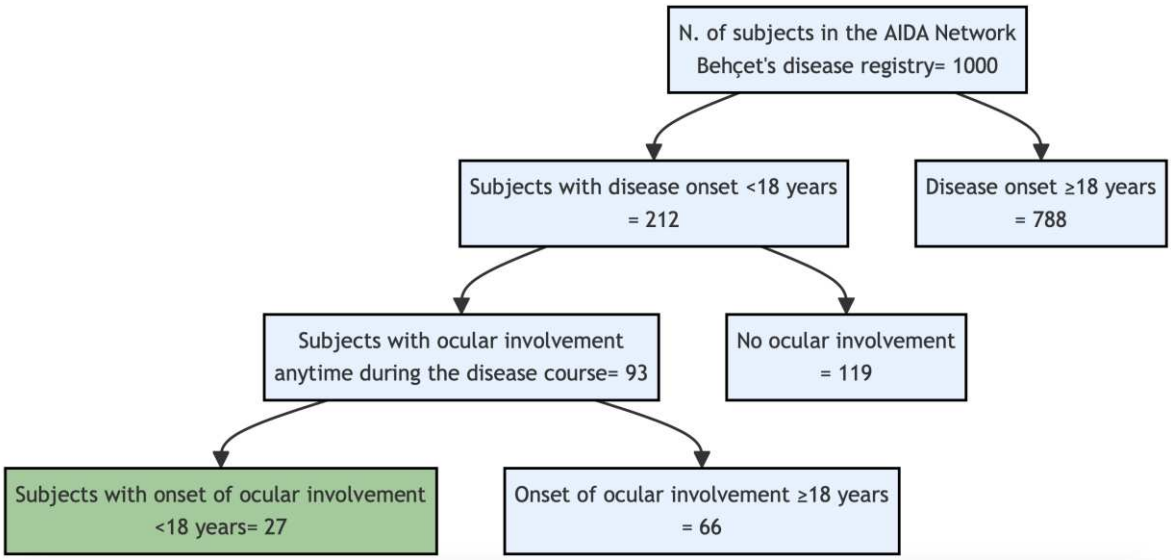
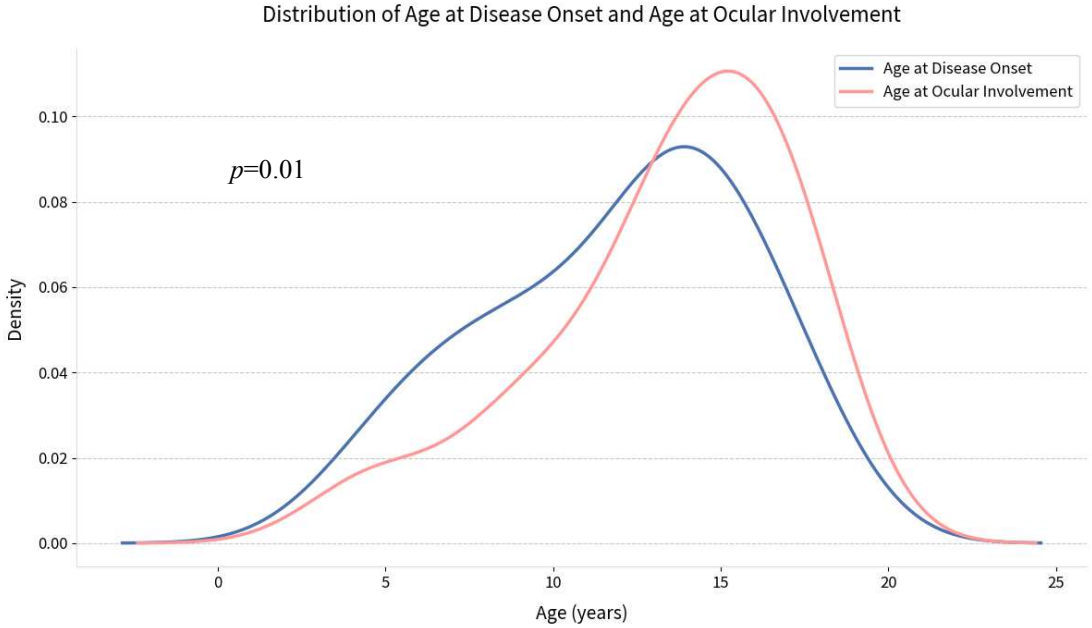


**Figure 7**

**(a)** Distribution of the age at BD onset and age at the onset of BD-associated ocular manifestations in the study group. The difference between the two distributions was statistically significant by paired-T-test with $p$=0.01.




**b)** Scatterplots for age at BD onset and age at the onset of BD-associated ocular manifestations. Subjects are ordered by age at BD onset (ascending order). The delay of ocular involvement is represented by a dashed line and its length is negatively correlated with the age at BD onset with moderate strength (Pearson's r = -0.43; $p$=0.02).

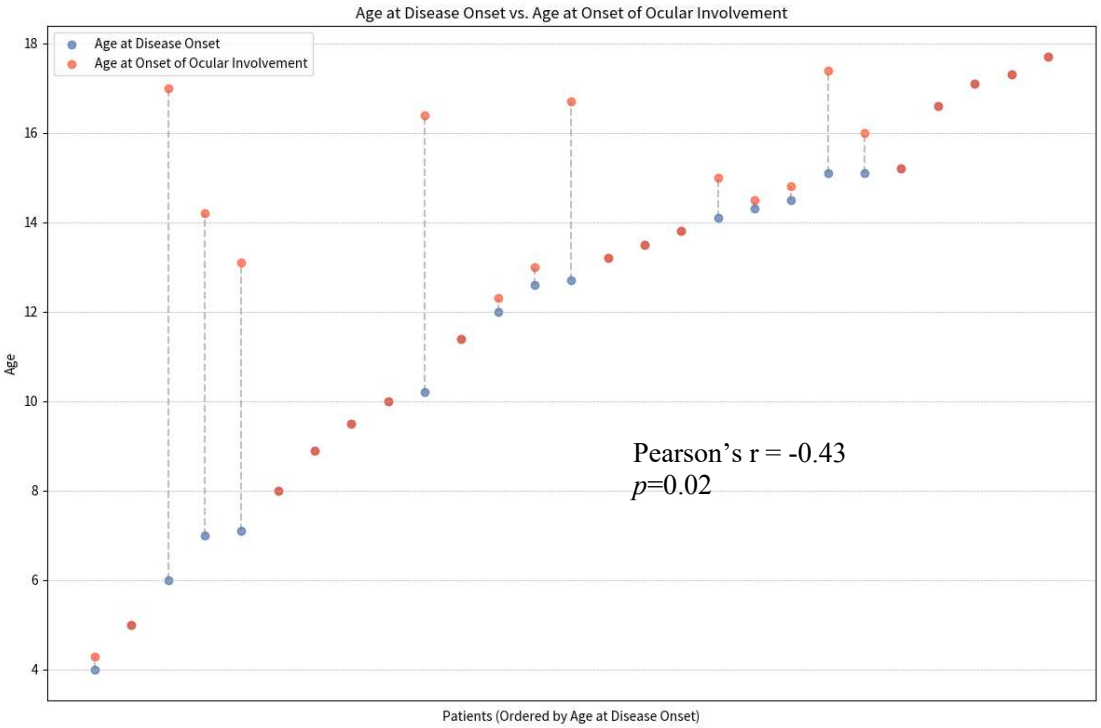


**Figure 8**

Frequency of major organ manifestations and minor symptoms of BD in the study group. The fulfilment of clinical classification criteria for BD and jBD is also represented. Data are presented split by gender, showing statistically significant differences in the frequency of skin manifestations and headache.

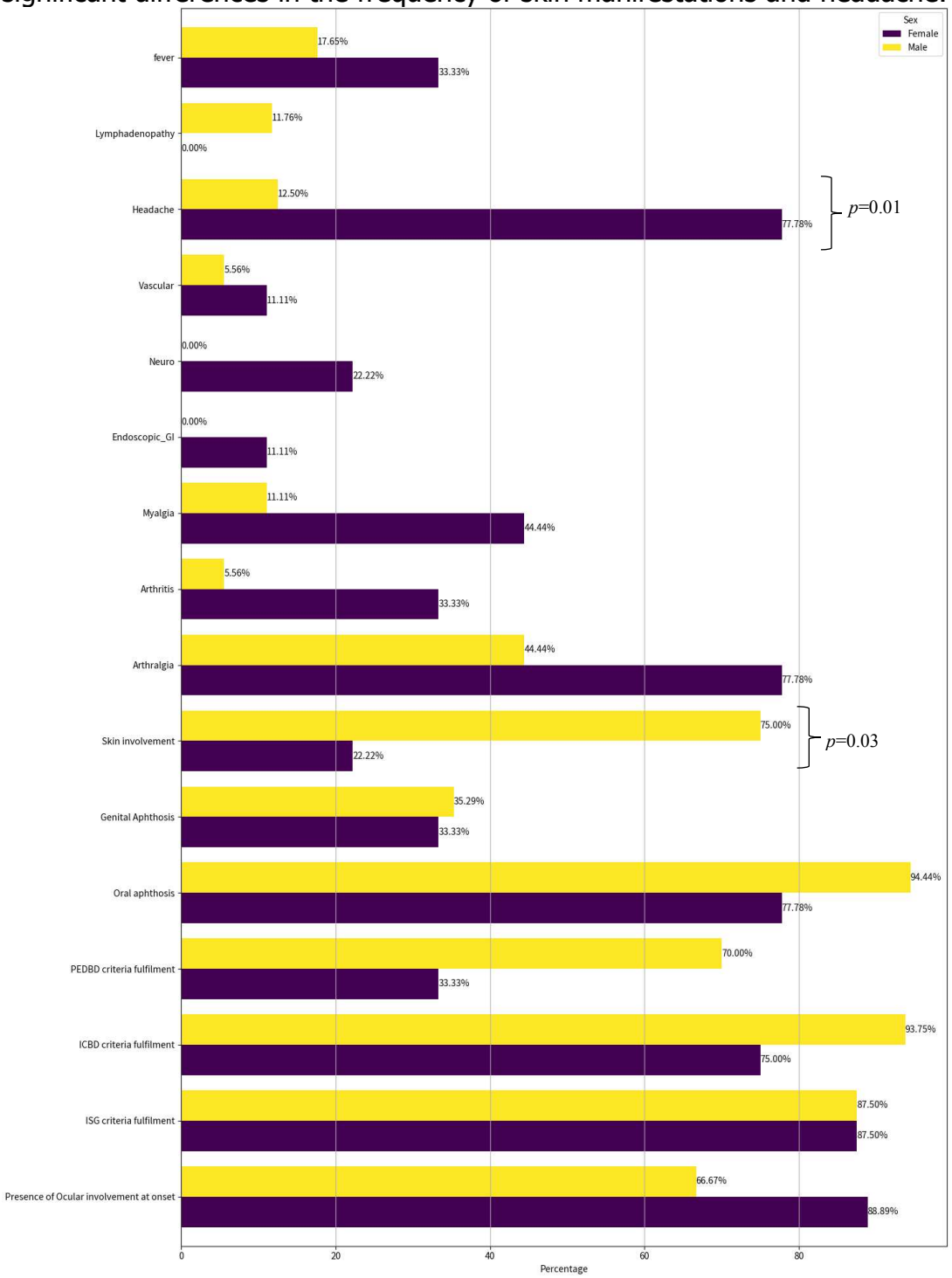


**Figure 9**
Visualization of the different distribution of age at BD onset according to the presence of specific clinical manifestations: arthritis, fever and recurrent genital aphthosis. The difference resulted statistically significant according to the Mann-Whitney test.

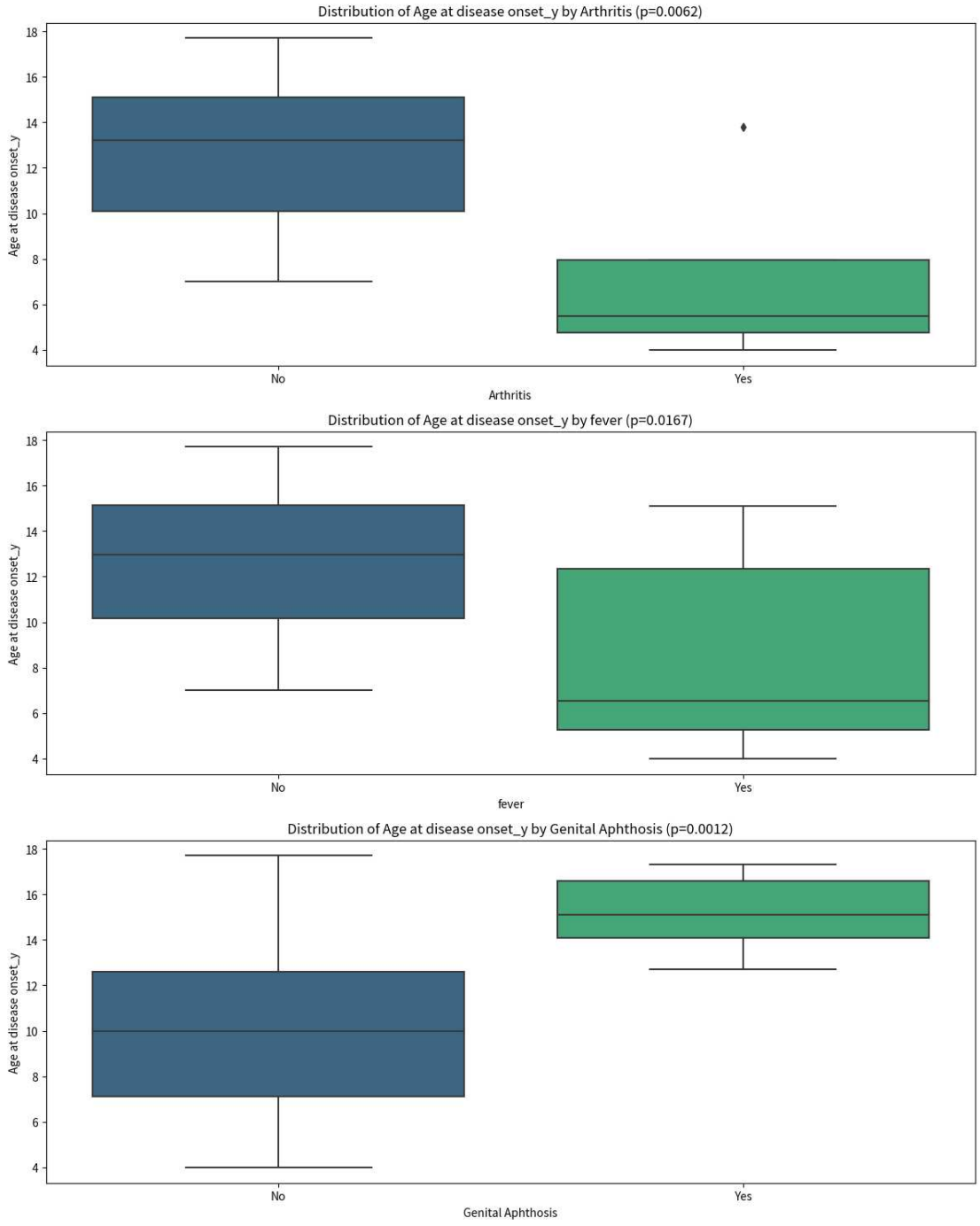


**Figure 10**
Visualization of the distribution of age at BD onset and age at ocular involvement according to the anatomical classification of uveitis.

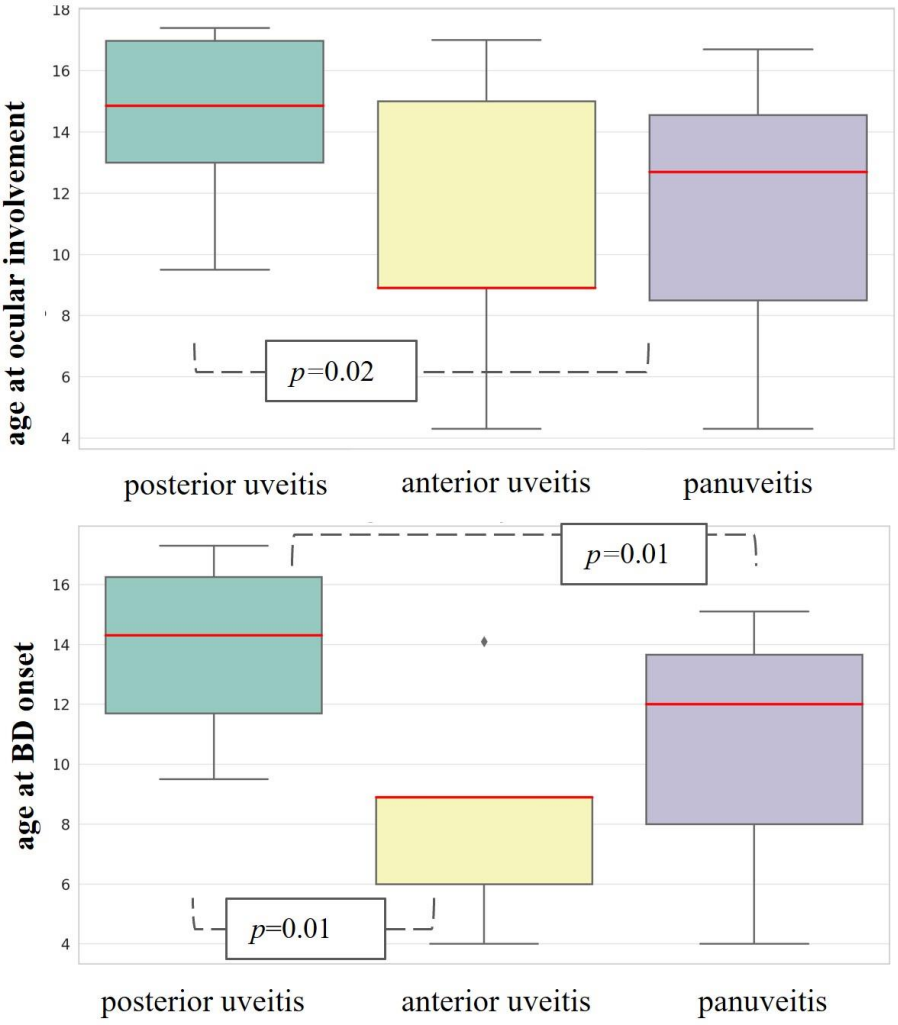


**Figure 11**
The anatomical classification of uveitis was remarkably different between sexes, with a prevalence of posterior uveitis in males.

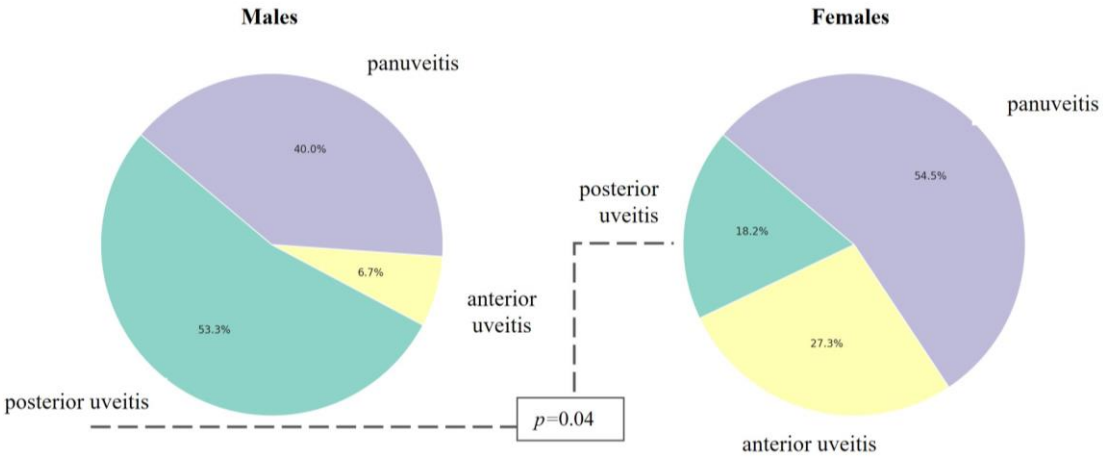



**Figure 12**
Visualization of the distribution of the number of ocular relapses in children with different anatomical patterns of uveitis. The difference among the three groups does not reach statistical significance ($p$>0.05).

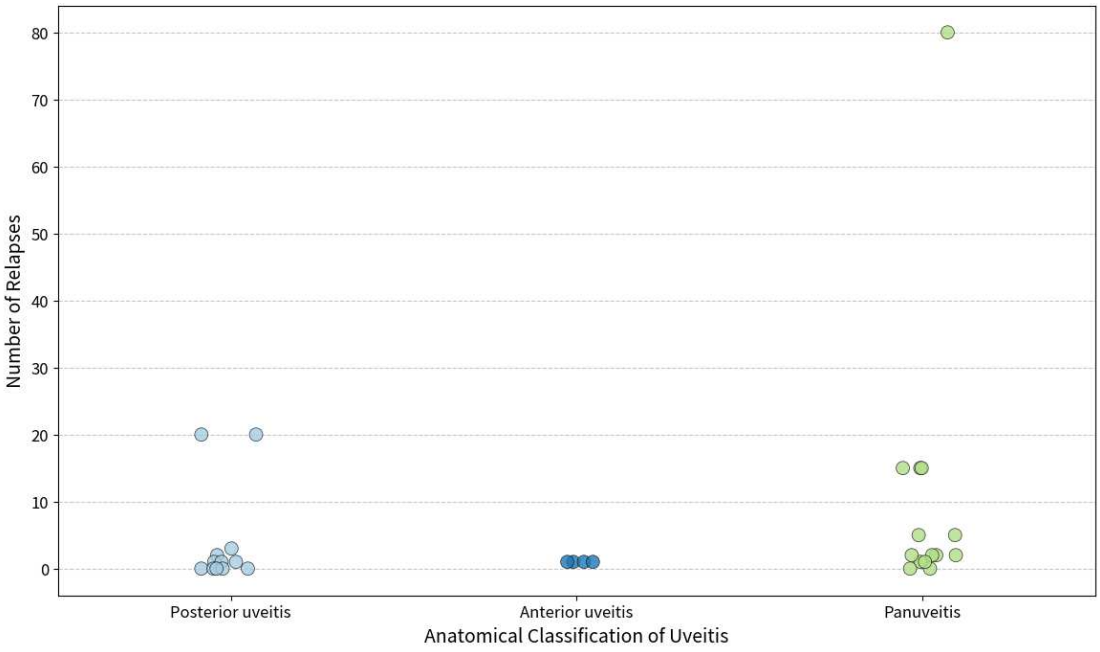
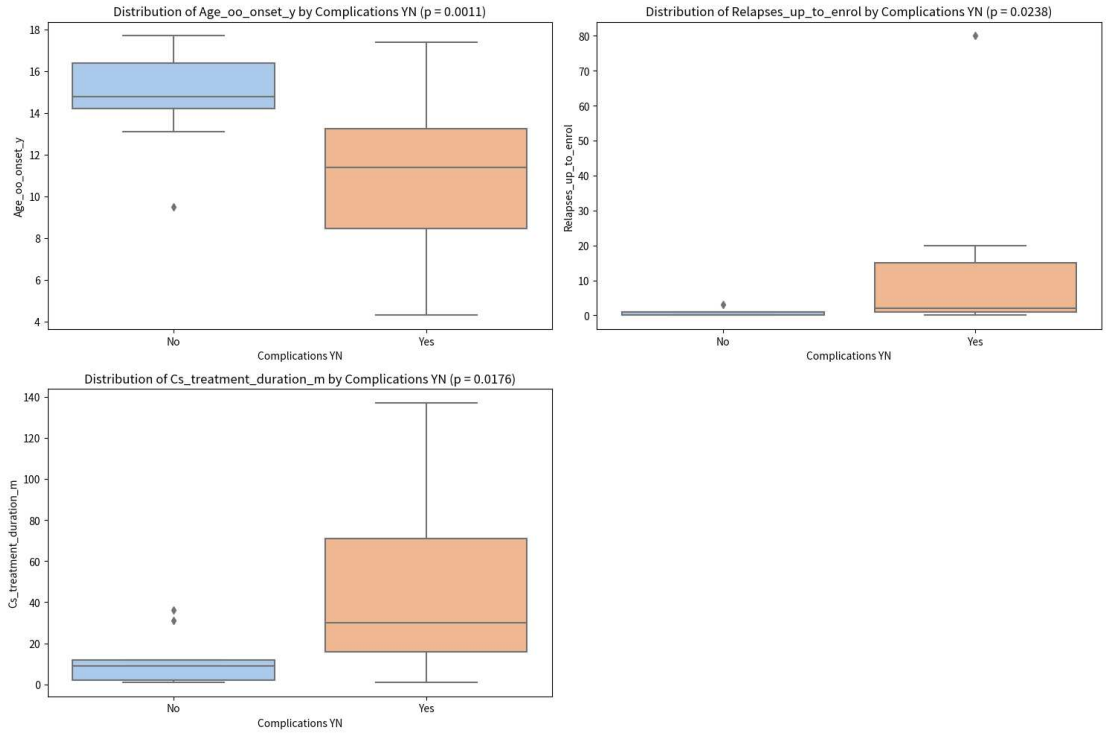


**Figure 13**

**a)** Different distribution of age at the onset of ocular manifestations, number of ocular relapses and durations of systemic CS therapy in subjects with and without ocular complications.




**b)** Association of ocular complications with the use of bDMARDs and TNFα inhibitors.

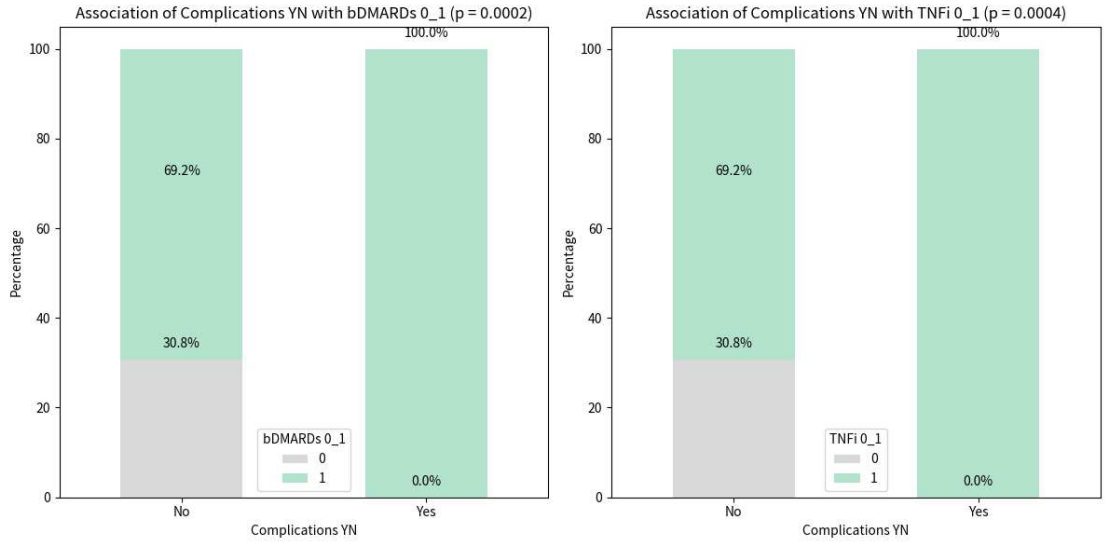


**Figure 14** (courtesy of Dr. Claudia Fabiani)
Ultra-wide field retinal imaging showing findings of retinal vasculitis in a 13 year-old boy **(a)** and in a young adult (22 year-old) as comparator **(b)**.

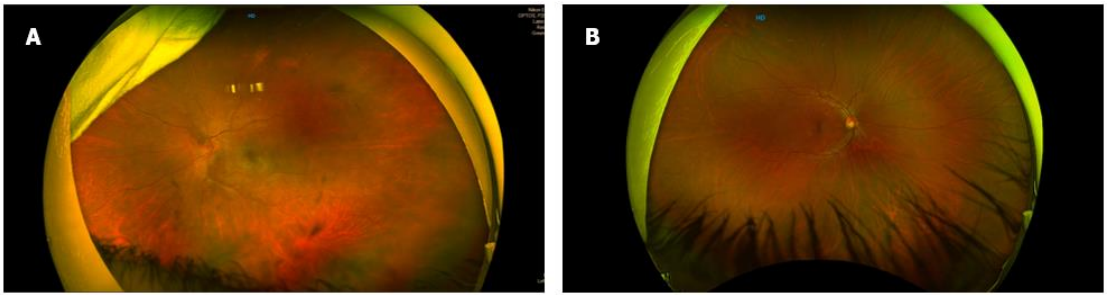



**Figure 15**
Fundus oculi alterations were mostly reported in eyes affected by posterior uveitis and panuveitis, less in case of anterior uveitis. The 2 eyes included in the "None" column ad been affected by retrobulbar optic neuritis, but fundus oculi was normal at the time of the evaluations recorded in the registry. The difference reached the statistical significancy threshold with $p$=0.03.

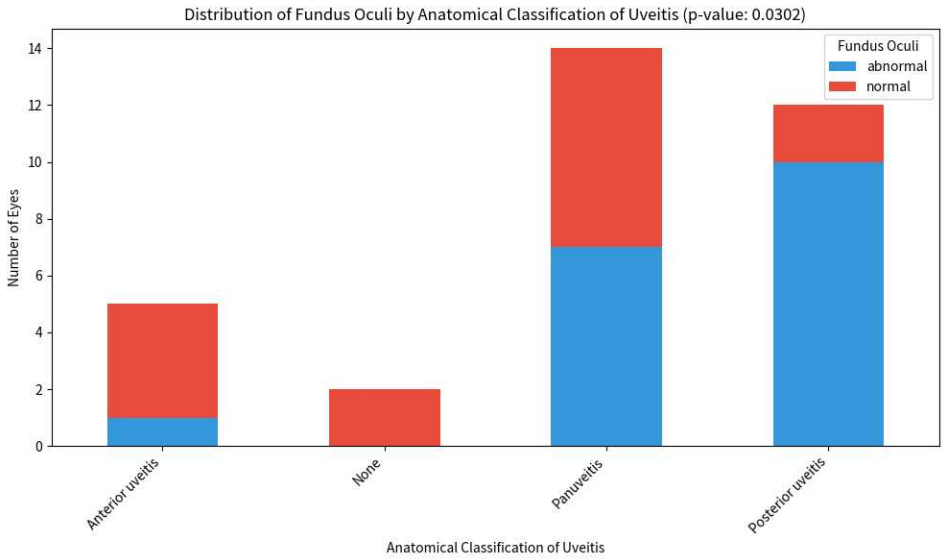
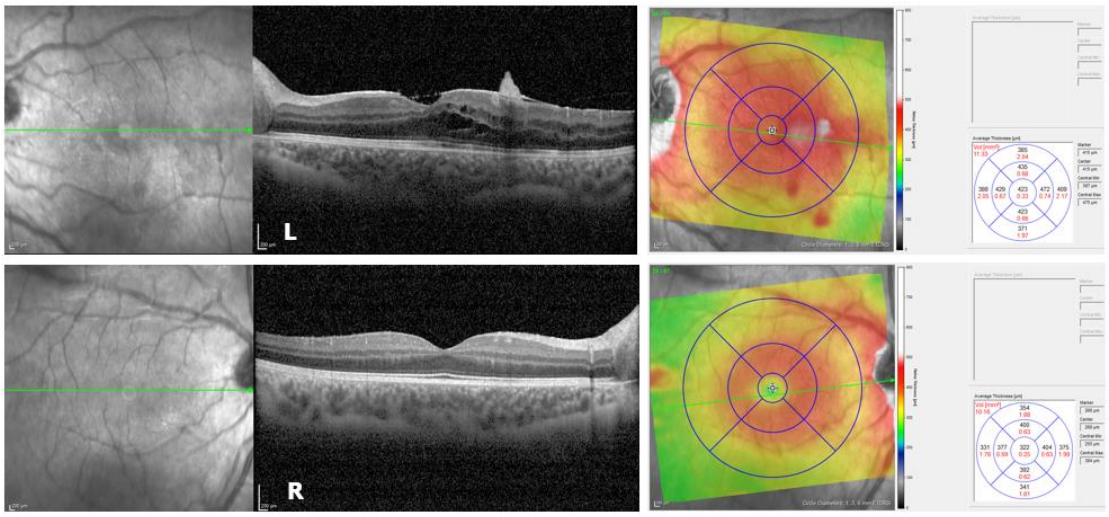


**Figure 16** (courtesy of Dr. Claudia Fabiani)
**a)** The OCT examination shows diffuse macular edema of the left eye in a 13-year-old boy with recurrent vitritis and bilateral retinal vasculitis (the left eye worse than the right one).




**b)** The OCT examination shows left eye epiretinal membrane in a 26 year-old girl as a complication of vitreoretinal inflammation with onset at 4.3 years.

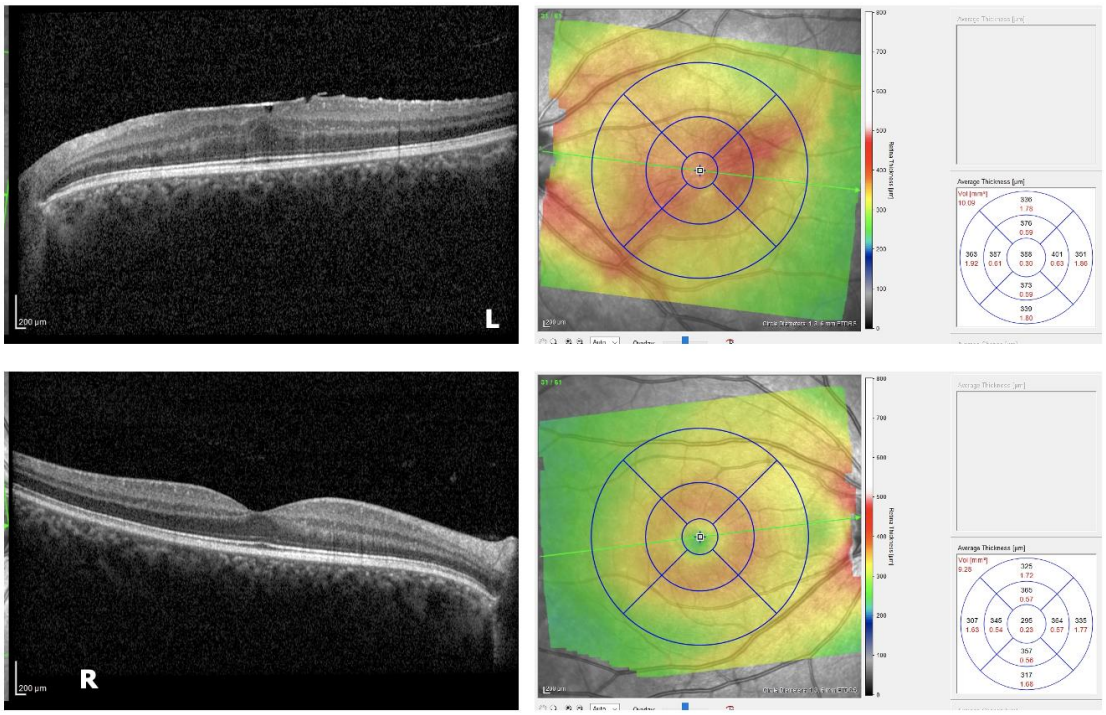


**Figure 17**
Frequency of detection of pathologic findings at the FFA. Percentages are calculated on the total number of procedures performed (19 procedures in 7 eyes).

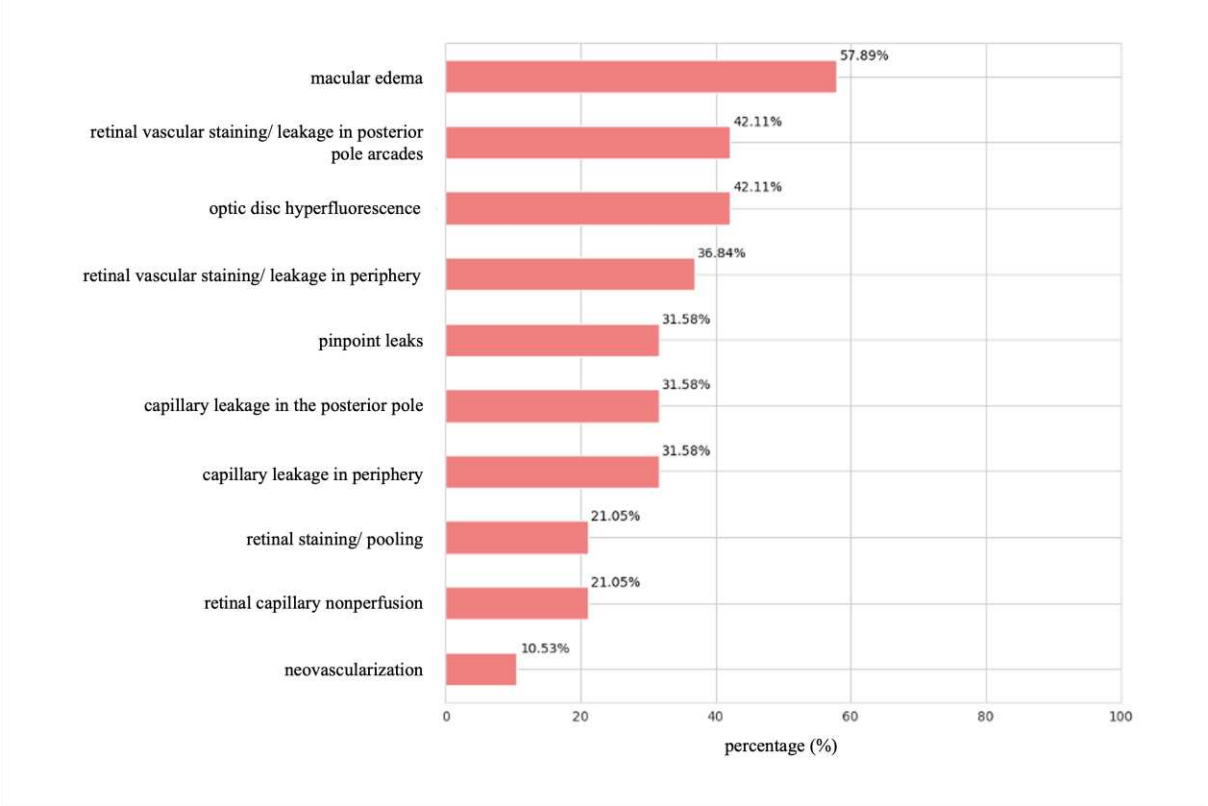
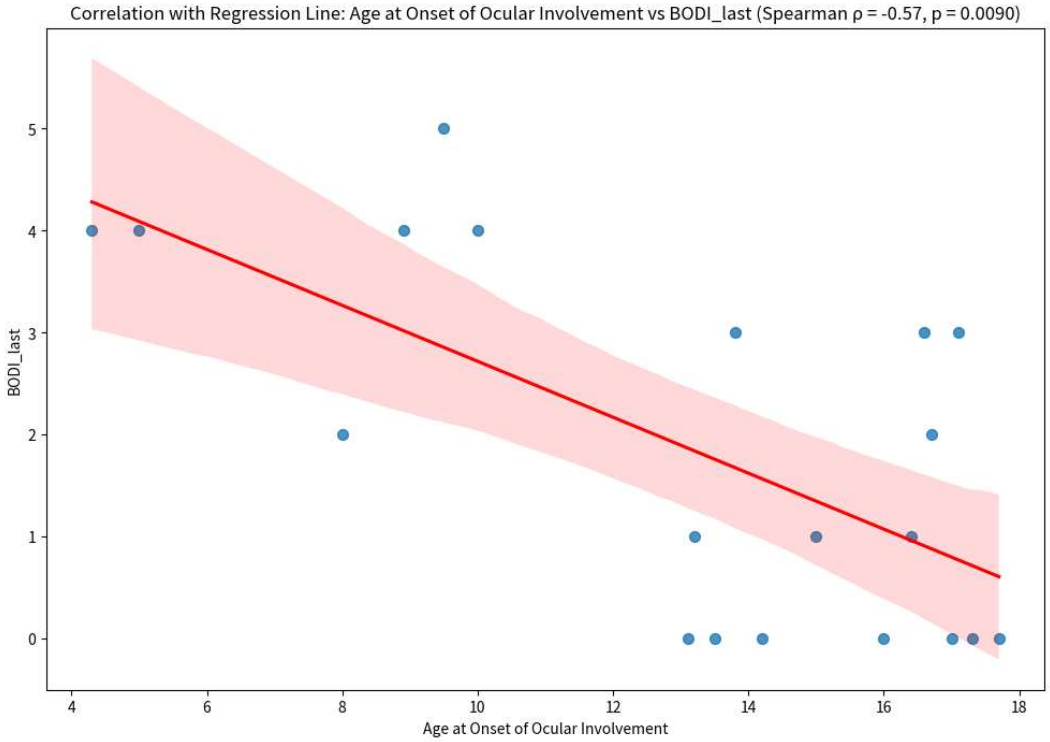


**Figure 18**

**a)** Visualization of the inverse correlation between age at the onset of BD-associated ocular manifestations and total BODI score at the end of the follow-up.




**b)** Children with bilateral ocular involvement had a higher total BODI score at the end of the follow-up than those with unilateral disease.

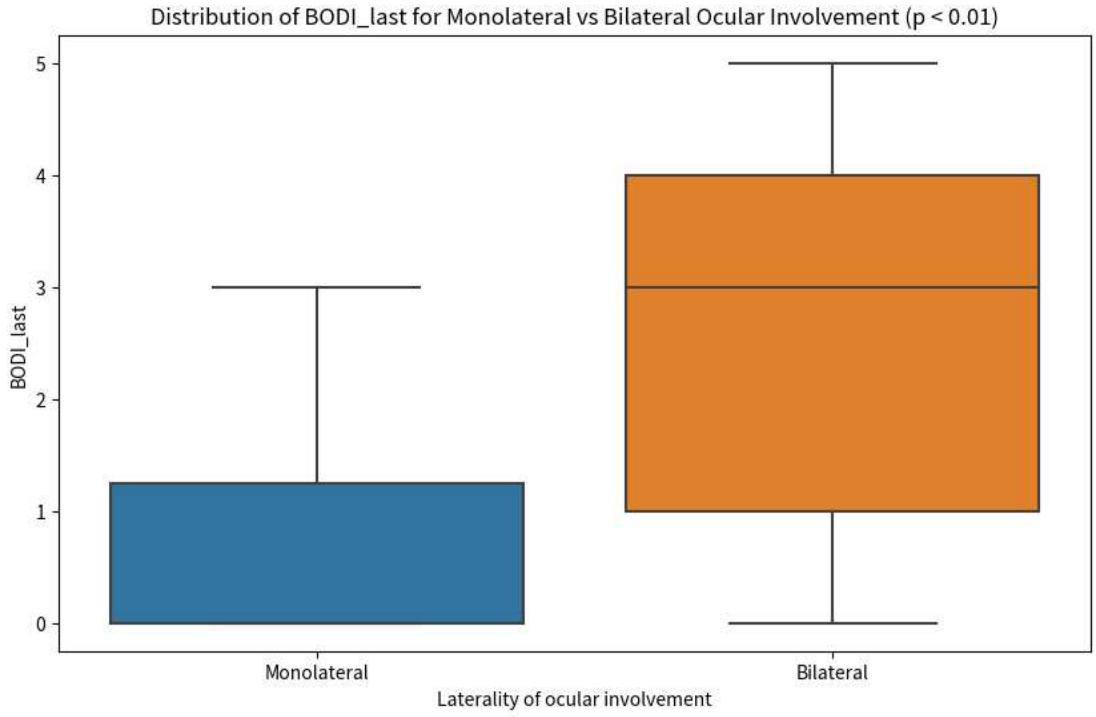


**Figure 19**
The age at onset of BD-associated ocular inflammation was lower in the group of children who developed permanent changes in the anterior segment or cataract during the disease course.

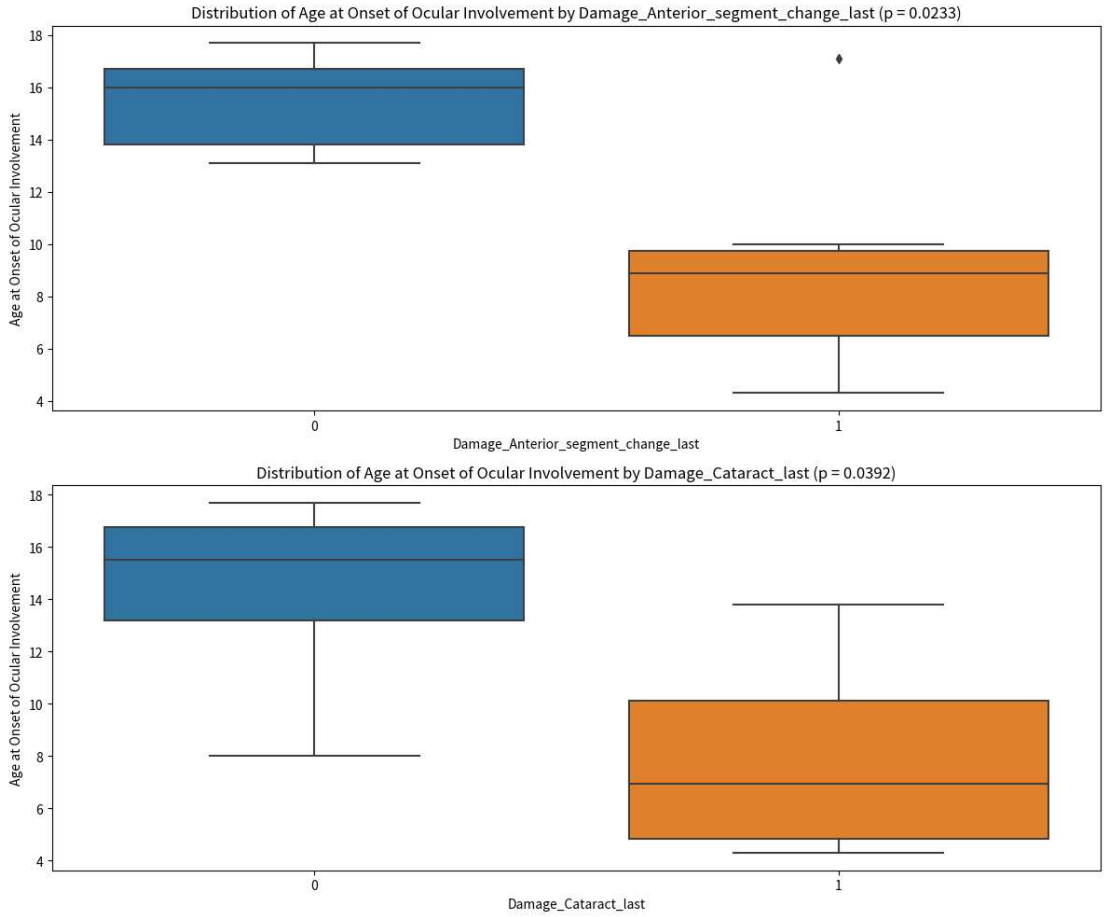
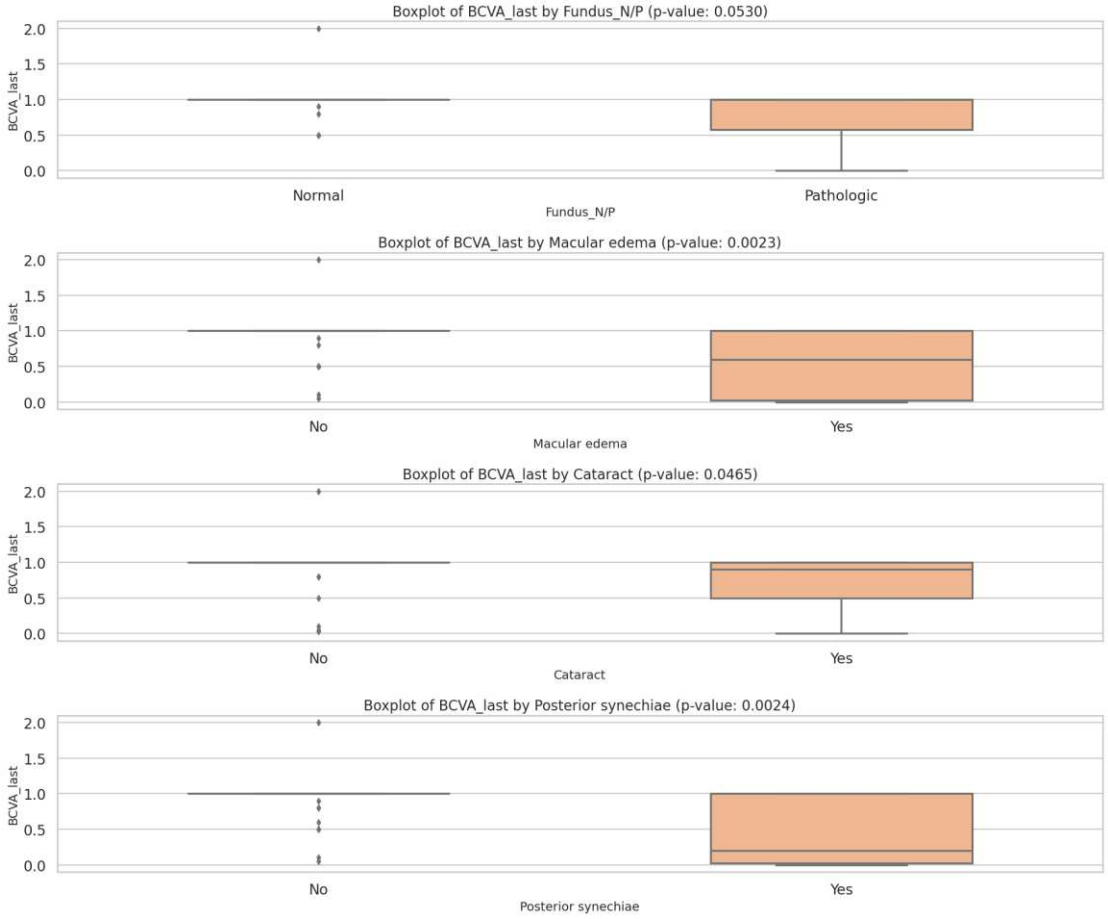


**Figure 20**
Visualization of the variables associated with a lower BCVA at the end of the follow-up: abnormal fundus oculi examination, macular edema, cataract and posterior synechiae. The presence of HLA-B51 was also found in association with a lower BCVA at the last follow-up.



## 8. List of acronyms

ADA, adalimumab
AIDA, autoinflammatory diseases alliance
Ala, alanine
ANA, anakinra
ASUWOG, angiography scoring for uveitis working group
AZA, azathioprine
BCVA, best corrected visual acuity
BD, Behçet's disease
bDMARDs, biologic disease-modifying antirheumatic drugs
BODI, Behçet's syndrome overall damage index
CAN, canakinumab
cDMARDs, conventional disease-modifying antirheumatic drugs
CMT, central macular thickness
CNS, central nervous system
CS, corticosteroids
CsA, cyclosporine A
CYC, cyclophosphamide
CZP, certolizumab Pegol
E, endpoint
ELSI, ethical, legal, and social issues
ERAP, endoplasmic reticulum aminopeptidase
ETN, etanercept
EULAR, European league against rheumatism
FFA, fundus fluorescein angiography
GDPR, general data protection regulation
GOL, golimumab
GWAS, genome-wide association studies
HCQ, hydroxychloroquine
HLA, human leukocyte antigen
HSPs, heat shock proteins

ICBD, international criteria for Behçet’s disease

ICGA, indocyanine green angiography

IFN, interferon

IFX, infliximab

IL, interleukin

IQR, interquartile range

ISG, international study group

jBD, juvenile Behçet’s disease

MHC, major histocompatibility complex

MMF, mycophenolate mofetil

MRI, magnetic resonance imaging

MTX, methotrexate

N., number

NET, neutrophil extracellular traps

NGS, next generation sequencing

NK, natural killer

NSAIDs, non-steroidal anti-inflammatory drugs

O, objective

OCT, optical coherence tomography

OR, odds ratio

PEDBD, pediatric Behçet's disease

PNS, peripheral nervous system

Pro, proline

RNFL, retinal nerve fiber layer

SD, standard deviation

SUN, standardization of uveitis nomenclature

TCZ, tocilizumab

TLD, thalidomide

TLR, toll-like receptors

TNFα, tumor necrosis factor α

Treg, regolatory T cells

Vs, versus

## 9. Annex

**I**

List of the investigator centers enrolling subjects for this study (alphabetical order):

- Ankara - Gazi University, Faculty of medicine
- Athens - Laikon University Hospital - National Kapodistrian University of Athens Medical School
- Bari - Policlinico di Bari I
- Bari - Policlinico di Bari II
- Cagliari - AOU di Cagliari
- Cairo - El Sayeda Nafeesa Hospital, New Giza University, El-Sayeda Zainab, Cairo Governorate; Cairo University
- Ciudad de México - Instituto Nacional de Ciencias Médicas y Nutrición
- Mansoura - Mansoura University, Faculty of Medicine
- Messina - A.O.U. Policlinico G. Martino
- Milano - ASST Gaetano Pini/CTO
- Milano - Ospedale Fatebenefratelli e Oftalmico I
- Milano - Ospedale Fatebenefratelli e Oftalmico II
- Riyadh - King Saud University
- Siena - Azienda Ospedaliero Universitaria Senese

**II**

List of the investigator centers enrolling subjects with juvenile-onset Behçet's disease in the AIDA Network Behçet's disease registry (alphabetical order):

- Ankara - Gazi University, Faculty of medicine
- Ankara - Hacettepe University Faculty of Medicine
- Athens - Evangelismos General Hospital
- Athens - Laikon University Hospital - National Kapodistrian University of Athens Medical School

- Bari - Policlinico di Bari
- Brescia - ASST degli Spedali Civili di Brescia
- Bucharest - Sf. Maria Hospital - University of Medicine and Pharmacy "Carol Davila"
- Cagliari - AOU di Cagliari
- Cairo - El Sayeda Nafeesa Hospital, New Giza University, El-Sayeda Zainab, Cairo Governorate; Cairo University
- Catania - A.O.U. Policlinico Vittorio Emanuele
- Chieti - Ospedale SS. Annunziata
- Ciudad de México - Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
- Ferrara - AOU di Ferrara - Arcispedale Sant'Anna
- Istanbul - İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine
- Istanbul - Marmara University, Research And Education Hospital
- L'Aquila - ASL 1 Avezzano, Sulmona, L'Aquila - P.O. San Salvatore
- L'Aquila - Università degli Studi di L'Aquila
- Latina - Sapienza University of Rome - Polo Pontino
- Mansoura - Mansoura University, Faculty of Medicine
- Messina - A.O.U. Policlinico G. Martino
- Milano - ASST Gaetano Pini/CTO
- Milano - Ospedale Fatebenefratelli e Oftalmico
- Napoli - A.O.U. dell'Università degli studi della Campania "Luigi Vanvitelli"
- Palermo - ARNAS Ospedali Civico-Di Cristina-Benfratelli - P.O. Ospedale dei Bambini G. Di Cristina
- Pavia - Fondazione IRCCS Policlinico San Matteo
- Perugia - AO di Perugia - Ospedale S. Maria della Misericordia
- Riyadh - King Saud University
- Roma - Ospedale Pediatrico Bambino Gesù
- São Paulo - Hospital das Clinicas da Faculdade de Medicina HCFMUSP, University of São Paulo

- Siena - Azienda Ospedaliero Universitaria Senese
- Sivas - Sivas Cumhuriyet University, School of Medicine
- Sousse - Farhat Hached Hospital
- Tehran - Shariati Hospital
- Torino - AO Ordine Mauriziano
- Verona - AOUI Verona

## 10. Acknowledgements


- The principal investigators from Azienda Ospedaliero-Universitaria Senese and General Hospital of Athens "LAIKO" – two of the centers providing data for this study – are members of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA).
- The doctoral thesis was prepared following a 6-month research stay at the University Medical Center of Ljubljana (Slovenia) in the context of the ERN RITA Research Mobility Fellowship.
- I acknowledge the use of ChatGPT [https://chat.openai.com/] to edit my writing at the final stage of preparing this essay. I entered the following prompt: "Improve my academic English writing style." ChatGPT was also used as interface to access the Jupiter Notebooks to create graphic contents.
- I am deeply thankful to these persons for their critical support in the planning, execution, discussion and presentation of this research: Prof. Luca Cantarini, coordinator of the AIDA Network, for allowing access to the AIDA Network Behçet's disease registry, fostering scientific connections and promoting this study; Dr. Claudia Fabiani, uveitis expert, for sharing her personal iconographic collection of Behçet's disease patients and constructive discussion about the topic; Dr. Alberto Balistreri, biomedical engineer, for providing technical support to the AIDA Network and challenging external insights; the principal investigators and sub-investigators of the AIDA Network, for investing time, trust and resources in the project; Prof. Tadej Avčin and Prof. José Hernández-Rodríguez for the time and effort they dedicated to reviewing this manuscript.