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Socioeconomic status among patients with uveitis: Association with Vogt-Koyanagi-Harada disease

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Abstract:

Purpose: Uveitis is an important cause of visual impairment and blindness worldwide. Vogt-Koyanagi-Harada disease (VKH) is a common cause of uveitis in East Asia and Southern Cone countries. Although studies regarding uveitis epidemiology have been published, the relationship between socioeconomic status and VKH has not been described.

Methods: We conducted a cross-sectional, observational, multicenter study at two tertiary referral centers in Santiago, Chile, over a three-year period. The study included 270 patients diagnosed with uveitis. Data were obtained from electronic medical records and included demographic characteristics, etiological diagnosis, health insurance type (public or private), and the Multidimensional Poverty Index (MPI) and Human Development Index (HDI) corresponding to each patient's area of residence.

Results: Of 270 patients with uveitis, 128 (47.4%) had idiopathic uveitis, with idiopathic anterior uveitis being the most common anatomical subtype (93 [34.4%]). A specific etiology was identified in 142 (52.6%) patients, with VKH being the most common identified etiology (28 [10.4%]). Patients with VKH resided in areas with a higher median MPI than those with non-VKH uveitis (23.5 [IQR 13.2–24.9] vs 17.2 [4.2–24.5]; p=0.0287) and a lower median HDI (0.609 [IQR 0.580-0.733] vs 0.630 [0.600-0.972]; p=0.0041).

Conclusion: Patients with VKH resided in areas characterized by greater MPI and lower HDI than patients with non-VKH uveitis. These findings suggest a potential association between socioeconomic status and VKH in Chile. Future studies with larger and more representative populations incorporating individual-level socioeconomic measures are needed to confirm this association and explore its underlying determinants.

Keywords: Uveitis, Vogt-Koyanagi-Harada disease (VKH), Multidimensional Poverty Index (MPI), Human Development Index (HDI)

Introduction

Uveitis encompasses a diverse spectrum of intraocular inflammatory conditions of infectious and non-infectious etiologies, affecting the uveal tract as well as adjacent structures, including the retina, optic nerve head, and vitreous humor[1]. It can cause visual loss and is the fifth commonest cause of visual loss in the developed world, accounting for about 10–15% of the cases of blindness and up to 20% of legal blindness[1].

The distribution of the types, clinical associations, and causes of uveitis in a given population is strongly influenced by diverse genetic, geographic, and environmental factors[2]. For instance, Behcet's disease demonstrates a particularly high prevalence in the Silk Road region, from East Asia to the Middle East and countries around the Mediterranean Basin, particularly Iran and Turkey[3]. Similarly, Birdshot chorioretinopathy is prevalent among Western European Caucasian populations[4], whereas Vogt-Koyanagi-Harada disease (VKH) primarily affects individuals of East Asian descent[2], and it has also been reported in populations from Southern Cone countries, such as Chile and Argentina[5,6,7]. Moreover, among the countries included in the analysis, Chile had the highest reported frequency of VKH, although this estimate was based on a single-center study[5,6].

VKH is characterized by bilateral granulomatous panuveitis, exudative retinal detachments, and extraocular manifestations in the auditory, integumentary, and central nervous systems[8]. The primary ocular pathological feature of VKH is a diffuse thickening of the uveal tract, caused by a non-necrotizing granulomatous inflammation[9]. Multiple therapeutic regimens have been used to treat VKH, including oral and intravenous corticosteroids (CS), immunomodulatory therapy, and biologic therapies[9].

Despite epidemiological studies of ocular inflammatory diseases conducted in Chile and Argentina, the higher prevalence of VKH in these countries compared with other geographical regions is not well understood[7,10]. A study by Yalçındağ et al. found that patients with Behçet disease had lower socioeconomic status and education level than patients with other non-infectious uveitis entities[11]. Another study reported an association between socioeconomic factors and poorer clinical outcomes in pediatric non-infectious uveitis[12]. A study by Oh et al. has highlighted lower household income as a significant risk factor for blindness in uveitis patients[13].

To our knowledge, no studies have evaluated the association between socioeconomic status and VKH. Therefore, this study aimed to characterize the demographic and socioeconomic

profiles of patients with uveitis treated at two tertiary referral centers in Chile, and to compare socioeconomic status between patients with VKH and those with non-VKH uveitis.

Materials and Methods

This study employed a multicenter, analytic, cross-sectional, and observational design to investigate the epidemiology and socioeconomic status of uveitis in Chile. Two national tertiary referral healthcare centers in Santiago de Chile (Clínica Alemana de Santiago and Hospital Clínico Félix Bulnes) were included.

Data were collected between 2018 and 2021. The study protocol obtained ethical approval from the Clinical Research Ethics Committees of participating institutions, ensuring compliance with international ethical standards. The institutions granted authorization to access patient information in their databases, in accordance with ethical guidelines[14]. Given the use of anonymized data, informed consent was considered unnecessary.

Study population:

The inclusion criterion for our study was confirmation of the diagnosis of uveitis by an ophthalmologist with expertise in the field (CAU), together with a comprehensive study to determine etiologies. Eligible patients included individuals of all ages and genders, whether they were newly diagnosed or had pre-existing diagnoses and continued to seek medical care during the study period. Newly diagnosed patients underwent ophthalmological examinations and complementary tests to establish an etiological diagnosis. Patients diagnosed solely with scleritis and/or episcleritis, without any signs or symptoms of an intraocular inflammatory disorder, were excluded from the analysis. Additionally, cases of uveitis induced by surgery or endophthalmitis were also excluded.

Data collection, measurements, and variables

Comprehensive data extraction was conducted from electronic medical records and subsequently transferred to a standardized electronic form. To ensure consistency and accuracy, investigators received training in data collection procedures, aligned with ophthalmological examinations and laboratory findings documented in the records. Information collected encompassed age at presentation, laterality, gender, demographic characteristics, socioeconomic indicators, and health insurance status (public or private).

All patients underwent a comprehensive ophthalmological examination. Laboratory and ancillary tests, including ocular imaging, were performed according to the clinical presentation and suspected differential diagnoses. Etiological diagnoses were established based on characteristic clinical findings and appropriate complementary testing, according to previously described diagnostic criteria [5]. Anatomical classification of uveitis (anterior, intermediate, posterior, or panuveitis) was determined based on standardized criteria established by the International Uveitis Study Group[15] and the Uveitis Nomenclature Working Group (SUN) criteria[16]. Patients with confirmed etiological diagnoses were categorized accordingly. Cases in which the cause could not be determined, despite evaluation described above, were classified as idiopathic[5].

Specifically, tuberculosis-associated uveitis (TAU) required exclusion of other causes, a tuberculin skin test (TST) ≥15 mm, and improvement of ocular inflammation within 2–4 weeks of initiating antituberculous treatment[17]. Ocular syphilis was diagnosed in patients with intraocular inflammation, a reactive VDRL test, and positive serum FTA-ABS test[18]. Vogt–Koyanagi–Harada disease was diagnosed according to the revised diagnostic criteria published in 2001[19]. The diagnosis of Behcet's disease (BD) was based on the international study group BD criteria[20]. Acute retinal necrosis was diagnosed based on the criteria published by the American Uveitis Society[21]. Presumed ocular sarcoidosis required compatible clinical features (i.e. bilateral, granulomatous, multifocal retinochoroiditis, periphlebitis), elevated serum angiotensin-converting enzyme (ACE) levels, and chest image findings compatible with sarcoidosis. Toxoplasmosis was diagnosed if there was a compatible clinical feature (focal retinochoroiditis with or without a pigmented scar) and serology (IgM and/or IgG) positive for toxoplasmosis[5].

The diagnoses for other specific conditions were made according to eye features, clinical course, and treatment response (e.g. Fuchs uveitis, white dot syndrome, sympathetic ophthalmia, Posner–Schlossman syndrome), or in collaboration with other specialists (e.g. rheumatologist for connective tissue diseases) when appropriate. HLA-B27-associated uveitis required compatible clinical features (i.e. anterior, acute, nongranulomatous) and a positive HLA-B27 test. Diabetes mellitus (DM)-associated uveitis was diagnosed if the patient had poor metabolic control at diagnosis and there was a clinical improvement with topical steroids and improved glycemic control. The diagnosis of herpetic uveitis required suggestive clinical signs (i.e. iris atrophy, cornea hyposensitivity, compromised cornea, elevated intraocular pressure); aqueous humor PCR was performed when the clinical presentation or course was unclear[5].

Healthcare insurance system in Chile

Chile has a mixed healthcare system comprising public and private health insurance. The public system is administered by the National Health Fund (FONASA), whereas private health insurance is provided by Health Insurance Institutions (ISAPREs). Private insurance is more commonly used by individuals with higher socioeconomic status and generally provides direct access to private healthcare facilities and specialists[22]. In contrast, the public healthcare system follows a tiered model of care, in which patients are typically referred from primary care to secondary and tertiary care according to clinical needs[22].

Socioeconomic status classification:

Socioeconomic status was assessed based on patients' area of residence, incorporating Multidimensional Poverty Index (MPI) and Human Development Index (HDI) values[22,23]. The MPI assesses education, health, and standard of living indicators, such as years of schooling, child mortality, nutrition, and access to basic amenities[22]. These data were calculated using the Small Area Estimation (SAE) methodology and sourced from the National Socioeconomic Characterization Survey conducted by the Ministry of Social Development and Family of the Republic of Chile[24]. Households with MPI scores indicating 22.5% or more deficiencies across all indicators were classified as multidimensionally poor[25].

In the socioeconomic analysis, the HDI was included for each area where the patients lived. HDI comprises three dimensions: a long and healthy life (measured by life expectancy at birth), knowledge (measured by expected years of schooling and mean years of schooling), and a decent standard of living (measured by gross national income per capita)[26]. HDI classifications are based on HDI fixed cutoff points, which are derived from the quartiles of distributions of the component indicators. The cutoff-points are HDI of less than 0.550 for low human development, 0.550-0.699 for medium human development, 0.700-0.799 for high human development and 0.800 or greater for very high human development[26]. HDI data for Chilean areas are publicly available from the Chilean Public Health Observatory (OCHISAP), which reported HDI estimates for each area in its latest review[27].

Our group analyzed the differences between patients in public and private health insurance, since higher income has been linked to an increased probability of being privately insured[28].

Statistical analysis:

The analysis was performed with Prism 9 software (GraphPad Inc., San Diego, California). All information and variables were tabulated using descriptive statistics, including frequency distribution and means or medians as appropriate. Shapiro-Wilk test was used to test for normality. The Mann-Whitney U test was used to compare MPI and HDI values between VKH and non-VKH uveitis groups. A two-sided P value < 0.05 was considered statistically significant.

Results:

A total of 270 patients with uveitis were included from two tertiary hospitals. The mean age of the patients was 41 years old (range: 4-92 years). Analysis of the overall number of cases revealed that the vast majority occurred in adults (≥ 18 years; 240 cases, 88.9%), while only a small portion of cases (30 cases; 11.1%) were pediatric patients (<18 years). Distribution by gender showed a higher frequency of cases in women than in men (61.1% vs 38.9%), resulting in a female-to-male ratio of 1.57:1. Regarding age distribution, the highest number of cases occurred in the 31-44 age group (73 cases; 27%), followed by the 45-54 age group, the 18-30 age group, and the 55-64 age group. The ≥65 age group presented the lowest number of cases (23 cases; 8.5%). Table 1 summarizes the main demographic features.

A specific etiology was identified in 142 patients (52.6%), including 109 cases (76.8%) with non-infectious etiologies and 33 cases (23.2%) with infectious etiologies. The most common identified etiologies were VKH (28 cases; 10.4%), Human Leukocyte Antigen-B27-associated uveitis (20 cases; 7.4%), and Herpes Simplex Virus-associated uveitis (13 cases; 4.8%). Additional etiologies included sarcoidosis, toxoplasmosis, Behcet's disease, and juvenile idiopathic arthritis, among others, as detailed in Table 2.

Conversely, in 128 patients (47.4%), the diagnosis was idiopathic uveitis, since no specific cause could be identified, after a comprehensive evaluation. Among this group, anterior uveitis was the most prevalent anatomical pattern (n=93; 34.4%), followed by idiopathic intermediate uveitis, panuveitis, and anterior-intermediate uveitis. Posterior uveitis represented the least common idiopathic classification.

The health insurance classification revealed a slight disparity between individuals with private insurance (161 cases; 59.6%) and those covered under the public healthcare system (109 cases; 40.4%) (Table 3). The median MPI of the patients' areas of residence was 17.2 (interquartile range (IQR): 5.4-24.5). Similarly, the median HDI value for the areas was 0.626 (IQR: 0.600-0.924), reflecting the level of human development in these areas.

In the VKH group, 78.6% of patients had public health insurance, whereas 21.4% had private insurance. In contrast, among patients with non-VKH uveitis, 36.0% had public health insurance and 64.0% had private insurance. The median MPI of the patients' areas of residence was higher in the VKH group than in the non-VKH group (23.5 [IQR, 13.2–24.9] vs. 17.2 [IQR, 4.2–24.5], respectively; Table 3). This difference was statistically significant (p=0.0287; Figure 1). HDI of the patients' areas of residence was lower in the VKH group than in the non-VKH group (0.609 [IQR, 0.580-0.733] vs. 0.630 [IQR, 0.600-0.972], respectively; Table 3). This difference was statistically significant (p=0.0041; Figure 2).

Discussion:

This study provides insights into the demographic, etiological, and socioeconomic characteristics of patients with uveitis treated at two tertiary referral centers in Chile, with a particular focus on the socioeconomic status of patients with VKH. The age stratification analysis showed that uveitis predominantly affected individuals of working age, consistent with findings reported in previous studies[29]. Among cases with an identified etiology, VKH was the most frequent cause of uveitis in our study, consistent with findings from a previous local study by Liberman et al.[5]. Importantly, patients with VKH resided in areas with lower socioeconomic status than those with non-VKH uveitis, as reflected by higher MPI and lower (HDI) values.

Tsirouki et al. studied the regional patterns of uveitis worldwide, finding that VKH is one of the most common causes of uveitis in Asia, particularly in countries such as China, Thailand and Singapore[30]. In contrast, Europe and North America had among the lowest reported frequencies of VKH[30]. Similarly, Cholaky-Mejia et al. reported geographic variations in VKH frequency, with higher frequencies in Southeast Asia, East Asia, and Africa, and lower frequencies in North America, Europe, and Oceania[6]. Liberman et al. conducted the only study about uveitis etiologies in Chile. In this single-center study, among cases with an identified etiology, VKH was the most frequent cause of uveitis[5], as in our cohort. A study by Tan et al. found that economic development in mainland China was negatively associated with uveitis onset, but this association was related to the overall epidemiology of uveitis rather than to specific etiologies[31]. Yalçındağ et al. found that patients with Behçet disease had lower socioeconomic status and education level than patients with other non-infectious uveitis entities[11].

This is the first multicenter study of uveitis etiologies in Chile and supports previous observations regarding the importance of VKH as the most commonly identified etiology of uveitis in the country, consistent with the findings of Liberman et al.[5]. Chile has one of the highest frequencies of VKH in the world [6]. The majority of studies on uveitis epidemiology have been conducted in developed countries[32]. To our knowledge, this study represents the first formal assessment of socioeconomic differences between patients with VKH and those with other uveitis etiologies. Therefore, understanding the potential association between socioeconomic status and VKH in Southern Cone populations is particularly relevant to the healthcare systems of Chile and Argentina[6]. The mechanisms underlying these differences remain uncertain and may involve genetic, ancestry, environmental, socioeconomic, and healthcare-related factors[31]. These findings may be partially explained by the association between socioeconomic status and genetic ancestry, as previous studies have reported socioeconomic disadvantages among individuals of Mapuche origin in Chile[33,34]. This hypothesis is particularly relevant given that Chile has one of the highest reported frequencies of VKH worldwide, as documented in the meta-analysis by Cholaky-Mejía et al[6]. A similar epidemiological pattern may be observed in gallbladder cancer, as Chile has one of the highest mortality rates from this malignancy worldwide[35], and Mapuche ancestry has been associated with an increased risk of gallbladder cancer [36]. These observations raise the possibility that genetic ancestry may partially contribute to the association between socioeconomic conditions and VKH observed in our study. However, further studies incorporating individual-level socioeconomic measures and genetic ancestry data are needed to investigate this hypothesis and determine whether Mapuche ancestry is associated with VKH.

This study has several limitations. First, it was conducted at two tertiary centers located in Santiago, the capital of Chile, which may limit the generalizability of our findings to the overall Chilean population. Patients covered by public health insurance typically require several medical appointments and referrals to access tertiary care, whereas patients with private insurance may have more direct access to subspecialty care. Consequently, differences in referral patterns between the public and private healthcare systems may result in differences in disease complexity and in the proportion of patients with VKH included in each setting[5]. Second, the relatively small number of VKH cases compared with non-VKH uveitis cases (28 of 270 patients) may have limited the statistical power of the comparisons and increased the uncertainty of the estimates. In addition, potential confounding factors, including nutritional, environmental, and educational factors, were not fully assessed. Finally, because access to specialized ophthalmologic care may vary across Chile, patients with VKH from regions

outside Santiago may be underrepresented in our dataset, particularly those living in rural or geographically underserved areas[27]. Furthermore, MPI and HDI were assigned according to the area of residence and therefore represent area-level rather than individual-level socioeconomic measures. Consequently, the observed associations should not be interpreted as direct measures of individual socioeconomic status.

In conclusion, VKH was the most commonly identified etiology of uveitis in this multicenter Chilean cohort. Patients with VKH resided in areas with lower socioeconomic status than those with non-VKH uveitis, as reflected by higher MPI and lower HDI values. These findings suggest a potential association between socioeconomic status and VKH in Chile. Future studies with larger and more representative populations incorporating individual-level socioeconomic measures are needed to further investigate this association and explore potentially contributing factors, particularly genetic, ancestry, nutritional, and environmental factors.

Statements and Declarations:

Funding Statement

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Clínica Alemana de Santiago and Hospital Clínico Félix Bulnes.

Consent to participate

The institutions granted authorization to access patient information in their databases, in accordance with ethical guidelines[14]. Given the use of anonymized data, informed consent was considered unnecessary.

Table 1: Characteristics of patients with uveitis in this sample.

Variable	Total
Number of patients, n (%)	270 (100)
Sex, n (%)	
Female	165 (61.1)
Male	105 (38.9)
Age category, n (%), years	
< 18	30 (11.1)
18-30	45 (16.7)
31-44	73 (27)
45-54	58 (21.5)
55-64	41 (15.2)
≥65	23 (8.5)

Table 2: Causes and clinical disease associations of uveitis.

Etiology	**Cases, n (%)**
Vogt-Koyanagi-Harada disease	28 (10.4)
HLA B27+	20 (7.4)
HSV	13 (4.8)
Sarcoidosis	8 (3)
Toxoplasmosis	8 (3)
Behcet's disease	7 (2.6)
Fuchs heterochromic iridocyclitis	6 (2.2)
JIA	6 (2.2)
Diabetes mellitus associated uveitis	5 (1.9)
Sympathetic ophthalmia	5 (1.9)
Tuberculosis	5 (1.9)
Connective tissue diseases	3 (1.1)
Masquerade Syndromes	3 (1.1)
Multifocal choroiditis	3 (1.1)
Acute retinal necrosis	2 (0.7)
APMPPE	2 (0.7)
AZOOR	2 (0.7)
Multiple evanescent white dot syndrome	2 (0.7)
Pharmacologic	2 (0.7)
Serpiginous choroiditis	2 (0.7)
TINU	2 (0.7)
Blau syndrome	1 (0.4)
Candidiasis	1 (0.4)
CMV Retinitis	1 (0.4)
HZV	1 (0.4)
Multiple Sclerosis	1 (0.4)
Syphilis	1 (0.4)
Traumatic	1 (0.4)
Toxocariasis	1 (0.4)
Idiopathic anterior uveitis	93 (34.4)
Idiopathic intermediate uveitis	11 (4.1)
Idiopathic anterior-intermediate uveitis	10 (3.7)
Idiopathic posterior uveitis	5 (1.9)
Idiopathic panuveitis	9 (3.3)
Total	270 (100)

HLA B27+: Human leukocyte antigen, HSV: Herpes simplex virus, JIA: Juvenile idiopathic arthritis, APMPPE: Acute posterior multifocal placoid pigment epitheliopathy, AZOOR: Acute zonal occult outer retinopathy, TINU: Tubulointerstitial nephritis with uveitis, CMV: Cytomegalovirus, HZV: Herpes zoster virus.

Table 3: Socioeconomic characteristics of patients with Vogt–Koyanagi–Harada (VKH) and non-VKH uveitis.

Variable	VKH (n=28)	Non-VKH uveitis (n=242)	Total (n=270)
Health insurance, n (%)			
Public	22 (78.6)	87 (36)	109 (40.4)
Private	6 (21.4)	155 (64)	161 (59.6)
MPI, median (IQR)	23.5 (13.2-24.9)	17.2 (4.2-24.5)	17.2 (5.4-24.5)
HDI, median (IQR)	0.609 (0.580-0.733)	0.630 (0.600-0.972)	0.626 (0.600-0.924)

MPI: Multidimensional Poverty Index, HDI: Human Development Index, IQR: Interquartile range

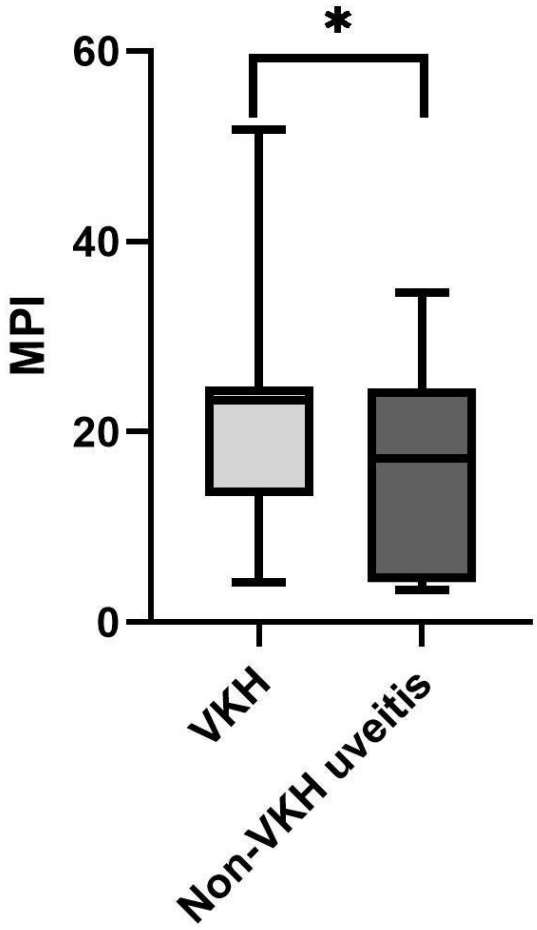


Figure 1: Multidimensional Poverty Index (MPI) in VKH and non-VKH uveitis
Box and whisker plot showing the MPI in two groups of patients: those diagnosed with Vogt-Koyanagi-Harada (VKH) disease (n=28) and those with non-VKH uveitis (n=242) in our sample. (Mann-Whitney U test, *: p value = 0.0287). Boxes represent the median and interquartile range, and whiskers indicate the minimum and maximum values.

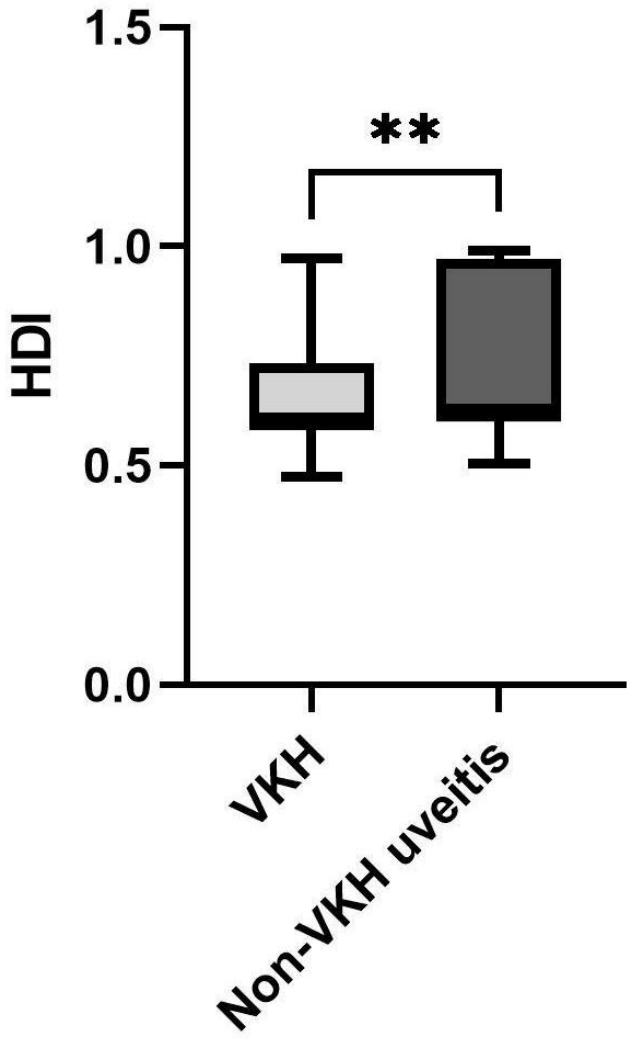


Figure 2: Human Development Index (HDI) comparison between VKH and non-VKH uveitis

Box and whisker plot showing the HDI in two groups of patients: those diagnosed with Vogt-Koyanagi-Harada (VKH) disease (n=28) and those with non-VKH uveitis (n= 242) in our sample. (Mann-Whitney U test, **: p value = 0.0041). Boxes represent the median and interquartile range, and whiskers indicate the minimum and maximum values.

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