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# Approach to uveitis in Bulgaria

**ABSTRACT**

ON A DISSERTATION PAPER FOR OBTAINING AN EDUCATIONAL AND SCIENTIFIC DEGREE "DOCTOR OF SCIENTIFIC SPECIALTY "OPHTHALMOLOGY", CODE 03.01.36

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The dissertation contains 212 pages, including 22 tables and 60 figures. 217 literary sources are cited. 5 chapters are presented, corresponding to the purpose and tasks and meeting the requirements for the layout of the dissertation work.

The dissertation work was discussed and proposed for defense to the departmental council of the Department of Eye Diseases and Visual Sciences at the MU "Prof. Dr. Paraskev Stoyanov" - Varna on 15/01/2025.

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The official defense of the dissertation work will take place at a meeting of the Scientific Jury on 15/01/2025 at 8:30 at the Department of Eye Diseases and Visual Sciences of the University of Varna. The defense materials are available at the Scientific Department of the Medical University - Varna and are published on the website of the Medical University - Varna.

**CONTENTS**

Abbreviations used……..….4
I. Introduction.....5
II. Aim, tasks and hypotheses.....7
2.1 Purpose.....7
2.2 Tasks.....7
2.3 Hypothesis..... .....7
III. Methodology…….....8
IV. Results…….....9
4.1. Research and analysis of the socio-demographic characteristics and etiological factors of patients with uveitis.....9
4.2. Analysis of diagnostics in patients with uveitis.....15
4.3. Analysis of the treatment of patients with uveitis.....21
4.4. Analysis of the course of the disease - relapses.....27
4.5. Creating a risk profile of the studied patients with uveitis and predicting the risk of recurrence and a behavior algorithm in patients with infectious and non-infectious uveitis.....25
V. Discussion.....29
Summary.....46
Conclusions.....47
Contributions.....48
Applications.....49
Publications and participation in scientific forum on the topic of the dissertation……53
Bibliography……..…….....53

Note: The numbering of the figures and tables in the abstract does not correspond to the numbering in the dissertation work.

Note: The team and principal investigator declare that they have no financial interest or affiliation with any of the mentioned trademarks of the products used in the study, devices or sites cited.

**USED ABBREVIATIONS**

AAO - American Academy of Ophthalmology

ACE – Angiotensin-converting Enzyme

ANCA – Antinuclear cytoplasmic antibodies

ANA/ АНА – Antinuclear antibodies

ANOVA - Analysis of Variance

ARMD – Age-Related Macular Degeneration

ARN - Acute Retinal Necrosis

CMV/ CMB - Cytomegalovirus

CT – Computer tomography

EBV - Epstein-Barr Virus

ELISA - Enzyme-linked immunosorbent assay

FHI – Fuchs'heterochromic iridocyclitis

HLA - Human Leukocyte Antigen

HSV - Herpes Simplex Virus

HZV - Herpes Zoster Virus

IUSG – International uveitis study group

MANOVA - Multivariate Analysis of Variance

MLI/ МЛИ – Membrana Limitans Interna

MTB - Mycobacterium tuberculosis

OCT - Optical Coherence Tomography

PCR – Polymerase Chain Reaction

PORN - Progressive Outer Retinal Necrosis

PPV/ ППВ - Pars Plan Vitrectomy

RA – Rheumatoid arthritis

SLE/ СЛЕ - Systemic Lupus Erythematosus

SUN - Standardization of Uveitis Nomenclature

TST - Tuberculin Skin Tests

VEGF - Vascular Endothelial Growth Factor

VZV - Varicella-zoster Virus

ВКХ/ VKH синдром - Vogt Koyanagi Harada Syndrome

ВОН/ IOP – Intraocular pressure

ИМТ/ IMT – Immunosupressive therapy

КС/CS - Corticosteroids

МС/MS – Multiple sclerosis

РПЕ/ RPE – Retinal pigment epithelium

ХИВ/HIV – Human Immunodeficiency Viruses/ Човешки имунодефицитни вируси

## I. Introduction

Uveitides are ocular diseases caused by disorders of diverse etiology from infectious and non-infectious agents that could lead to impaired vision, blindness and reduced quality of life. Inflammatory processes in the uvea and the underlying structures, namely the iris, ciliary body and choroid, can be the result of infections, inflammatory diseases, trauma and even occur idiopathically. Sometimes they are representatives of already accompanying systemic diseases, and it is their ocular manifestation that signifies the first sign of the underlying disease. Like its multifaceted etiology, the range of symptoms is diverse, from redness, changes in the color of the iris, reduced and blurred vision, photophobia, irritation and pain to total vision loss.

Their successful treatment is a complex process which includes a thorough examination, detailed anamnesis, performance of highly specialized tests, correct and timely diagnosis, precise selection of treatment and follow-up of the response to it. Historically, this meticulous cycle of activities provides crucial information regarding the differentiation of the possible etiology involved in the pathophysiology of the intraocular inflammation and promotes the healing process, reducing the negative consequences for the eye structures and vision. A stepwise approach to managing the condition includes a thorough examination of the patient's general systemic diseases, ruling in or ruling out infectious agents and considering the apparent biomarkers to diagnose the specific causative agent that triggers the choice of treatment.

The manifestation of uveitis in the pediatric population is relatively low - about 5-10% of all cases, which indicates that the disease mostly affects the population of working age, reducing its working capacity for an unlimited period of time, emphasizing its social significance. Uveitis is among the leading causes of blindness in developed countries, ranking 5th or 6th, and unlike glaucoma and age-related macular degeneration, which mainly affect the elderly population, it can occur in any age group. Often patients develop depression or anxiety and choose self-isolation due to the problems related to impairments and lack of vision.

The uveitis management market is expected to grow by 6.7% during the period from 2023 to 2030 year. Globally, the increasing number of clinical trials for the treatment of eye inflammation, uveitis and refractory cases and the established application of biological therapy are increasing the demand for new agents and driving the market growth significantly. Key

market trends are an increased focus on the development of innovative therapies for uveitis, including biologic and immunosuppressive therapy; increased adaptation of intraocular implants for prolonged drug delivery; personalized approach from the individual ophthalmology practice; integration of systems with artificial intelligence and telemedicine; carrying out highly specialized research and cooperation between different personnel, units and institutions for adequate diagnosis and treatment of the condition.

Complications associated with uveitis can include retinal detachment, secondary glaucoma and cataracts, and as the presentation worsens, the examination of these patients becomes significantly more difficult due to the inability of proper fundus visualization in a standard manner. Fundus photography, optical coherence tomography, fluorescein angiography and B-scan are of utmost importance to specialists in establishing the diagnosis and monitoring the response to treatment.

Effective diagnosis and management of uveitis require a collaboration between various healthcare professionals. After a successful diagnosis, a consecutive choice of therapy follows. Current treatment of patients includes cycloplegics, corticosteroids, immunomodulatory therapy, etc. It requires long-term continuation in order to prevent relapse and ensure effective remission. The long-term use of corticosteroids and the responsibility for patient safety lead to efforts for creating new therapeutic agents such as immunosuppressants, gene therapy and new methods of drug administration for higher biological activity on target tissues with minimal systemic effect.

These new approaches, the training of artificial intelligence systems for its incorporation into imaging diagnostics, the modern clinical trials and the trials of new drugs, successfully place the disease and its management in the present, and even in the future. The cascade of activities - time-proven, modern, tested and set in the future, aims to restore the anatomical and visual function, influence the expressed subjective and objective symptoms, improve the quality of life of the population, the successful reintegration of able-bodied patients into society and is a step in the individual approach of personalized ophthalmology.

We have directed our scientific interests to the study of the problem - uveitis, due to the multifaceted nature of the disease and the still open number of questions that seek answers. We hope that through our research, although limited by time and place, we will contribute to clarifying the characteristics of uveitis in Northeastern Bulgaria.

# II. AIM, TASKS AND HYPOTHESIS

## 2.1. Aim

The aim of the present study is to evaluate the socio-demographic characteristics, diagnostic and therapeutic algorithms and complications in patients with uveitis, based on a retrospective analysis and prospective follow-up over a period of 8 years.

## 2.2. Tasks

To meet our aim, the following tasks were set:

1) to review the publications in the literature and evaluate the modern diagnostic approaches in patients with uveitis and the therapeutic approaches applicable to them;

2) to examine and analyze the socio-demographic characteristics and etiology of patients with uveitis for a period of 8 years;

3) to analyze the course of uveitis, diagnostic approaches and therapeutic algorithms in patients with uveitis who underwent treatment at USBOBAL-Varna;

4) to evaluate the complications of the course of the disease, concomitant diseases and side effects of the therapy;

5) to analyze the duration and course of the disease (relapses, remission intervals);

6) to create a risk profile of the studied patients with uveitis and to predict the risk of relapse and to create a behavior algorithm for patients with infectious and non-infectious uveitis.

## 2.3. Hypothesis

The course of uveitis nowadays is characterized by changed etiology and characteristics, with a predominance of anterior uveitis, a moderate and severe form of course with an autoimmune etiology and a shift of the curve of the affected individuals to a lower age group.

## III. METHODOLOGY

The present study was conducted on the territory of the University Specialized Hospital for Eye Diseases for Active Treatment - Varna for a period of 8 years - 2014-2018 and 2019-2021. The conducted study includes 219 patients who underwent treatment in hospital and pre-hospital care. The selection of patients is based on precisely defined criteria - patients with uveitis as an independent or accompanying disease, patients under or over 18 years of age and who have completed the informed consent form.

Exclusion criteria is applied to patients without uveitis, patients with other ophthalmic diseases not accompanied by uveitis, patients with uveitis and mental disabilities and those who did not complete the informed consent form.

The research methodology includes a documentary method through research and analysis of the published scientific literature on the prevalence and risk factors of the disease, diagnostic methods and therapeutic algorithms. The sociological method included the formulation of a questionnaire corresponding to the objectives of the study and conducting a survey among patients. Clinical methods include anamnesis and physical examination covering a number of examinations such as autorefractometry (HRK-1, HUVITZ Co., Ltd., Republic of Korea), tonometry (TONOPACHY™ NT-530P, Nidek Co., LTD, Japan), biomicroscopy (Carl Zeiss, Meditec AG), ophthalmoscopy (Jena HO 110, Carl Zeiss Meditec, AG, Germany), optical coherence tomography Cirrus HD-OCT 5000, Carl Zeiss Meditec, AG, Germany) and fluorescein angiography (Visucam 224/Visucam 524, Carl Zeiss Meditec AG, Germany). The collected data was processed using the following statistical methods – analysis of variance (ANOVA, MANOVA), correlation, regression and comparative analysis and risk assessment analysis (OR, RR). In all analyzes conducted, an acceptable significance level of $p<0.05$, $p<0.01$, $p<0.001$ with a confidence interval CI of 95% was accepted. The data was processed statistically using SPSS v.20, using descriptive indicators for quantitative and qualitative variables and presented in tabular and graphical form.

## IV. RESULTS

### 4.1. Research and analysis of the socio-demographic characteristics and etiological factors of patients with uveitis.

This uveitis study covers two time periods – first between 2014-2018 year and then between 2019-2021y., with total number of examined patients being 219. The analysis of patients who underwent treatment in USBOBAL - Varna for the period 2014-2018 is 12,906, with the relative share of patients with uveitis being 0.9% and for the period 2019-2021 - 8,704 patients out of whom the relative share of patients with uveitis is 1.2%. The results show that the number of patients with uveitis is increasing. The average age of the examined patients for both periods is 54.21 years. ± 17.66 years, with the minimum age being 6 years and the maximum being 92 years. The study of the age indicator shows that during the second studied period there is a tendency towards migration to a younger age group (respectively 56.04 years for the period 2014-2018 and 52.07 years for the period 2019-2021). The analysis of the results according to gender shows that there is a slight predominance of men (respectively 57.3% for males and 42.7% for females). No significant difference was found according to gender in the two studied periods.

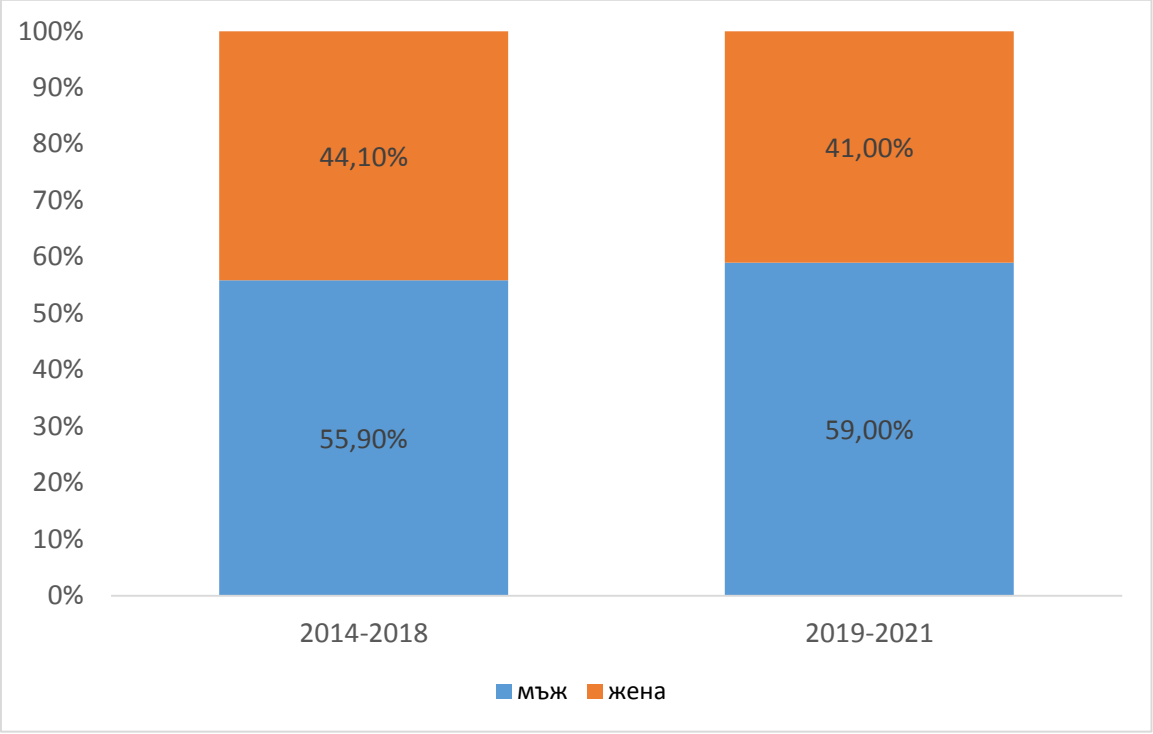



**Figure 1. Distribution of study participants by gender and study period.**

Analysis of patients according to age and gender in the two periods studied showed that male patients with uveitis were younger than females with uveitis; the difference between the two periods being about 4 years for women and about 2 years for men.

The majority of patients with uveitis are from the cities (85.3%), and the city:rural ratio is preserved in both periods (83.9% for the cities for 2014-2018 and 86.9% for 2019-2021, respectively). No difference was found in the place of residence according to gender. The analysis of uveitis patients according to place of residence and age shows that patients from rural areas are younger than those from the cities (respectively 49.3 years for villages and 55.0 for cities).

In slightly more than half of the patients, the uveitis is chronic (52.4%) with unilateral eye involvement prevailing (94.5%).

No significant difference was found in the average age of the patients according to the type of uveitis, with the average age of the patients with acute form of uveitis being 52 years and of the chronic form being 55.5 years. No difference in age was found regarding the affected eye either - with patients with unilateral eye involvement having a mean age of 54.6 years and those with bilateral involvement having a mean age of 48.1 years.

A significant difference was found regarding the affected eye and gender (p=0.046), with bilateral involvement being more characteristic of men (83.3%) and male gender carrying a nearly 4-fold higher risk of bilateral uveitis involvement (OR= 3.9 (0.836-18.308); p<0.005) (Fig. 2).

According to the type of uveitis, no significant gender difference was found, as in both the acute and chronic forms men were more affected (Fig. 3).

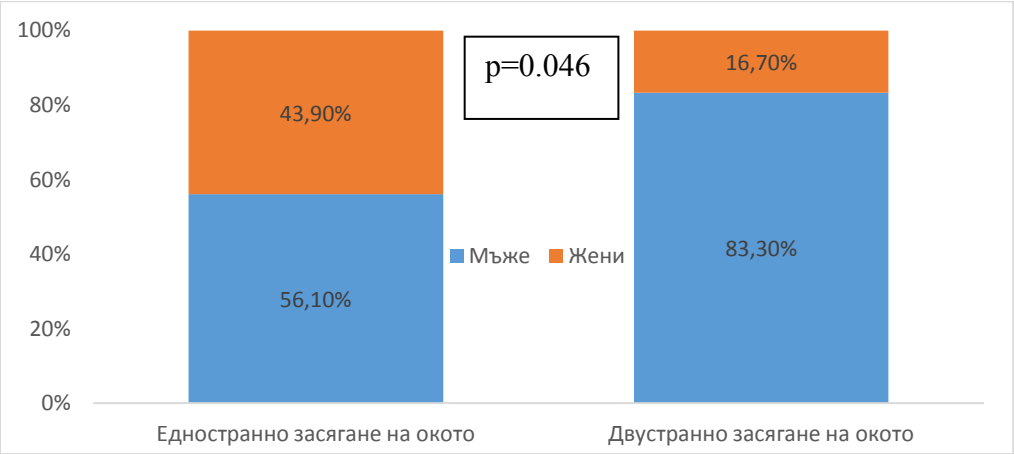



**Figure 2. Distribution of patients by eye involvement and gender.**

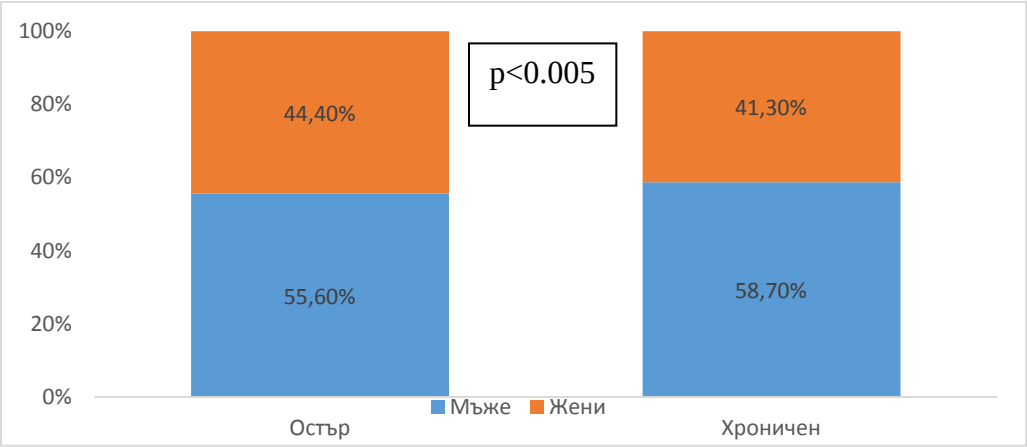



**Figure 3. Distribution of patients according the type of uveitis and gender.**

A significant difference was also found regarding the type of uveitis according to the studied period ($p<0.001$), as in 2014-2018 y. the chronic form of uveitis prevails (66.4%) and in 2019-2021 is the acute form (65.2%).

Half of the examined patients had a moderate severity of uveitis (50.9 %) (Fig. 4). No significant difference was found in the severity of uveitis according to the gender and age of the patients.

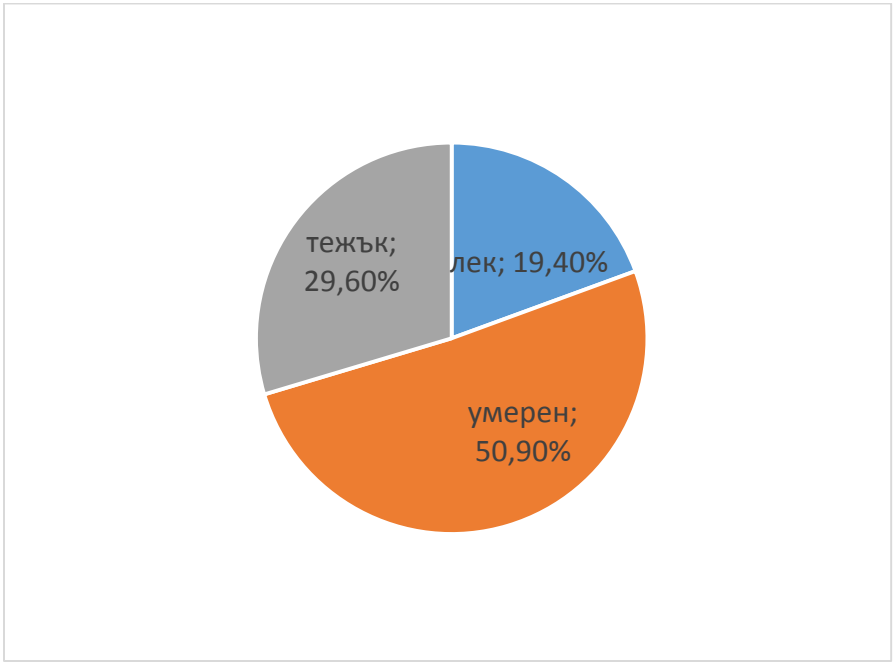



**Figure 4. Distribution by severity of uveitis.**

The study of the severity of uveitis according to the considered period showed the presence of a significant difference ($p<0.001$), as for the years 2014-2018 moderate uveitis predominates (57.6%), while in 2019-2021 there is a slight preponderance of severe uveitis (44.9%) (Fig. 5).

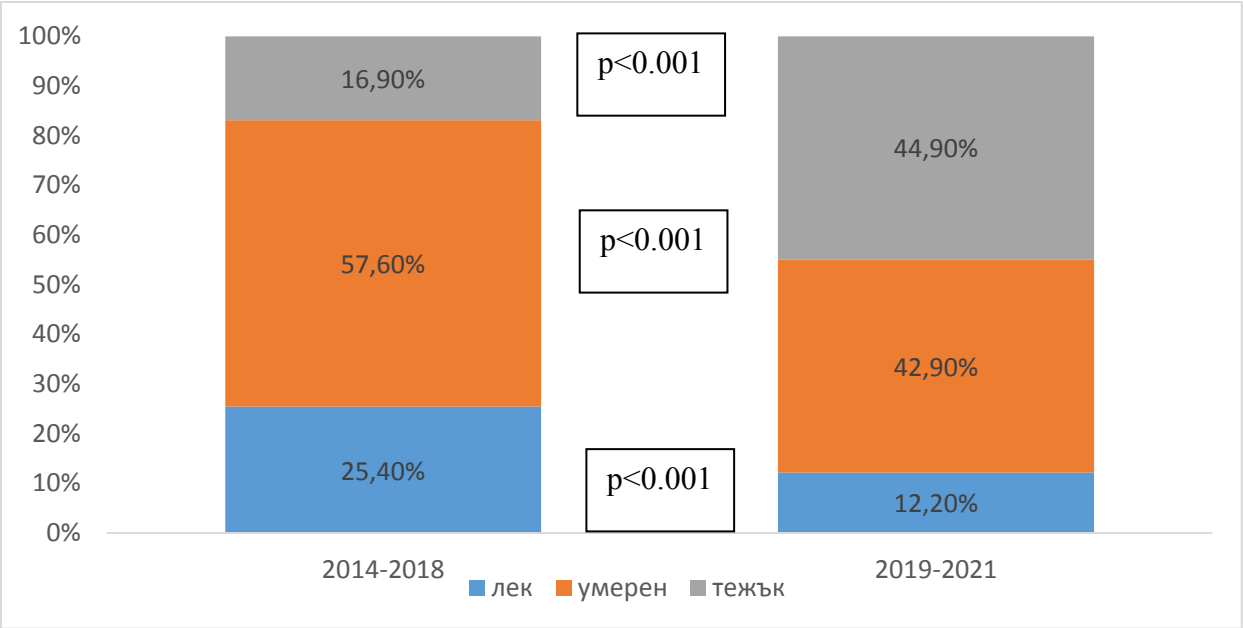



**Figure 5. Distribution of patients according to the studied period and the severity of uveitis.**

A significant difference was also found regarding the severity of uveitis and the place of residence of the patients (p=0.047), with the majority of patients from cities having moderate severity of uveitis (52.2%), while 46.9% of patients from rural areas had severe uveitis (Fig . 6).

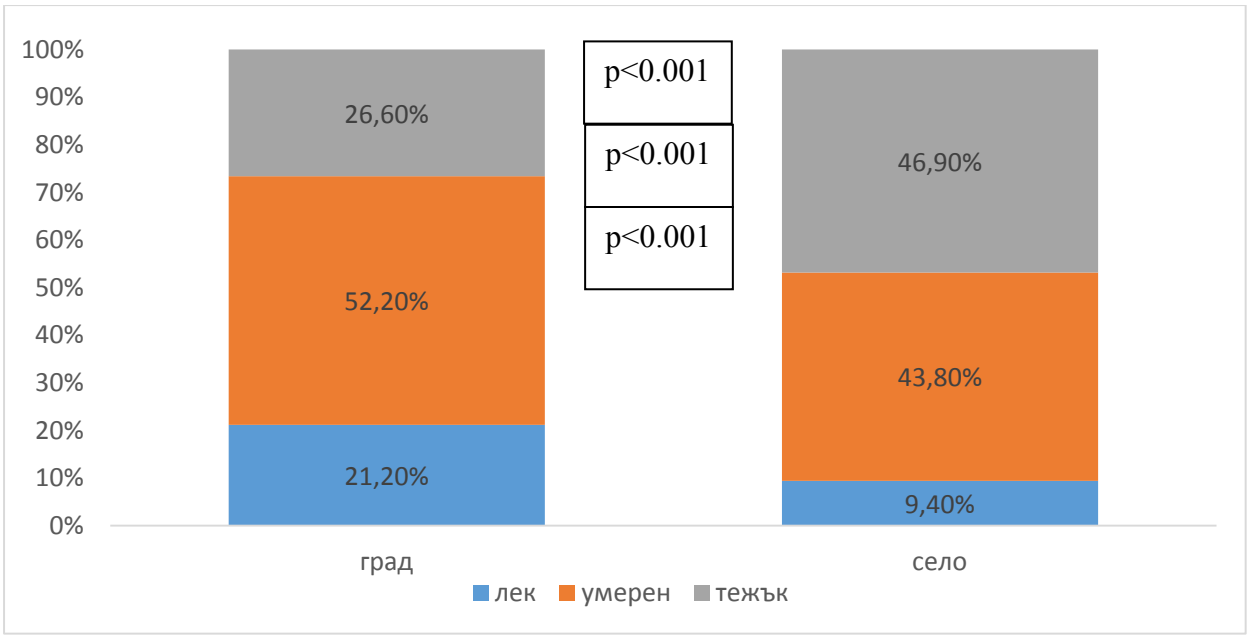



**Figure 6. Distribution of patients according to place of residence and severity of uveitis.**

According to the localization of uveitis, it can be said that patients with anterior uveitis predominate (91.2%) (Fig. 7).

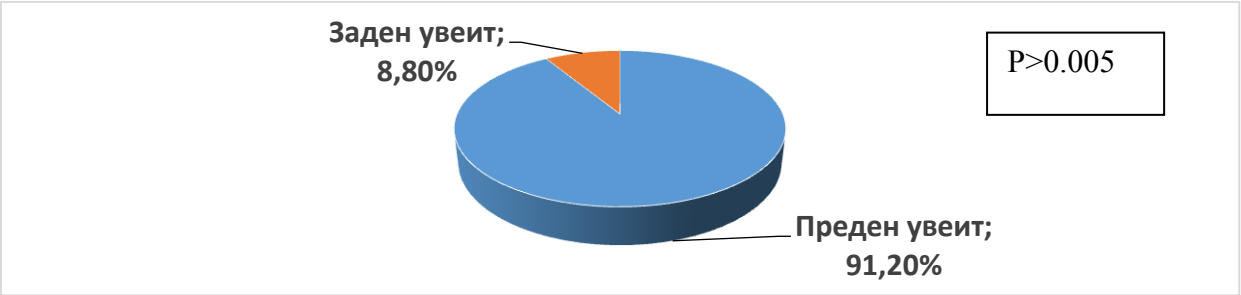



**Figure 7. Localization of uveitis.**

A significant difference was noticed in the age of patients with anterior and posterior uveitis (p=0.003) with posterior uveitis mostly affecting younger patients (respectively, 42.8 years for posterior uveitis vs. 55.3 years for anterior uveitis). A weak correlation was found between the age of the patients and the location of the uveitis (r=0.200; p=0.003).

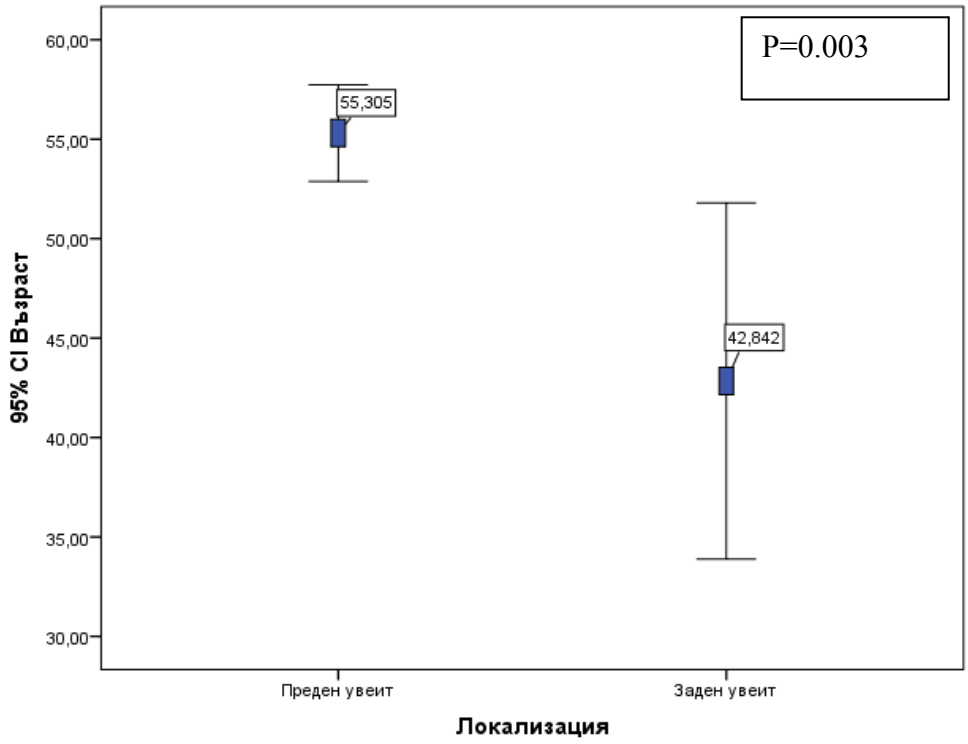



**Figure 8. Mean age of patients according to uveitis location.**

A significant difference was also observed regarding the localization and severity of the uveitis (p<0.001) with anterior uveitis being mostly of moderate severity (54.8%), while posterior uveitis being predominantly severe (89.5%) (Fig. 9). A moderate correlation was found between localization and severity of uveitis (r=0.364; p<0.001).

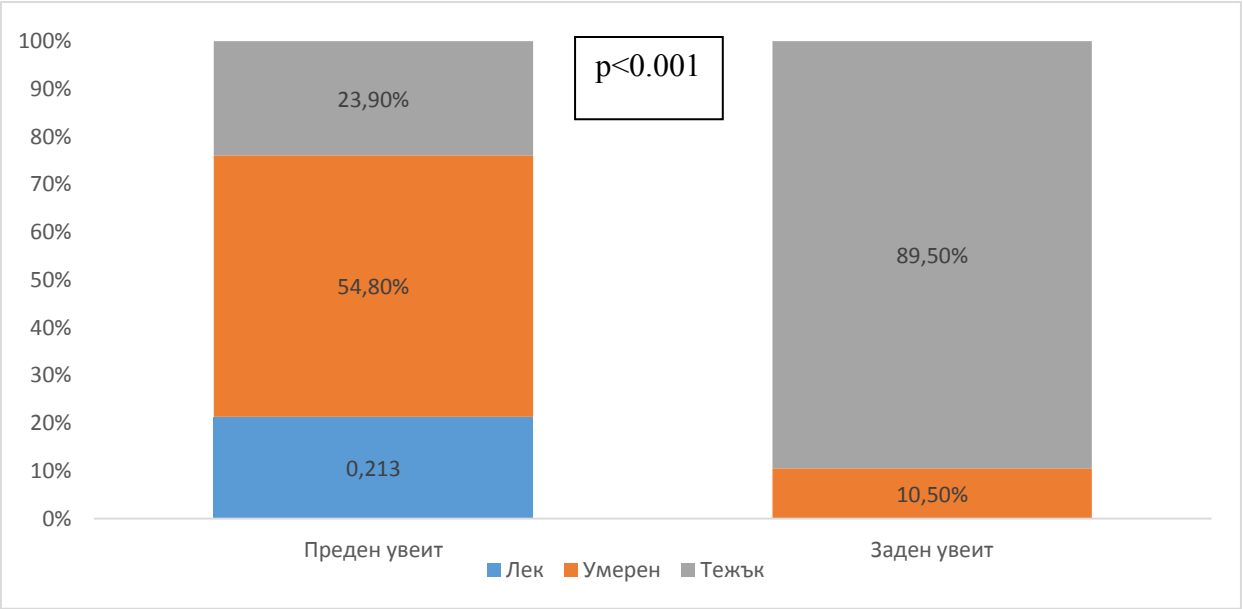



**Figure 9. Distribution of patients according to location and severity of uveitis.**

Most commonly observed is the idiopathic uveitis (42.2%) as shown on Fig. 10, where the etiological factors of patients with uveitis are presented. The most common causes are herpes zoster, ankylosing spondylitis, herpes simplex and rheumatoid arthritis.

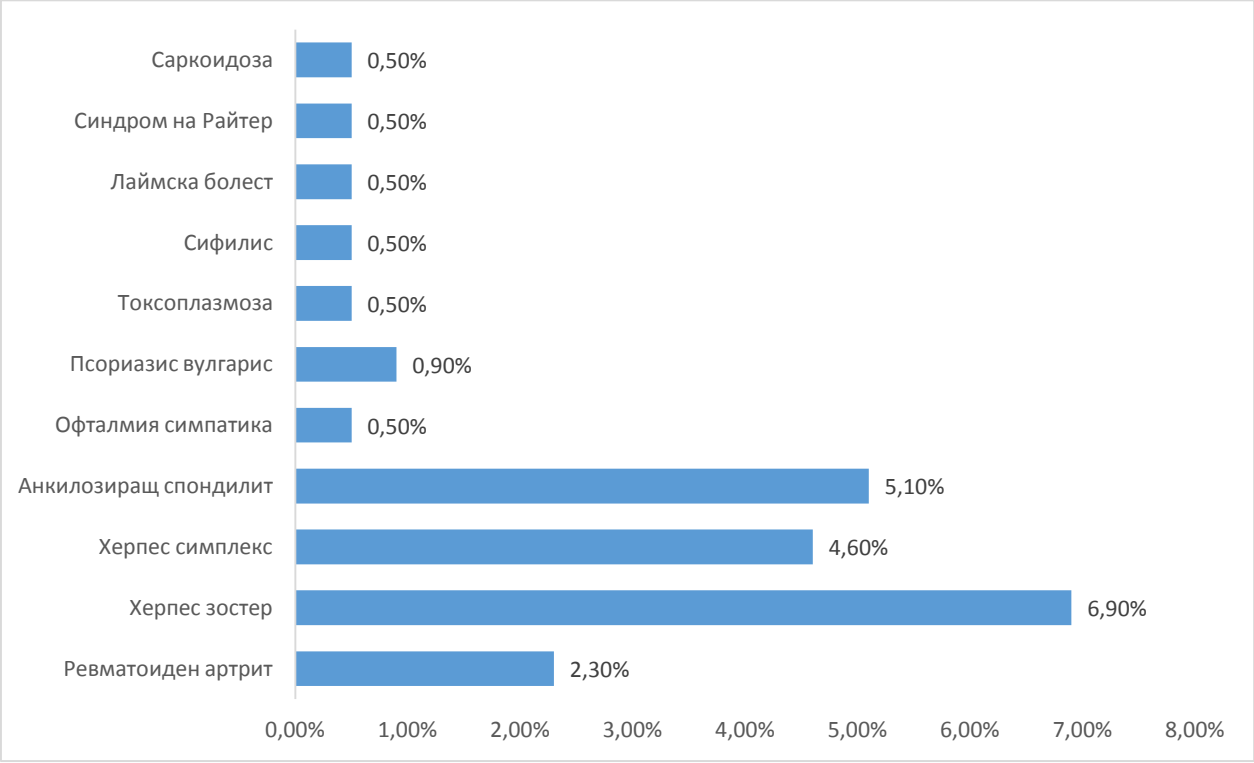



**Figure 10. Distribution according to etiological factors.**

**4.2. Analysis of diagnostics in patients with uveitis.**

The examination of ocular manifestations also exhibited the existence of a significant difference during the two studied periods and in 2014-2018 these manifestations were more pronounced ($p<0.05$) (Fig. 11).

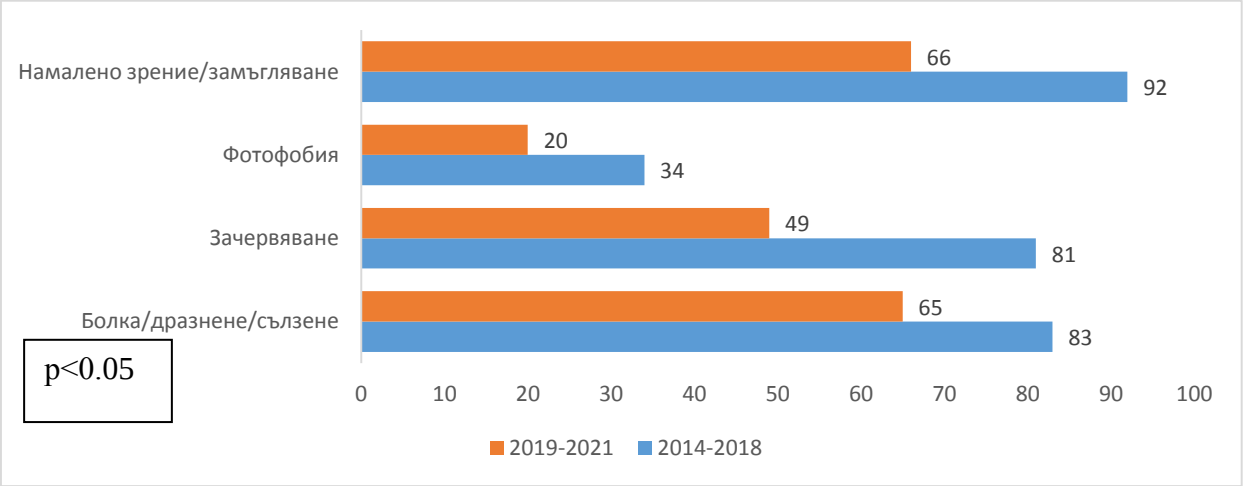



**Figure 11. Distribution of patients according to the ocular manifestation and the studied period (number of patients).**

The examination of visual acuity revealed a tendency for improvement during the second study period in both the right and left eyes (Fig. 12).

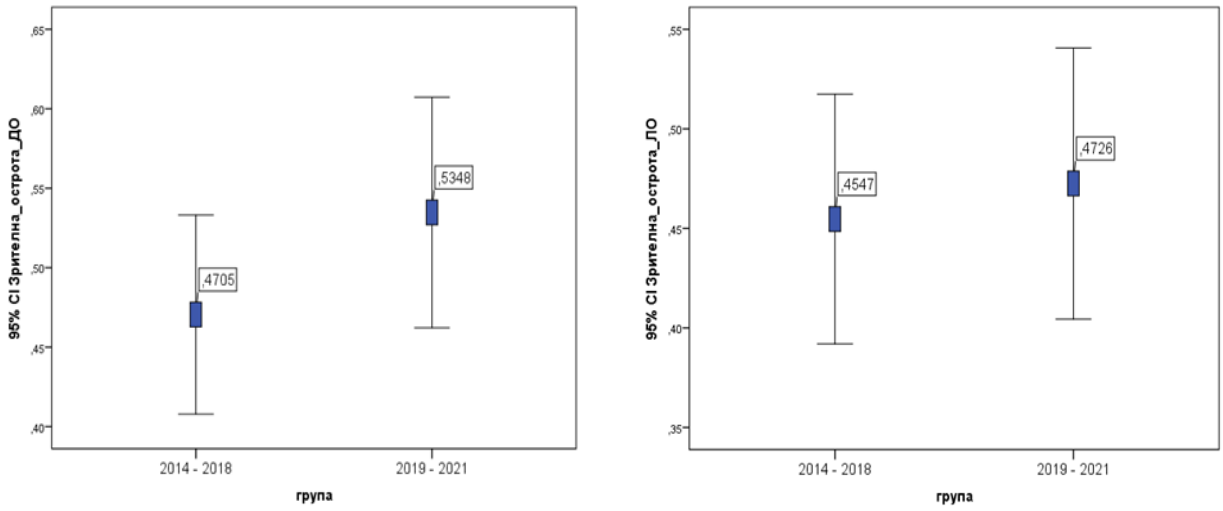



**Figure 12. Average value of visual acuity during the two studied periods.**

On Fig. 13 the findings established by biomicroscopy of the cornea in patients with iridocyclitis for the two studied periods are presented. The results exhibit the existence of a statistically

significant difference in relation to patients with normal cornea ($p<0.05$); patients with a smooth, shiny and transparent cornea having a larger number in the second studied period.

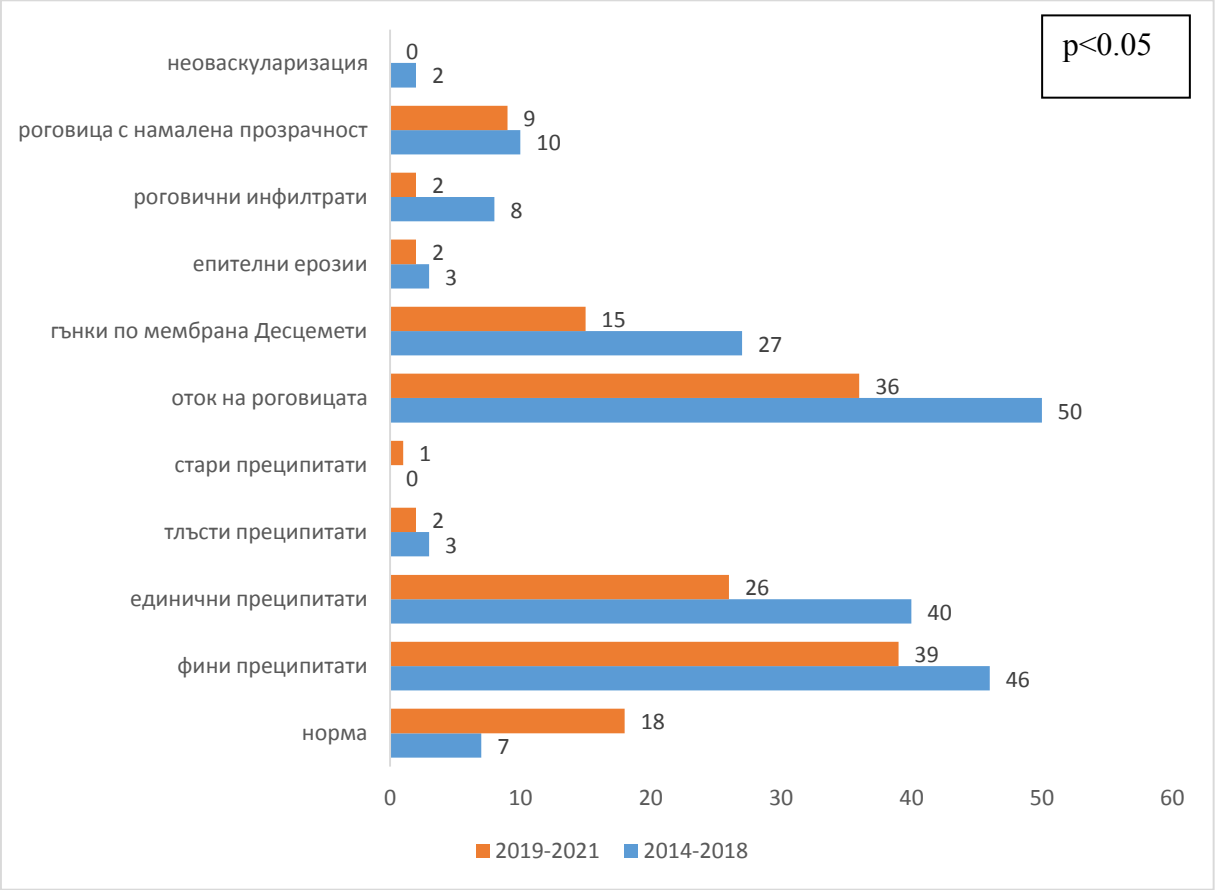



**Figure 13. Corneal biomicroscopy findings (number of patients).**

In the period 2014-2018, single findings of patients with old precipitates were established. There is also a small number of patients with fatty precipitates, epithelial erosions and corneal infiltrates - 2 patients each. No patients with neovascularization were identified. In 2019-2021, no findings such as old precipitates are found. A minimal number of patients have fatty precipitates, epithelial erosions and neovascularization. Findings such as fine precipitates, single precipitates, corneal edema and folds of Descemet's membrane were most frequent for both studied periods, but a significant difference was found in the number of patients ($p<0.05$); all the exhibited findings prevailed during the first study period. A significant difference was also found with regard to corneal infiltrates ($p<0.05$), where again the number of patients during the first examined period predominated (respectively, 8 for 2014-2018 and 2 for 2019-2021). Corneas with opacities were observed with almost equal frequency during the two periods studied (10 for 2014-2018 and 9 for 2019-2021, respectively). According to the presented results of

biomicroscopy of the conjunctiva for the two periods, it can be said that in the first period the patients with normal conjunctival surface, ciliary injection ($p<0.05$) and mixed injection ($p<0.05$) predominated (Fig. 14).

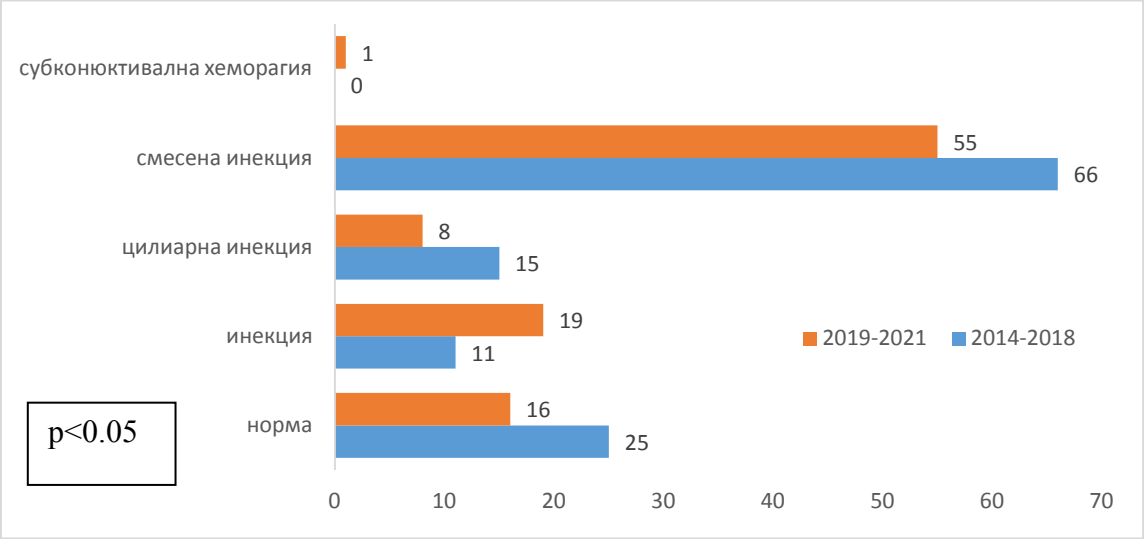



**Figure 14. Conjunctival biomicroscopy findings (number of patients).**

In the second studied period, patients with conjunctival injection predominated ($p<0.05$) and a single case of subconjunctival hemorrhage was also found. On fig. 15 the anterior chamber biomicroscopy findings are presented. The results show that no abnormalities in the mentioned structure predominated in the second studied period ($p<0.05$).

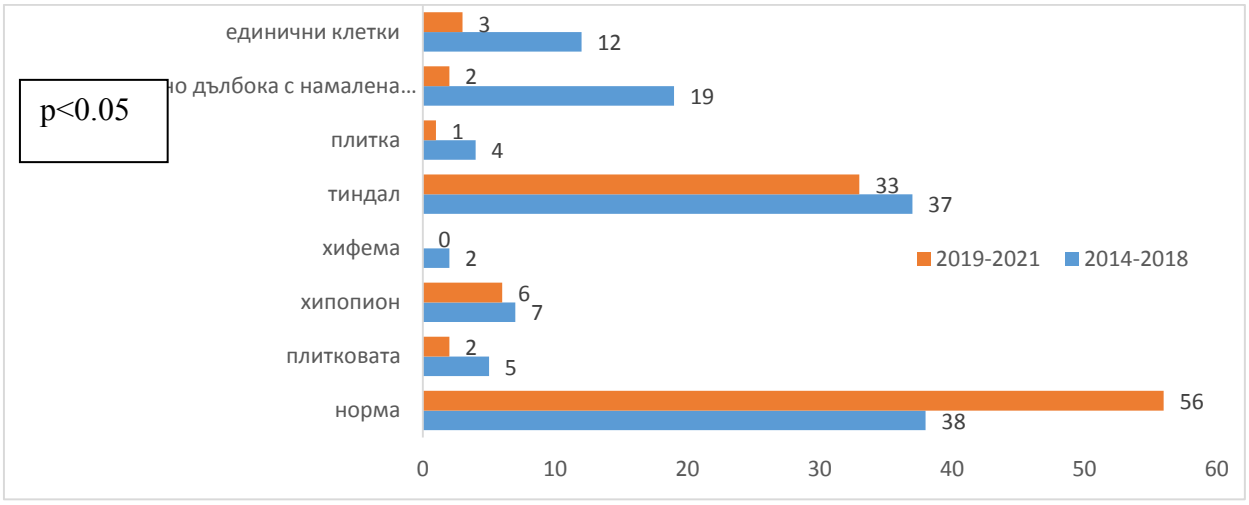



**Figure 15. Manifestations found in anterior chamber by biomicroscopy (number of patients).**

A significant difference was displayed only in terms of a moderately deep anterior chamber with reduced pellucidity ($p<0.01$) and the presence of single cells ($p<0.01$), where patients from

the first period predominated. The most frequent occurrence for both periods was the positive Tyndall and no difference was found between the two periods. As for other findings, the frequency is relatively small and no significant difference was observed between the two groups of patients. On fig. 16 the results of biomicroscopy of the iris are presented; with the most common finding in both periods being a smoothed surface of the iris, followed by adhesion to the anterior chamber. Although no significant difference is found, it can be said that the number of patients is slightly higher in the period 2014-2018. On the other hand, in 2019-2021, findings such as atrophy, nodules and iridectomy are observed.

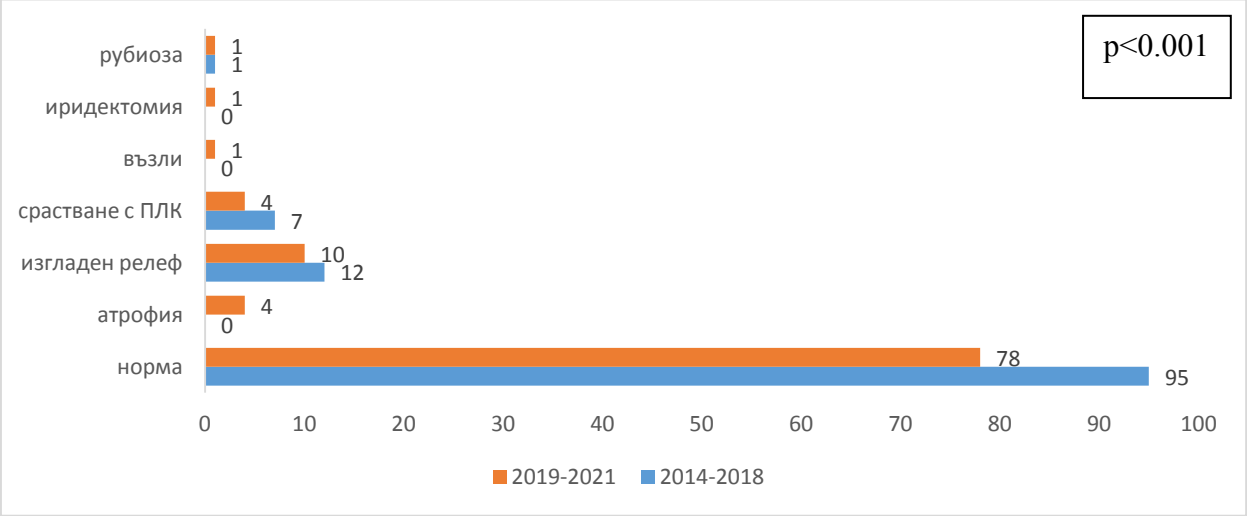



**Figure 16. Iris: biomicroscopy findings (number of patients).**

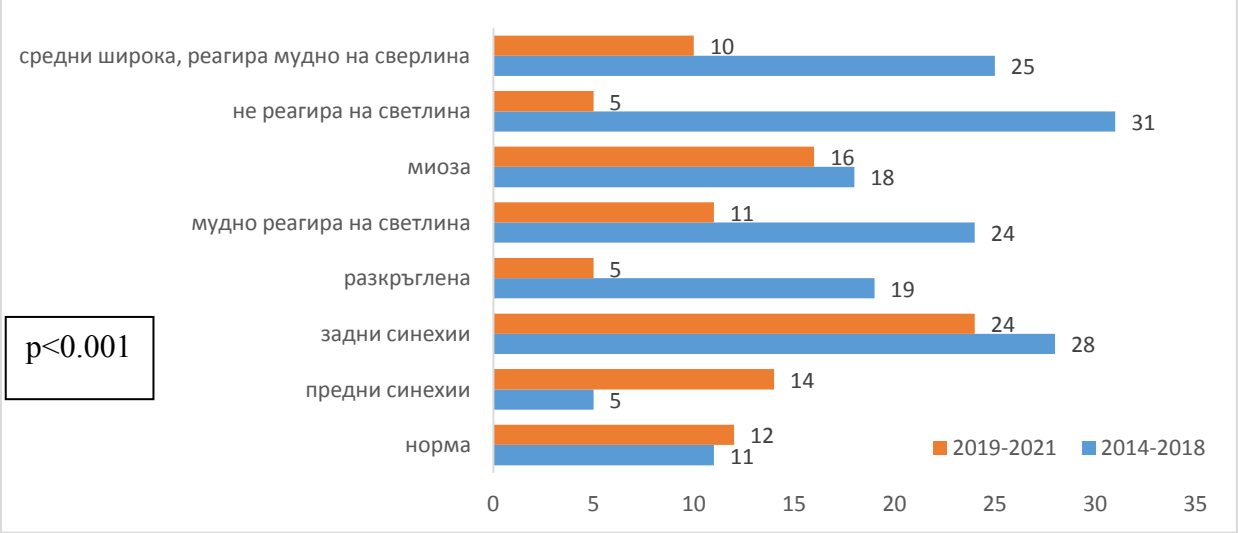



**Figure 17. Pupil: biomicroscopy findings (number of patients).**

The data presented on Fig. 17 displays that there is a significant difference between the frequency of individual findings during the two studied periods ($p<0.001$). Anterior synechiae

were more common in 2019-2021, while the other findings were mostly seen in 2014-2018, with the most prominent being round pupil, sluggish or no light response and moderately wide pupil.

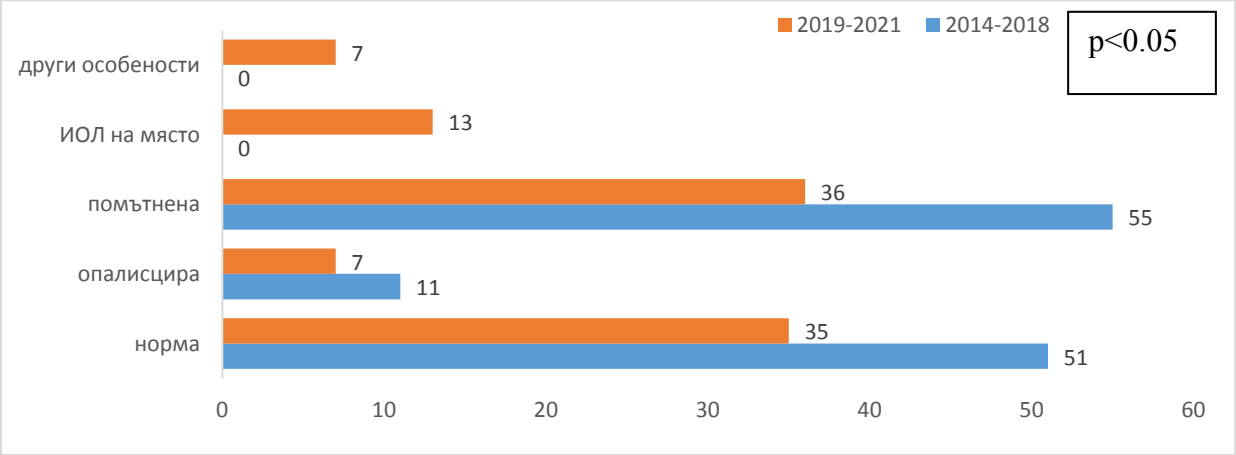



**Figure 18. Lens: biomicroscopy findings (number of patients).**

Lens biomicroscopy findings for the two studied periods also present a significant difference ($p<0.05$) with opalescent and opaque lens occurring more frequently in 2014-2018, while IOL and other features occurred only in 2019-2021 (Fig. 18). In the biomicroscopy findings in the vitreous body, several manifestations stand out, the frequency of which differs during the two investigated periods ($p<0.05$) (Fig. 19). In 2014-2018, findings with a lack of illumination predominate, while haemorrhages are twice as many in 2019-2021; some other features are also exhibited only in the second studied period.

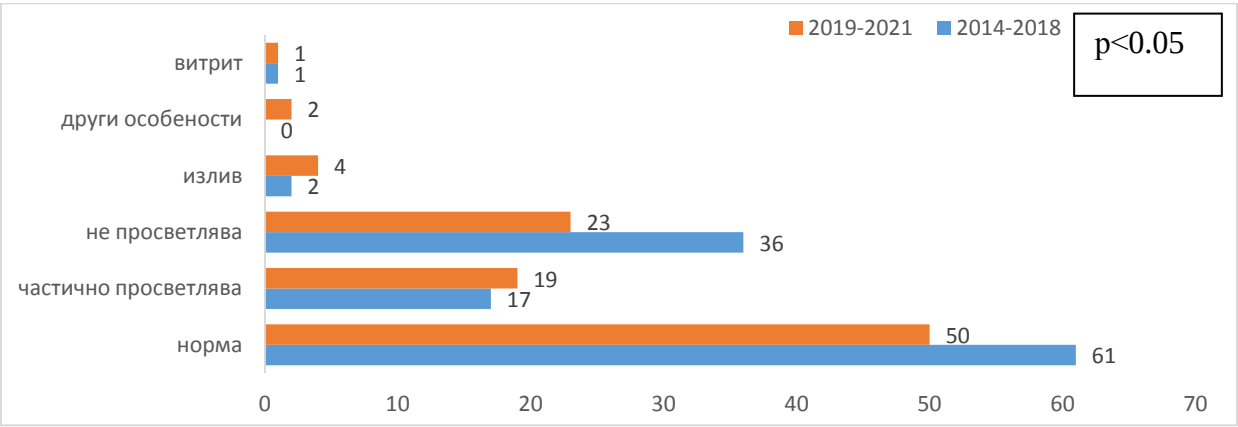



**Figure 19. Vitreous body: biomicroscopy findings (number of patients).**

Variations in manifestation are also observed in the fundus observation (Fig. 20).

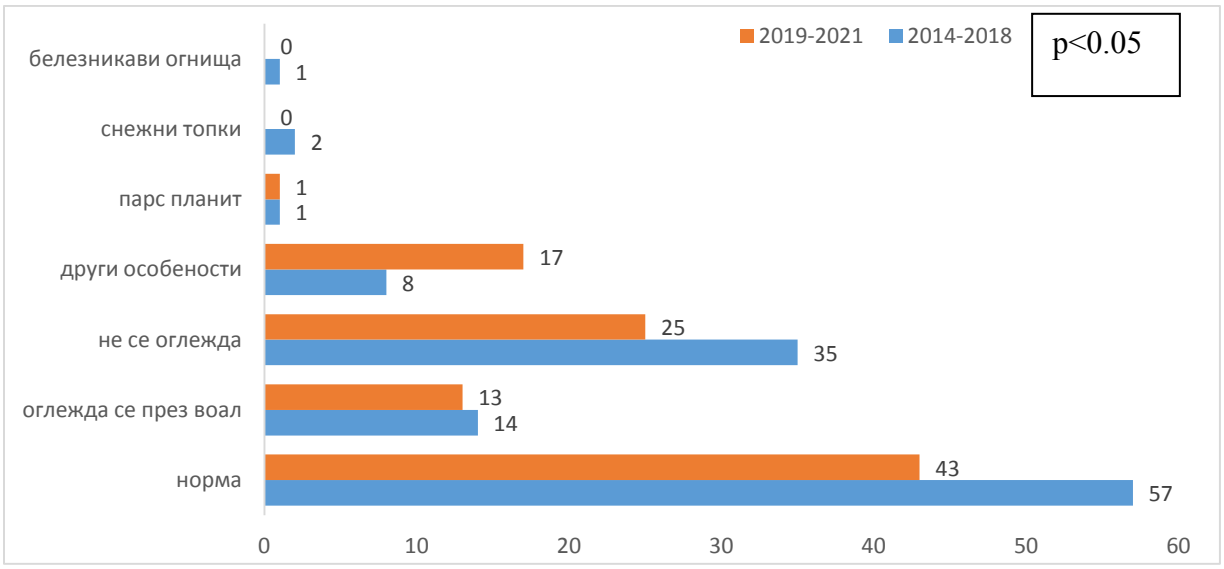



**Figure 20. Present manifestations during fundus ophthalmoscopy (number of patients).**

During the first period, 2014-2018, the frequency of patients in whom the fundus was not able to be examined, or opacities such as "snowball" type were present, prevailed. In the second period, 2019-2021, patients with other characteristics predominate.

On Fig. 21 the visual acuity according to eye symptoms is presented, and no significant difference is found between the two eyes, as well as between the individual symptoms.

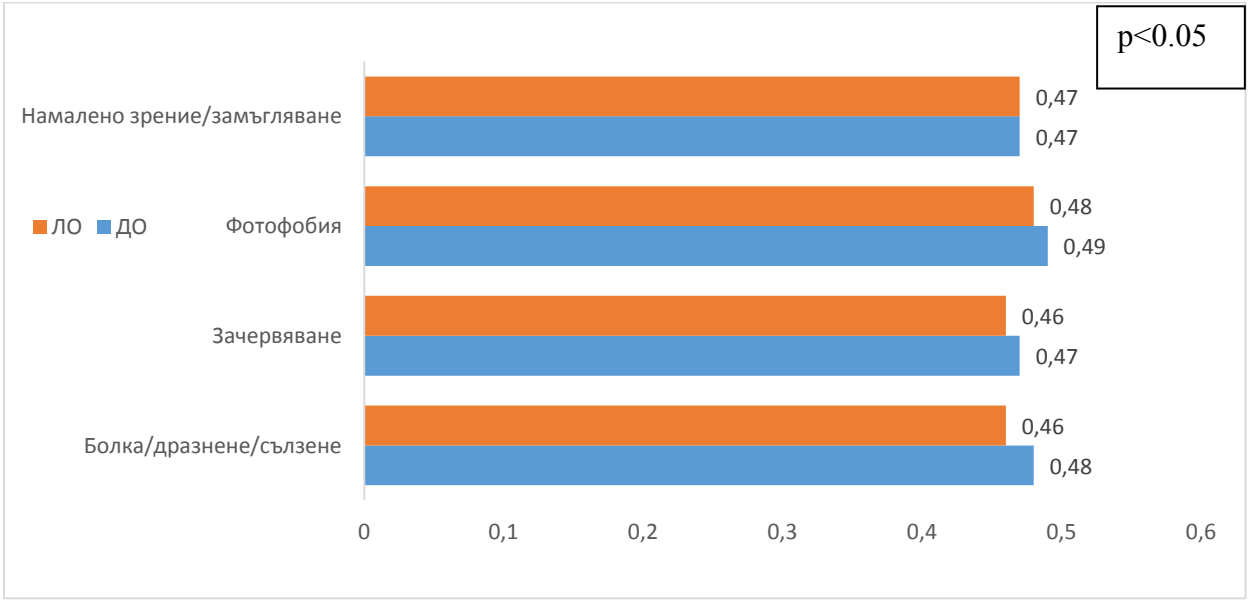



**Figure 21. Symptoms and its reflection on visual acuity.**

On Fig. 22 the IOP according to the ocular symptoms is presented and no significant difference was found between the two eyes, as well as between the individual symptoms.

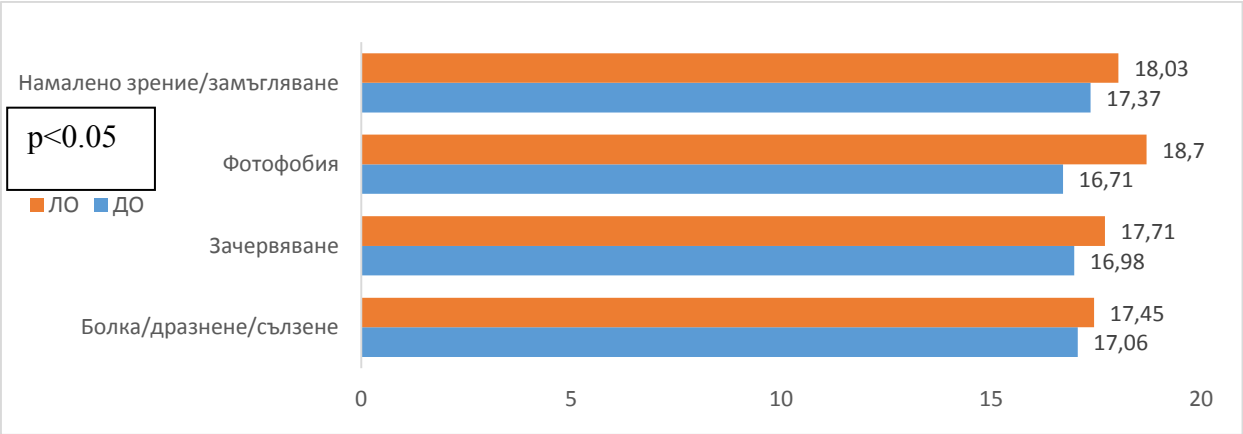



**Figure 22. Dynamics of IOP depending on the manifested eye symptoms.**

### 4.3. Analysis of the treatment of patients with uveitis

On fig. 23 the application of local medications in patients with uveitis for the two studied periods is displayed.

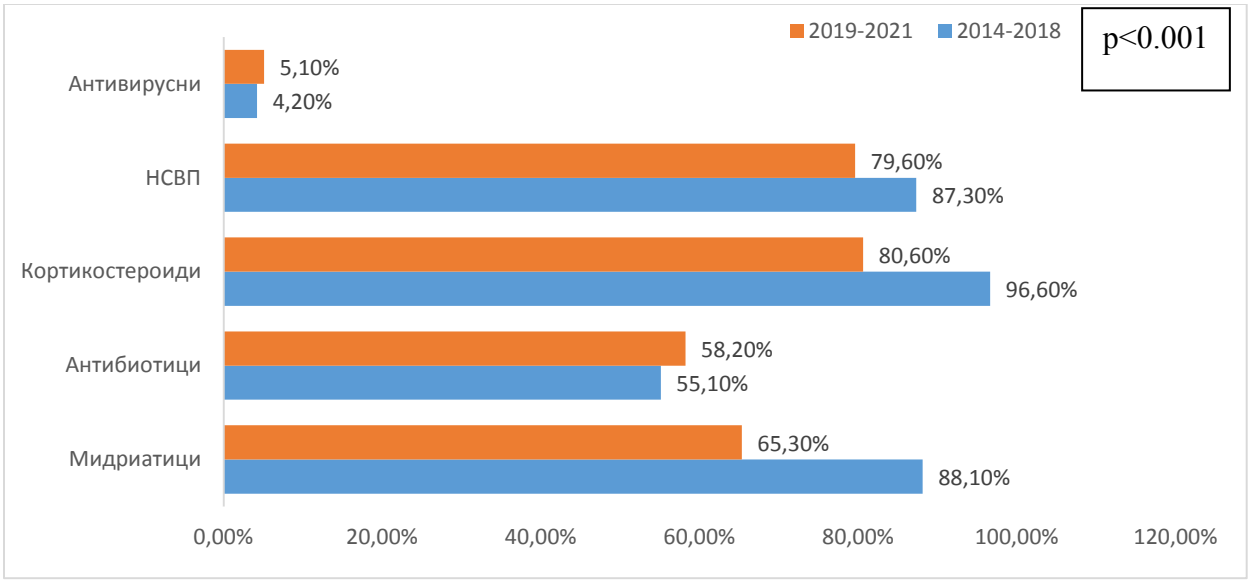



**Figure 23. Distribution of patients according to the local application of medication for the two studied periods.**

From the data presented on Fig. 23, it can be seen that there is a significant difference between the two studied periods in the local application of mydriatics ($p<0.001$) and corticosteroids ($p<0.001$), where the relative share of patients in 2014-2018 prevails. On the other hand, a slight preponderance of the use of antibiotics and antiviral medications during the second period under study - 2019-2021, but the difference is not significant.

From the administration of systemic medications, a significant difference between the two studied periods was found only in the administration of antibiotics ($p<0.003$), where in 2019-2021 a greater frequency of use of this group of medications was observed (Fig. 24).

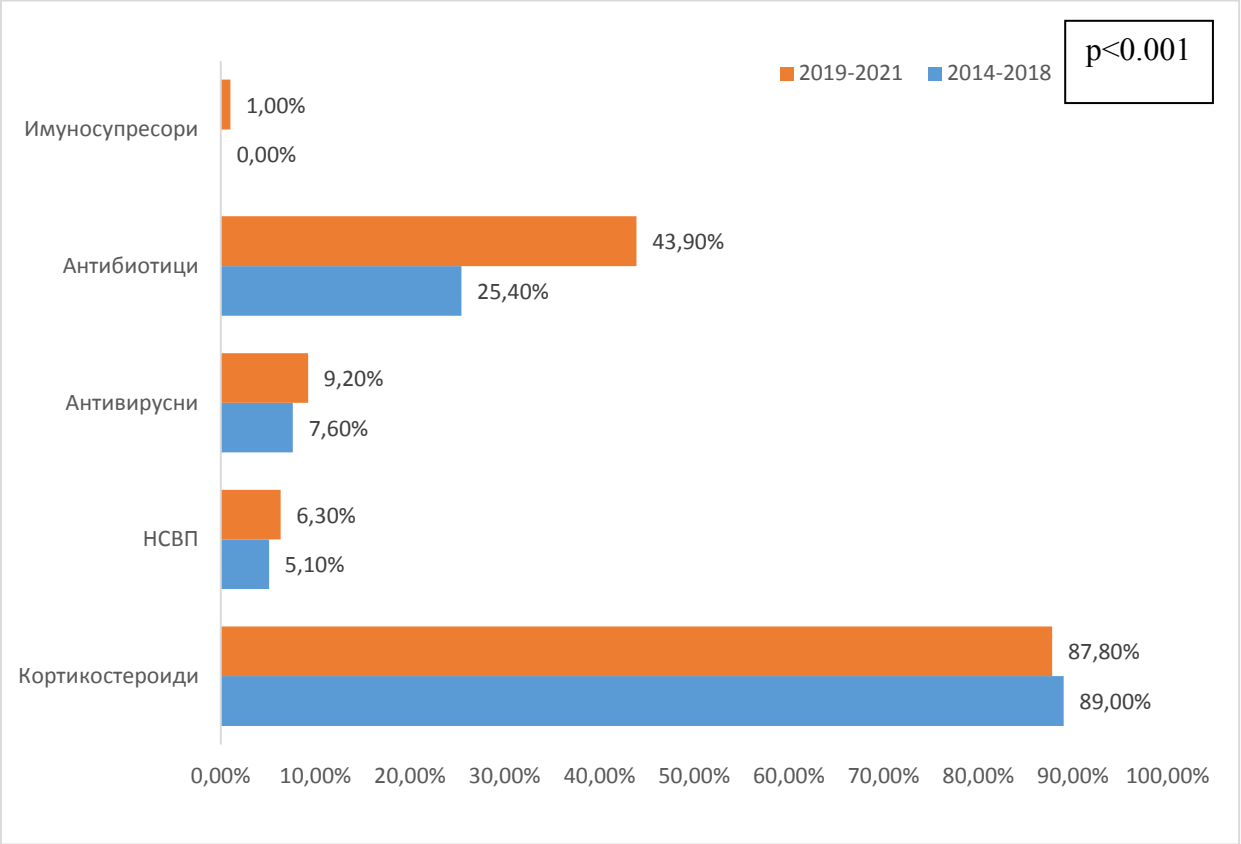



**Figure 24. Distribution of patients according to the systemic administration of medication for the two studied periods.**

When comparing the use of topical and systemic corticosteroids, no significant difference was found. Systemic NSAIDs are applied significantly less compared to topical NSAIDs ($p<0.001$), on the other hand, systemic and topical antibiotics for 2019-2021 maintain a high frequency of use, while for 2014-2018 a lower frequency of use of systemic antibiotics was observed compared to local ones ($p<0.001$). The frequency of use of antiviral medications remained below 10% for both local and systemic use for both periods studied. On Fig. 25 it can be seen that there is a significant difference in the use of biological medications ($p<0.05$) and their use increases significantly in 2019-2021.

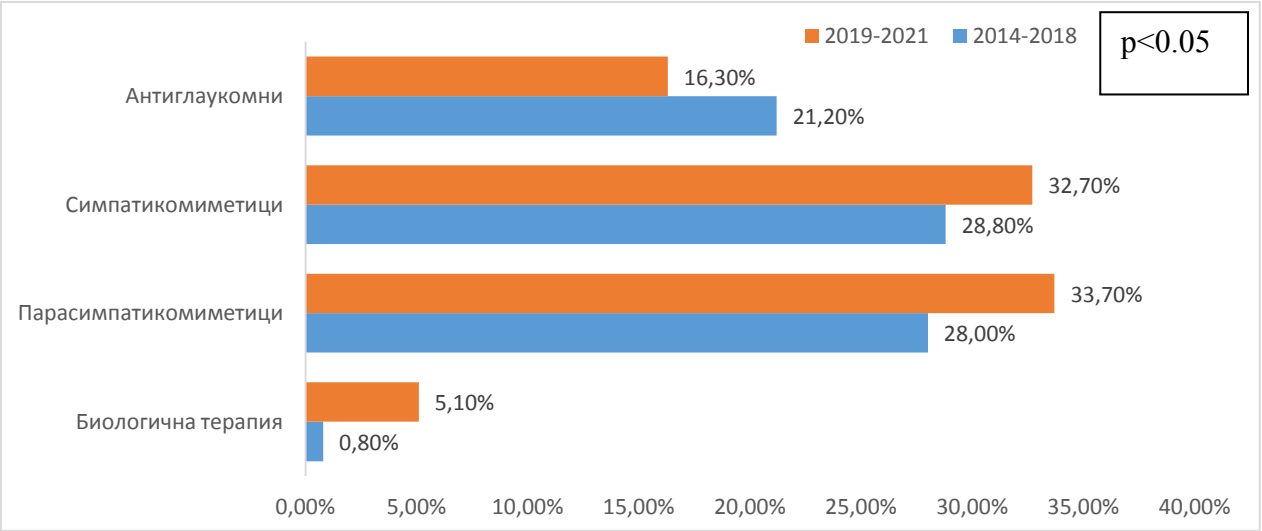



**Figure 25. Distribution of patients according to other types of therapy for the two studied periods.**

The use of parasympathomimetics and sympathomimetics also showed a higher frequency for 2019-2021, but the difference was not statistically significant. Anti-glaucoma medications are more widely used in therapy for 2014-2018 with a non-significant difference again. Examination of uveitis therapy by disease severity displays that biologic therapy is primarily used in patients with moderate to severe uveitis (Fig. 26). For the other types of therapy, a higher relative proportion of patients with moderate uveitis was observed. On Fig. 27 the presentation of the use of topical medications according to the severity of uveitis is shown, with all of them exhibiting an increase in the frequency of use in patients with moderate uveitis.

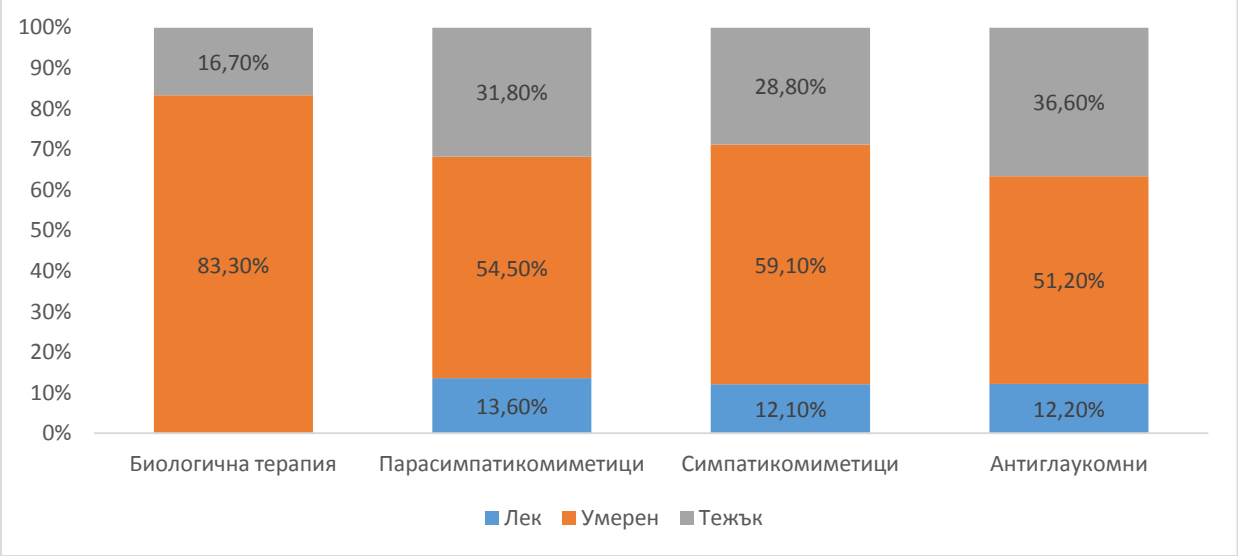


**Figure 26. Distribution of patients according to other types of therapy and the severity of uveitis.**

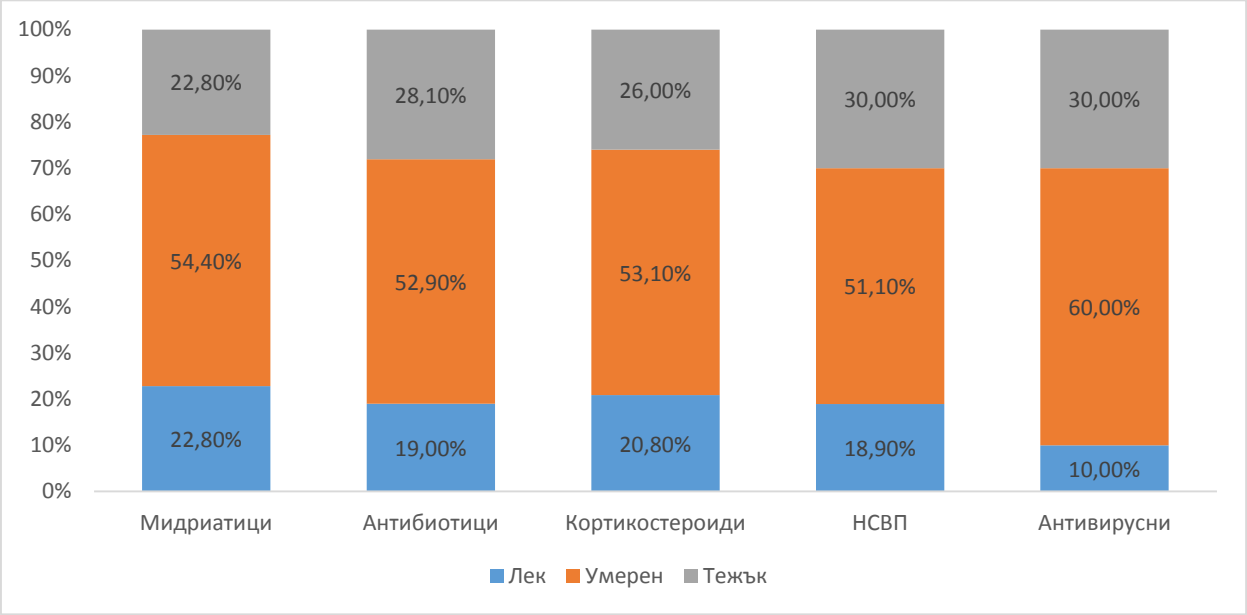



**Figure 27. Distribution of patients according to use of topical medication and uveitis severity.**

The use of systemic corticosteroids, antivirals and antibiotics was most frequent in patients with moderate uveitis (Fig. 28). The use of systemic NSAIDs increases with the severity of uveitis and immunosuppressants are only used in patients with severe uveitis according to the collected data.

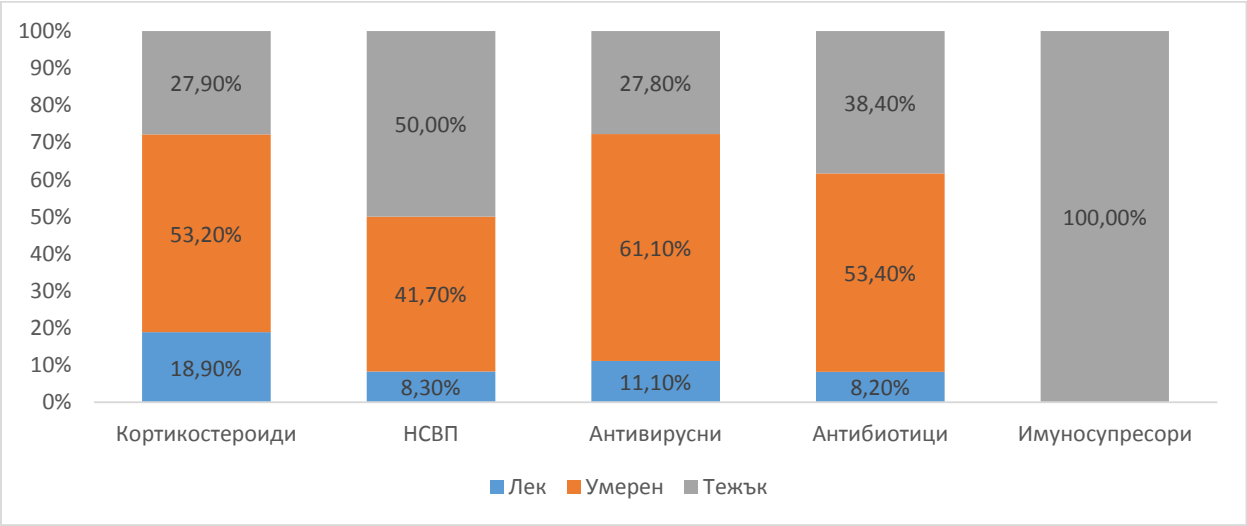



**Figure 28. Distribution of patients according to systemic medication administration and uveitis severity.**

### 4.4. Analysis of the course of the disease - relapses

About 1/5 (20.8%) of the patients had relapses and a significant difference was found between the two studied periods (p<0.001). In 2019-2021 the recurrence rate was significantly higher than in 2014-2018 (31.3% for 2019-2021 and 12.0% for 2014-2018, respectively) (Fig. 29).

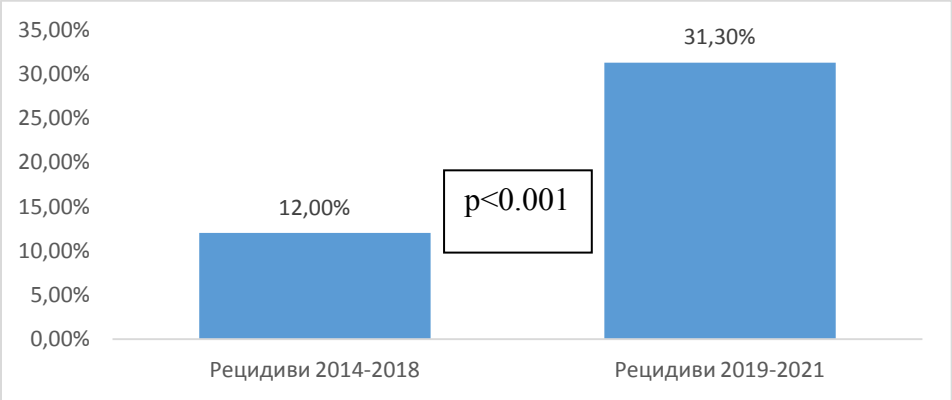



**Figure 29. Distribution of patients according to recurrences and uveitis and the study period.**

Although there is no significant difference, it can be said that in 2014-2018 uveitis recurrences occurred in younger individuals. No significant difference was found in the occurrence of relapses according to gender with males predominating in both periods studied (Fig. 30).

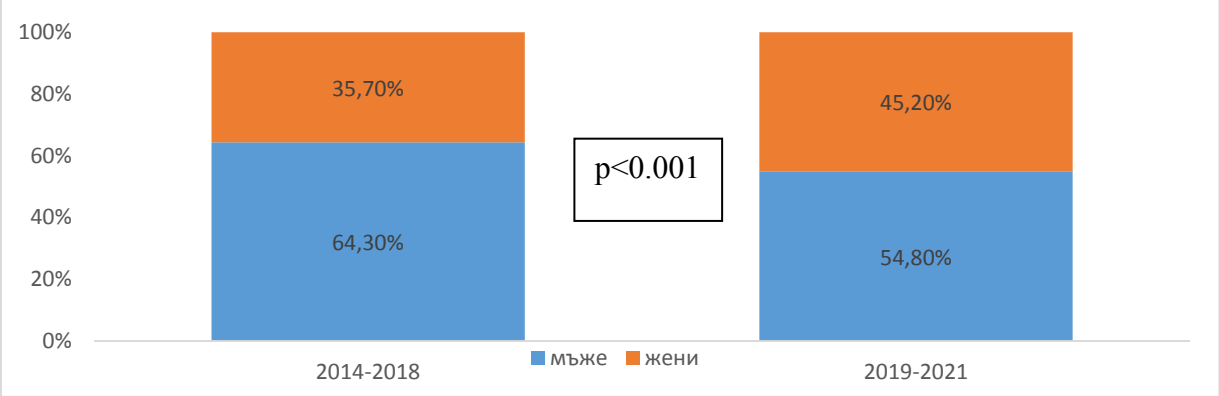



**Figure 30. Distribution of patients by gender and the occurrence of relapses for the two studied periods.**

No subordination was found between the severity of the disease and the occurrence of relapses according to both studied periods. On the other hand, there is a difference between the two studied periods, as for 2014-2018 there is a tendency of decreased recurrences in regard of the severity of uveitis; while in 2019-2021 there is a tendency of increased frequency of relapses with the severity of the disease (Fig. 31).

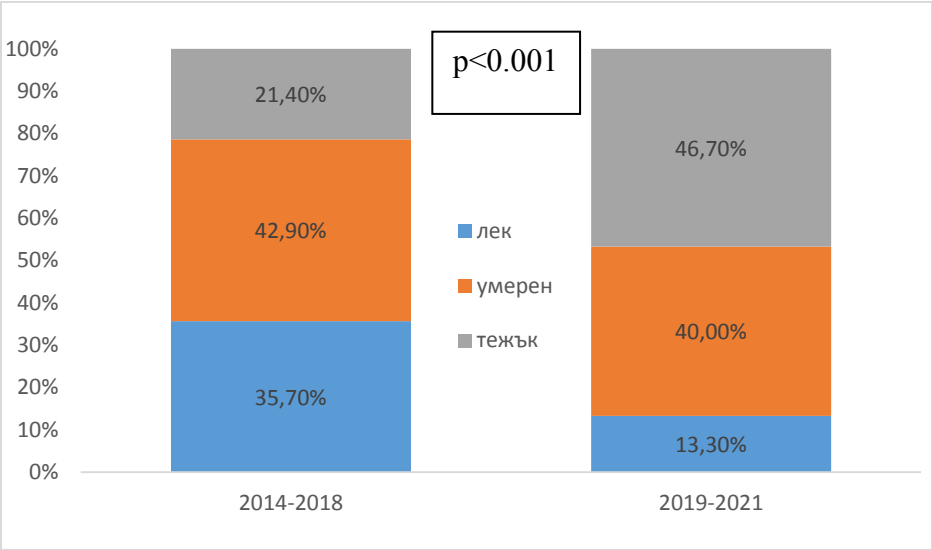



**Figure 31. Frequency of uveitis recurrence according to the disease severity and the studied period.**

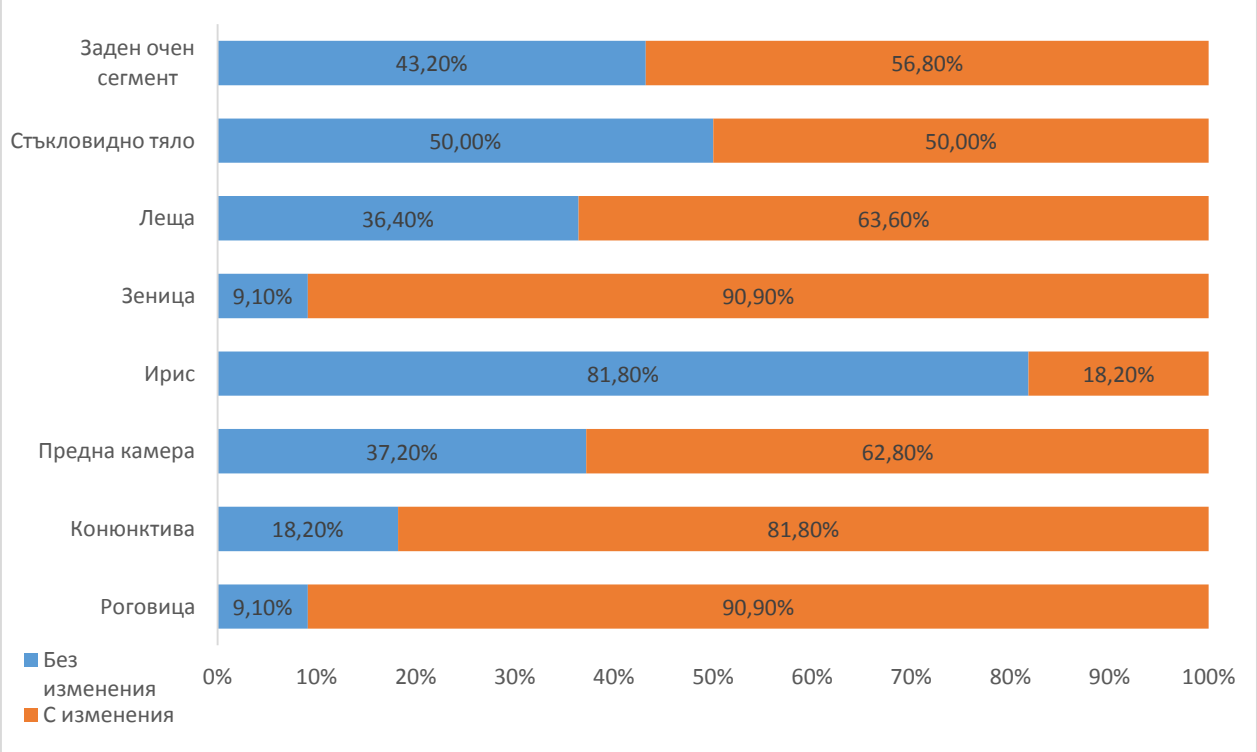



**Figure 32. Recurrence rates according to anterior and posterior eye segment changes.**

A moderate correlation was found between the presence of rheumatoid arthritis and the occurrence of relapses in patients with uveitis ($r=0.311$; $p<0.001$) with a significant difference ($p<0.01$) observed between the two studied periods (Fig. 33).

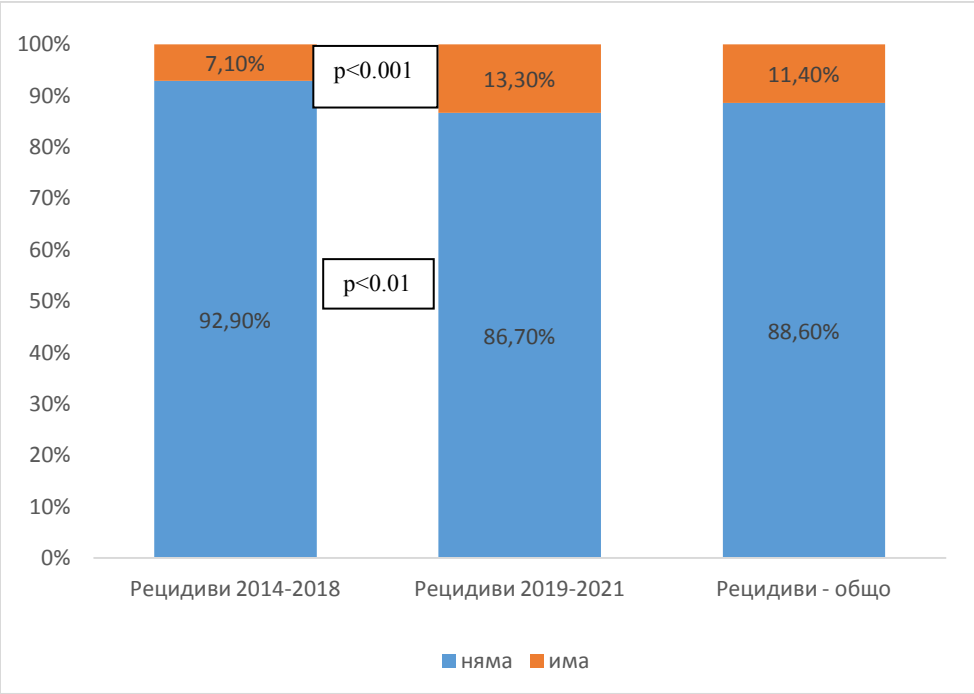



**Figure 33. Frequency of relapses according to the presence of rheumatoid arthritis.**

No significant difference was found in the frequency of recurrence regarding the presence of herpes zoster with only 4.5% of the studied patients with the mentioned disease having uveitis recurrence. Results in patients with herpes simplex were identical with only 6.5% having uveitis recurrence. Contrarily, it is striking that there is a difference in the risk assessment indicator, as for 2014-2018 herpes simplex carries a 2.56 times greater risk for uveitis recurrences (OR=2.56 (0.248-26.506); $p<0.05$), while for 2019-2021 this risk indicator decreased to 1.14 (OR=1.14 (0.198-6.606); $p<0.05$). These results may be due to better disease control in these patients group.

Ankylosing spondylitis can be considered as a risk factor for the development of recurrences in uveitis, carrying a 3.53 greater risk of recurrence (OR=3.53 (1.023-12.147); $p<0.05$). It is also noted that there is a difference regarding the risk of relapses in the patients with ankylosing spondylitis and uveitis during the two studied periods, such as for 2014-2018 the autoimmune disease carries a 5.56 times higher risk of uveitis recurrence (OR=5.56 (0.842-36.654); $p<0.05$), while for 2019-2021 this risk decreased to 2.41 (OR=2.41 (0.457-12.687); $p<0.05$). This difference is also observed in terms of the recurrence rate in the two studied periods, which decreases in the second studied period (2019-2021). This can be explained by the good results that are achieved in the control of the disease when using modern biological therapy.

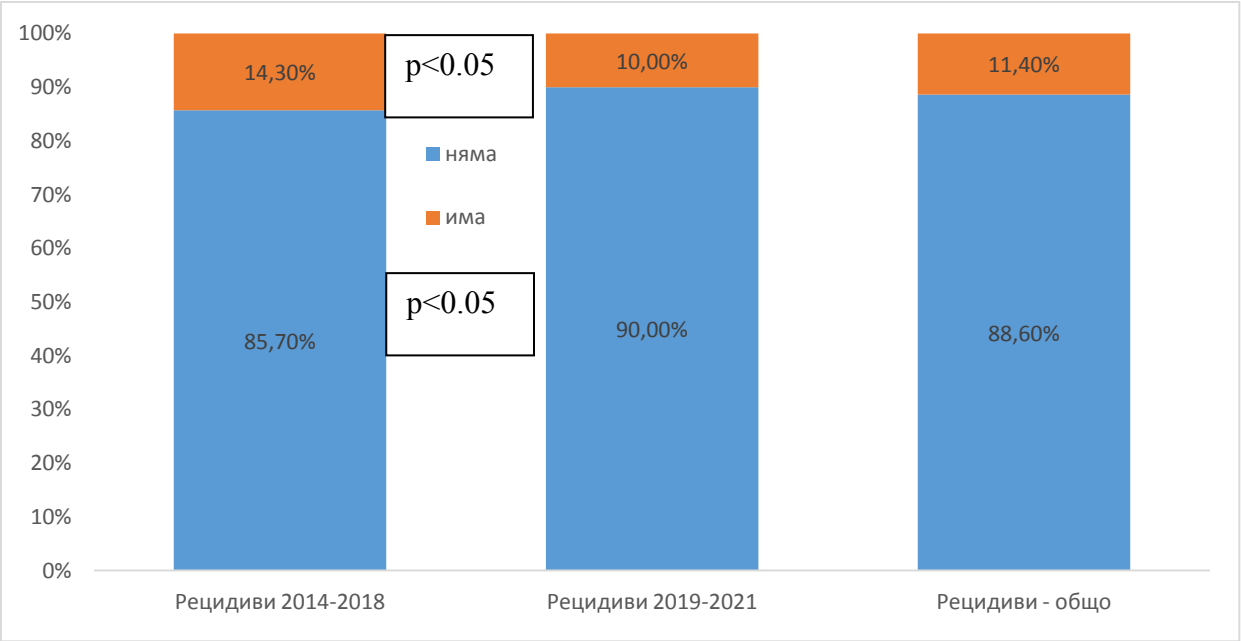



**Figure 34. Frequency of relapses according to the presence of ankylosing spondylitis.**

Single patients, in whom recurrences of uveitis are found, have ophthalmia sympatica, psoriasis vulgaris, toxoplasmosis and Reiter's syndrome. Examination of the symptoms in uveitis patients who have relapses shows that pain, irritation and tearing are the most prominent and photophobia occurs in about 1/3 of patients (Fig. 35).

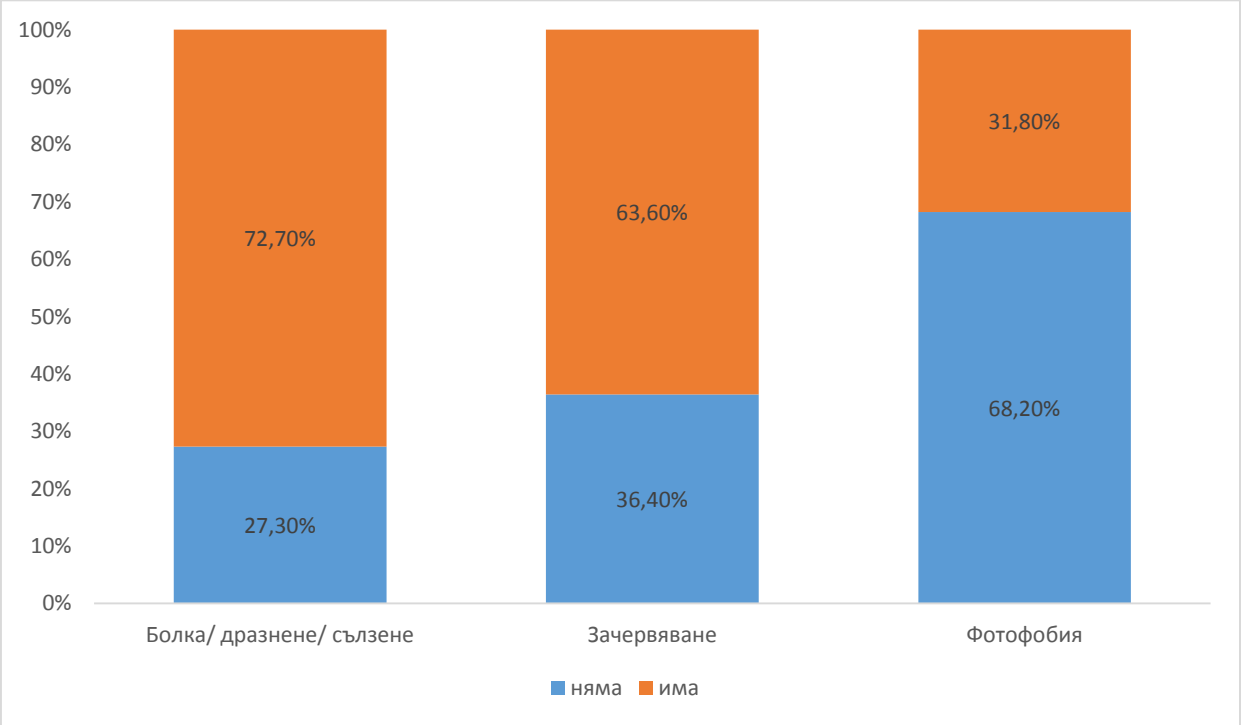



**Figure 35. Frequency of relapses regarding the eye symptoms.**

**4.5. Creating a risk profile of the studied patients with uveitis and predicting the risk of recurrence and a behavior algorithm in patients with infectious and non-infectious uveitis**

Uveitis is caused by diseases of various etiologies, including a wide range of infectious and non-infectious causes. The inflammatory process mainly affects the uveal tissues with subsequent damage to the retina, optic nerve and vitreous body. In several cases, it reflects diseases that develop in the patient's body and can be the first evidence of such systemic diseases, creating a challenge for the ophthalmologist in reaching the etiologic diagnosis. Furthermore, because several manifestations share common clinical symptoms and signs, etiological diagnosis can be a difficult task.

Table 1 presents the risk profile of patients with uveitis for recurrence of the disease and the development of severe disease.

**Table 1. Risk analysis for the development of severe type of disease and recurrence of uveitis.**

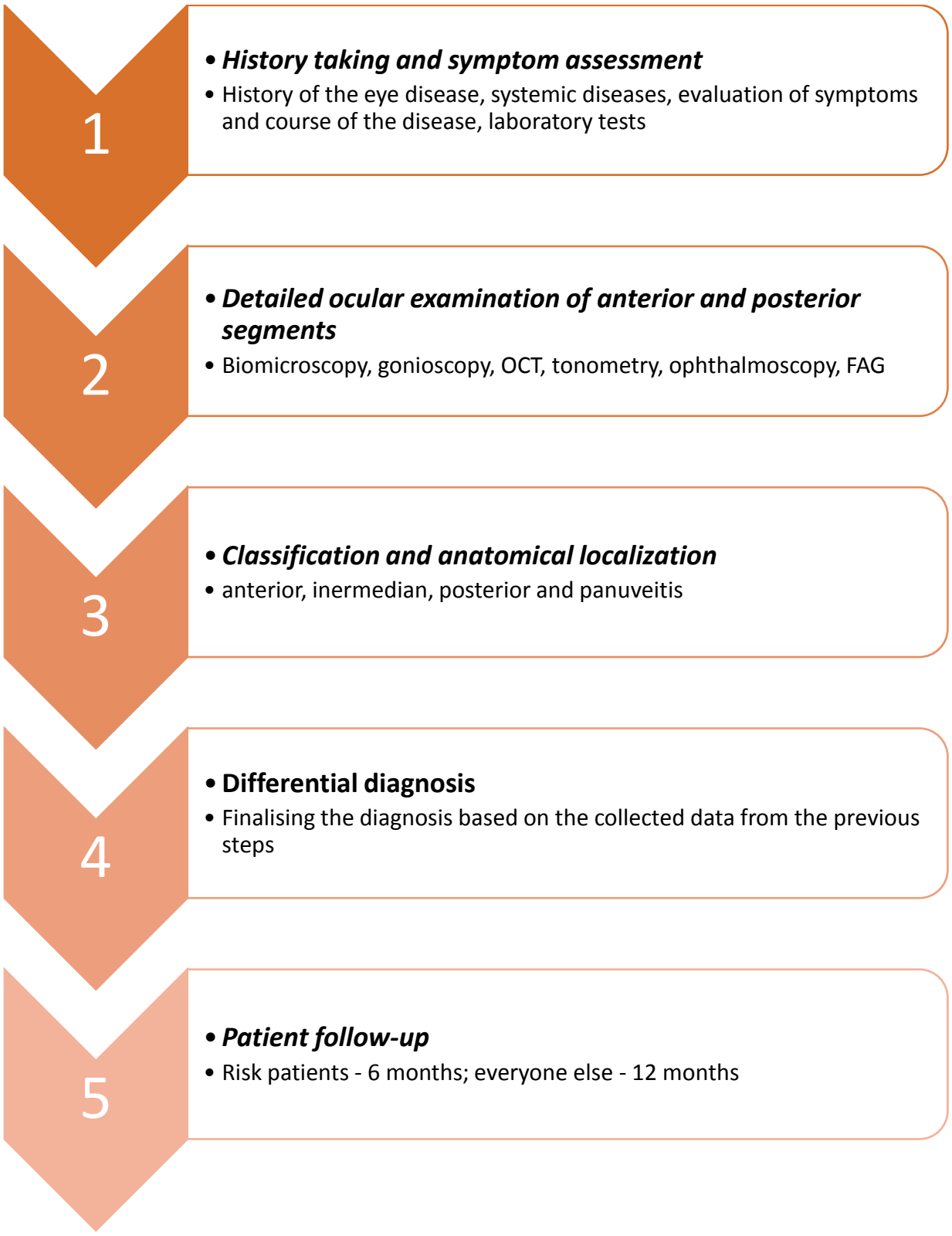
| Indicator | OR | 95% CI | P |
|---|---|---|---|
| **Rural area** | 2.6 | 0.752-8.986 | < 0.05 |
| **Bilateral course** | 2.76 | 0.347-22.049 | < 0.05 |
| **Ankylosing spondylitis** | 3.53 | 1.023-12.147 | < 0.05 |
| **Herpes zoster** | 3.61 | 0.461-28.256 | < 0.05 |
| **Rheumatoid arthritis** | 8.8 | 0.797-30.985 | < 0.001 |
| **Psoriasis vulgaris** | 21.0 | 0.895-71.018 | < 0.001 |

Algorithms solve the problem by showing the critical paths to take. The steps in building an algorithm include the following:

- Defining the problem and deriving a clinical diagnosis using a naming technique given by Nozik.
- Review all possible causes of the condition and compare with existing known models of uveitis, also known as linking technique.
- Proving the diagnosis by presenting the diagnostic modalities in a logical manner.

The etiologic diagnosis of uveitis begins with the first step of a detailed history taking, followed by a systemic and eye examination to reach a clinical conclusion. Subsequently, a differential diagnostic list is created to decide on laboratory tests to rule out or determine the possible

etiology. Sometimes other specialists may need to be consulted, such as a rheumatologist, infectious disease specialist, pulmonologist, dentist or dermatologist.



**History taking and symptom assessment**

Making a final diagnosis of uveitis begins with a thorough collection of anamnestic data. Subsequently, a precise systemic and ocular examination will offer a clinical conclusion. It is estimated that over 70% of the diagnosis can be made only on the basis of a detailed medical history and a thorough clinical work-up. Systemic history suggests a possible association of systemic disease with ocular involvement. It is often the clinical acumen of the ophthalmologist that indicates the diagnosis, which is further confirmed or rejected by a specific laboratory approach.

- **Importance of age**

Certain diseases are more prevalent for certain age groups. Juvenile arthropathies and parasitic uveitis are the most common diseases in patients under 16 years of age [3]. In general, infection-based secondary uveitis is common in the elderly and immunological diseases are common in middle age [3]. Some of the examples are:

- Children: juvenile rheumatoid arthritis, toxocarosis.
- Young patients: Behcet's uveitis associated with human leukocyte antigen B27, Fuch's uveitis.
- Old age: Vogt-Koyanagi-Harada (VKH) syndrome, Herpes Zoster Ophthalmicus, Tuberculosis.

- **Importance of gender**

Certain diseases have a gender predilection as given below [4].

- Males - ankylosing spondylitis, Reiters disease, Behcet's disease, sympathetic ophthalmia.
- Women - rheumatoid arthritis, juvenile rheumatoid arthritis.

Demographic characteristics such as race and ethnicity may predispose to the development of specific conditions, for example [5]:

- Ankylosing spondylitis, Reiters - Caucasian race;
- Sarcoidosis – Afro-American race;
- VKH syndrome, Behcet syndrome – Middle-Eastern race.

### Importance of socioeconomic factors and lifestyle

Activities such as swimming in open water bodies can expose individuals to water-borne diseases that can eventually lead to uveitis. The best example is leptospirosis and trematode granulomas. Patients who own or care for dogs or cats may be exposed to intestinal parasites. Toxoplasma gondii and Toxocara canii occur after ingestion of contaminated food sources or contact with soil. People whose profession is related to work on sewage systems may be at risk of various zoonoses [5]. Some examples of zoonotic diseases result from contact with the following animals:

- Toxoplasmosis - cats;
- Toxocarosis - dogs;
- Leptospirosis, cysticercosis - cattle;
- Cysticercosis, leptospirosis - pigs.

Lifestyle can be a predisposing factor for the development of: HIV, leptospirosis and trematode granuloma in children [6] [7] [8].

### Importance of systemic disorders

Vascular disorders as seen in collagenoses are the best examples of noninfectious systemic disease that can cause severe ocular morbidity. Other examples include sarcoidosis, Behcet's syndrome, Reiter's syndrome and VKH syndrome. Tuberculosis, leprosy, syphilis are common systemic infections that can cause uveitis [9]. Endogenous endophthalmitis is more common in diabetes, kidney disease and immunosuppressed patients.

### Significance of eye symptoms

Pain, redness, and photophobia are the important symptoms for anterior uveitis, while floating opacities, with or without reduced vision, are important for intermediate and posterior uveitis [10].

**Detailed eye examination**

1) A systematic eye examination is a requirement for all patients with uveitis, starting with an assessment of the patient's best-corrected visual acuity.

2) Examination of the conjunctiva, episclera, sclera and pupil.

3) Biomicroscopy - Examination of the anterior surface of the eye should first be performed with direct focal illumination. The reaction of the conjunctiva and episclera is associated with ciliary injection - livid, diffuse, localized. In cases of uveitis, congestion of the perilimbal area is more than the palpebral and fornix conjunctiva. We examine the cornea with focal illumination, slit beam and retrograde illumination. Anterior chamber is to be checked for presence of cells, Tyndall effect, presence of hypopyon/hyphema. The pupil is examined with oscillating light, looking for a reaction to light, occlusion or seclusion. In biomicroscopy, depending on the finding, uveitis can be classified as granulomatous or non-granulomatous (presence or absence of nodules on the iris). The examination can display the severity, timeline and possible complications of the disease.

4) Anterior chamber reaction - The presence of cells and inflammation in the anterior chamber is a marker of inflammation of the iris and ciliary body. The field size recommended for examination is a 1 mm by 1 mm slit beam to classify anterior chamber cells and extension.

| Cells in anterior chamber | |
|---|---|
| Degree | Cells in field |
| 0 | <1 |
| 0.5+ | 1-5 |
| 1+ | 6-15 |
| 2+ | 16-25 |
| 3+ | 26-50 |
| 4+ | >50 |
| **Inflammation** | **Description** |
| 0 | It is completely missing |
| 1+ | Mild (barely noticeable) |
| 2+ | Moderate (iris and lens details are clear) Marked (iris |
| 3+ | and lens details are unclear) Severe (fibrin in the intraocular |
| 4+ | fluid) |

**Figure 36. Classification scheme of the SUN* working group [11] for anterior chamber cells and extension.** Free access.

1) Iris - Evaluation of the iris may include areas of discoloration, presence of granulomas, synechiae, edema, posterior synechiae and increased IOP. Atrophy of the iris is often associated with herpetic uveitis. Varicella zoster virus usually causes sectorial iris atrophy due to occlusive vasculitis, while herpes simplex virus usually causes macular iris atrophy. Other causes of atrophy include anterior segment ischemia, Hansen's disease trauma, and previous episodes of angle-closure glaucoma. Granulomas can be located in the stroma of the iris or choroid. Iris nodules are most commonly seen at the edge of the pupil and are described as Koeppe nodules, while those on the surface of the iris are called Busacca nodules. Sarcoidosis, tuberculosis, VKH syndrome, sympathetic ophthalmia and syphilis can lead to iris nodules. The normal radial vessels of the iris may be seen dilated in acute inflammation causing hyperemia of the iris, as in rubeosis of the iris; they disappear when the inflammation is controlled. Iris heterochromia can be either hypochromic (the abnormal eye is lighter than the other eye), as seen in Fuch's heterochromic iridocyclitis, or hyperchromic (the abnormal eye is darker than the other eye), as seen in iris melanosis.

2) Tonometry - The disease can occur with both increased and decreased IOP. IOP in patients with uveitis is most often decreased due to impaired production of ventricular fluid due to involvement of the ciliary body. Factors that can affect IOP include accumulation of inflammatory material in the trabecular meshwork, inflammation of the trabecular meshwork (trabeculitis), venous obstruction and steroid therapy.

Causes of elevated IOP include:

- Posner-Schlossman syndrome;
- Herpetic uveitis;
- Toxoplasmosis;
- Fuchs' heterochromic iridocyclite;
- Sarcoidosis.

3) Gonioscopy - Gonioscopy can reveal the presence of peripheral anterior synechiae. Cells can that clog the trabecular meshwork and lead to an increase in IOP can be found. Abnormal iris vessels, neovascularization or fine branching vessels, as seen in Fuch's heterochromic iridocyclitis, are easily identified by gonioscopy and their presence can guide to an appropriate therapy. In cases where traumatic uveitis is suspected, recession of the angle and the presence of a foreign body may be seen.

4) Fundoscopy - During fundoscopy, the state of the fundus reflex is assessed.

- Lens - The most common type of cataract in patients with uveitis is posterior subcapsular. Changes in the anterior lens capsule, pigment deposits at the site of iris adhesion can be observed. Clouding of the anterior lens capsule after extreme IOP elevations (glaukome flecken) provides information about a past acute glaucomatous attack.
- Vitreous body - In active vitritis the cells appear white and are evenly distributed. Old cells are small and pigmented. Active cells can be found in front of the chorioretinal focus. Focal accumulation of inflammatory cells around vessels is seen in active retinal vasculitis. Inflammatory cells that accumulate (snowball-type) may deposit on the lower peripheral retina, as seen in intermediate uveitis associated with sarcoidosis. Cells can accumulate in the retrovitreal space after shrinkage of the vitreous fibrils and posterior vitreous detachment.

If there is an area of active chorioretinitis in one quadrant, the red reflex is replaced by a yellowish reflex. If there is choroidal hemorrhage in an area, the red reflex is dark only in that area. During fundoscopy, the finding in the fundus is objectified - multiple and cotton-like opacities with unclear boundaries in an active inflammatory process and clearly outlined with pigment clusters, whitish cuffs along the course of the vessels - in vasculitis, hyperemia, edema of the optic disc nerve, areas of necrosis.

- Pars plana - Examination of the peripheral retina and pars plana for the presence of an inflammatory reaction - snowball type.
- Retina and choroid – Retinitis presents with a yellow-white appearance and poorly defined margins, often associated with hemorrhage and exudation. The involvement can be focal or multifocal. In retinal vasculitis, whitish cuffs are seen around the vessels, usually in cases of retinitis, but also in Wegener's granulomatosis, systemic lupus erythematosus, viral retinitis, including herpes infection, or viruses, including Chikungunya or West Nile virus infections. Vascular involvement can alter the blood-retinal barrier and lead to exudative retinal detachment.
- Optic disc - Inflammation of the optic disc can occur with or without other signs of uveitis. Optic disc involvement is in the form of papillitis or disc swelling and neovascularization. Neovascularization occurs in ischemic conditions and is characterized with vessels that bleed

easily. Sarcoidosis and leukemia can infiltrate the optic disc, mimicking a picture of papillitis. Optic neuritis can occur in multiple sclerosis.

- Macula - Chronic inflammation can lead to the following pathologies of the macula:
  - Cystoid macular edema;
  - Macular lamellar holes;
  - Clumping of epithelium;
  - Choroidal neovascular membrane;
  - Exudative detachment of the macula.

**Anatomy localization of uveitis: help of the ophthalmologist in prehospital care**

Based on the thorough eye examination, we also determine the anatomical localization of the inflammatory process.

**Anterior uveitis**

Anterior uveitis causes inflammatory changes mainly in the anterior chamber as a result of inflammation of the iris and the ciliary body. Inflammation of the iris - iritis includes hyperemia of the iris, smoothing of the surface of the iris due to edema. Adhesion in the anterior chamber, precipitates, hypopyon, the presence of posterior synechiae presents the picture of iridocyclitis. The cornea can be secondarily involved in the inflammatory process with edema, m.Descemeti folds - keratouveitis. The sclera can be involved secondarily and then we speak of sclerouveitis.

Severe or chronic anterior uveitis can lead to secondary structural complications such as macular edema, optic disc edema, cataracts, corneal edema, band keratopathy or iris abnormalities.

**Intermediate uveitis**

Intermediate uveitis is an inflammation localized in the periphery of the vitreous body. Inflammation occurs in the ciliary body, pars plana and/or the peripheral retina. Clinical signs include vitreous opacities, which are often associated with peripheral retinal vasculitis. Macular edema is the most common complication; severe or chronic disease may cause peripheral exudative or tractional detachment, retinal neovascularization, cataract or epiretinal membrane formation. The diagnostic term, pars planitis, refers to the subset of intermediate uveitis in which

there are peripheral preretinal collections of exudates in the absence of associated infection or systemic disease.

**Posterior uveitis**

Posterior uveitis /chorioretinitis/ is an inflammation involving the retina and/or choroid. Inflammatory cells can be observed diffusely throughout the vitreous body or in front of the active inflammation area. Fundoscopy reveals focal, multifocal or diffuse areas of retinitis and/or choroiditis, often with retinal vasculitis. Subjects may have a similar clinical appearance, although some clinical disease patterns are almost pathognomonic for diagnosis. Structural complications such as macular edema, epiretinal membrane and retinal or choroidal neovascularization are not sufficient for the anatomical classification of posterior uveitis.

**Panuveitis**

In panuveitis, inflammation is present diffusely throughout the eye. Inflammation can be associated with an infectious or non-infectious systemic disease.

**Retinal vasculitis**

Retinal vasculitis is defined by the presence of vascular changes in the retina associated with ocular inflammation. The term retinal vasculitis is used in contrast to vasculopathy, in which there are changes in the vessels but no visible signs of inflammation. Retinal vasculitis includes perivascular sheathing, vascular leakage or occlusion demonstrated on fluorescein angiography studies. Retinal vasculitis is not considered a defining feature of the anatomical classification of uveitis.

**Differential diagnosis**

After carefully conducted history taking and performing a complete systemic examination, the specific clinical entity can be determined. A probable list of etiologies will be included based on the objective findings and history of comorbidities. Once we arrive at a probable cause of the illnesses, we must verify them with laboratory tests and other specialists. The overall workup leads the clinician to the differential diagnosis list and then to laboratory work before treatment is finalized.

## V. DISCUSSION

Uveitis is an extremely complex disease that can progress differently in each patient. There are many known causes for the development of the disease - infections, autoimmune diseases, systemic diseases, trauma, but the percentage of uveitis due to unclear origin remains high. The disease creates many differential-diagnostic problems and often therapeutic ones as well. Sometimes the unfavorable outcome of the disease also affects the social status of the patients and their quality of life. Therefore, uveitis carries its psychological and economic burdens for patients, their relatives and society. The spread of the disease depends on a number of factors - sex, age, place of residence, race, environmental influence, genetic factors, social habits, health status, state of the health care system. The localization of the inflammatory process, as well as the findings, can direct the ophthalmologist to a specific cause, but in most cases, a large set of tests must be performed to be correctly interpreted. All this requires good collaboration with general practitioners and specialists - infectious disease specialists, immunologists. Knowing the symptoms of the disease from the GP can shorten the response time and improve the outcome of uveitis. This also determines the interdisciplinary nature of uveitis. Therefore, studying the regional patterns of uveitis is useful and can give us a picture of the features of the disease in Northeastern Bulgaria.

Uveitis has always been in the field of challenges in ophthalmology - frequent relapses, unclear etiology, sometimes difficult to treat and their possible complications define their characteristics. Therefore, the interest in them and their analysis is justified. Each study of the disease has its own contribution and brings us even a small step forward. A study of uveitis patients who have passed through USBOBAL-Varna can help us refine our work related to diagnosis and treatment and eliminate at least some of the gaps in the management of these patients.

Although it is not the primary cause of blindness such as cataracts, age-related macular degeneration (ARMD) and glaucoma, it can cause blindness primarily through the disease process itself or through secondary complications such as cataracts and glaucoma. This makes optimal management of uveitis an important aspect of eye care. However, one of the main challenges in treating uveitis is reaching an accurate diagnostic conclusion early on. Over time, the development and advancement of diagnostic tools and techniques have improved the way we diagnose and manage patients with uveitis. There is wide epidemiologic variability for uveitis depending on age, ethnicity, gender and genetic predisposition, which may aid in the differential

diagnosis of uveitis. The frequency and prevalence of each type of uveitis differs in different regions of the world. Understanding the epidemiology and causes of uveitis in different regions will further assist clinicians in a targeted approach to the management of patients with diagnostic difficulty in the diagnosis of uveitis. Laboratory tests have an important role in supporting the etiological diagnosis. In most cases, they are conducted to support the clinical diagnosis or to aid in a differential diagnosis. On the other hand, the irrelevant results of these tests can make the diagnosis difficult. Therefore, there should be appropriate indications for the appointment of the relevant tests. Usually, a detailed history taking combined with a systemic examination can confirm the relevant diagnosis. Recent advances in ocular pathology have helped to understand the immunology of uveitis - the role of cytokines and methods of modulating cytokine genes in the pathology of uveitis, which in turn has led to new methods of treatment. The mean age of patients in this study (54.2 years) was higher than that reported in a study by researchers from Brazil (32.1 years) [12], as well as in other studies conducted in reference centers in Colombia (31.7 years) [ 13] [14], Tunisia (34.0 years) [15] [16], North America (45.0 years) [17] and Southeast Brazil (41.0 years) [18]. Most patients in our study were working adults, similar to patients in a study by other investigators [19] [20]. Retrospective study by Gürsoy and colleagues for the period 2015-2020. regarding the socio-demographic characteristics of patients from the Eastern Black Sea coast reported an average age of patients of 35.85±16.79 years, which once again confirms our hypothesis about the specificity of the disease, according to which uveitis covers different age groups [21]. The data support findings from population studies that describe an increasing incidence of uveitis with increasing age. Regarding the results relative to other developed countries, the data from our study is consistent with the reported results from Spain [22], Greece [23] and Germany [24], where the incidence of the disease increases with increasing age and uveitis in children and adolescents isn't as common. The mean age reported in our study is higher than that among developing and third world countries, possibly due to better access to health care, prevention and diverse infectious agents in regions of low socioeconomic status. Most epidemiological studies of uveitis show no significant difference between male and female gender [25] [26] [27] [28] [29] [30] [31] [32]. Similar results are reported in the present study, where no difference was found between the two sexes, despite the slight preponderance of men (57.3%). The most common location of uveitis worldwide is anterior uveitis. These results are also confirmed by the present study, where anterior uveitis represents 91.2% of the investigated

cases. The most common diagnosis among uveitis is idiopathic uveitis [33][34][35][36][37] [38][39][40] and acute anterior uveitis was reported as the most common cause in three other studies [41] [42] [43]. In the present study, idiopathic uveitis was found in 42.2% of cases and acute anterior uveitis was diagnosed in 44.7% of cases. In addition, viral uveitis can be named the second and third most common cause of uveitis.

The etiology of disease in the developed and developing world differs dramatically. In the developed world, the most common cause of unilateral involvement is uveitis associated with spondyloarthropathies [44], Fuch's heterochromic uveitis [45] and herpetic anterior uveitis [43]. In contrast, studies from the developing world have included a relatively high prevalence of traumatic uveitis, herpes, toxoplasmosis, phacolytic uveitis, parasitic anterior uveitis in children and leptospirosis as important causes of unilateral inflammation [46][47][48][49][50][51]. Bilateral uveitis is more common in some studies from the developed world, while some of the bilateral uveitis is specific to certain geographic locations in the developing world [45][48][49][50]. Those observed in our population are Vogt-Koyanagi-Harada, sympathetic ophthalmia, serpiginous choroiditis and leptospirosis uveitis. Overall, nongranulomatous uveitis, which has been reported to account for 51-89% of cases in previous articles, is more common than granulomatous uveitis, which is supported by the data of the present study at 74%. In a significant proportion of patients, the cause of uveitis remains unknown despite appropriate investigation, regardless of age, sex, or anatomical location; according to previous studies in approximately 30-60% of patients. In general, anterior and intermediate uveitis are more often idiopathic than posterior and diffuse forms of inflammation and uveitis is more often idiopathic in women than in men. In the current study, 44.6% of the total cohort with uveitis and 47.8% of women had idiopathic uveitis. In more than half of our patients, no causative agent of the inflammation was found and they are included in the idiopathic group. However, the unclassified cases of uveitis in this study may include true idiopathic uveitis as well as patients who underwent extensive investigations, but only within the capacity of the respective centers. Furthermore, given that the diagnosis was made primarily by ophthalmologists, some specific inflammatory or infectious entities may have been underdiagnosed. Approximately 35% of uveitis patients experience severe vision loss and blindness and it is the third leading cause of blindness (approximately 5–10% worldwide). Intermediate, posterior and panuveitis are responsible for visual impairment in most of these patients. The most common sight-threatening

complications are macular edema, retinal detachment, retinal vasculitis and optic neuropathy. Other causes include phthisis bulbi, hypotension, band keratopathy and glaucoma. The prevalence, phenotypic characteristics and distribution of the various types of uveitis depend on genetic and epidemiological factors such as age, sex, race, geographic and environmental influence and social habits. Uveitis can occur in any age group, from infancy to adulthood, but individuals aged 20–60 years are more susceptible [52]. Global studies have found that anterior uveitis is the most common type of involvement seen in both adults and children, but the underlying etiologies differ. Although the prevalence of some uveitis shows regional dependence, in general that of infectious uveitis is lower in developed countries. The pattern of uveitis may be influenced by several epidemiological factors, therefore any comparison should take these differences into account. Regional epidemiologic studies can be useful for both diagnostic and therapeutic guidance. Regardless of its great variety, uveitis shows dependence on a number of factors such as: climatic conditions, age structure of the population, economy, state of the health system. Onchocerciasis is not common for our latitudes. An increase in life expectancy causes a more frequent encounter with various infectious disease agents. Certain professions carry the risk of developing certain infections, on the other hand, the poor socio-economic status affects the ability of patients to pay for the need for expensive tests and medications. Last but not least, the state of the health system is also important, related to the possibility of expensive research and treatment being taken over by the state. Close collaboration with other specialists is necessary, both when interpreting the obtained research results and when conducting treatment, so we can safely say that uveitis is an interdisciplinary problem.

According to a number of studies in the literature, a thorough history taking and physical examination continue to play a key role in the diagnosis of uveitis [53]. The sources advise that upon examination, after establishing a certain finding, the diagnostic approach to uveitis in each patient should be adapted according to the epidemiological features and the resources of the health system. History taking and physical examination increase the efficiency of diagnosis, minimize harm to the patient and do not burden the health care system by not using its resources unnecessarily. The adaptation to the mentioned resources and the good awareness of general practitioners, who are a “bridge” between patients and ophthalmologists, would help to achieve useful communication between units, to reduce time and resources, and to improve the clinical prognosis of patients suffering from the disease.

In the present study, the treatment carried out was etiological - according to the etiology, symptomatic - in idiopathic uveitis, systemic in systemic diseases and according to the site of administration - systemic, local and intravitreal. Initiation of treatment with topical corticosteroids and cycloplegics is important after diagnosis of uveitis. In recent years, biologic agents, biologic response modifiers, anti-TNF-alpha necrosis factor therapies, anti-IL-6 therapies, and next-generation calcineurin inhibitors have provided new options for the treatment of uveitis. The most recent guidelines for the management of the condition advocate for a reduced use of topical, periocular and systemic corticosteroids due to their widely known side effects, however, corticosteroids remain a fundamental tool in the treatment of the acute phases of uveitis and when seeking a more rapid treatment effect . However, targeting biological therapy and adaptation of new therapeutic agents is associated with a very high cost, the need for additional follow-up examinations and highly specialized tests, which burdens the health care system. Nanoparticle therapy opens up new ways to approach treatment with harmless medications, potentiating the action of the base therapy. Studies should be continued and investment in new research should be made in order to achieve the most optimal treatment plan for uveitis patients, which is maximally efficient, harmless, safe and which provides the best visual and clinical results.

The integration of artificial intelligence (AI) in healthcare opens up new avenues for the diagnosis, treatment and management of various pathological conditions with remarkable precision. Management of uveitis requires specialized knowledge that is often lacking, especially in regions with limited access to health services. AI capabilities for pattern recognition, data analysis and predictive modeling offer significant potential to revolutionize uveitis management. However, incorporating AI models into clinical practice and meeting patient expectations involves overcoming a number of challenges. Furthermore, given the heterogeneity of clinical manifestations in uveitis and its potential impact on most ocular structures such as the iris, ciliary body, vitreous, retina and optic nerve, uveitis presents significant difficulties in the application of diagnostic technologies [54][55][56]. The complex nature of uveitis highlights the need for international research collaboration to accumulate adequate data for meaningful AI-based application, which is essential to develop innovative strategies that improve the quality of life of those affected by the condition. These models could potentially be trained to discriminate between different etiologies in the different phenotypes of anterior, intermediate, posterior and panuveitis based on clinical and imaging data, such as recognizing specific patterns of retinal

inflammation in fundus photographs or OCT images [55]. Artificial intelligence is applicable in the following areas of imaging eye diagnostics – anterior and posterior eye segment and vitreous body. The predictive capabilities can also be extended to assess the risk of complications, such as macular edema or cataract development, from the first visit by analyzing cross-sectional and longitudinal imaging data of patients [54][55]. Additionally, AI could estimate the likelihood of a patient responding to specific treatments such as biological therapy or corticosteroids using past treatment outcomes, genetic markers, and disease characteristics, supporting personalized treatment strategies [55]. In cases where uveitis presents a diagnostic challenge due to its diverse etiologies and clinical manifestations, these systems can assist professionals by rapidly summarizing relevant studies, identifying patterns in patient histories and suggesting evidence-based treatment strategies [56] . In addition to the advantages that AI offers in the management of uveitis, an essential aspect to consider is how it can improve the patient's freedom of action, especially since uveitis is a chronic condition in which the patient's participation and cooperation is critical. Language models such as ChatGPT and Bard hold promise for creating educational materials tailored to ophthalmic patients and addressing their concerns in a precise and empathetic manner—they can generate personalized content that explains the specifics of uveitis, its types, potential complications and various treatment options [56]. This personalized approach not only simplifies complex medical terminology, but also provides patients with the knowledge they need to actively participate in their treatment planning. The integration of artificial intelligence systems has the potential to significantly improve diagnostic accuracy and provide physicians and researchers with a deeper understanding of the disease’s mechanisms. This facilitates more personalized treatment approaches tailored to individual patients.

Specialists in uveitis and their management are few and often the distribution of personnel in relation to urban and rural regions is uneven. The literature reveals that this specialty has faced several challenges in terms of global positioning and understanding since its inception. This highlights the critical need for further research and increased awareness and experience of uveitis among healthcare professionals. A study by Mallem and colleagues shows that while specialist representation in the US is high in urban areas, there is a shortage of specialists in rural areas, significantly delaying the initiation of appropriate treatment for patients who cannot afford to travel, as well as for those in areas with large socio-economic differences. This is further supported by a study in Canada that demonstrated how general ophthalmologists have limited

experience with immunomodulatory drugs in patients with uveitis, presenting an increased risk of complications and highlighting the need to develop management guidelines. Interestingly, this correlates with observations in developing countries where, due to the limited number of uveitis specialists, the time between disease onset and evaluation by an uveitis specialist can exceed two years.

The literature shows that patients with uveitis face worse psychosocial outcomes and quality of life compared to the general population. Clinical factors such as visual impairment and ocular comorbidities, along with patient-related factors including advanced age and female gender, significantly contribute to this discrepancy. Stress, coping mechanisms, pain, health literacy, treatment adherence, patient empowerment, work and productivity, social support were identified as key areas affecting the lives of these patients. Critical aspects in patients with uveitis in studies include functional impact at work, psychological/emotional, social and financial/economic impact. The most commonly reported factor affecting psychosocial well-being and quality of life in patients with uveitis is decreased visual acuity [57]. The severity and complexity of uveitis, combined with its dynamic epidemiological trends and significant economic impact, highlight the urgent need for innovative solutions. That is why, based on the research conducted, we created guidelines for general practitioners to facilitate the early diagnosis of uveitis and help increase awareness, the initiation of effective treatment, the healing process and increase the quality of life of our patients.

Uveitis is an extremely complex disease that can progress differently in each patient. There are many known causes for the development of the disease - infections, autoimmune diseases, systemic diseases, trauma, but the percentage of uveitis of unclear origin remains high. The disease creates many differential-diagnostic problems, and often therapeutic ones. Sometimes the unfavorable outcome of the disease also affects the social status of the patients and their quality of life. Therefore, uveitis carries its psychological, economic burdens for patients, their relatives and society. The spread of the disease depends on a number of factors - sex, age, place of residence, race, environmental influence, genetic factors, social habits, health status, state of the health care system. The localization of the inflammatory process, as well as the finding, can direct the ophthalmologist to a specific cause, but in most cases, a large set of tests must be performed to be correctly interpreted. All this requires good collaboration with GPs and specialists - infectious disease specialists, immunologists. Knowing the symptoms of the disease

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Uveitis has always been in the field of challenges in ophthalmology - frequent relapses, unclear etiology, sometimes difficult to treat, possible complications define their characteristics. Therefore, the interest in them and their analysis is justified. Each study of the disease has its own contribution and brings us even a small step forward. A study of uveitis patients who have passed through USBOBAL-Varna can help us refine our work related to diagnosis and treatment and eliminate gaps in the management of these patients.

## SUMMARY

Uveitis as a potentially sight-threatening eye disease poses diagnostic and therapeutic challenges to general ophthalmologists as well as uveitis specialists. Epidemiological studies of the pattern and etiology of uveitis may help clinicists to diagnose, manage and treat the disease. However, epidemiological studies of the disease at the national level can help in assessing the burden of the disease on the health community of the country, making possible planning for the future. In contrast, studies on the incidence and prevalence of uveitis in our society are limited, especially in the general population. Based on the extensive review of the literature, to the best of our knowledge, no study has reported the epidemiological pattern of uveitis, as it has a dynamic characteristic and may change at any moment based on the altered factors discussed below. above in the analysis. The clinical pattern of uveitis can change over time for several reasons, including emerging diseases, new surgical procedures that can lead to uveitis as a complication and new laboratory equipment that can help better understand or more further diagnosis of the disease. Of course, limitations of laboratory equipment may make it difficult to detect some etiologies and cause some specific diagnoses to fall into the category of idiopathic uveitis. Thus, the pattern of uveitis in one community may be different from that in other societies and may also change over time. This justifies the need for national and regional studies and repeated epidemiological studies over time. Comparison of these studies may help identify predisposing factors in different regions and provide new insights into disease pathogenesis,

All published studies examined the epidemiology of uveitis in university referral ophthalmology centers. Due to the lack of a reference center in Bulgaria, the data from the study carried out are essential and key, but cannot be generalized to the public, as there are significant differences between the disease pattern in these studies compared to general ophthalmic practice or the community.

We hope that our study and the data we have collected and analyzed, help us unlock the secrets of uveitis and improve our approach in both diagnostic and therapeutic aspects.

## CONCLUSIONS

1. A tendency of increased frequency and recurrence of the incidence of uveitis, which passes from chronic to acute form, has been established, with an age line moving towards a younger group is observed mainly in men and persons from rural regions.
2. Male gender emerged as a risk factor (OR=3.9) for bilateral involvement in patients with uveitis.
3. The localization of uveitis correlates with the age of the patients and with the severity of the disease.
4. Idiopathic uveitis predominates with the most common causes being herpes zoster (6.9%), ankylosing spondylitis (5.1%), herpes simplex (4.6%) and rheumatoid arthritis (2.3%).
5. The results of the established findings during the performed biomicroscopy show a significant difference in the two periods in all the studied segments.
6. A significant difference was found in the medical treatment of uveitis, with the majority of patients treated with corticosteroids, NSAIDs and mydriatics in the first period, while the use of biological medications increased in the second studied period.
7. The results of the study according the treatment of uveitis display that biological medications are mainly used in patients with a moderate and severe form of the disease.
8. The use of systemic NSAIDs increases with the severity of uveitis and immunosuppressants are used only in patients with severe disease.
9. Rheumatoid arthritis, herpes simplex and ankylosing spondylitis were identified as risk factors for uveitis recurrence and their severity decreased during the second study period, which can be explained by improved disease control through the application of biological therapy.
10. The risk profile of uveitis patients for disease recurrence and development of severe disease includes the presence of systemic diseases (psoriasis vulgaris), autoimmune diseases (ankylosing spondylitis and rheumatoid arthritis) and viral agents (herpes zoster), bilateral involvement and residence in a rural area .

# CONTRIBUTIONS

## Contributions of scientific and applied nature

1) For the first time, an analysis of patients with uveitis in Northeastern Bulgaria was performed.

2) Epidemiological data regarding age, sex and risk factors in patients with uveitis was obtained.

3) Complications in patients with uveitis and their relationship with demographic characteristics, activity, treatment and outcome of the disease were analyzed.

4) A detailed analysis of activity, course, remission and medication control in patients with uveitis was performed.

5) A comprehensive analysis of the possibilities provided by artificial intelligence systems in the areas of diagnosis, awareness raising and patient tracking was carried out.

## Contributions of cognitive nature

1) A detailed analysis of the data in the scientific literature was made; the modern methods of treatment of uveitis were also described.

2) It has been proven that the trends related to the spread of uveitis in Northeastern Bulgaria correspond with the data from other sources for other countries.

3) It has been shown that patients with idiopathic uveitis continue to have high-risk diseases of idiopathic etiology.

## Contributions of practical nature

1) A situational analysis of uveitis in Northeastern Bulgaria was carried out and the advantages and disadvantages of good practices in the diagnosis and treatment of the disease on a European and global scale were established.

2) Agorithms have been created for diagnosis and treatment in patients with infectious and non-infectious uveitis.

3) A risk profile of patients with uveitis and prediction of recurrences was created.

4) A guideline for general practitioners with the aim of early diagnosis of uveitis, raising awareness, starting effective treatment and improving the quality of life of patients was designed.

## APPLICATIONS

## QUESTIONNAIRE

**Demographic data**

Age: ……..

Sex:  male  female

Ethnicity: ……

Employment:  employed  unemployed  retired  retired due to illness

Profession:……. Place of residence:……

**Ocular status:**

Visual acuity: OD ……. OS…….

IOP: TOD…….. TOS…….

Biomicroscopy of the affected eye:

Tyndall  effusion  precipitates  posterior synechiae  occlusion  seclusion

Description of the lens of the affected eye: ……

Vitreous body of the affected eye:  homogeneous  opacities  hemorrhage

Fundus:

 Vessels:  normal  cuffs along the course of the vessel

 Retina:  normal  inflamed

 Macula:  normal  pigmentation  atrophy  edema  neovascular membrane.

 epiretinal membrane

 Nerve:  normal  edematous

**History of the disease:**

Affected anatomical area of the eye:

 anterior  posterior  middle  retina  choroiditis  panuveitis

Anterior uveitis:  Iritis  Anterior cyclitis  Iridocyclitis

Intermediate uveitis:  Pars planitis  Hyalitis  Posterior cyclitis

Posterior uveitis:  Focal choroiditis  Multifocal choroiditis  Diffuse choroiditis

 Chorioretinitis and retinochoroiditis  Neurouveitis

Affected part of the eye:

 unilateral  unilateral variable  symmetrical bilateral  asymmetrical bilateral

Type of uveitis:  acute  acute recurrent  chronic

Disease severity: □ mild □ moderate □ severe

Disease duration: …….

Onset of disease (age at diagnosis): ……

Ocular symptoms: □ pain □ redness □ photophobia □ blurred vision

Pathology: □ non-granulomatous □ granulomatous

Structure: □ focal □ multifocal

Prevalence: □ no □ yes Range of spread: ……..

Etiological factors:

□ infections □ immunological □ trauma □ idiopathic □ result of another disease, and if yes, then what ……..…….

Diseases:

□ AIDS □ Ankylosing spondylitis □ Behcet's disease □ CMV retinitis

□ Herpes zoster infection □ Histoplasmosis □ Kawasaki disease □ Multiple sclerosis

□ Psoriasis □ Reactive arthritis □ Rheumatoid arthritis □ Sarcoidosis □ Syphilis

□ Toxoplasmosis □ Tuberculosis □ Ulcerative colitis □ Vogt-Koyanagi-Harada disease

Infectious etiology of uveitis:

□ Bacteria □ Viruses □ Fungi □ Protozoa □ Helminths

Immune-mediated etiology of uveitis – with and without systemic associations:

□ Ankylosing spondylitis □ Reiter's syndrome □ Psoriatic arthritis

□ Juvenile rheumatoid arthritis □ Crohn's disease □ Rheumatoid arthritis

□ Behcet's syndrome □ Sarcoidosis □ Polychondritis □ Vogt-Koyanagi-Harada syndrome

□ Sympathetic ophthalmia □ Multiple transient white spot syndrome

□ Multiple sclerosis □ Systemic lupus erythematosus □ Dermatomyositis

□ Temporal arteritis (Horton's disease) □ Takayasu's disease □ Buerger's disease

□ Wegener's granulomatosis □ Fuchs' heterochromic iridocyclitis □ Posner-Schlossmann syndrome

□ Lens-induced uveitis □ Pars planitis □ Eales' disease □ Idiopathic uveitis

Traumatic and toxic etiology of uveitis:

 Contusion  Penetration/perforation by a foreign body  Electrical trauma  Radiation  Toxicity.

Masking syndromes:

 Anatomical – retinal detachment, pigment-dispersion syndrome

 Congenital (congenital)

 Immune-mediated

 Infectious – chronic anaerobic endophthalmitis/ panophthalmitis, postoperative endophthalmitis/ panophthalmitis.

 Metabolic

 Neoplastic – carcinoma-associated retinopathy, intraocular lymphoma of the choroid or retina, juvenile xanthogranulomatosis, leukemia, metastatic carcinoma, retinoblastoma, uveal melanoblastoma.

**Treatment:**

Medications taken and dosage: ……

Patient's adherence to the treatment plan:

 no  yes  does not take the medication on time  misses taking the medication

Complications during treatment:  yes  no

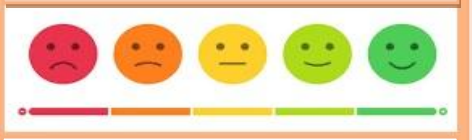
Types of side effects from treatment: …….

Operative intervention on the affected eye:  yes  no

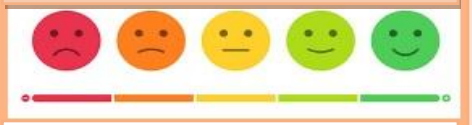
Relapses (number):……..

# Guidelines for general practitioners for patients with suspected uveitis

How strong is your pain?



How severe is the irritation?



How prominent is the redness?

How blurry is your vision?

- Do you take any medication?
- Have you had any relief from them?

**Symptoms**

- ◯ Ocular pain
- ◯ Light sensitivity
- ◯ Ocular redness
- ◯ Headache
- ◯ Eye irritation
- ◯ Other.....

**Do you have any of the following conditions?**

- ○ Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- ○ Juvenile idiopathic arthritis
- ○ Spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis)
- ○ Multiple sclerosis
- ○ Herpes
- ○ Toxoplasmosis
- ○ Tuberculosis
- ○ Syphilis
- ○ HIV
- ○ Lyme disease
- ○ Brucellosis
- ○ Laser eye surgery
- ○ Previous severe eye trauma or previous eye surgery
- ○ Lymphoma
- ○ Leukemia
- ○ Melanoma
- ○ Other

Are you a smoker?

◯ Yes ◯ No

Which of the following symptoms are the most prominent?

Blurred vision

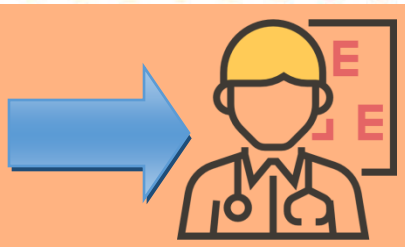
Eye “floaters” such as: “flies”, “spider webs”

Ocular pain

Irritated red eyes

Changed pupil size or shape

Feeling anxious/ depressed



## PUBLICATIONS AND PARTICIPATIONS IN SCIENTIFIC FORUMS

**Publications related to the dissertation**

1. Nikolaeva, S., & Nencheva, B. (2022). Quality of Life in Patients with Uveitis–An Overview. Bulgarian Review of Ophthalmology, 66(1), 13-18.

2. Nikolaeva, S., & Nencheva, B. (2021). Risk Factors for the Development of Uveitis. Bulgarian Review of Ophthalmology, 65(3), 31-38.

3. Nikolaeva, S., & Nencheva, B. (2021). Uveitis and systemic diseases. Izvestia Journal of the Union of Scientists-Varna. Medicine and Ecology Series, 26(1), 19-24.

**Participation in scientific forums on the topic**

1. "Risk factors for the development of uveitis" – S. Nikolaeva, B. Nencheva, poster presentation, BDO Congress, 2021

2. "Analysis of uveitis cases for the period 2014-2021 in a specialized hospital for eye diseases - Varna" – S. Nikolaeva, B. Nencheva, BDO Congress, 2022

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