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**Original Article / Оригинални рад**

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**Cost effectiveness analysis associated to the treatment of primary open-angle glaucoma according to disease severity**

Анализа ефеката трошкова повезани са третманом примарног глаукома отвореног угла према тежини болести

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### SUMMARY

**Introduction/Objective** POAG treatment should be individually tailored to the disease severity and type, effectiveness and secondary side effects of the medications used.

This research aimed to assess the direct medical costs and the cost effectiveness associated with pharmacotherapy in visually impaired people with primary open-angle glaucoma according to disease severity.

**Methods** This scientific study is designed as an observational cross-sectional study with a quantitative analytical approach and was conducted in the period from July 2020 to June 2021 on the territory of North Macedonia. The study included 157 patients with binocular POAG in the early, moderate and advanced clinical stage, up to the age of 67, with changes in visual acuity and work ability. During the assessment of the effects of pharmacotherapy were analyzed the types, mutual correlations and effectiveness of the most commonly prescribed antiglaucomatous medications and the cost benefit from their administration. Direct medical costs are calculated according to disease severity in the last 12 months using real-time data of public interest.

**Results** The beta blockers due to their affordable price and availability are the dominant option with high-cost benefit for primary treatment of POAG. Antiglaucoma medications and diagnostic procedures are major components of direct medical treatment costs.

**Conclusion** Pharmacotherapy is the dominant alternative compared to other types of treatment because it is safer and is associated with greater effectiveness and lower direct medical costs.

**Keywords:** pharmacotherapy; direct medical costs; antiglaucoma medications; economic burden

### САЖЕТАК

**Увод/Циљ** Третман примарног глаукома отвореног угла треба да буде индивидуално усаглашен са тежином болести, ефикасношћу и секундарним невољним реакцијама примењеним лековима.

Циљ рада је био да се процене директни медицински трошкови и ефикасност фармацеутских трошкова повезаних са третманом примарног глаукома отвореног угла према тежини болести.

**Метод** Научни рад је дизајниран као обсервацијска студија пресека са квантитативним аналитичким приступом и је спроведена у периоду јула 2020. до јуна 2021. на територији Северне Македоније. У истраживању су укључена 157 лица са биокуларним примарним глаукомом отвореног угла узраста до 67 год. у иницијалном, умереном и напредном клиничком стадијуму са променама у видној оштрини и радној способности. При процени ефеката фармакотерапије анализирани су видови, међусебне релације и корист најчешће примењиваних антиглаукоматозних лекова. Директни медицински трошкови у задњих 12 месеци су процењени коришћењем реалних ажурираних података од јавног интереса.

**Резултати** Бета блокатори због њихове прихватљиве цене и доступности су доминантна примарна опција са високим трошковним ефектима у третману примарног глаукома отвореног угла. Антиглаукоматозни лекови и офталмолошки прегледи сачињавају главне компоненте директних медицинских трошкова.

**Закључак** Фармакотерапија је доминантна алтернатива у односу на остале видове третмана јер је безбеднија, повезана је са већом ефикасношћу и мањим директним медицинским трошковима.

**Кључне речи:** фармакотерапија; директни медицински трошкови; антиглаукоматозни лекови; економски терет

## INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy which, due to untimely diagnosis and inadequate treatment, leads to irreversible loss of visual acuity. [1]

It is most commonly associated with increased intraocular pressure, but not always and requires lifelong therapy [2].

It has a prevalence of 1-2% in the population over 40 years of age and it is the second most common cause of vision loss and accounts for 13% of global blindness. [3]

About 70% of all glaucoma cases are patients with primary open-angle glaucoma (POAG) and female patients are more dominant [2, 4].

Due to long-term treatment, high treatment costs and low cost effectiveness, glaucoma generates individual and family financial burden [5, 6, 7] and has a huge socio-economic impact on the society and population [8].

Pharmacotherapy with antiglaucoma medications is the safest option for primary treatment of POAG. [9]

Surgical treatment performed at an early clinical stage prevents the progression of POAG and has lower or identical direct medical treatment costs compared to pharmacotherapy. [10]

Direct medical costs for treatment increase as the disease severity progresses [11, 12, 13], but stagnate or decrease over time [14, 15].

The treatment outcome and the height of direct medical costs are essentially related to timely diagnosis and individual approach to treatment according to disease severity. [16]

The untimely diagnosis, irregular control of IOP and visual acuity [6] and low level of patient awareness of the essence of POAG adversely affect the outcome of treatment [17].

This research aimed to assess the direct medical costs and the cost effectiveness associated with pharmacotherapy in visually impaired people with primary open-angle glaucoma (POAG) according to disease severity.

## **METHODS**

This scientific study was designed as a cross-sectional observational study with a

quantitative analytical approach (cross sectional study) and was conducted in the period July 2020-June 2021 on the territory of North Macedonia.

According to inclusion criteria, the study included 157 patients diagnosed with binocular POAG at an early, moderate and advanced clinical stage. The patients were up to 67 years old and treated with pharmacotherapy; whereas the patients in advanced clinical stage were socioeconomically predisposed and with reduced work ability.

The patients' diagnosis was confirmed by ophthalmological examination, while the visual acuity and disease severity (clinical stages) were determined according to ICD 10-CM: 40.11 in early, moderate and advanced clinical stage, in accordance with the classification guidelines of the European Glaucoma Society.

A specially designed questionnaire was used for the analysis of the clinical-demographic parameters, whereas a standardized visual analogue scale EQ VAS was used for self-assessment of the general health status.

The research was carried out during periodic health examinations in the Institute of Occupational Medicine and the Department of Ophthalmology at the University Clinical Hospital Bitola, Department of Ophthalmology at the Medical Faculty Skopje, Department of Ophthalmology at the Medical Faculty Stip and specialist ophthalmological hospitals in several cities in Macedonia.

The assessment of the effects of pharmacotherapy involved the following: type of most commonly prescribed antiglaucomatous medications, their mutual correlations, the effectiveness and the secondary side effects from their use. The effectiveness and outcome of the treatment were analyzed by controlling the height and normalization of the IOP and the preservation of visual acuity in the last 12 months.

Direct medical costs were calculated according to the disease severity in the last 12 months using realtime data of public interest presented by the HIF (Health Insurance Fund of

North Macedonia) and SSO (State Statistical Office).

Statistical data processing was performed by descriptive and comparative statistics procedures with SPSS software package version 22.0 for Windows (SPSS, Chicago, IL, USA).

The attributive (qualitative) series were analyzed by determining the coefficients of ratio, proportion and rate, and were presented as absolute and relative numbers. Numerical (quantitative) series were analyzed by finding the measures of central tendency (average value; median, minimum and maximum value; interactive range) and dispersion measures (standard deviation and standard error).

Pearson  $\chi^2$  test for homogeneity, Fischer exact test and Fisher-Freeman-Halton exact test were used to determine the association between certain variables in the groups of subjects.

The Shapiro-Wilk W test was used to determine the normality of frequency distribution of investigated variables. Risk factors were quantified using probability ratios, Odd ratio (OR).

In order to test the significance of the difference between the parameters analyzed, depending on the type and distribution of data, Student's t test for two independent samples, analysis of variance (ANOVA) for multiple independent samples and the non-parametric Mann-Whitney U test and Kruskal-Wallis H test for independent samples were used.

A value of  $p < 0.05$  was used to determine significance. The obtained results from the analysis were compared with scientific reference literature in the world and are presented numerically, with tables and figures.

## RESULTS

The highest proportion of the patients included in the research were in the initial clinical stage 38.22% and the mean age of the patients was  $57.51 \pm 6.28$  years. (Table 1)

Regarding the demographic parameters, 77.71% of the patients lived in a city; 89.17% in a married community; 50.32% had a secondary education; 43.31% were a clerk/administrator

by profession, without statistical significance between the two sexes.

17.91% of the patients had a family history of eye diseases; 21.06% had registered comorbid diseases, while 15.29% were not informed about the essence of POAG.

The patients were treated with pharmacotherapy, with prescription of various anti-glaucomatous medications (Figure 1, Table 2).

The type and method of administration of antiglaucoma medications depend on the disease severity, the level of intraocular pressure (IOP) and their effectiveness. The medications are individually tailored and in our research the predominant type of pharmacotherapy were the beta blockers.

In the early stage, the predominant option was mono pharmacotherapy 60%, in the moderate stage, combination therapy of two medications 55.77% and, in the advanced stage, combination therapy of two 33.33% or three or more anti-glaucomatous medications 66.67%.

The effectiveness of pharmacotherapy is manifested by regression, slow progression or worsening of disease severity.

Significant association of with the highest number of regression outcome of the disease was observed in patients in initial (early) when compared to advanced clinical stage,  $p = 0.00001$ .

Over 20% of the patients did not adhere to regular treatment due to economic reasons or lack of information and ignorance about the essence of POAG.

Loss of visual acuity and reduced work ability are the reasons for non-fulfillment or poor fulfilment of work responsibilities and eventual relocation of patients to job positions with lower personal income (Table 3).

Considering the fact that this concerned adult population of up to the age of 67, the average self-assessment of the general health status of the patients was low,  $7.68 \pm 1.56$ . Of whom, 36.94% due to reduced visual acuity and work ability received a low monthly income

of up to 250 euros, without significance between the two sexes,  $p = 0.316$ .

Antiglaucoma medications were a major component of direct medical costs 80,86% and imposed an economic burden from  $3.05\% \pm 0.75$  to  $10.52\% \pm 0.62$ , which was significantly associated with patients who received low monthly income (nonparametric ANOVA:  $F = 6.38$ ;  $p = 0.0001$ ).

## DISCUSSION

The patients included in the research were aged 40-67, predominated by females 55.41%, while over 50% of the patients were older than 59.

Previous studies show that POAG is most often manifested binocularly with the highest frequency over the age of 60, while 55-60% of the patients are female [2, 4].

POAG is diagnosed between the age of 40-50 in 46.91% of the patients, while in 7.63% younger than 40. According to the available studies, POAG is most often diagnosed after 40 [18], although that limit is gradually lowering to a younger age under 40 years old [19].

Of the registered comorbid conditions, 33.33% were due to diabetes mellitus and the rest to hypertension, cardiovascular and metabolic diseases and were 2.47 times more common in patients with advanced stage [OR = 2.47 (1.20–5.07) 95% CI].

84.71% were fully/partially informed about the essence of POAG, but not all of them, without statistical significance between the two sexes,  $p = 0.195$ .

Studies in Egypt and Nigeria showed that 40-50% of illiterate and uninformed people had been treated for glaucoma. [6, 13]

Antiglaucoma medication of choice in the treatment of POAG were beta blockers (Thymolol) which were administered in 132 cases (84.08%), and their alternative were analogues of prostaglandins 95 (60.51%), carbonic anhydrase inhibitors 83 (52.87%) and alpha<sub>2</sub> agonists 24 (15.29%), which are prescribed as mono or combination therapy.

Beta blockers were usually prescribed as monotherapy 16.56%, while in combination therapy of two medications, beta blockers and carbonic anhydrase inhibitors 22.29%, and in combination of three medications, beta blockers, carbonic anhydrase inhibitors and prostaglandin analogues 30.57%. Combined use of more than one antiglaucoma medication is an effective way to normalize IOP, but it increases the treatment cost and the possibility of secondary side effects. [7, 20]

Adverse drug reactions were reported in 40 cases (25.48%). Of these, 23 (14.65%) were secondary local reactions in the form of irritation, allergy, dry eye and eye pain, and secondary cataract in 7 cases (4.46%). Of the patients treated with non-selective beta-blockers, 5 (3.18%) showed complications in the form of primary bronchial asthma, exacerbation of asthma and deviations in functional spirometry tests.

In long-term studies for the treatment of POAG in patients who have used medications with preservatives and non-selective beta-blockers (Thymolol) the following was observed: local adverse drug reactions 12-20% [21] and 2.7%, systemic reactions in the form of bronchial asthma exacerbation [7, 22]. Pharmacotherapy with prostaglandin analogues is the most effective way to normalize IOP and has the highest cost benefit for treatment and the lowest percentage of secondary side effects. [20]

The treatment outcome in 78.98% was successful with normalization of IOP and regression of the disease, in 12.10% was partially successful with slow progression, and in 8.92% the outcome was unsuccessful with deterioration and progression of the disease,  $p = 0.00001$ , without significance between the two sexes,  $p = 0.772$ .

Increased disease severity in the last 12 months has been registered in all clinical stages, 13,33% of whom were patients in advanced clinical stage.

Studies conducted in Egypt and Nigeria report unsuccessful normalization of IOP in glaucoma patients treated with pharmacotherapy 42-50%. [6, 13]



21.02% of the patients did not adhere to regular treatment. Of whom, 15.15% were uninformed about the essence of POAG and the benefits of regular treatment, while 84.85% due to economic reasons used generic alternative anti-glaucomatous medications with inadequate dosage.

Many people with POAG are partially blind due to untimely diagnosis [13], poor health care [17] and low levels of health education and awareness, especially in developing countries [5].

Long-term treatment, high medication prices and lack of information about the essence of POAG are most common reasons for patients' non-adherence to medication. [16]

In 75.75% of the patients who did not adhere to treatment, the IOP height in the last 12 months was usually higher than 28 mmHg. Patients who adhere to regular treatment have 5.14 times higher chance of a successful outcome compared to patients with irregular treatment [OR = 5.14 (2.36-14.63) 95% CI].

According to several studies in case of unfavorable outcome and increased disease severity, the possibility of non-adherence to medication must be taken into account. [23]

Significant association was established between low monthly income and patients in advanced clinical stage,  $p=0.00001$ , without statistically significant association between the two sexes,  $p=0.955$ .

There are numerous studies regarding the connection of the advanced clinical stage with the reduced personal income, high treatment costs, decreased visual acuity and low cost effectiveness for treatment. [13, 14, 24]

Monthly and annual direct medical costs for treatment were significantly lower in the initial, whereas the highest in the advanced clinical stage (Kruskal-Wallis H test,  $p = 0.00001 / 0.0002$ ).

Most of the direct medical costs 80.86% were for anti-glaucoma medications which were

significantly higher in the advanced clinical stage,  $p = 0.0001$ , while similar findings were referred to in other studies related to the economic burden of glaucoma treatment. [11, 12]

Treatment costs for patients with advanced clinical stage were 2.4 times higher compared to those for patients with initial stage [OR = 2,4 (9,79–60,93) 95% CI].

Beta-blocker pharmacotherapy is associated with low and prostaglandin analogues with high cost treatment. Identical cost findings have been reported in other comparative studies of glaucoma treatment with medications. [25, 26]

Significantly higher direct medical costs for treatment and low cost benefit were observed in patients with comorbid conditions/diabetes mellitus,  $p = 0.00001$ , compared to other patients.

Patients over the age of 60 have insignificantly higher direct medical costs for treatment,  $p=0.0612$ . Parallel studies on the economic burden of glaucoma treatment have reported a significant association between higher treatment costs, advanced disease severity and older mean age. [24]

The Health Insurance Fund (HIF) of North Macedonia partially subsidizes the costs of non-selective beta-blockers and carbonic anhydrase inhibitors, but not the costs of prostaglandin analogues, other expensive medications and diagnostic procedures used to treat POAG.

Available studies depending on the economic development of the countries indicate annual direct medical costs of 45-809 euros. [5, 12, 13, 15, 27]

The burden of direct medical costs on the monthly personal income is significantly higher in patients with advanced clinical stage, who receive low monthly personal income (One Way ANOVA:  $A_v = 6.38$ ;  $p = 0.0001$ ).

Low cost effectiveness and individual economic burden on the monthly personal income, from 1.3-61.5%, are referred to in numerous studies conducted in different geographical

regions. [6, 7, 13]

## CONCLUSION

POAG treatment should be individually tailored to the disease severity and type, effectiveness and secondary side effects of the medications used.

Pharmacotherapy is the dominant alternative compared to other types of treatment because it is safer and is associated with greater effectiveness, lower direct medical costs and higher cost effectiveness during treatment.

Beta-blockers, due to their availability and low cost, are the most common option as a primary type of pharmacotherapy in the initial (early) stage of the disease.

The progression of the disease severity is associated with change, intensification of treatment and increased direct medical costs.

Long-term IOP control with the initial treatment without modifications will allow regression of the disease, slow disease progression and reduced treatment costs. Screening programs for early detection of POAG, subsidizing the cost of expensive anti-glaucoma medications and increased awareness of the essence of POAG are essential.

**Conflict of interest:** None declared.

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Paper accepted

**Table 1.** Clinical and demographic characteristics of patients

Parameters	Sex			P Difference test
	Total N = 157 (100%)	Male N = 70 (44.59%)	Female N = 87 (55.41%)	
<b>Disease severity</b>				
<b>Early</b>	60 (38.22%)	27 (45%)	33 (55%)	$\chi^2 = 0.837$ ; df=2; p = 0.667
<b>Moderate</b>	52 (33.12%)	23 (44.23%)	29 (55.77%)	
<b>Advanced</b>	45 (28.66%)	20 (44.44%)	25 (55.56%)	
<b>Age</b>	57.51 ± 6.28	57.60 ± 6.10	57.40 ± 6.46	Z = 0.332; p = 0.739
<b>Age when diagnosed</b>	47.53 ± 5.61	47.71 ± 5.51	47.34 ± 5.70	Z = 0.339; p = 0.734
<b>Duration of therapy.</b>	9.54 ± 4.27	9.62 ± 4.12	9.46 ± 4.41	$\chi^2 = 0.235$ ; df = 2; p = 0.715
<b>Comorbid diseases / N (%)</b>	33 (21.06%)	15 (21.43%)	18 (20.69%)	$\chi^2 = 0.152$ ; df = 1; p = 0.697
<b>Genetic Predisposition / N (%)</b>	28 (17.91%)	13 (18.57%)	15 (17.24%)	$\chi^2 = 0.002$ ; df = 1; p = 0.988
<b>Side effects</b>				
Local	35 (22.35%)	16 (22.86%)	19 (21.84%)	$\chi^2 = 0.023$ ; df = 2; p = 0.989
Systemic	5 (3.16%)	2 (2.86%)	3 (3.45%)	
<b>Health informed/ N (%)</b>				
Yes / partially	133 (84.71%)	60 (85.71%)	73 (83.91%)	$\chi^2 = 0.235$ ; df = 2; p = 0.889
No	24 (15.29%)	11 (15.71%)	13 (14.94%)	

$\chi^2$  – Pearson Chi-square test; Z – Mann–Whitney U test; \*significant for p < 0.05

**Table 2.** Treatment outcome of the patients

Parameters	Treatment Outcome				P Difference test
	Total	Regression	Slow Progression	Worsening	
<b>Treatment Method / N (%)</b>					
pharmacotherapy / 12 months	157 (100%)	124 (78.98%)	19 (12.1%)	14 (8.92%)	†p = 0.00001*
<b>Adherence to Treatment/ N (%)</b>					
Yes	124 (78.98%)	56 (45.16%)	43 (34.68%)	25 (20.16%)	$\chi^2 = 69.049$ ; df=2; p=0.0001*
No	33 (21.02%)	3 (9.09%)	5 (15.15%)	25 (75.76%)	
<b>Treatment outcome according to disease severity / 12 months / N (%)</b>					
Early	60 (38.22%)	51 (85%)	6 (10%)	3 (5%)	†p = 0.00001*
Moderate	52 (33.12%)	41 (78.85%)	6 (11.54%)	5 (9.61%)	
Advanced	45 (28.66%)	32 (71.11%)	7 (15.56%)	6 (13.33%)	

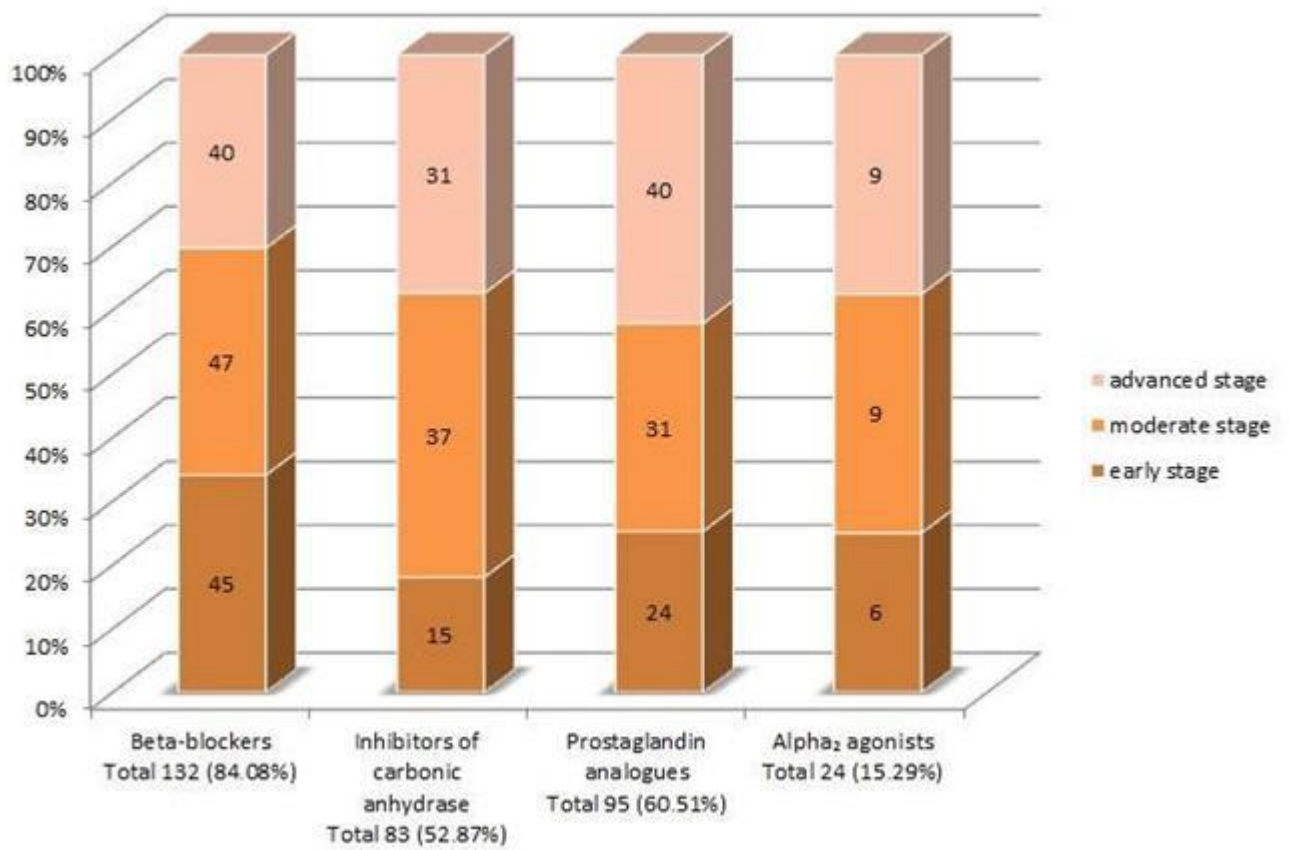
$\chi^2$  – Pearson Chi-square; †Fisher Freeman Halton exact test; \*significant for p < 0.05

**Table 3.** Economic burden associated with primary open-angle glaucoma pharmacotherapy

Parameters	Primary open-angle glaucoma severity				P Difference test
	Total	Initial	Moderate	Advanced	
<b>Self-assessment of health condition / EQ VAS Mean/ %</b>	7.68 ± 1.56	8.25 ± 1.19	7.65 ± 1.55	7.15 ± 1.95	†p = 0.00001* advanced / early
<b>Reduced personal income / N (%)</b>	25 (15.92%)	0	8 (5.1%)	17 (10.83%)	†p = 0.00001* moderate / advanced
<b>Monthly personal income / N (%)</b>					
Low ≤ 250 euros	55 (35.03%)	13 (23.64%)	16 (29.09%)	26 (47.27%)	†p = 0.00001*
<b>Direct medical costs/ euros</b>					
Monthly	15.13 ± 1.6	6.1 ± 1.2	14.4 ± 1.7	24.9 ± 1.9	1p = 0.00001*
Annual	181.56 ± 19.2	73.2 ± 14.4	172.8 ± 20.4	298.8 ± 22.8	1p = 0.0002*
<b>Types of costs / Mean/ %</b>					
Specialist ophthalmological examinations	19.14	25.5	18.89	13.03	$\chi^2 = 66.752$ ; df = 4; p = 0.00001*
Antiglaucomatous medications	80.86	74.5	81.11	86.97	
<b>Economic burden on low monthly income / %</b>	6.68 ± 0.70	3.05 ± 0.75	6.47 ± 0.73	10.52 ± 0.62	<sup>1</sup> F = 6.38 p = 0.0001*

1p – Kruskal-Wallis H test;  $\chi^2$  – Pearson Chi-square; F – nonparametric ANOVA; †Fisher exact test; \*significant for p < 0.05





**Figure 1.** Antiglaucomatous medications prescribed in the treatment

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