THE EFFECT OF CERTAIN SYSTEMIC DISEASES ON THE OCCURENCE AND PROGRESSION OF GLAUCOMA

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Abstract

Glaucoma is a progressive optic neuropathy, most commonly characterized by morphological changes in the papillae of the optic nerve and retinal nerve fibers, without the presence of other eye diseases or congenital anomalies. The risk factors for glaucoma can be divided into systemic and local. A case-control study was performed, which included patients aged 25 to 70. The study was conducted at the Clinic for Eye Diseases, in Skopje, in the Glaucoma Cabinet, in the period from 2015-2019.

The study included 100 patients, who were divided into two groups. An exhaustive medical history was made about the involved patients. Regarding the systemic diseases in the patients included in our study, most of the patients 24.00% had increased blood pressure, 10.00% patients had heart disease, 5.00% patients had diabetes and the other category (10 different diseases) was registered in 10.00% patients. Due to a large standard error, the analysis excluded diabetes, high blood pressure and heart disease, and the category "others" was excluded because it contains various systemic diseases. It was found that patients who had heart disease 7.09 times had a slightly (p = 0.071) higher risk of glaucoma than patients who did not have systemic disease. Patients who had high blood pressure and diabetes by 1.97 times had a slightly higher risk (p = 0.439) of glaucoma than patients without systemic disease. The lowest predictive value for glaucoma prediction was registered in patients with increased blood pressure (0.93 times), insignificant (p = 0.883).

Key words: systemic diseases, glaucoma, association

Introduction

Glaucoma, one of the leading causes of irreversible blindness in the elderly population worldwide, is a progressive optic neuropathy [1]. According to the European Glaucoma Association, glaucoma is a group of chronic progressive neuropathies most commonly characterized by morphological changes in the papillae of the optic nerve and retinal nerve fibers, without the presence of other eye diseases or congenital anomalies.

According to the American Academy of Ophthalmology, glaucoma is a group of conditions characterized by damage to the optic nerve and loss of nerve axons, through atrophy of ganglion cells and preservation of the neurofibrillary layer of the retina. Because glaucoma ranks second on the highest morbidity list of ophthalmic diseases, there are many definitions that characterize its importance in the scientific world and in seeking opportunities for its treatment, and thus reducing the percentage of blindness that glaucoma can cause [2].

According to Murray-Lewis, about 67 million people were diagnosed with glaucoma in 2000, making glaucoma the second leading cause worldwide. The number of patients with visual acuity in both eyes equal to/ or less than 0.1 is about 6 million. According to Weinerb [3], about 3 million patients are blind in both eyes from glaucoma, which makes glaucoma part of the group of diseases that lead to severe disability. Globally, the latest research on the prevention of blindness shows that the number of people with blindness in the world is increasing for 1-2 million people per year [4]. Glaucoma as an etiological factor for blindness occupies 22% -36% of all causes. This percentage varies depending on the geographical localization. The global prevalence of glaucoma worldwide is expected to reach 80 million by 2020 [5].

According to Burr [6], the population screening for glaucoma is not expensive, the risk factor screening is more expensive but especially important for the prognosis and choice of therapy. In a population with diabetes, heart disease and heredity, screening has major effects in saving the funds of a

country, up to over 40%.Primary open-angle glaucoma (POAG) is the most common type of glaucoma in the population according to recent studies.

The pathogenesis of glaucoma is still poorly understood. The increase in intraocular pressure may be caused by increased production of aqueous humor or its decreased leakage. There are several major theories about the initial mechanisms of POAG: "mechanical theory", "vascular theory", "excitotoxicity theory" and "genetic theory".The disease has, if left untreated or if it is resistant to therapy, often a bad ending with ganglion cell loss, gradual loss of vision and blindness.

Glaucoma risk factors have been studied and published in many studies. Increased intraocular pressure (IOP) is, as is well known, the highest risk for glaucoma [7]. Studies show that reducing IOP reduces the risk of developing the disease or slows the progression of glaucoma [8]. There is growing evidence that other risk factors such as age, sex, race, refraction, heredity, and systemic diseases play a role in the pathogenesis of glaucoma.

The risk factors for glaucoma can be divided into systemic and local. Systemic risk factors are blood pressure: hypotension or hypertension, vasospasm, diabetes, chronic heart disease, hypercholesterolemia, thyroid disease, etc. Local risk factors are: parapapillary atrophy, intraocular pressure, papillary escalation, certain diseases of the anterior or posterior segment of the eye, central corneal thickness, fluctuations in IOP, etc.

The aim of the study is to determine the impact of certain systemic diseases as risk factors for the occurrence and progression of glaucoma.

Resources and methods

A case-control study was performed, which included patients aged 25 to 70.The study was conducted at the Clinic for Eye Diseases, in Skopje, in the Glaucoma Cabinet, in the period from 2015-2019.The study included 100 patients, who were divided into two groups:

1. The first group of respondents (group 1 / Patients with Primary open-angle glaucoma) included: 60 patients diagnosed with glaucoma. Entry criteria for this group were the following:

- increased intraocular pressure (EOP) -over 24mmHg, without therapy;
- changes in the papilla of the optic nerve;
- vision field defects;
- anti - glaucoma therapy.

2. The second group of respondents (group 2 / Control group) included: 40 patients without glaucoma. Entry criteria for this group were the following:

- patients without glaucoma;
- normal intraocular pressure;
- normal vision field;
- neat optic nerve results (fundus).

An exhaustive medical history and history of systemic disease (blood pressure, diabetes, heart disease) was made about the involved patients, and it was determined whether the patient was using anti-glaucoma treatment.

The following statistical methods were used: In the series with attributive features (systemic diseases) percentages of structure (%) are determined. Association & Differences - in attribute series have been tested using Pearson Chi-Square / (p) and Fisher's Exact Test / Monte Carlo Sig. (2-sided) / (p). The predictive values of the analyzed risk factors for glaucoma prediction were analyzed using Univariate (Enter) and Multivariate Binary Logistic Regression Analysis (Wald, (Exp (B), 95% C.I., p) (Forward: Conditional).The significance is determined by $p < 0.05$.The data are presented in tabular and graphical format.

Results

Table 1 and Graph 1 show systemic diseases in patients with primary open-angle glaucoma.
Out of 60 patients, 11 (18.30%) had high blood pressure, 5 (8.30%) had diabetes, 9 (15.00%) had heart disease, 8 (13.30%) had other diseases (various diseases / 2 patients had thyrotoxicosis, hypothyroidism, chronic bronchitis, osteoporosis, thyroid disease, paranoid schizophrenia, Hashimoto), 5 (8.30%) hypertension & diabetes, 1 (1.70%) patient had hypertension & heart disease and 21 (35.00%) patients had no systemic disease.

Table 1. Systemic disease

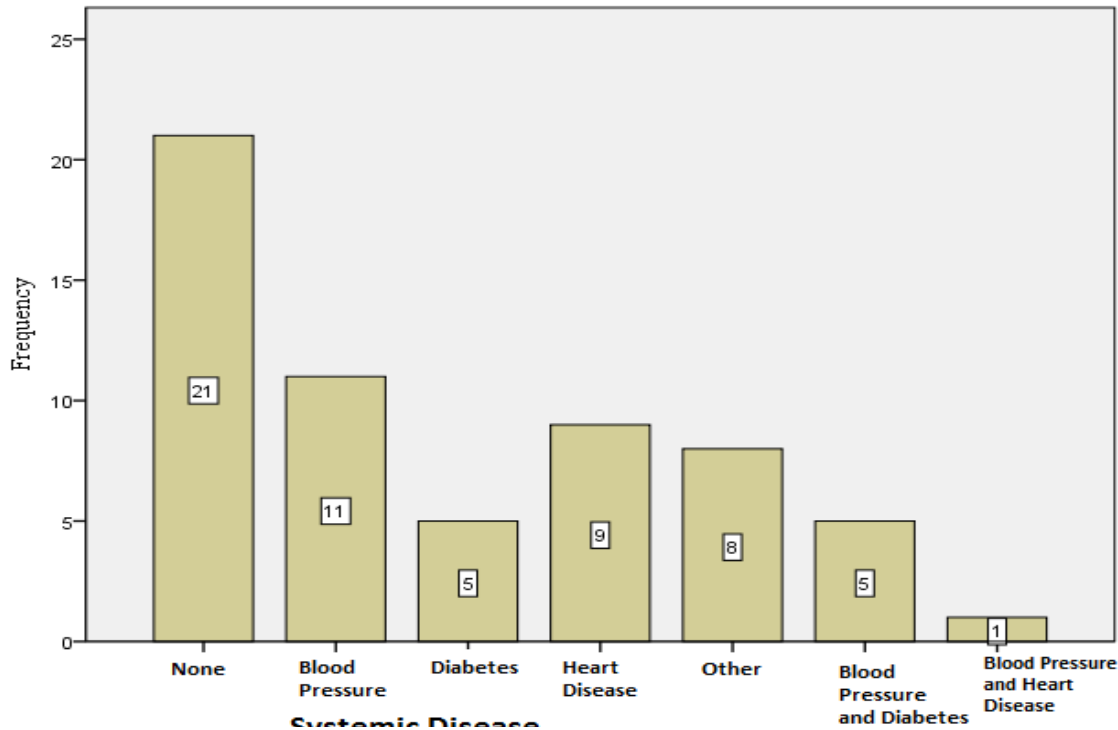|		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	None	21	35,0	35,0	35,0
	Blood pressure	11	18,3	18,3	53,3
	Diabetes	5	8,3	8,3	61,7
	Heart disease	9	15,0	15,0	76,7
	Other	8	13,3	13,3	90,0
	Blood pressure and diabetes	5	8,3	8,3	98,3
	Blood pressure and heart disease	1	1,7	1,7	100,0
	Total	60	100,0	100,0	

Chart 1. Systemic disease

Table 2 and Chart 2 show systemic diseases in patients in the control group. Out of 40 patients, 11 (27.50%) had increased blood pressure, 1 (2.50%) had heart disease, 4 (10.00%) had diseases in the other category (various diseases / 2 patients had hysterectomy; thyrotoxicosis, arthritis), 2 (5.00%) had high blood pressure & diabetes, 1 (2.50%) patient had high blood pressure & diabetes & heart disease and 21 (52.50%) patients had no systemic disease.

Table 2. Systemic disease

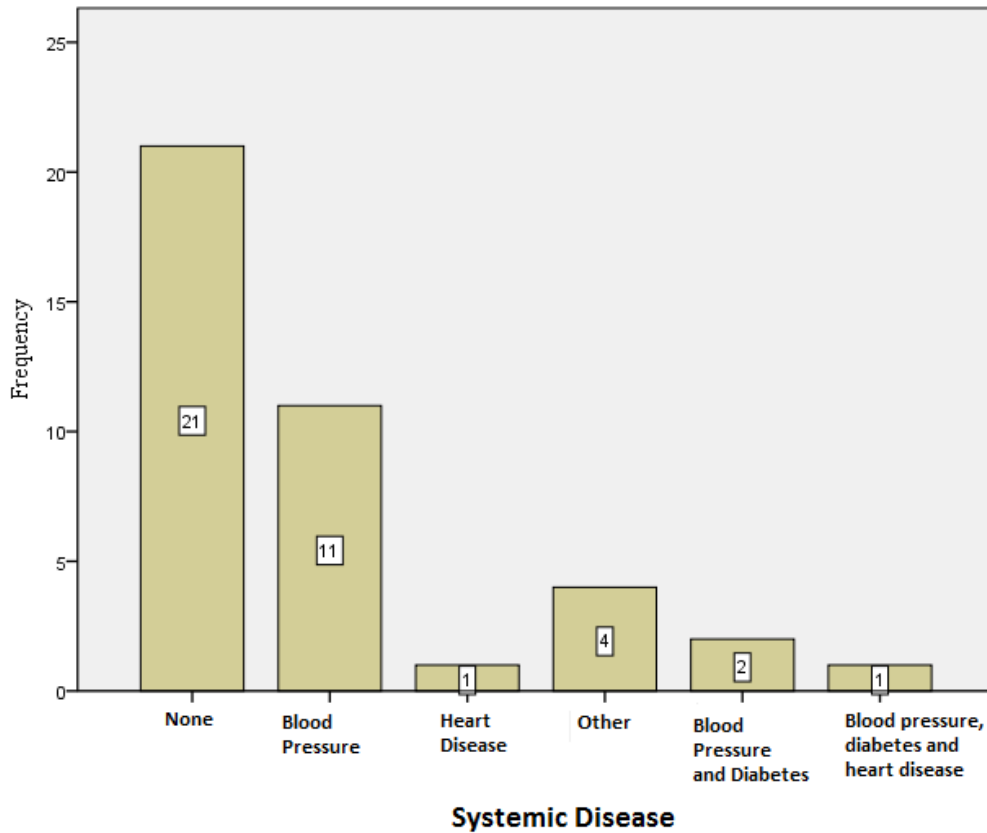|		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	None	21	52,5	52,5	52,5
	Blood pressure	11	27,5	27,5	80,0
	Heart disease	1	2,5	2,5	82,5
	Other	4	10,0	10,0	92,5
	Blood pressure and diabetes	2	5,0	5,0	97,5
	Blood pressure, diabetes and heart disease	1	2,5	2,5	100,0
	Total	40	100,0	100,0	

Chart 2. Systemic disease

The results shown in Table 3 and Chart 3 refer to the difference in systemic diseases between the examined group (has glaucoma) and the control group (no glaucoma).

Out of 60 patients, 11 (18.30%) had high blood pressure, 5 (8.30%) had diabetes, 9 (15.00%) had heart disease, 8 (13.30%) had other diseases (various diseases / 2 patients had thyrotoxicosis, hypothyroidism, chronic bronchitis, osteoporosis, thyroid disease, paranoid schizophrenia, Hashimoto), 5 (8.30%) hypertension & diabetes, 1 (1.70%) patient had hypertension & heart disease and 21 (35.00%) patients had no systemic disease.

Out of 40 patients, 11 (27.50%) had increased blood pressure, 1 (2.50%) had heart disease, 4 (10.00%) had other diseases (various diseases / 2 patients had a hysterectomy; thyrotoxicosis, arthritis), 2 (5.00%) had high blood pressure & diabetes, 1 (2.50%) patient had high blood pressure & diabetes & heart disease and 21 (52.50%) patients had no systemic disease.

In the shown cross-tabulation the examined group (has glaucoma) * the control group (no glaucoma) for Fisher's Exact Test = 11,363 and p> 0.05 (p = 0.081) / Monte Carlo Exact Sig. (2-sided) / 0.074-0.088 / there is no significant difference between the two groups in terms of systemic diseases.

Table 3. Systemic diseases / Difference / Examined group and Control group

			Glaucoma		Total
			Doesen't have	Has	
Systemic diseases	None	Count	21	21	42
		%	52,5%	35,0%	42,0%
	Blood pressure	Count	11	13	24
		%	27,5%	21,7%	24,0%
	Diabetes	Count	0	5	5
		%	0,0%	8,3%	5,0%
	Heart disease	Count	1	9	10
		%	2,5%	15,0%	10,0%
	Other	Count	4	6	10
		%	10,0%	10,0%	10,0%
	Heart disease and diabetes	Count	2	5	7
		%	5,0%	8,3%	7,0%
	Blood pressure and heart disease	Count	0	1	1
		%	0,0%	1,7%	1,0%
	Blood pressure and diabetes and heart disease	Count	1	0	1
		%	2,5%	0,0%	1,0%
	Total	Count	40	60	100
		%	100,0%	100,0%	100,0%

The enter method was used to determine the predictive values of systemic diseases for glaucoma. The global accuracy of this model for predicting glaucoma is 60.00%. The sensitivity is 100.00% and the specificity is 0.00%

The analysis of the contribution to the prediction of glaucoma as systemic diseases the following were included: hypertension, diabetes, heart disease, hypertension & diabetes, hypertension & heart disease, hypertension & diabetes & heart disease and others. Due to a large standard error, the analysis excluded diabetes, high blood pressure & heart disease, high blood pressure & diabetes & heart disease, and the category "others" was excluded because it contains various systemic diseases.

In determining the significance of the contribution to the prediction of glaucoma, it was found that the the heart disease has the greatest influence (Wald = 3.25 / p> 0.05 (p = 0.07), followed by increased blood pressure & diabetes (Wald = 0.60 / p> 0.05 (p = 0.44) and the weakest is the effect of increased blood pressure (Wald = 0.02 / p> 0.05 (p = 0.88) .
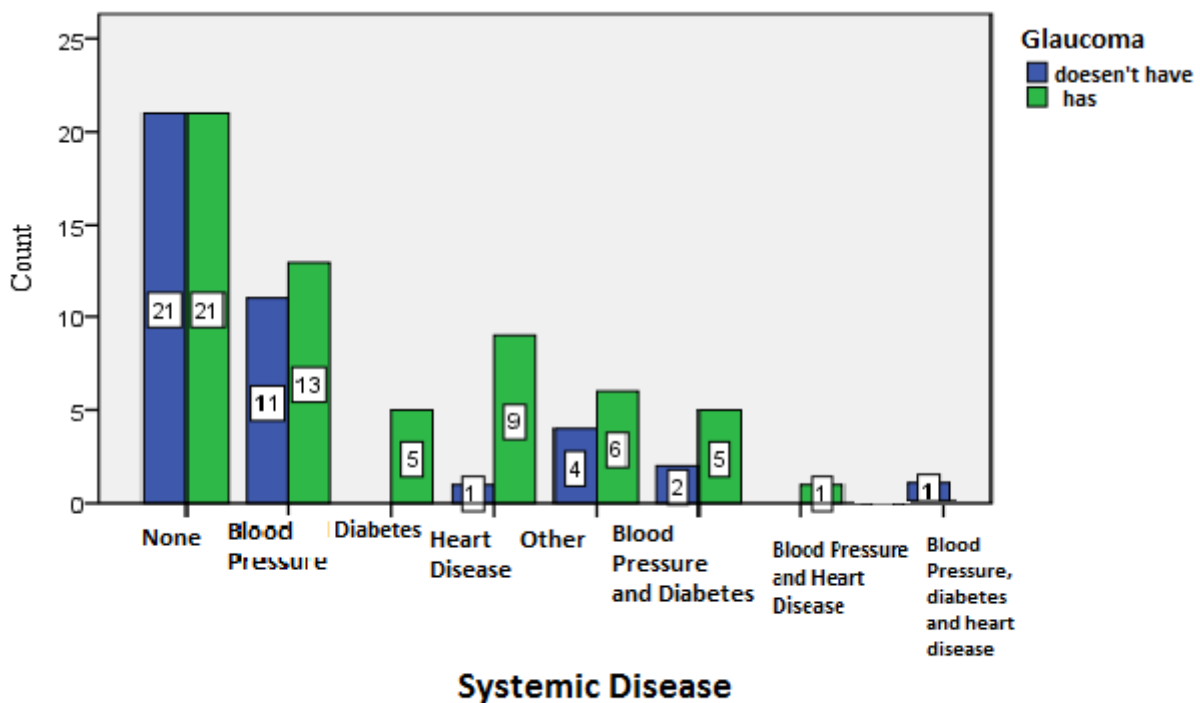

Chart 3. Systemic diseases / Difference / Examined group and Control group

Table 4. Predictive values of systemic disease for glaucoma / Discrimination Model

Observed			Predicted		
			Glaucoma		
			Doesen't have	Has	Percentage Correct
Step 1	Glaucoma	Doesen't have	0	40	.0
		Has	0	60	100.0
	Overall Percentage				60.0

a.   The cut value is .500

Patients who have heart disease (1) 7.09 times (Exp (B) = 7,091) have a slightly higher risk of glaucoma than patients who do not have systemic disease, the impact of heart disease [1] is not significant / 95% CI: 0.84-59.61 / p> 0.05.

Patients who have increased blood pressure & diabetes (1) by 1.97 times (Exp (B) = 1.970) have a slightly higher risk of glaucoma than patients who do not have systemic disease, the impact of high blood pressure & diabetes [1] is not significant / 95% CI: 0.35-10.98 / p> 0.05.

Patients who have increased blood pressure [1] by 0.93 times (Exp (B) = 0.93) have a slightly lower risk of glaucoma than patients who do not have systemic disease, the impact of high blood pressure [1] is not significant / 95% Cl: 0.36-2.42 / p> 0.05.

Table 4.1 Binary Logistic Regression Analysis for Glaucoma Prediction / Systemic Diseases

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a] Elevated Blood pressure (1)	-.071	.486	.022	1	.883	.931	.359	2.416
Heart disease(1)	1.959	1.086	3.252	1	.071	7.091	.844	59.607
Elevated Blood Pressure and Diabetes	.678	.877	.598	1	.439	1.970	.353	10.983
Constant	.238	.262	.827	1	.363	1.269		

Variable(s) entered on step 1: Increased Blood Pressure, Heart Disease, Increased Blood Pressure & Diabetes.

The ROC area is 0.587 which means that in 58.70% / 95% CI: 0.476-0.698 / p> 0.05 (p = 0.141) / of all possible pairs of patients in whom one has glaucoma and the other has no glaucoma, this model will determine a higher probability of glaucoma).
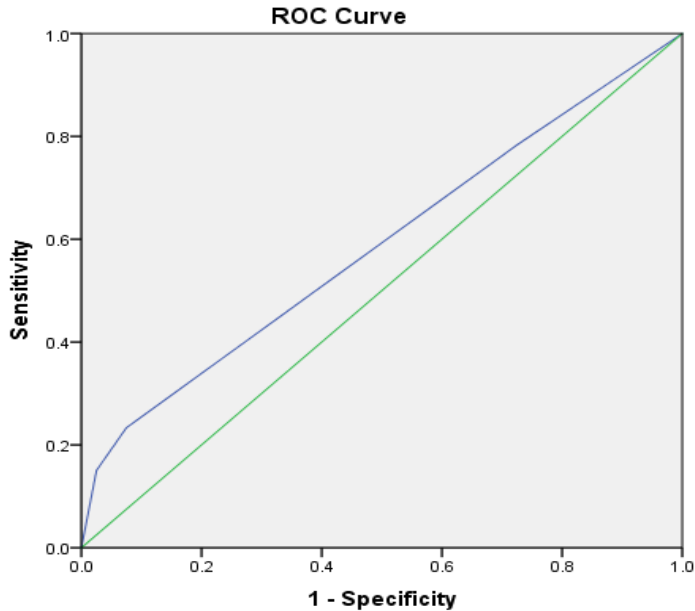
Chart 4. Binary Logistic Regression Analysis for Glaucoma Prediction / Systemic Diseases

Discussion

Glaucoma as a multifactorial disease is closely related to a number of risk factors that contribute to its progression. According to Werne [9], systemic and nocturnal blood pressure are very important for the ocular nerve deterioration. According to Tarkkanen, the prevalence of glaucoma in patients with diabetes mellitus and chronic heart disease is higher than in other groups. According to Sacca [10], glaucoma as a degenerative disease is characterized by Oxidative stress and DNA damage play an important role in inducing the degeneration of these well-differentiated tissues, with DNA damage resulting in progressive cell loss. So in this disease risk factors show genotoxic behavior. When these factors affect individuals susceptible to genetic predisposition, a specific eye disease occurs depending on the ocular tissue affected.According to Mackey [11], family history is present in 60% of glaucoma patients, and in 27% of these families glaucoma is more severe.According to Salaun [12], the most common factors associated with retinal venous occlusion are, in addition to glaucoma, hyperchomocystinaemia, arterial hypertension, and hypercholesterolemia.

According to Yucel, hypercholesterolemia as a risk factor is important for the development of glaucomatous optic neuropathy through induction of nitrite oxide synthesis. According to Steward [13,14], elevated lipoproteins and total cholesterol worsen the condition of a glaucomatous patient as well as those with heart disease, but topical beta-blockers used in glaucoma reduce HDL and raise triglycerides. According to McMonnies, scleral tissue and lamina cribrosa in myopia are more susceptible to variations in altered IOP.According to Rivera [15], the level of recognition and monitoring of risk factors is essential in the treatment of glaucoma in those patients who have a lower neuroretinal margin and a larger beta-zone of parapapillary atrophy.

Regarding the systemic diseases in the patients included in our study, most of the patients 24 (24.00%) had increased blood pressure, 10 (10.00%) patients had heart disease, 5 (5.00%) patients had diabetes , increased blood pressure & diabetes had 7 (7.00%) patients, increased blood pressure & heart disease had 1 (1.00%) patients, increased blood pressure & diabetes & heart disease had 1 (1.00%) and the other category (10 different diseases registered) was registered in 10 (10.00%) patients. From the systemic diseases in the unitary binary logistic regression for the prediction of glaucoma were analyzed heart diseases, increased blood pressure and diabetes and increased blood pressure. It was found that

patients who had heart disease 7.09 times had a slightly ($p = 0.071$) higher risk of glaucoma than patients who did not have systemic disease. Patients who had high blood pressure & diabetes by 1.97 times had a slightly higher risk ($p = 0.439$) of glaucoma than patients without systemic disease. The lowest predictive value for glaucoma prediction was registered in patients with increased blood pressure (0.93 times), insignificant ($p = 0.883$).

Several studies have been performed to determine the correlation of glaucoma with systemic diseases. In a study conducted in Australia [16], it was found that there is a significant association of glaucoma with atherosclerosis (OR: 1.42 95% CI: 1.05-1.92), and its correlation with hypertension, diabetes, and thyroid disease is insignificant.

Another study in Greece [17] found that glaucoma was significantly associated with arterial (systolic) hypertension ($p = 0.033$) and diabetes mellitus ($p = 0.003$), as well as age. There was no association between glaucoma and low diastolic blood pressure and migraine.

A study of the association between systemic disease and glaucoma in Japan [18] found that there was a significant association between glaucoma and arterial hypertension ($p = 0.0094$), and age ($p < 0.0001$), while there was no significant association with diabetes mellitus ($p = 0.85$).

A study in Sweden [19] found that there was no risk of glaucoma progression in patients with arterial hypertension ($p = 0.1279$), and there was a risk of progression in patients with low diastolic blood pressure. It confirmed a significant correlation between age and glaucoma ($p = 0.027$).

In a study of the African population [20], systolic blood pressure ($p < 0.0001$) and diastolic blood pressure ($p < 0.0001$) were significantly associated with glaucoma.

In the Barbados Eye Study [21], it was found that patients with lower systolic blood pressure were more likely to develop glaucoma (RR, 0.91; 95% CI, 0.84-1.00 mmHg).

Conclusion

Based on the results of our study, the following conclusions were made that there is no significant difference ($p > 0.05$) between the examined (group with glaucoma) and the control group (group without glaucoma) in terms of systemic diseases. In the Univariate Logistic Regression Analysis for Glaucoma Prediction, systemic diseases are not significantly associated with glaucoma.

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