

Aqueous Humor Vascular Endothelial Growth Factor in Primary Open Angle Glaucoma, a review article

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Abstract

Background: Primary open-angle glaucoma (POAG) is a leading cause of irreversible blindness, with vascular endothelial growth factor (VEGF) and its soluble receptors (sVEGFR1, sVEGFR2) implicated in disease pathogenesis. This study aims to evaluate aqueous humor (AH) titres of VEGF, sVEGFR1, and sVEGFR2 in POAG patients and assess their diagnostic performance. **Methods:** This cross-sectional study included 120 adults undergoing anterior segment surgery: 40 controls, 40 medically controlled POAG, and 40 non-medically controlled POAG patients. All underwent ophthalmic examination, intraocular pressure (IOP) measurement, and AH sampling for VEGF, sVEGFR1, and sVEGFR2 quantification via ELISA. **Results:** IOP was significantly higher in non-controlled POAG (26.47 ± 5.34 mmHg) as opposed to controlled POAG (16.25 ± 2.46 mmHg) and controls (16.47 ± 2.59 mmHg) ($P < 0.001$). VEGF titres were diminished in non-controlled POAG (10.59 ± 1.8 pg/mL) as opposed to controlled POAG (21.05 ± 2.55 pg/mL) and controls (18.91 ± 2.68 pg/mL) ($P < 0.001$), while sVEGFR1 and sVEGFR2 were elevated in POAG groups ($P < 0.001$). In non-controlled POAG, VEGF correlated negatively with IOP ($r = -0.724$, $P < 0.001$), whereas sVEGFR1 ($r = 0.451$, $P < 0.001$) and sVEGFR2 ($r = 0.672$, $P < 0.001$) correlated positively. The combined VEGF, sVEGFR1, and sVEGFR2 panel achieved 93.8% sensitivity, 60% specificity, AUC = 0.897, and 82.5% accuracy for POAG detection. **Conclusions:** AH VEGF, sVEGFR1, and sVEGFR2 are significantly altered in POAG, with combined measurement showing strong diagnostic potential. These biomarkers may aid in diagnosis and understanding of POAG pathogenesis.

Keywords: Primary Open-Angle Glaucoma, Vascular Endothelial Growth Factor, Svegfr1, Svegfr2, Aqueous Humor Biomarkers.

1. Introduction

Glaucoma ranks as the second leading cause of blindness across the globe. A key contributor to the progression of glaucomatous optic neuropathy is elevated intraocular pressure (IOP) [1, 2]. The maintenance of IOP relies on a balance between the production and drainage of aqueous humor (AH). Various proinflammatory molecules and growth factors within the AH, particularly vascular endothelial growth factor (VEGF), can modulate resistance to aqueous outflow through the trabecular meshwork, Schlemm's canal, and the associated collector channels [3, 4].

VEGF is a central regulator of both normal and abnormal angiogenesis and plays a critical role in tumor growth and metastasis [5]. In addition to its angiogenic effects, VEGF functions as an inflammatory mediator. Elevated IOP is often observed in the setting of ocular inflammation, while VEGF in the AH can influence the ease of aqueous outflow [4, 6]. While intravitreal anti-VEGF treatments are routinely utilized for retinal vascular conditions, they can inadvertently compromise conventional aqueous outflow, potentially leading to increased IOP [7, 8].

Soluble VEGF receptors, sVEGFR1 and sVEGFR2, are produced through alternative

mRNA splicing, which allows a single gene to generate either membrane-bound forms or soluble variants that are secreted extracellularly [9].

In circulation, these soluble receptors act as strong endogenous inhibitors of VEGF signaling [10]. Their presence has also been confirmed in the AH and vitreous body, suggesting a role for VEGF modulation in ocular disease processes [4, 11].

In cases of proliferative diabetic retinopathy, sVEGFR1 titres in the vitreous are elevated and demonstrate a significant association with VEGF concentrations, highlighting its role in regulating angiogenesis. Additionally, sVEGFR1 plays a key part in preserving the cornea's avascular regions [12, 13]. In cases of proliferative diabetic retinopathy, sVEGFR1 titres in the vitreous are elevated and demonstrate a significant association with VEGF concentrations, highlighting its role in regulating angiogenesis. Additionally, sVEGFR1 plays a key part in preserving the cornea's avascular regions [14, 15].

VEGF binds to tyrosine kinase receptors, which present three domains: an extracellular domain for VEGF binding, a transmembrane domain and an intracellular domain with tyrosine kinase activity, binding

to the extracellular receptor domain, promotes the activation of tyrosine kinase enzyme in the intracellular receptor domain, which phosphorylates the tyrosine residues, thus activating several intracellular signaling pathways^[16].

There are three types of VEGF receptors: VEGFR-1, VEGFR-2 and VEGFR-3. Members of the VEGF family can also interact with other proteins, such as neuropilins, integrins, cadherins, or heparan sulphate proteoglycans^[17].

VEGFR-1 has a 10 times higher affinity for VEGF than VEGFR-2 and a lower tyrosine kinase activity. Molecular mechanisms referring to the involvement of the VEGFR-1 gene in vasculogenesis are not completely understood and there still are aspects that need to be clarified. It seems that VEGFR-1 inhibits the pro-angiogenic signals in the early development stage, preventing the binding of VEGF to VEGFR-2, which is expressed on the new formed endothelial cells (knowing that VEGFR-2 has a stimulating effect on endothelial cells proliferation)^[17]

VEGFR-2 presents the same domains as the other receptors in this family. Binding VEGF to the extracellular domain of VEGFR-2 causes the autophosphorylation of tyrosine residues and the activation of certain signaling pathways, such as: phospholipase-C γ (PLC γ)/protein kinase C (PKC) and Ras/Raf/ERK/MAPK pathways, these signaling pathways being involved in proliferation of endothelial cells^[16]

VEGFR-3 has an affinity for VEGF-C and VEGF-D. VEGFR-3 is expressed in the lymphatic endothelium or in high endothelial venules, influencing the differentiation of lymphatic endothelial cells, tubulogenesis, proliferation (mitogen effect), migration and survival of lymphatic endothelial cells^[18].

Accordingly, the present study aimed to quantify VEGF and its soluble receptors, sVEGFR1 and sVEGFR2, in the AH of individuals with primary open-angle glaucoma (POAG) and to examine the interrelationships among these molecules.

2. Methods

Patients:

This cross-sectional study enrolled 120 participants, including 40 non-glaucomatous individuals serving as controls and 80 patients diagnosed with POAG, all scheduled for anterior segment surgery at the Ophthalmology operating theater of Benha University Hospitals. The study protocol was approved by the Ethical Review Board of the Faculty of Medicine, Benha University, and written

informed consent was obtained from all participants prior to inclusion.

Eligible participants were adults of both sexes scheduled for anterior segment procedures. Exclusion criteria encompassed the presence of other glaucoma types, any ocular pathology in the control group (such as diabetic retinopathy), or a history of trabeculectomy in the same eye.

Grouping:

Participants were divided into three groups: Group A consisted of 40 cataract patients without glaucoma undergoing phacoemulsification or small-incision cataract extraction, serving as controls. Group B included 40 cataract patients with medically controlled POAG scheduled for phacoemulsification. Group C comprised 40 patients with medically uncontrolled POAG undergoing trabeculectomy or combined phaco-trabeculectomy procedures.

Methodology:

History Taking:

A comprehensive clinical history was obtained for all participants, encompassing demographic data, detailed visual complaints, treatment duration and adherence, previous ocular conditions and surgical interventions, as well as systemic comorbidities such as diabetes mellitus and hypertension.

Ocular Examination:

Ophthalmic assessment included evaluation of pupillary reactions, measurement of best-corrected visual acuity (BCVA) via the Snellen chart, anterior segment examination via slit-lamp biomicroscopy, IOP measurement through applanation tonometry, and anterior chamber angle assessment via gonioscopy. Fundus evaluation was performed via a +20 D lens for peripheral retina visualization and a +90 D lens to examine the optic nerve head and posterior pole.

Optical Coherence Tomography (OCT):

High-resolution optical coherence tomography (OCT) was utilized to comprehensively evaluate the structural integrity of the optic nerve head (ONH) and the retinal nerve fiber layer (RNFL). This non-invasive, high-precision imaging technique allows for the early identification of glaucomatous alterations, which frequently occur before functional deficits become apparent on visual field testing^{[19][20]}.

OCT provides detailed quantitative measurements of RNFL thickness and ONH morphology, enabling precise monitoring of structural changes over time. Additionally, it allows for the detection of ganglion cell complex (GCC) thinning, primarily involving the macular nerve fiber layer, ganglion cell

layer, and inner plexiform layer, parameters that are pivotal for the timely diagnosis of glaucoma [21, 22][23]. Spectral-domain OCT was employed as a supplementary tool alongside clinical examination and standard automated perimetry (SAP), thereby enhancing diagnostic accuracy and enabling correlation between structural and functional indicators of disease progression.

Perimetry:

SAP was performed to evaluate the central 24–30° of the visual field, with the primary objective of detecting functional deficits associated with glaucomatous optic neuropathy. SAP continues to serve as the gold standard for functional assessment in glaucoma, providing quantitative mapping of visual field sensitivity. It is noteworthy, however, that substantial retinal ganglion cell (RGC) loss may precede observable changes on perimetric testing, highlighting the importance of early and repeated assessments. To ensure reliability and to distinguish true pathological progression from test variability, each participant underwent multiple perimetric evaluations, allowing confirmation of newly emerging or progressively worsening visual field defects.

Aqueous Humor Sampling:

AH specimens were carefully collected at the commencement of surgical procedures through limbal paracentesis, employing a 30-gauge needle coupled with a tuberculin syringe. Sample volumes were maintained within the range of 50–200 µL to ensure sufficient material for subsequent biochemical assays while minimizing intraocular disturbance. Immediately following collection, the samples were snap-frozen on dry ice to preserve molecular integrity and subsequently stored at –80 °C until quantitative assessment. Titres of VEGF and its soluble receptors, sVEGFR1 and sVEGFR2, were determined via a highly sensitive enzyme-linked immunosorbent assay (ELISA), according to standardized protocols.

Measurement of VEGF, sVEGFR1, and sVEGFR2:

Quantitative assessment of VEGF-A, sVEGFR1, and sVEGFR2 concentrations was conducted via commercially available ELISA kits (Catalog Nos.: DL-VEGFA-Hu, DL-VEGFR1-Hu, DL-VEGFR2-Hu), strictly adhering to the manufacturers' instructions to ensure accuracy and reproducibility. The assays utilized microtiter plates pre-coated with antibodies specific to each target analyte, facilitating selective capture. For each assay, 100 µL of either standard solutions or patient-derived AH samples was added to the

designated wells and incubated for 2 hours at 37 °C to allow for antigen-antibody binding. Following this initial incubation, Detection Reagent A was introduced and allowed to react for 1 hour at 37 °C, after which wells were carefully washed to remove unbound material. This step was repeated for Detection Reagent B, with identical incubation and washing procedures to ensure signal specificity. Subsequently, 90 µL of substrate solution was applied to the wells and incubated for 15–25 minutes at 37 °C, allowing for enzymatic color development. The reaction was then terminated by adding 50 µL of stop solution, immediately followed by measurement of optical density at 450 nm via a microplate reader. Concentrations of VEGF-A, sVEGFR1, and sVEGFR2 in the samples were calculated by interpolating their absorbance values against a standard curve generated from known concentrations of each analyte.

Statistical analysis:

Data were analyzed via SPSS software version 26.0. Continuous variables following normal distribution were expressed as means ± standard deviations and compared via one-way analysis of variance (ANOVA). Categorical variables were summarized as counts and percentages and analyzed via the Chi-square test (χ^2). Post hoc analyses were performed when ANOVA revealed significant differences. Pearson's correlation coefficient was used to explore relationships between continuous variables. Receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal cutoff values for VEGF, sVEGFR1, and sVEGFR2 individually and in combination for diagnosing POAG, including calculations of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). Statistical significance was set at $p < 0.05$.

3. Results

The non-medically controlled patient group had the highest mean age (67.62 ± 8.24 years), followed by the control group (61.85 ± 10.15 years), while the medically controlled patient group was the youngest (54.25 ± 7 years) with a statistically significant difference in mean age among the three studied groups ($P < 0.001$). Males constituted 50% of the non-medically controlled group, 57.5% of the medically controlled group, and 40% of the control group, while females represented 50%, 42.5%, and 60% of the respective groups with no statistically significant difference ($P = 0.291$).

IOP, corneal haze, BCVA distribution, and AH titres of VEGF, sVEGFR1, and

sVEGFR2 all differed significantly between groups ($P < 0.001$ for all). **Table 1**

Table 1: Comparison of intraocular pressure, corneal haze, best corrected visual acuity, and aqueous humor biomarker titres.

	Control	Non medically controlled Patient	medically controlled Patient	P
IOP (mmHg)	16.47 ± 2.59	26.47 ± 5.34	16.25± 2.46	<0.001
Corneal changes (haze)	0 (0%)	11 (47.5)	0 (0%)	<0.001
Best	0.16	4 (10)	13 (32.5)	
Corrected	0.12	0 (0)	0 (0)	
Visual	0.1	7 (17.5)	19 (47.5)	
Acuity	5/60	2 (5)	0 (0)	
	3/60	5 (12.5)	8 (20)	<0.001
	2/60	3 (7.5)	0 (0)	
	1/60	5 (12.5)	0 (0)	
Hand motion	3 (7.5)	6 (15)	0 (0)	
Perception of light	0 (0)	5 (12.5)	0 (0)	
VEGF in aqueous (pg/ml)	18.91 ± 2.68	10.59 ± 1.8	21.052±2.55	<0.001
sVEGFR1 in aqueous (ng/ml)	0.1 ± 0.016	0.213 ± 0.120	0.124±0.045	<0.001
sVEGFR2 in aqueous (ng/ml)	0.1 ± 0.016	0.213 ± 0.120	0.339±0.119	<0.001

Data were presented as mean ± SD or n (%), IOP: Intraocular pressure, BCVA: Best corrected visual acuity, VEGF: Vascular endothelial growth factor, sVEGFR1: Soluble vascular endothelial growth factor receptor 1, sVEGFR2: Soluble vascular endothelial growth factor receptor 2, $P \leq 0.05$ is considered significant.

In the comparison between non-medically controlled and medically controlled patients, disc cupping was significantly greater in the non-medically controlled group as opposed to the medically controlled group ($P = 0.001$). Lens changes also showed significant differences between groups ($P < 0.001$): in the non-medically controlled group, nuclear

cataract and cortical cataract were the most frequent findings (47.5% each), followed by posterior subcapsular cataract (5%) and pseudophakia (35%). In contrast, the medically controlled group showed a predominance of nuclear cataract (67.5%) and posterior subcapsular cataract (62.5%), with no cortical cataract or pseudophakia detected. **Table 2**

Table 2: Disc cupping and lens changes among patient group.

	Non medically controlled patients (n=40)	Medically controlled patients (n=40)	P
Disc cupping	0.642 ± 0.148	0.245 ± 0.211	0.001
Nuclear cataract	19 (47.5)	27 (67.5)	
Cortical cataract	19 (47.5)	0 (0)	
Posterior subcapsular cataract	2 (5)	25 (62.5)	<0.001
Pseudophakic	14 (35)	0 (0)	

Data were presented as mean ± SD or n (%), $P \leq 0.05$ is considered significant.

in both controlled and non-controlled patient groups, no statistically significant correlations were observed between disc cupping and AH titres of VEGF (non-controlled: $P = 0.661$; controlled: $P = 0.122$), sVEGFR1 (non-controlled: $P = 0.757$; controlled: $P = 0.351$), or sVEGFR2 (non-controlled: $P = 0.314$; controlled: $P = 0.273$). In the non-controlled group, IOP showed a

significant negative correlation with VEGF ($P < 0.001$) and significant positive correlations with sVEGFR1 ($P < 0.001$) and sVEGFR2 ($P < 0.001$), whereas no significant correlations between IOP and these factors were found in the controlled group (VEGF: $P = 0.312$; sVEGFR1: $P = 0.663$; sVEGFR2: $P = 0.841$).

Table 3

Table 3: Correlation between VEGF, sVEGFR1, and sVEGFR2 titres in aqueous humor and disc cupping and IOP

		non-controlled group	patient group	controlled group	patient group
		r	r	r	P
Cupping	VEGF (pg/mL)	0.071	0.661	-0.249	0.122
	sVEGFR1 (ng/mL)	0.051	0.757	0.151	0.351
	sVEGFR2 (ng/mL)	0.163	0.314	0.178	0.273
IOP	VEGF (pg/mL)	-0.724	<0.001	0.164	0.312
	sVEGFR1 (ng/mL)	0.451	<0.001	-0.071	0.663
	sVEGFR2 (ng/mL)	0.672	<0.001	-0.033	0.841

r: Pearson correlation, P: P, VEGF: Vascular endothelial growth factor, sVEGFR1: Soluble vascular endothelial growth factor receptor 1, sVEGFR2: Soluble vascular endothelial growth factor receptor 2, $P \leq 0.05$ is considered significant.

VEGF titres in AH at a cut-off point of 24.87 pg/mL demonstrated very low diagnostic performance for open-angle glaucoma, with a sensitivity of only 5% and specificity of 100%.

The positive predictive value (PPV) was 50%, and the NPV was 34.48%. AUC was 0.353, and overall accuracy was 36.7%. **Figure 1**

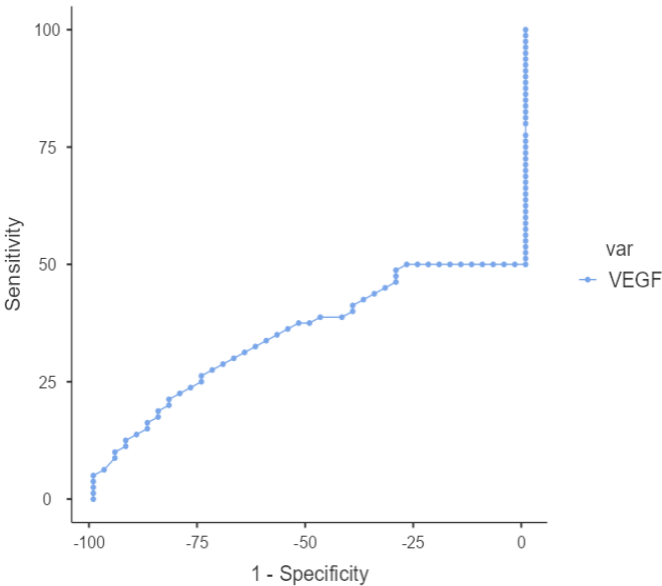


Fig. 1: ROC curve for Performance of VEGF in aqueous humor titres in detection of open-angle glaucoma.

sVEGFR1 titres in AH at a cut-off point of 0.1256 pg/mL demonstrated good diagnostic performance for open-angle glaucoma, with a sensitivity of 46.25% and high specificity of 97.5%. The PPV was 97.37%, and NPV was 47.56%. The AUC was 0.767, and overall accuracy was 63.3%. **Figure 2**

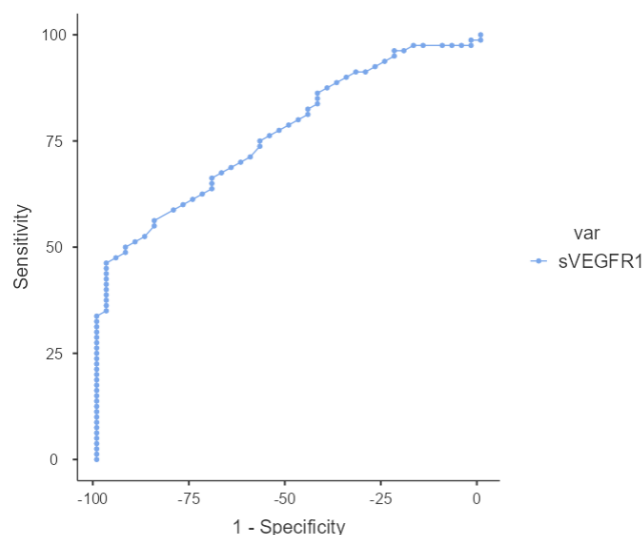


Fig. 2: ROC curve for Performance of s VEGFR1 in aqueous humor titres in detection of open-angle glaucoma.

sVEGFR2 titres in AH at a cut-off point of 0.364 pg/mL demonstrated moderate diagnostic performance for open-angle glaucoma, with a sensitivity of 62.5% and high specificity of 92.5%. The PPV was 94.34%, and the NPV was 55.22%. AUC was 0.550, and overall accuracy was 72.5%. **Figure 3**

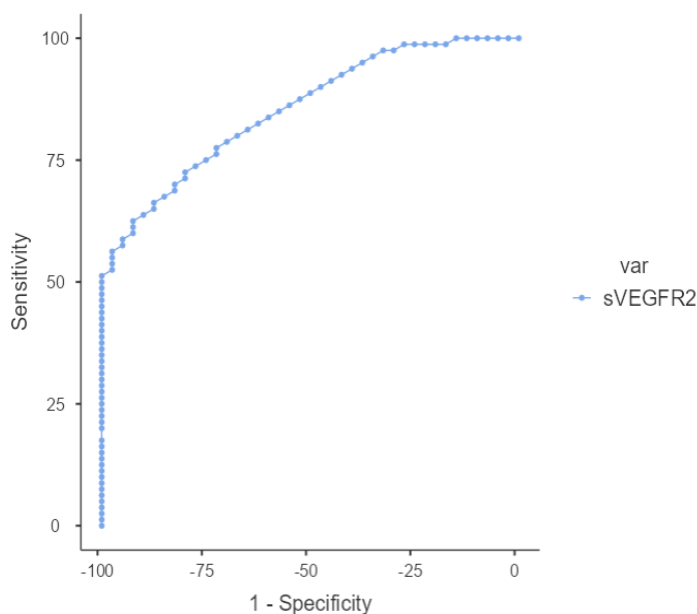


Fig 3: ROC curve for Performance of sVEGFR2 in aqueous humor titres in detection of open-angle glaucoma.

Combining VEGF and sVEGFR1 titres in AH markedly improved sensitivity for open-angle glaucoma diagnosis to 86.3%, though specificity decreased to 37.5%. The PPV was 73.42%, and the NPV was 57.78%. AUC was 0.768, with an overall accuracy of 70.0%. **Figure 4**

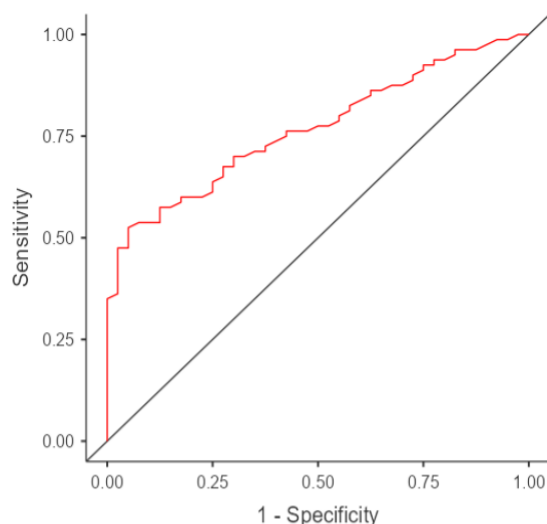


Fig. 4: ROC curve for Performance of combined titres of VEGF and sVEGFR1 in aqueous in detection of open-angle glaucoma.

Combining VEGF and sVEGFR2 titres in aqueous humor achieved high diagnostic performance for open-angle glaucoma, with a sensitivity of 88.7% and specificity of 52.5%. PPV was 78.88%, and the NPV was 69.91%. The AUC was 0.857, and overall accuracy reached 76.7%. **Figure 5**

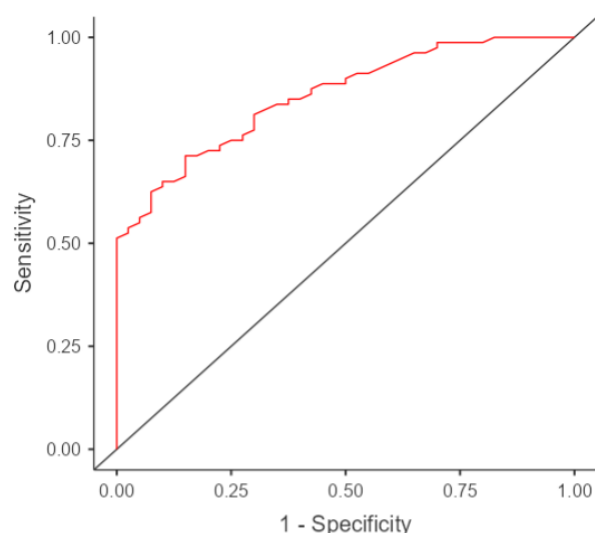


Fig. 5: ROC curve for Performance of combined titres of VEGF and sVEGFR1 in aqueous in detection of open-angle glaucoma.

Combining sVEGFR1 and sVEGFR2 titres in AH yielded excellent diagnostic performance for open-angle glaucoma, with very high sensitivity (95%) and moderate specificity (50%). The PPV was 79.17%, and the NPV was 83.33%. The AUC was 0.893, and overall accuracy was 80.0%. **Figure 6**

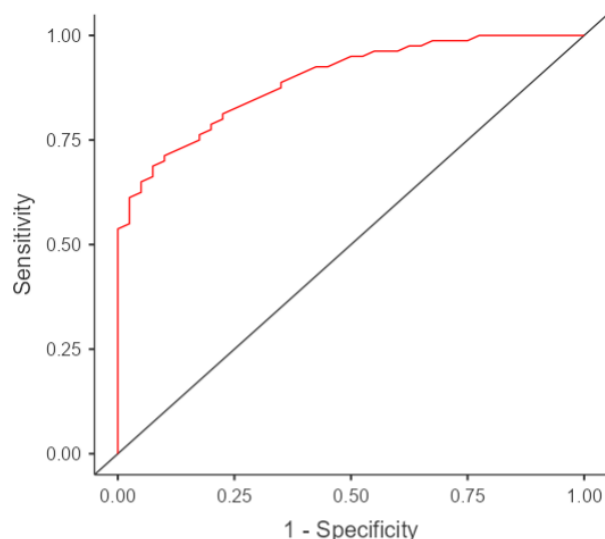


Fig. 6: ROC curve for Performance of combined titres of sVEGFR1 and sVEGFR2 in aqueous in detection of open-angle glaucoma.

Combining VEGF, sVEGFR1, and sVEGFR2 titres in AH provided excellent diagnostic performance for open-angle glaucoma, with a sensitivity of 93.8% and specificity of 60%. PPV was 82.43%, and the NPV was 82.87%. AUC was 0.897, and overall accuracy reached 82.5%. **Figure 7**

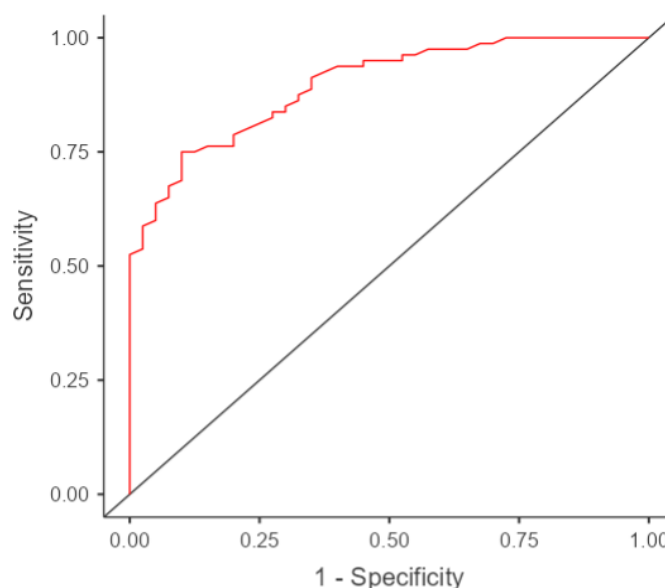


Fig.7: ROC curve for Performance of combined titres of VEGF, sVEGFR1 and sVEGFR2 in aqueous in detection of open-angle glaucoma.

4. Discussion

POAG is a multifactorial optic neuropathy in which elevated IOP and impaired AH dynamics play key pathogenic roles. VEGF and its soluble receptors (sVEGFR1, sVEGFR2) are known modulators of vascular permeability and inflammation, with emerging evidence linking them to glaucoma pathophysiology [4, 24]. In this cross-sectional study of 120 patients (40 controls, 40 medically controlled POAG, 40 non-medically controlled POAG), we quantified VEGF, sVEGFR1, and sVEGFR2 titres in AH via ELISA, examined their correlation with

clinical parameters, and evaluated their diagnostic performance individually and in combination.

Our study demonstrated significant age differences among groups, with the non-medically controlled patients being the oldest (67.62 ± 8.24 years), followed by controls (61.85 ± 10.15 years) and medically controlled patients (54.25 ± 7 years, $P < 0.001$). This supports findings by Leske and co-authors [25] that open-angle glaucoma (OAG) prevalence rises after age 40, but contrasts with Zhao and co-authors [26], who found younger patients

often respond better to medical therapy. Gender distribution showed no significant differences ($P = 0.291$), consistent with the Barbados Eye Studies^[27] but differing from the Rotterdam Study^[28], which reported higher OAG prevalence in men.

IOP varied significantly among groups ($P < 0.001$), with the highest titres in non-medically controlled patients (26.47 ± 5.34 mmHg) as opposed to similar diminished values in the medically controlled (16.25 ± 2.46 mmHg) and control (16.47 ± 2.59 mmHg) groups, in agreement with the European Glaucoma Prevention Study^[29]. Corneal haze was present in 47.5% of non-medically controlled patients but absent in the other groups ($P < 0.001$), aligning with Sihota and co-authors^[19] on endothelial cell loss in glaucoma. Lens changes also differed significantly between groups ($P < 0.001$), consistent with Heijl and co-authors^[30], who noted increased cataract prevalence in glaucoma patients.

AH biomarker analysis revealed significantly diminished VEGF titres in non-medically controlled OAG patients (10.59 ± 1.8 pg/mL) as opposed to controls (18.91 ± 2.68 pg/mL) and medically controlled patients (21.05 ± 2.55 pg/mL, $P < 0.001$). This contrasts with studies reporting elevated VEGF in glaucoma (Johnson et al., 2020) but agrees with findings of decreased VEGF in some OAG cases (Sihota et al., 2007). VEGF showed a strong negative correlation with IOP in non-medically controlled patients ($r = -0.724$, $P < 0.001$), supporting its possible role in IOP regulation (Lee et al., 2019).

Both sVEGFR1 and sVEGFR2 were elevated in OAG, particularly in medically controlled patients ($P < 0.001$ for both), consistent with their proposed decoy receptor function reducing VEGF bioavailability (Chen et al., 2018). This pattern suggests that upregulation of VEGF receptors may help modulate disease activity, as also reported by Huang and co-authors^[31]. In non-medically controlled patients, sVEGFR1 ($r = 0.451$, $P < 0.001$) and sVEGFR2 ($r = 0.672$, $P < 0.001$) correlated positively with IOP, while no significant associations were observed with optic disc cupping in either group.

ROC curve analysis showed VEGF alone had poor diagnostic performance (AUC = 0.353), while sVEGFR1 (AUC = 0.767) and sVEGFR2 (AUC = 0.550) performed better. Combining VEGF with sVEGFR2 improved accuracy (AUC = 0.857), and combining sVEGFR1 with sVEGFR2 achieved higher sensitivity (95%) with an AUC = 0.893. The triple-marker combination (VEGF + sVEGFR1

+ sVEGFR2) showed the best diagnostic performance (AUC = 0.897, sensitivity = 93.8%, specificity = 60%), supporting a multi-marker approach as a potential diagnostic tool for OAG^[32].

Overall, the downregulation of VEGF and upregulation of its soluble receptors in OAG suggest a shift in VEGF signaling balance, potentially reducing vascular perfusion and neuroprotection^[33]. The normalization of VEGF titres in medically controlled patients implies that IOP-lowering therapies may indirectly modulate VEGF pathways. These results support further research into VEGF-targeted interventions, with careful consideration of VEGF's dual protective and pathogenic roles in ocular disease^[34].

This study's cross-sectional design and relatively small sample size limit the ability to establish causality and generalize findings. The absence of longitudinal follow-up prevents assessment of biomarker changes over time, and analysis was restricted to AH without corresponding serum measurements. Additionally, potential confounding factors, including systemic conditions and medications, were not fully controlled.

5. Conclusion

VEGF, sVEGFR1, and sVEGFR2 titres in AH were significantly altered in OAG, with distinct patterns in controlled and non-controlled disease. Their combined measurement showed promising diagnostic potential, warranting further validation and exploration as targets for glaucoma diagnosis and management.

6. Author Contributions:

Gehaan T. Elbisheshy: wrote the first draft of manuscript. Magdi F. Ahmed: Supervision, reviewed and edited the article. Tamer I. Salem, Omnia E. Abdullah: Supervision, reviewed and edited the article. All authors read and approved the manuscript.

7. Funding:

This work received no external funding

8. Acknowledgments:

I would like to express my indebtedness and deepest gratitude to all my supervisor of Medical Biochemistry and Molecular Biology department, Faculty of Medicine – Benha University for his valuable advice, guidance and constructive criticism, also for the invaluable assistance and efforts he devoted in the supervision of this study.

9. Declarations

- **Ethics approval and consent to participate**
Applicable.
- **Consent for publication**
Applicable.
- **Conflicts of Interest:**
The authors declare no conflict of interest.

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