

A New Glaucoma Severity Score Combining Structural and Functional Defects

Systematische Einteilung des Glaukomstadiums unter Berücksichtigung struktureller und funktioneller Defekte

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Bibliography

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ABSTRACT

Background In order to assess glaucoma severity and to compare the success of surgical and medical therapy and study outcomes, an objective and independent staging tool is necessary. A combination of information from both structural and functional testing is probably the best approach to stage glaucomatous damage. There has been no universally accepted standard for glaucoma staging. The aim of this study was to develop a Glaucoma Severity Score (GSS) for objective assessment of a patient's glaucoma severity, combining both functional and structural information.

Materials and methods The Glaucoma Severity Score includes the following 3 criteria: superior and inferior Retinal Nerve Fibre Layer (RNFL) thickness, perimetric mean defect (MD), and agreement of anatomical and perimetric defects, as assessed by two glaucoma specialists. The specialists defined a staging tool for each of the 3 criteria in a consensus process, assigning specific characteristics to a scale value between 0 and 2 or 0 and 3, respectively. The GSS ranges between 0 and 10 points. In a prospective observational study, the data of 112 glaucoma patients were assessed independently by the two specialists according to this staging tool.

Results The GSS was applied to 112 eyes and patients (59.8% female) with a mean age of 66.3 ± 13.1 years. Mean GSS was 4.73 points.

Cohen's kappa coefficient was determined to measure inter-rater agreement between glaucoma specialists for the third criterion. With $\kappa = 0.83$, the agreement was very good. Thus, all 3 criteria of the GSS may be regarded as objective.

Conclusions The Glaucoma Severity Score is an objective tool, combining both structural and functional characteristics, and permitting comparison of different patients, populations and studies. The Glaucoma Severity Score has proven effective in the objective assessment of 112 glaucoma patients and is relatively user-friendly in clinical practice. A comparative study of the GSS with the results of the FORUM® Glaucoma Workplace (Carl Zeiss Meditec AG, Jena, Germany) will be the next step. If outcomes match, the Glaucoma Severity Score can be accepted as a promising tool to stage glaucoma and monitor changes objectively in patients when comparing glaucoma progression in study analyses.

ZUSAMMENFASSUNG

Hintergrund Zur Beurteilung des Glaukomstadiums, zum Vergleich von operativen und medikamentösen Therapieerfolgen sowie von Studienergebnissen ist ein objektives Graduierungssystem notwendig. Von Vorteil ist ein Ansatz, der funktionelle und strukturelle Untersuchungsergebnisse kombiniert. Bis dato hat sich international kein Beurteilungssystem des Glaukomstadiums durchsetzen können. Das Ziel dieser Studie war die Entwicklung eines Glaucoma Severity Scores (GSS), der Funktion, Struktur und objektive Beurteilung kombiniert.

Material und Methoden Der Glaucoma Severity Score beinhaltet folgende 3 Kriterien: retinale peripapilläre Nervenfaserschichtdicke (superior und inferior), perimetrischer mittlerer Defekt und den Konsens über anatomische und perimetrische Defekte durch 2 Glaukomspezialisten. Für jede der 3 Dimensionen werden spezifische Merkmale festgelegt, die eine Zuordnung zu einem Skalenwert zwischen 0 und 2 resp. 3 Punkten pro beurteilter Domäne erlauben. Das Graduierungssystem reicht von 0 bis zu 10 Punkten. Der GSS wird in einer prospektiven Beobachtungsstudie an 112 Patienten getestet.

Ergebnisse Der GSS wurde anhand von 112 Patienten (59,8% Frauen) mit einem durchschnittlichen Alter von $66,3 \pm 13,1$ Jahren getestet. Der durchschnittliche GSS betrug 4,73 Punkte. Cohens Kappa-Koeffizient als statistisches Maß für die Interrater-Reliabilität zwischen den Glaukomspezialisten für das 3. Kriterium betrug $\kappa = 0,83$. Dies entspricht einer sehr guten Übereinstimmung, weshalb alle 3 Kriterien des Index als objektiv betrachtet werden können.

Schlussfolgerungen Der Glaucoma Severity Score erlaubt eine objektive Beurteilung des Glaukomstadiums verschiedener Patienten und bietet somit eine optimierte Vergleichsmöglichkeit von Studienergebnissen und Therapieerfolgen. Für die optimale Beurteilung des Glaukomstadiums sind im GSS strukturelle und funktionelle Eigenschaften kombiniert. In einem nächsten Schritt soll der GSS mit dem FORUM® Glaucoma Workplace (Carl Zeiss Meditec AG, Jena, Deutsch-

land) verglichen werden. Stimmen die Resultate überein, ist der GSS ein erfolgsversprechendes Instrument zur objektiven Beurteilung von Glaukomsta-

dium und Progression, und könnte zum Vergleich verschiedener Patienten und Studienergebnisse dienen.

Introduction

Early diagnosis and appropriate treatment of glaucoma are essential in the management of the disease in order to prevent glaucomatous damage with irreversible vision loss. Therefore, objective and standardized assessment of glaucoma severity is important. A quantitative staging system enables evaluation of inter-individual surgical and medical therapy, definition of intra- and inter-individual progression rates, and the comparison of independent studies [1].

Until present day, there has been no universally accepted standard for glaucoma staging. Many systems have been proposed, but none have been sufficiently convincing to become established in clinical practice [2, 3]. The difficulty may be that glaucoma cannot be defined accurately by one single criterion. Cup-to-disc ratio, visual field damage, or intraocular pressure (IOP) may vary individually and cannot be used solely for the diagnosis of glaucoma [1]. Either changes in optic disc and retinal nerve fiber layer may precede visual field changes, visual field defects may be caused by conditions other than glaucoma, or IOP may be elevated in the absence of glaucoma or normal in the presence of glaucoma [1, 2, 4]. However, staging of the disease is important for treatment decisions and the objective monitoring of changes.

Standard automated perimetry (SAP) is the clinical standard for the diagnosis and monitoring of glaucoma, providing functional information [5]. Structural information is given by Optical Coherence Tomography (OCT) addressing retinal nerve fiber layer (RNFL) thickness and optic nerve head (ONH) appearance. Objective assessment of RNFL has been shown to improve detection of glaucoma and is useful in monitoring disease progression [6, 7]. Accordingly, the diagnosis and evaluation of glaucoma are currently based primarily on the results of perimetry and spectral domain Optical Coherence Tomography (OCT) [8]. In addition, the ophthalmologist must take into account factors such as age, disease severity, risk factors (e.g. IOP), and life expectancy in order to assess the patient's glaucomatous disease [8]. The aforementioned factors and others are left to the ophthalmologist's personal experience and subjective evaluation. Most proposed staging systems assess either functional or structural damage, although not both [9].

The aim of this study is to develop a Glaucoma Severity Score for objective assessment of a patient's glaucoma severity, combining both functional and structural information.

Materials and Methods

This observational prospective study was approved by the local ethics committee (Ethics Committee of the Canton Zurich, KEK-ZH-No. 2011-0311) and adhered to the tenets of the Declaration of Helsinki and local law.

The Glaucoma Severity Score was developed by two glaucoma specialists (CK, MT) at two affiliated centers in Zurich, Switzerland. A total of 112 glaucoma patients, who were recruited for another study conducted by the authors of this paper, were examined between July 2011 and May 2016. Inclusion criteria were age of 18 years or older with confirmed or suspected open angle glaucoma or ocular hypertension (OHT). All patients were Caucasians. Exclusion criteria were contact lens wear, acute or chronic corneal diseases, corneal astigmatism, hypermetropia or myopia > 2.0 dpt., a history of laser refractive surgery, or other corneal interventions. All patients underwent a full ophthalmologic examination, including refraction, visual acuity, slit lamp examination and fundus biomicroscopy, biometry, pachymetry (echographic and optic), Optical Coherence Tomography (Cirrus™ HD-OCT 5000, Carl Zeiss Meditec AG, Jena, Germany), and Dynamic Octopus Perimetry (Haag-Streit Octopus 900, Haag-Streit, Koenitz, Switzerland). Intraocular pressure was measured by Goldmann Applanation Tonometry (IOP_{GAT}) and Dynamic Contour Tonometry (IOP_{DCT}) (DCT/Pascal®, Ziemer Ophthalmic Systems, Port, Switzerland).

After a review of the literature on existing glaucoma staging systems, the two specialists (CK, MT) defined a Glaucoma Severity Score (GSS), combining both structural and functional information. The GSS is composed of the following three criteria: superior and inferior Retinal Nerve Fiber Layer (RNFL) thickness, perimetric Mean Defect (MD), and agreement of anatomic and perimetric defect, assessed by the two specialists. The specialists defined a staging tool for each of the 3 criteria in a consensus process, assigning specific characteristics to a scale value between 0 and 2 or 0 and 3, respectively. The GSS ranges from 0 to a maximum of 10 points. ► **Table 1** gives an overview of GSS criteria and definition.

RNFL thickness (Zeiss Cirrus™ HD-OCT 5000) was staged objectively according to the standardized color levels green (0 points), yellow (1 point) and red (2 points). Perimetric mean defect [dB] (Haag-Streit Octopus 900) was categorized as follows: 0–1.9 dB = normal (0 points), 2–5.9 dB = early defect (1 point), 6–11.9 dB = moderate defect (2 points), ≥ 12 dB = severe defect (3 points). The third criterion, accordance of OCT and perimetric defect, was staged independently by the two specialists as no agreement/no defect (0 points), suspected agreement/defect (1 point), moderate agreement/small defect (2 points), good agreement/advanced defect (3 points).

The data of 112 glaucoma patients (112 single eyes) of both centers were assessed independently by the specialists (CK, MT) according to this staging tool. While GSS OCT and GSS MD criteria are fully objective, inter-rater agreement was evaluated for the third criterion in order to assess its objectivity.

Statistical methods

Data was coded in Excel and analyzed with SPSS version 22 (IBM Corporation, New York City, NY, USA). Descriptive statistics, such

► **Table 1** Criteria of the Glaucoma Severity Score.

GSS criteria	Description	GSS points	Total GSS
GSS OCT superior & GSS OCT inferior	Superior and inferior peripapillary Retinal Nerve Fiber Layer thickness	0–2 points 0–2 points	GLAUCOMA SEVERITY SCORE 0–10 points
GSS MD	Mean Deviation/defect from normal perimetric sensitivity	0–3 points	
GSS Agreement	Agreement of congruent anatomic and perimetric defect	0–3 points	

GSS = Glaucoma Severity Score; OCT = Optical Coherence Tomography; MD = Mean Defect

as mean, standard deviation (SD), median and interquartile range (IQR), as well as absolute and relative frequencies were computed. An agreement between the two specialists CK and MT was investigated by the kappa statistic. According to Altman (1991), kappa value > 0.8 indicates a very good agreement. For the analysis at patient level, one eye per patient was randomly chosen to guarantee that the observations are independent. Association between GSS and factors (IOP, axial length, CCT, age and gender) was investigated by a non-parametric Spearman correlation and a multiple linear regression. The results were visualized by scattergrams. For the analysis of the full dataset with dependent observations (all eyes), the linear mixed-models methodology adjusting for two observations per patient was used. Results of statistical analysis with p-value < 0.05 were interpreted as statistically significant.

Results

The Glaucoma Severity Score was applied to a total of 112 eyes and patients, with 45 (40.2%) male and 67 (59.8%) female patients. Mean age was 66.3 ± 13.1 years (26–90 years). The majority of eyes (60.7%) was diagnosed with primary open-angle glaucoma (POAG). Secondary glaucoma, mostly pseudoexfoliation glaucoma, was seen in 21.4%, and 17.9% suffered from ocular hypertension (OHT). Mean central corneal thickness (CCT) was 536.8 µm (SD ± 36.4), mean axial length (AL) was 23.9 mm (SD ± 1.9), and mean IOP measured by GAT was 17.0 mmHg (SD ± 4.1) and 20.3 mmHg (SD ± 4.5) measured with DCT, respectively.

The mean GSS of our study population was 4.73 points. ► **Table 2** summarizes the mean measures for each of the 3 GSS criteria. Cohen's kappa coefficient was determined to measure interrater agreement between the two glaucoma specialists (CK and MT) for the third criterion. With $\kappa = 0.83$, the degree of agreement was very good. Therefore, all 3 criteria of the GSS may be regarded as objective. For statistical analysis, one specialist's rating was selected (CK Agreement GSS) to avoid half point scores.

Spearman's rank-order correlation showed a strong negative correlation between both the OCT superior ($r_s = -0.79$, $p < 0.001$) and inferior ($r_s = -0.78$, $p < 0.001$) RNFL thickness and GSS score. For perimetric MD, there was a strong positive correlation with the GSS score ($r_s = 0.78$, $p < 0.001$). These findings correspond with the expected increase in MD and decrease of RNFL thickness with glaucoma progression and higher GSS, respective-

► **Table 2** Results of Perimetry, OCT and GSS Criteria

Parameter	Mean (± SD)* or Median (Min, Max, IQR)**
Perimetric Mean Defect (MD) [dB]	3.75 (0, 27.3, 6.35) **
▪ OCT RNFL superior [µm]	86.2 (± 26.2)*
▪ OCT RNFL inferior [µm]	89.3 (± 26.6)*
Glaucoma Severity Score (GSS)	
▪ MD GSS (0–3 points)	1.31 (± 0.99)*
▪ OCT superior GSS (0–2 points)	1.05 (± 0.94)*
▪ OCT inferior GSS (0–2 points)	1.0 (± 0.92)*
▪ CK Agreement GSS (0–3 points)	1.38 (± 1.23)*
▪ GSS (0–10 points)	4.73 (± 3.37)*

* (± SD) = standard deviation, ** (IQR) = Interquartile Range; GSS = Glaucoma Severity Score; OCT = Optical Coherence Tomography; MD = Mean Defect; RNFL = Retinal Nerve Fiber Layer

► **Table 3** Multiple linear regression analysis for GSS.

Outcome	Predictor	β-slope	p-value
Glaucoma Severity Score	Age	0.06	0.013
	Gender	1.21	0.037
	IOP	-0.22	0.002
	CCT	-0.02	0.014

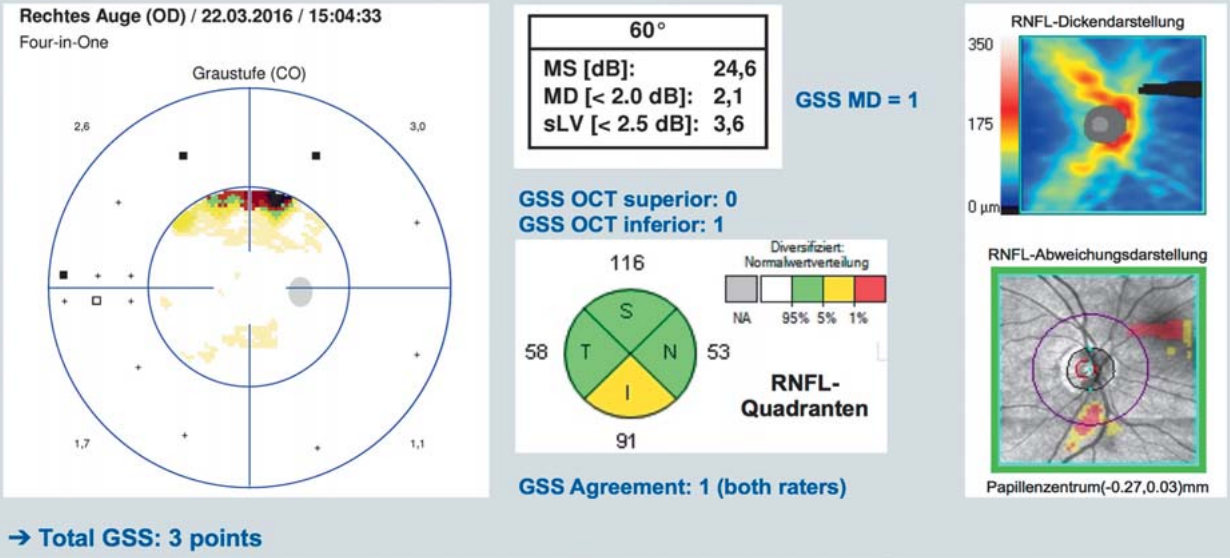
IOP = Intraocular Pressure; CCT = Central Corneal Thickness

ly. Multiple linear regression results for the influence of age, gender, CCT and IOP on GSS are given in ► **Table 3**.

Spearman's rank-order correlation showed a negative correlation between CCT and GSS ($r_s = -0.38$, $p < 0.001$). Thus, patients tended to have thinner corneas with progressed GSS. Analyzing mean CCT by glaucoma diagnosis resulted in a mean CCT of 531.3 µm (± 35.2) for POAG eyes, 548.6 µm (± 32.7) for secondary glaucoma types, and 541.2 µm (± 42.2) for OHT patients. There was no significant difference in CCT among these three groups as determined by one-way ANOVA ($p = 0.112$). A scatterplot showed even distribution of all 3 diagnostic groups from thin to thick corneas.

CASE 1 – EARLY GLAUCOMA

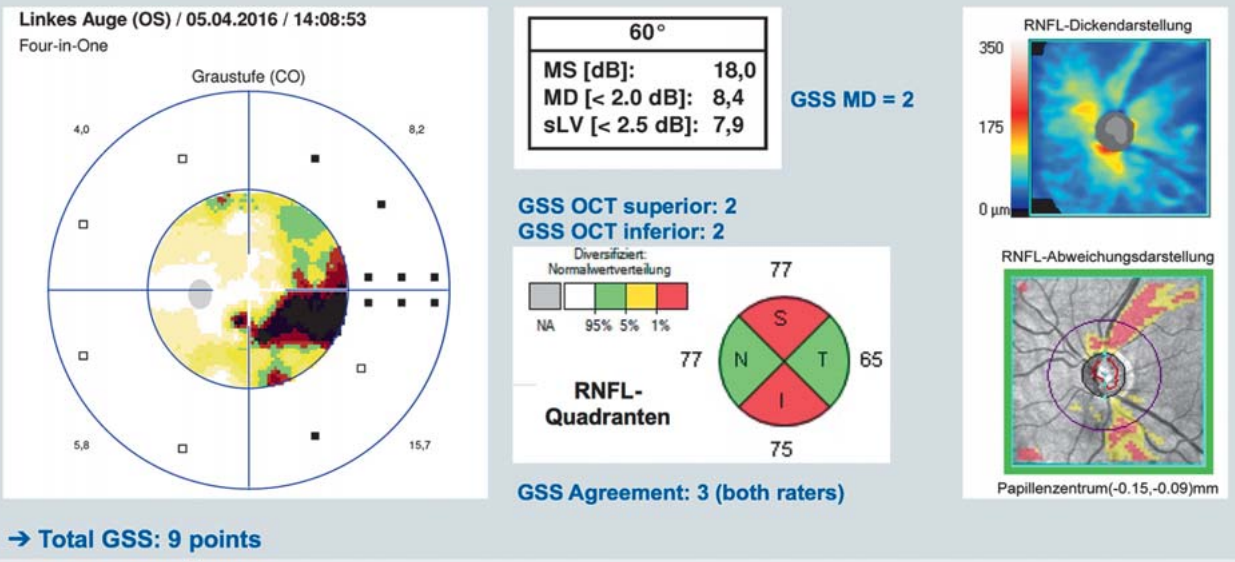
63 years old male patient with diagnosis of ocular hypertension (OHT), right eye



► Fig. 1 Application example of the GSS for a case of early glaucoma. GSS = Glaucoma Severity Score; OCT = Optical Coherence Tomography; MD = Mean Defect; RNFL = Retinal Nerve Fiber Layer.

CASE 2 – ADVANCED GLAUCOMA

67 years old female patient with primary open-angle glaucoma (POAG), left eye



► Fig. 2 Application example of the GSS for a case of advanced glaucoma. GSS = Glaucoma Severity Score; OCT = Optical Coherence Tomography; MD = Mean Defect; RNFL = Retinal Nerve Fiber Layer.

► **Figs. 1 and 2** are application examples of the GSS for a case of early glaucoma (► **Fig. 1**) and a case of advanced glaucoma (► **Fig. 2**).

Discussion

Objective assessment of a patient's glaucoma stage is important in clinical practice and for study purposes. The Glaucoma Severity Score is a tool, combining both objective structural and functional characteristics, thereby permitting comparison of different patients, populations and studies.

Staging the severity of glaucoma is essential for therapeutic decisions and monitoring the disease progression. While many staging systems only consider the functional results of perimetry [9–13], other methods have been proposed, assessing solely structural results of optic disc appearance [1, 14–17]. The first approach may overlook early glaucoma because patients typically first develop structural damage before detectable functional ones. Studies have shown that structural information may not be sensitive enough in patients with advanced glaucomatous damage compared to visual field testing [18, 19]. The European Glaucoma Prevention Study emphasizes the possible disagreement between functional and structural examination results [20]. Hence, a combination of information from both structural and functional testing is probably the best approach to stage glaucomatous damage. A few combined staging systems have been developed. In 2012, Medeiros et al. presented a combined index of structure and function measuring disease severity based on an estimate of the retinal ganglion cells (RGC) lost in glaucoma compared to age-matched healthy eyes as obtained by SAP and OCT [3, 21]. The index showed a better performance compared to the isolated use of functional or structural measures. [3, 18] The GSS introduced in this paper does not include estimates of RGC loss, but provides a combination of both structural OCT and functional SAP information, together with a criterion connecting both, the agreement of the anatomic and perimetric defect as assessed by specialists. RNFL thickness is declining over time in any individual. Hence, the GSS does not use RNFL thickness but the color code (green, orange, or red) provided by the normative database of the OCT software. This database takes change of RNFL thickness with age of individuals into account.

The Glaucoma Severity Score has proven effective in the assessment of 112 glaucoma patients. The GSS has several advantages. The standardized definitions of GSS criteria enable the use of different models of perimeters and OCT. With a minimum of 0 and a maximum of 10 points, the GSS is uncomplicated to use and may allow detection of disease alteration over time. Regarding early, moderate, and severe disease, larger intervals may be easier to apply, yet involve the risk of neglecting clinically relevant changes [1]. The third criterion of the GSS – agreement of anatomic and perimetric defect – appeared to be in good correspondence between the two glaucoma specialists. All of these aspects cause the GSS to be relatively user-friendly and a promising tool in the staging of glaucoma patients in our study setting. A change in GSS over time may be an indicator for disease progression, but its

usefulness and reliability, especially in a clinical setting, needs to be investigated.

There are some limitations of the GSS. As with any scoring system in medicine, individuality of the patient, the disease and possible risk factors may be lost. In a clinical setting, it is mandatory to observe and follow the patient including all available individual variables. As it is generally hard to detect glaucoma and glaucoma progression in patients with tilted disc, extensive peripapillary atrophy, high myopia, and small optic discs, these cases have been excluded in this preliminary investigation of the GSS. Furthermore, high astigmatism as well as high refractive errors are known to influence OCT measurement in an unpredictable manner. Therefore, both modalities have been excluded. The clinical use of the GSS is therefore unknown in these conditions. Subsequent evaluation is necessary.

By integrating the results of both structural and functional testing into one single index, the Glaucoma Severity Score may be useful in the staging of glaucoma and detection of disease progression. The GSS shall be further assessed to guarantee the quality and objectivity of the proposed staging score. A study comparing inter-rater agreement of 40 glaucoma specialists is in planning, in addition to a comparative study of the GSS with the results of the FORUM® Glaucoma Workplace (Carl Zeiss Meditec AG, Jena, Germany), which Zeiss recently introduced. The FORUM® Glaucoma Workplace integrates data from Humphrey® Field Analyzer (HFA) and CIRRUS™ analysis in one report, allowing for the combination of structural and functional information in a single report, analogous to the GSS. If outcomes match, the Glaucoma Severity Score is a promising tool to stage glaucoma and monitor changes objectively in patients while comparing glaucoma progression in study analyses.

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Conflict of Interest

None.

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