Categorizing the Stage of Glaucoma From Pre-Diagnosis to End-Stage Disease

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● PURPOSE: To provide a reliable, comprehensive staging system to assess glaucoma stage in the absence of an universally accepted glaucoma staging system (GSS) on the basis of visual field results.
● DESIGN: Literature review and GSS adaptation.
● METHODS: After a review of published GSSs was conducted, the Bascom Palmer (Hodapp-Anderson-Parrish) GSS was selected as an appropriate platform for a retrospective GSS on the basis of visual fields. The system was modified by a panel of glaucoma specialists, and additional modifications were made after pilot testing to cover the full range of disease progression, from preglaucoma diagnosis to complete blindness; the ordered stages reflect the typical progression of glaucoma.
● RESULTS: The GSS is comprised of six ordered stages and is on the basis of the Humphrey visual field. The completed GSS was validated by reviewing patient charts from 12 US glaucoma centers.
● CONCLUSIONS: The GSS allows accurate staging of 100% of glaucoma on the basis of visual fields and other data, enabling evaluation of disease progression and resource utilization at various glaucoma stages. Additionally, treatment costs may be assigned to determine cost-effectiveness of treatment. Research utilizing the GSS has found that cost of care increases with increasing disease severity. The GSS may be used as the basis for creating treatment guidelines, which have the potential to delay glaucoma progression and lower treatment costs. (Am J Ophthalmol 2006;141:24–30. © 2006 by Elsevier Inc. All rights reserved.)

In the United States, glaucoma is the second leading cause of blindness in the general population, and the leading cause of blindness in black patients.1 Although only half of the individuals who have the disease are aware of their condition, glaucoma affects approximately 2.5 million people, including three percent of those age 55 years and older.1 Annual US healthcare costs for glaucoma total an estimated $2.5 billion, including $1.9 billion in direct costs and $0.6 billion in indirect costs.2 Additionally, costs for the treatment of a newly diagnosed case of open-angle glaucoma have been estimated at $1055 per year.3 For the approximately 120,000 patients who have become blind as a result of glaucoma, costs for benefits, healthcare, and reduced tax revenues total $1.5 billion per year.4

Primary open-angle glaucoma (POAG), accounting for more than 90% of US cases of glaucoma, is a chronic, progressive disease characterized by optic disk cupping and visual field loss.5 Although this form of glaucoma is commonly associated with elevated intraocular pressure (IOP), more than two-thirds of patients with IOP exceeding 21 mm Hg do not have glaucoma.1 As 15% of patients with glaucoma have a normal IOP of 21 mm Hg or less on a consistent basis, there are factors other than IOP that likely contribute to disease development.1,6–8

A glaucoma staging system (GSS) provides a way of measuring the progress of glaucoma in patients who have the disease. With clearly defined stages of disease progression, it becomes possible to observe disease progression, and thus gauge the effectiveness of treatment at each stage. The definition of each disease stage needs to be adequately precise to allow patients at different stages of disease and from different glaucoma treatment centers to be meaningfully compared. Further, such a system must allow for precise categorization without ambiguity, and must be easily usable and provide consistent (reliable) results.

The purpose of this article is to report the development of this GSS from an existing GSS. We aimed to create a staging system that can be used to stage patients retrospectively by chart review without physician inter-
interpretation of a patient’s clinical presentation by adapting an existing GSS. By assigning cost of treatment, and reviewing its effectiveness at each stage, the relative cost-effectiveness of glaucoma treatment at various stages of disease progression can also be quantified and compared using this GSS.

METHODS

● PRELIMINARY RESEARCH: A literature review was conducted to evaluate previously developed GSSs. Examined GSSs included the staging systems used in the Advanced Glaucoma Intervention Study (AGIS)\textsuperscript{9–11} and the Collaborative Initial Glaucoma Treatment Study (CIGTS).\textsuperscript{10–12} Esterman binocular scale,\textsuperscript{13} and the Bascom Palmer system.\textsuperscript{11,14–16} These existing GSSs were considered as potential “seed systems” for modification. Consideration was also given to the American Academy of Ophthalmology GSS, but this was not used because it was limited to only three stages (no field loss, moderate field loss, severe field loss).

● AGIS: AGIS used the central 24 to 2 total deviation printout of the Humphrey Field Analyzer to determine a patient’s visual field score.\textsuperscript{10} This study scored three visual field sectors: the nasal, superior, and inferior areas. Where visual field threshold values were depressed from the normal values, as measured in decibels (dB) by five to nine dB, this was considered abnormal, depending on the field location. To qualify as abnormal, a depression had to be greater in the superior field than in the inferior, and a depression had to be greater in the periphery than centrally. Scores were assigned on the basis of the dB depressions found in the various areas. A score of zero indicated no visual field loss, while 20 was the maximum possible score. One stage of field loss progression was arbitrarily defined as an increase in score of four.

● CIGTS: The CIGTS staging system used a scoring methodology similar to that used by the AGIS.\textsuperscript{10,12,17} Glaucoma staging in this study was also on the basis of the central 24 to 2 program of the Humphrey Field Analyzer, but the categories of probability values on the total deviation probability plot rather than dB deviations as in AGIS were used. Scores were scaled from 0 to 20. A patient was considered to have progressed when the CIGTS score increased by three or more.

● ESTERMAN BINOCULAR SCALE: Mills and Drance used an Esterman visual function score derived from an automated binocular visual field test on the CooperVision Diagnostics Dicon AP2000 perimeter (CooperVision, Fairport, New York).\textsuperscript{13} The scoring system included both central and peripheral visual field and was weighted according to the functional importance of different areas of the visual field. The American Medical Association accepted the Esterman scoring system in 1984 as a standard for rating vision capabilities.\textsuperscript{18} Patients with advanced glucomatous loss also responded to a 15-item quality of life questionnaire to assess problems in activities of daily living they encountered as a result of their visual field loss. The authors, however, did not attempt to use Esterman test scores to assign standardized stages of disease progression.\textsuperscript{13}

● BASCOM PALMER (HODAPP-ANDERSON-PARRISH) GSS: The Bascom Palmer staging system was chosen as the foundation for development of a new GSS (Table 1).\textsuperscript{15,16,19} Like the CIGTS and AGIS systems, this system allows for stage assignments on the basis of HVF testing, making it easily applicable to a multicenter retrospective chart review. This staging system assigns glaucoma patients to different stages of disease progression on the basis of a combination of mean defect (MD) score and one of the following: pattern deviation probability plot score (indicating deviation from a normalized visual field pattern), dB plot (stages 2 to 4) or, for stage 1, either corrected pattern standard deviation/pattern standard deviation (CPDS/PSD) or glaucoma hemifield test results. Despite the utility of this system on the basis of its use of visual field loss as an indication of progression, pilot testing found that this GSS fails to capture the full range of stages in glaucoma progression, from patients with early and minimal visual field defects to patients who are blind from end-stage disease.

● DRAFT GSS DEVELOPMENT: Following review of the literature on existing GSSs, an expert panel was assembled, consisting of four glaucoma specialists. The use of expert panels to create guidelines has been used in a number of fields of medical inquiry,\textsuperscript{20–24} including ophthalmology.\textsuperscript{25} The panels use shared medical literature and initial algorithms to form drafts of final algorithms, typically for treatment, formulating a standard of care.\textsuperscript{22,26}

Among existing GSSs considered, the Bascom Palmer GSS was deemed most appropriate by the expert panel as it allowed for structured severity stage assignment based primarily on Humphrey visual field parameters in a relatively simplified manner. The AGIS and CIGTS scoring systems involve more complex calculations and were thus felt to be more susceptible to errors in scoring. Additionally, those scoring systems have not been used to any significant degree in clinical practice. In contrast, the Bascom Palmer GSS has been used clinically for routine patient care. While there has been no comparison of the Bascom Palmer GSS to the other systems, Katz and associates did find that the AGIS and CIGTS scoring systems diverged considerably in their evaluation of visual field progression.\textsuperscript{27} The panel initially
<table>
<thead>
<tr>
<th>Stage</th>
<th>Humphrey MD Score</th>
<th>Probability Plot/Pattern Deviation</th>
<th>dB Plot (Stages 2–4) or CPSD/PSD (Stage 1)</th>
<th>dB Plot (Stages 2–4) or Hemifield Test (Stage 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 – Ocular hypertension/earliest glaucoma</td>
<td>&gt;0.00</td>
<td>Does not meet any criteria for Stage 1.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 – Early glaucoma</td>
<td>−0.01 to −5.00</td>
<td>Points below 5%: &gt;3</td>
<td>CPSD/PSD significant at ( P &lt; 0.05 )</td>
<td>Glaucoma hemifield test “outside normal limits”</td>
</tr>
<tr>
<td></td>
<td>( (P &lt; 0.05) )</td>
<td>contiguous AND &gt;1 of the points below 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2 – Moderate glaucoma</td>
<td>−5.01 to −12.00</td>
<td>Points below 5%: 19–36 AND Points below 1%: 12–18</td>
<td>Point(s) within the central 5° with sensitivity of &lt;15 dB: &gt;1 AND point(s) within the central 5° with sensitivity of &lt;0 dB: OR</td>
<td>Point(s) with sensitivity &lt;15 dB within 5° of fixation: Only 1 hemifield (1 or 2)</td>
</tr>
<tr>
<td>Stage 3 – Advanced glaucoma</td>
<td>−12.01 to −20.00</td>
<td>Points below 5%: 37–55 AND Points below 1%: 19–36</td>
<td>Point(s) within the central 5° with sensitivity of &lt;0 dB: 1 only</td>
<td>Point(s) with sensitivity &lt;15 dB within 5° of fixation: Both hemifields, at least 1 in each</td>
</tr>
<tr>
<td>Stage 4 – Severe glaucoma</td>
<td>−20.01 or worse</td>
<td>Points below 5%: 56–74 AND Points below 1%: 37–74</td>
<td>Point(s) within the central 5° with sensitivity of &lt;0 dB: 2–4</td>
<td>Point(s) with sensitivity &lt;15 dB within 5° of fixation: Both hemifields, 2 in each (ALL)</td>
</tr>
<tr>
<td>Stage 5 – End-stage glaucoma/blind</td>
<td>No HVF in “worst eye”</td>
<td>HVF not possible attributable to central scotoma in “worst eye” OR “worst eye” acuity of 20/200 or worse attributable to glaucoma. “Best eye” may fall into any of above stages.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CPSD/PSD = Corrected pattern standard deviation/pattern standard deviation; dB = decibel; HVF = Humphrey visual field; MD = mean deviation.
Stage 0: No or minimal defect/ocular hypertension
Does not meet any criteria for stage 1.

Stage 1: Early defect
MD $\geq -6.00$ dB and at least one of the following:
A On pattern deviation plot, there exists a cluster of 3 or more points in an expected location of the visual field depressed below the 5% level, at least 1 of which is depressed below the 1% level
B Corrected pattern standard deviation/pattern standard deviation significant at $P < .05$
C Glaucoma hemifield test “Outside Normal Limits”

Stage 2: Moderate defect
MD of $-6.01$ to $-12.00$ dB and at least one of the following:
A On pattern deviation plot, greater than or equal to 25% but fewer than 50% of points depressed below the 5% level, and greater than or equal to 15% but fewer than 25% of points depressed below 1% level
B At least 1 point within central 5° with sensitivity of $<15$ dB but, no point within central 5° with sensitivity of $<0$ dB
C Only 1 hemifield containing a point with sensitivity $<15$ dB within 5° of fixation

Stage 3: Advanced defect
MD of $-12.01$ to $-20.00$ dB and at least one of the following:
A On pattern deviation plot, greater than or equal to 50% but fewer than 75% of points depressed below the 5% level and greater than or equal to 25% but fewer than 50% of points depressed below 1% level
B Any point within central 5° with sensitivity of $<0$ dB
C Both hemifields containing a point(s) with sensitivity $<15$ dB within 5° of fixation

Stage 4: Severe defect
MD of $-20.00$ dB and at least one of the following:
A On pattern deviation plot, greater than or equal to 75% of points depressed below the 5% level and greater than or equal to 50% of points depressed below 1% level
B At least 50% of points within central 5° with sensitivity of $<0$ dB
C Both hemifields containing greater than 50% of points with sensitivity $<15$ dB within 5 degrees of fixation

Stage 5: End-stage disease
Unable to perform Humphrey visual fields in “worst eye” attributable to central scotoma or “worst eye” visual acuity of 20/200 or worse attributable to primary open-angle glaucoma. “Best eye” may be any stage.

Staging definitions are based on Humphrey visual field printouts. dB = Decibels; MD = mean deviation.

### RESULTS

GSS decision rules were created to determine which parameters should be used to assign patients to stage 0 through stage V. MD was decided on as the primary measure for assigning stages 0 through IV, with three additional criteria for stage adjustments depending on the CPSD/PSD and hemifield test results for stages 0 through I, dB plot for stages II through IV, and pattern deviation plot for stages I through IV (Table 2). Additional criteria were included on the basis of decision rules, which apply to both the GSS stage definitions.
and the staging table. These decision rules are defined as follows: if a patient meets the MD criteria for a particular stage (stages I to IV) but fails to meet one of the additional criteria for that stage, then the patient is categorized in the preceding stage; if a patient meets the MD criteria for a particular stage (stages I to IV), and meets one of the additional criteria for a succeeding stage, then the patient is categorized in the succeeding stage; if a patient meets the MD criteria for a particular stage (stages I to IV), and meets one or more of the additional criteria for a preceding stage as well as one or more of the criteria for a succeeding stage, then the patient is categorized in the original stage on the basis of MD criteria.

**DISCUSSION**

A MODIFIED VERSION OF THE BASCOM PALMER GSS WAS developed to enable disease severity assignment of all glaucoma patients on the basis of historical visual field data recorded in patient charts, and to create a GSS that can be used to retrospectively stage patients without clinical judgment by a physician. The GSS was successfully applied by retrospectively assigning unambiguous stages using HVFs from a total of 98 glaucoma charts across seven centers in the United States. Automated visual field testing with HVFs has been the gold standard for visual field testing for the past decade.28–30 Our GSS may be used to monitor the long-term progression of disease in glaucoma patients; however, it requires further validation by comparison to other systems, including those in use outside the United States, to determine its ultimate applicability.

Despite the modifications made to the Bascom Palmer GSS and the improved staging across all stages of glaucoma these modifications allowed, there are several limitations to our new GSS and its application. This GSS is based primarily on visual field criteria and does not consider other clinical factors that may be used to assess progression of disease such as optic nerve head examination, nerve fiber analyzer, or disk photographic findings. Thus, the GSS serves as a practical tool for assigning severity categories but is not necessarily a complete proxy for glaucoma disease progression.11 Additionally, because the developed GSS requires use of HVFs, this restricts the population for which the GSS can be used. In line with this, it is likely that the stages do not represent equal intervals in the progression of glaucoma; in other words, there may be more damage occurring when a patient progresses from stage 0 to stage I, compared with moving from stage III to stage IV. We also do not know the functional significance of these stages of disease in terms of vision-related functioning and quality of life.

The need for a standardized GSS, nevertheless, remains pressing. We chose to use a modification of the Bascom Palmer system because it is one with which the glaucoma community in the United States has at least passing familiarity, is easy to score, and is currently used clinically (as opposed to only in trials). With a GSS in place, it becomes possible to do many analyses, includ-
ing measuring the costs of treatment at each stage. Direct costs for the treatment of open-angle glaucoma include (1) patient visits to the ophthalmologist, (2) surgery for glaucoma, (3) medication use, (4) visual field examinations, and (5) other related services (for example, gonioscopy, optic disk photographs, nerve fiber thickness analysis, and IOP diurnal curve testing). Despite the widespread applicability of this modified system as a tool to retrospectively assign disease severity and analyze progression retrospectively, this GSS does not account for the association between IOP and disease progression. Determination of patient stage may allow modification of patient treatment regimens, but IOP and other individual patient factors must be included in such treatment decisions.

Because glaucoma is often asymptomatic in its earlier stages, this may result in delayed diagnosis followed by increased medical vigilance in care through the later stages of the disease. It is important, therefore, to realize the value of early diagnosis accompanied by early treatment, as research has found that moderate or advanced visual field losses found in glaucoma patients at the time of diagnosis is a strong predictor of disease progression leading to blindness. Using the modified GSS, a retrospective analysis of 151 patient charts from 12 sites was conducted in the United States. This study found the estimated average annual direct cost of treatment to range from $623 per patient with early-stage disease to $2511 per patient with end-stage disease. Medication costs were found to be the largest portion of total direct healthcare costs at each stage.

The transformed Bascom Palmer GSS was further modified for use in European countries, such as Germany and Austria, where patients’ visual field testing ordinarily is conducted with Octopus perimeters. A panel of glaucoma specialists from the United States and Germany used formulas from published literature to convert the Humphrey threshold values to Octopus values (Table 3). This modified GSS was applied to a retrospective chart review of 194 patients with glaucoma among 16 sites in Austria, France, Germany, Italy, and the United Kingdom. In this study, as in the US study, increasing use of healthcare resource utilization was found at each succeeding stage of glaucoma, accompanied by increasing treatment costs.

This staging system has already demonstrated its usefulness in analyzing the breakdown of costs associated with different stages of disease progression in patients with POAG. It may provide an even greater service in providing a new standard for diagnosing, monitoring, and cost-effectively treating this devastating disease. If early treatment can considerably delay disease progression and save costs, then this new staging system may serve as a model to encourage early diagnosis and careful, standardized monitoring of disease progression, accompanied by a stage-by-stage strategy for treatment.

REFERENCES


