RATE OF PROGRESSION IS A CLINICALLY IMPORTANT yet difficult-to-measure parameter in glaucoma disease management. An accurate indication of rate of progression of glaucomatous disease would allow clinicians to identify patients who are at most risk of suffering a significant decline in their quality of life from the disease. Despite numerous studies assessing the methods of measuring disease progression, there is still currently little consensus, with major randomized controlled trials using different methods.1–13

A major issue that prevents the accurate measurement of glaucoma disease progression is that it is hidden by the short- and long-term variability that is inherent in visual field testing.9,14–17 Trend-based analysis, although imperfect, enables clinicians to detect subtle visual field progression despite significant variability.18

Rates of progression vary greatly among individuals. The average rate of progression is between −0.3 and −0.5 dB decline in mean deviation (MD) per year and not all patients become visually impaired during their lifetime.18–24 A rate of progression characterized by a decline in MD of greater than or equal to 1 dB/year has been considered by several studies as the criterion for rapidly progressive disease.25–29 This rate of progression is significant, as it would result in advancement of disease from early to advanced stage in the space of 10–15 years, resulting in considerable negative personal and societal impact.30

A number of theories have been postulated regarding the reasons behind glaucoma disease progression, as well as the pathogenesis of the disease. The most widely known is the mechanical theory, whereby glaucoma is caused by decreased ocular perfusion pressure, which affects ganglion cells at the optic nerve head. Disease progression is then enhanced following this primary insult by impaired vascular autoregulation and dysfunctional neurovascular coupling.52 Evidence supporting this theory has been mixed, with systemic hypotension,
METHODS

THIS STUDY IS A RETROSPECTIVE REVIEW OF PATIENTS recruited from 5 private ophthalmology clinics in Sydney and the Central Coast in New South Wales, Australia. Patients were eligible if they had a working diagnosis of glaucoma from their treating ophthalmologist and if they had greater than or equal to 5 Humphrey visual fields (24-2) conducted during their period of treatment at the clinic. Full-threshold SITA standard and SITA fast fields were accepted, with the majority of fields being SITA standard. Patients were excluded if their sequential visual fields showed an improvement in MD or if they had greater than 5 dB MD variation in between visits. Visual fields were manually screened by the author and any fields with an obvious neurologic scotoma were also excluded. The data from both the subject’s right and left eye were used if they individually satisfied the inclusion and exclusion criteria. Rates of progression were calculated by taking the MD difference between the most recent and initial visual fields and dividing that by the number of years that have lapsed between the fields. Patients received a level of treatment that was deemed clinically appropriate as per the managing ophthalmologist.

For every eligible patient, clinical data from visits where a visual field test was conducted were recorded in a database. Information collected includes the subject’s age, sex, refraction, IOP (measured with Goldmann tonometry), and CCT. Furthermore, the medical, ocular, surgical, and medication histories of the subjects were obtained from patient files and recorded. Medical conditions were confirmed usually via correspondence from general practitioners, optometrists, or previous treating ophthalmologists. Particular note is made of any condition that is suspected of being related to glaucoma progression from previous literature. These presumed risk factors include ocular conditions such as high myopia, pseudoexfoliation syndrome (PXF), and disc hemorrhages. Systemic factors include hypertension, hypotension, diabetes mellitus, CVD (including hypercholesterolemia, hypertriglyceridemia, ischemic heart disease, cerebrovascular disease, transient ischemic attack, valvular heart disease, arrhythmia, heart failure, and vascular disease, including peripheral vascular disease and thromboembolic disease), migraines, vasospasm, and steroid use.

- **STATISTICAL ANALYSIS:** Statistical analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, Illinois, USA). We compared differences in frequency of risk factors in the rapid progressor and nonrapid progressor groups using the independent t-test for continuous variables and Wald χ² test for categorical variables. Risk factors that showed a P value of less than .05 between the rapid progressor and nonrapid progressor groups from the above statistical analyses were then selected and a binomial regression analysis was used to investigate which of these risk factors

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### TABLE 1. Demographics and Risk Factor Profiles of Rapid Progressors and Nonrapid Progressors (Continuous Variables)

<table>
<thead>
<tr>
<th>Variable (number of eyes)</th>
<th>Rapid Progressors</th>
<th>Nonrapid Progressors</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (number of eyes)</td>
<td>54</td>
<td>486</td>
<td>.01</td>
</tr>
<tr>
<td>Average age, years (± SD)</td>
<td>83 (± 9.83)</td>
<td>79 (± 10.63)</td>
<td>.01</td>
</tr>
<tr>
<td>Average number of medication changes per patient (± SD)</td>
<td>4.30 (± 4.65)</td>
<td>2.50 (± 2.59)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Average number of IOP-lowering surgeries per patient (± SD)</td>
<td>1.02 (± 1.45)</td>
<td>0.21 (± 0.78)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Average baseline IOP, mm Hg (± SD)</td>
<td>18.80 (± 4.29)</td>
<td>20.99 (± 4.94)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Range of baseline IOP, mm Hg</td>
<td>12–34</td>
<td>8–40</td>
<td></td>
</tr>
<tr>
<td>Average IOP, mm Hg (± SD)</td>
<td>16.75 (± 2.74)</td>
<td>16.94 (± 2.74)</td>
<td>.63</td>
</tr>
<tr>
<td>IOP fluctuation, mm Hg (± SD)</td>
<td>3.10 (± 1.44)</td>
<td>2.90 (± 1.19)</td>
<td>.24</td>
</tr>
<tr>
<td>Baseline MD, dB (± SD)</td>
<td>−6.86 (± 5.48)</td>
<td>−3.63 (± 4.63)</td>
<td>.01</td>
</tr>
<tr>
<td>Average CCT, μm (± SD)</td>
<td>512.96 (± 40.40)</td>
<td>532.21 (± 35.78)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation.

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nocturnal blood pressure dipping, low diastolic perfusion pressure, and low ocular perfusion pressure being implicated in rapid disease progressors, especially in normotensive glaucoma. However, other systemic contributors to decreased blood flow, such as hypertension, use of antihypertensive medications, atherosclerosis, and vasospastic phenomena (such as migraines, chilblains, and Raynaud syndrome), have not been reliably associated with rapid progression. Furthermore, vascular diseases such diabetes and cardiovascular disease (CVD) have not been consistently shown to be correlated with rapid disease progression.

Our current study aims to expand on the current understanding of how systemic and intraocular risk factors correlate with glaucoma disease progression by studying a cohort of rapid progressors (decline of MD greater than or equal to 1 dB/year) and comparing them to nonrapid progressors (decline of MD less than 1 dB/year).
were most predictive of glaucoma disease progression while taking into account all other selected variables. To allow for the correlation of observations arising from the same patient, the logistic regression was conducted within the framework of generalized estimating equations. A receiver operating characteristic (ROC) curve was then constructed to test the performance of the binomial regression analysis, first on the whole dataset and then on 2 subgroups of the dataset, split based on clinic location.

### RESULTS

**FROM 1991 TO 2015, VISUAL FIELD AND CLINICAL DATA WERE AVAILABLE FROM 11 254 EYES. OF THESE, 54 EYES WITH COMPLETE DATASETS SATISFIED THE PROGRESSION CRITERIA AND WERE INCLUDED IN THE ANALYSIS AS RAPID PROGRESSORS. A TOTAL OF 486 EYES WITH COMPLETE DATASETS SATISFIED THE INCLUSION CRITERIA BUT DID NOT SATISFY THE PROGRESSION CRITERIA AND WERE INCLUDED AS NONRAPID PROGRESSORS. FIELDS WERE CONSIDERED RELIABLE IF THEY HAD FEWER THAN 15% FALSE-POSITIVES AND LESS THAN 20% FIXATION LOSS. UNDER THESE CRITERIA, 80% OF RAPID PROGRESSORS HAD RELIABLE FIELDS ON AVERAGE WHILE 88% OF NONRAPID PROGRESSORS HAD RELIABLE FIELDS ON AVERAGE. WHEN ONLY THE MOST RELIABLE FIELD OF EACH EYE WAS CONSIDERED, 100% OF RAPID PROGRESSORS AND 99.6% OF NONRAPID PROGRESSORS HAD RELIABLE FIELDS.

The overall demographics and risk factor profile for progressors and nonrapid progressors are shown in Tables 1 and 2. The sex distributions between the 2 groups were not significantly different. The mean rate of progression for rapid progressors was $-1.55$ dB/year, while for nonrapid progressors it was $-0.24$ dB/year. The average age of progressors was significantly older compared with nonrapid progressors. Rapid progressors had a significantly worse baseline MD compared with nonrapid progressors.

Patients with rapidly progressive disease had significantly lower CCT and baseline IOPs and were more likely to have pseudoexfoliation syndrome, disc hemorrhages, and ocular medication changes. They also had significantly higher rates of cardiovascular disease and hypotension. Patients with a history of cardiovascular disease displayed significantly lower mean IOP (20.6 mm Hg; 19.8 mm Hg, $t = 2.21, P < .02$). Furthermore, CVD patients who rapidly progressed also had significantly lower baseline IOPs (18.27 mm Hg; 20.48 mm Hg, $t = 2.38, P < .02$). Rapid progressors had a higher mean number of medication changes and IOP-lowering surgeries per patient, both of which were statistically significant (Table 1).

Average IOP and IOP fluctuation were not significantly different between rapid progressors and nonrapid progressors. Reported rates of hypertension, diabetes mellitus, migraines, vasospasm, steroid use, and high myopia were also not significantly different between the 2 groups.

A logistic regression analysis was then performed to examine the effect of each of these risk factors in contributing to the likelihood of rapidly progressive glaucoma disease. The model was statistically significant.

**TABLE 2. Demographics and Risk Factor Profiles of Rapid Progressors and Nonrapid Progressors (Categorical Variables)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rapid Progressors, N (%)</th>
<th>Nonrapid Progressors, N (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (number of eyes)</td>
<td>54</td>
<td>486</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.62</td>
</tr>
<tr>
<td>Male</td>
<td>21 (38.8%)</td>
<td>206 (42.3%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (61.2%)</td>
<td>280 (57.7%)</td>
<td></td>
</tr>
<tr>
<td>PXF</td>
<td>7 (13.0%)</td>
<td>19 (3.9%)</td>
<td>.03</td>
</tr>
<tr>
<td>Disc hemorrhage</td>
<td>12 (22.2%)</td>
<td>56 (11.5%)</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (70.3%)</td>
<td>301 (61.9%)</td>
<td>.22</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (11.1%)</td>
<td>89 (18.3%)</td>
<td>.19</td>
</tr>
<tr>
<td>Migraines</td>
<td>8 (14.8%)</td>
<td>58 (11.9%)</td>
<td>.54</td>
</tr>
<tr>
<td>Vasospasm</td>
<td>1 (1.9%)</td>
<td>4 (0.8%)</td>
<td>.45</td>
</tr>
<tr>
<td>Steroid use</td>
<td>11 (2.0%)</td>
<td>101 (2.1%)</td>
<td>.94</td>
</tr>
<tr>
<td>High myopia (≥−5.00 D)</td>
<td>3 (5.6%)</td>
<td>22 (4.5%)</td>
<td>.73</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (7.4%)</td>
<td>12 (2.5%)</td>
<td>.04</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>30 (55.6%)</td>
<td>157 (32.3%)</td>
<td>.01</td>
</tr>
</tbody>
</table>

D = diopter; IOP = intraocular pressure; PXF = pseudoexfoliation syndrome.


<table>
<thead>
<tr>
<th>Variable (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.03 (0.99 – 1.06)</td>
</tr>
<tr>
<td>Baseline MD (per 1-dB improvement)</td>
<td>0.93 (0.88 – 0.99)</td>
</tr>
<tr>
<td>Medication changes (per change)</td>
<td>1.15 (1.02 – 1.30)</td>
</tr>
<tr>
<td>IOP-lowering surgery (per surgery)</td>
<td>1.91 (1.50 – 2.44)</td>
</tr>
<tr>
<td>Baseline IOP (per mm Hg)</td>
<td>0.88 (0.81 – 0.96)</td>
</tr>
<tr>
<td>IOP fluctuation (per unit SD)</td>
<td>1.07 (0.67 – 1.71)</td>
</tr>
<tr>
<td>Average CCT (per μm)</td>
<td>0.99 (0.98 – 1.00)</td>
</tr>
<tr>
<td>PXF (reference no PXF)</td>
<td>2.65 (0.95 – 7.44)</td>
</tr>
<tr>
<td>Disc hemorrhage (reference no hemorrhage)</td>
<td>0.93 (0.43 – 2.00)</td>
</tr>
<tr>
<td>Hypertension (reference not hypertensive)</td>
<td>1.21 (0.55 – 2.63)</td>
</tr>
<tr>
<td>Diabetes (reference no diabetes)</td>
<td>0.64 (0.20 – 2.04)</td>
</tr>
<tr>
<td>Hypotension (reference not hypotensive)</td>
<td>2.40 (0.60 – 9.80)</td>
</tr>
<tr>
<td>Cardiovascular disease (reference no cardiovascular disease)</td>
<td>2.33 (1.03 – 5.27)</td>
</tr>
</tbody>
</table>

CCT = central corneal thickness; IOP = intraocular pressure; MD = mean deviation; PXF = pseudoexfoliation syndrome.
(χ² [25] = 74.32, P < .01), and explained 27% of the variance in glaucoma progression (Nagelkerke R²). The logistic regression model correctly predicted 91% of cases. The results of the logistic regression analysis are presented in Table 3. Accounting for all other risk factors, rapidly progressive disease was associated with a worse baseline MD, lower baseline IOP, more frequent medication changes and higher rates of IOP-lowering surgery. The odds of developing rapidly progressive glaucomatous disease in those with cardiovascular disease history is twice that compared to those without a history.

The area under the curve for the ROC graph used to test the binomial regression analysis obtained from all subjects in this study was 0.80 (0.72–0.86), P < .01 (Figure). This was reproducible when validated with 2 subsets of patients obtained from the complete dataset. The area under the curve obtained from subjects from clinics 1 and 2 (306 eyes) was 0.78 (0.67–0.90), P < .01. The area under the curve obtained from subjects from clinics 3, 4, and 5 (234 eyes) was 0.77 (0.69–0.86), P < .01.

### DISCUSSION

**TO OUR KNOWLEDGE, THIS IS THE FIRST STUDY THAT COMPARES THE RISK FACTOR PROFILE DIFFERENCES BETWEEN 2 GROUPS OF GLAUCOMA PATIENTS THAT DIFFER IN THEIR RATE OF DISEASE PROGRESSION IN A REAL-WORLD CLINICAL ENVIRONMENT.** Our study confirms that cardiovascular disease is a major risk factor in predicting rapid disease progression in glaucomatous patients. Additionally, worse baseline MD, lower baseline IOP, more frequent ocular antihypertensive medication changes, and number of IOP-lowering surgeries were also robust predictors for rapid progression in our cohort. Although other risk factors including lower CCT, pseudoexfoliation, disc hemorrhages, and hypotension were more common in the rapid progressor cohort, they did not have a significant effect in predicting disease progression in the multivariate regression analysis.

- **CARDIOVASCULAR DISEASE:** One of the most striking results from our analysis is that CVD is a major determinant of glaucoma disease progression. The risk of having rapidly progressive disease is doubled in those with a cardiovascular history. All of the risk factors included under the CVD umbrella in our study either can cause or are a result of poor blood circulation. This fits well with the “vascular theory” of glaucoma.

  The majority of large population trials that have been published in the literature concentrate on the prevalence and effects of CVD in patients with glaucoma, with very few studies focusing on how CVD actually relates to disease progression. The conclusions regarding the significance of CVD as a risk factor for progression derived from these few studies are mixed. Most studies currently available have advocated no link between cardiovascular disease history and glaucoma progression. A previous study based on the Early Manifest Glaucoma Trial (EMGT) exhibited similar findings to our current study, with CVD patients having a hazard ratio of 2.75 for glaucoma disease progression compared with non-CVD patients. The CVD patients in the EMGT trial who progressed were more likely to have higher baseline IOP compared with those that did not. This is a major point of difference to the conclusion derived from our current study, which showed that CVD subjects that progressed had significantly lower IOP. This observation could indicate that CVD is a strong risk factor for rapid glaucoma progression, independent of IOP control, which also fits with the vascular theory.

  The EMGT study relied on subjects self-reporting their cardiovascular history. Therefore the conditions that constituted cardiovascular disease in this study were not known. Our study used a clearer definition of cardiovascular disease, which may explain why we detected an association, compared with other studies. This work can provide some ideas for future studies to determine which particular CVD conditions, if any, could contribute to greater glaucoma disease progression.

- **INTRAOCULAR PRESSURE:** Three domains related to IOP were analyzed in our study: baseline IOP, average IOP, and long-term IOP fluctuation. Interestingly, subjects who experienced rapid glaucoma disease progression in our cohort had...
lower baseline IOPs. Average IOP and IOP fluctuation were not statistically significantly different between the 2 groups.

Higher IOP is undoubtedly related to disease progression and has been shown in a large volume of literature.33–38 This observation had not been replicated in our study. There are several possible reasons for this. First of all, our study compares 2 groups of patients, both of whom have glaucoma. Our nonrapid progressor cohort still showed a considerable amount of progression, with the mean rate of progression only slightly lower than the average glaucoma population progression rate of −0.3 to 0.5 dB/year.

Therefore, any potential differences in IOP between the 2 groups would be reduced, especially when compared to studies that measured differences between glaucoma subjects and normal controls. Rapidly progressing glaucoma patients might also be treated more aggressively with lower target IOPs in a real-world clinical environment. This is evidenced by the greater number of medication changes and surgical interventions. Rapidly progressing patients might also have seen another health care provider before attending the study clinics, which would give an artificially lower IOP at first presentation to the clinic. The rapidly progressing group also had lower average CCT, which could account for a lower IOP. Finally the baseline IOP represents a single reading, which could have been low by chance.

**Other Risk Factors:** All other risk factors studied, including sex, age, refraction, CCT, PXF, disc hemorrhage, hypertension, diabetes, migraine, vasospasm, steroid use, and hypotension, were not shown to be statistically significant predictors of rapid progression in our study. This could again be a result of our comparing 2 groups of glaucoma patients, both of which have considerable rates of progression.

**Strengths and Limitations of the Study:** Our study used strict criteria for inclusion. Only patients with a complete dataset were included in the analysis, and we recruited a representative glaucoma patient sample from a real-world clinic scenario.

The main limitation of our study was the fact that it was a retrospective chart review, which could introduce some bias and confounders implicit to this study design. These are negated in part by our very strict criteria for inclusion of subjects into the study. Also, given the study design, useful information such as medical treatment adherence, compliance, and family history were often not found in the notes and were therefore omitted from the study. We chose not to include cup-to-disc ratios because they are quite subjective and will differ depending on the practitioner. Furthermore, although the study numbers for nonrapid progressors were quite large, the number of rapid progressors was limited, which makes the conclusions less generalizable. However, our results are definitive, with large differences between the cohorts, and this could pave the way for future studies with larger patient numbers.

Patients affected by cataracts and who had cataract surgery were not excluded in this study. This could affect MD and can act as a confounder. The effect of this is minimized by excessive variability being included as part of our exclusion criteria, which would act to exclude the majority of these patients. The SITA algorithm was not available throughout the 25-year period from which data were collected. As a result, MD values from some full-threshold fields were compared with MD values from SITA fields to determine rate of progression, which is a source of error. This error would tend to underestimate the rate of progression in our study, and as such will not alter the significance of our results.67–69 An alternative method of measuring rates of progression would be through the Humphrey guided progression analysis (GPA) software. However, only 88% of our subjects had GPA on file; therefore, using this method would result in some loss of data. Unfortunately, we were unable to correlate structural changes to visual field progression, as many of our subjects did not have OCT technology available to them at the time of review, given that we recruited patients from 1991. This would be a good direction for future research.

In conclusion, our study suggests that cardiovascular disease is an important predictor for rapidly progressive glaucomatous visual loss, irrespective of IOP. Our results support clinicians managing glaucoma taking a comprehensive past medical history and highlight the importance of optimizing cardiovascular risk factors so as to reduce the risk of rapidly progressive disease.

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**References**


