

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

### Noncycloplegic Measurements in Students

July 2022

Measuring cycloplegic refraction in school settings can pose logistical and consent challenges, leading to suboptimal participation in school-based vision programs. Although noncycloplegic refraction in the same setting is less complicated, it's unclear if this parameter is a viable starting point for prescribing glasses. Guo et al. explored differences between autorefractometer measurements, with and without cycloplegia, among predominantly Black and Hispanic students in Chicago. They found that spherical equivalents (SEs) for cycloplegic and noncycloplegic measurements varied by less than a diopter in three-fourths of their study group. Concordance was more likely in myopic and older participants.

This cross-sectional review included 11,119 participants (mean age,  $10.8 \pm 4$  years). In addition to documenting differences between cycloplegic and noncycloplegic measurements for each participant, the authors explored factors linked to significant discrepancies between the two types of measurements. They collected demographic data during eye exams and performed

autorefractometer before and after the cycloplegic state. Myopia, hyperopia, and astigmatism were established from cycloplegic and noncycloplegic measurements.

Slightly more than half (52.4%) of the participants were female, 62.9% were Black, and 32.3% were Hispanic. Noncycloplegic SE measurements were found to be  $.65 \pm 1.04$  D more myopic than cycloplegic SE measurements. After adjusting for demographics and refractive error, individuals with at least

1 D of more myopic SE refraction by noncycloplegic autorefractometer (25.9%) tended to be younger than 5 years of age (odds ratio [OR], 1.45; 95% confidence interval [CI], 1.18-1.79) or between 5 and 10 years of age (OR, 1.32; 95% CI, 1.18-1.48). An

SE difference of at least 1 D was more common in Hispanics (OR, 1.23; 95% CI, 1.10-1.36) and in those with hyperopia (OR range, 4.20-13.31). Factors linked to a cylindrical difference of at least .75 D (5.1%) between refractions were young age (<5 years); male sex; the presence of mild, moderate, or high myopia; and the presence of moderate to high hyperopia.

Understanding differences in the measurements used to assess refractive error may be helpful for future studies

and school-based vision programs, said the authors. They cautioned that the generalizability of their findings may be limited by the racial/ethnic makeup of their study cohort.

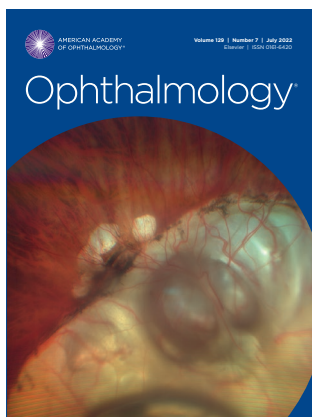
### Tumor Staging: Conjunctival Melanoma Outcomes

July 2022

Although conjunctival melanoma (CM) is a rare cancer, it has grown in prevalence and has the potential to metastasize. Jia et al. studied the predictive value of the tumor staging system described in the *AJCC Cancer Staging Manual* (8th edition) and explored histologic features linked to outcomes and metastasis patterns in patients with CM. In their review, the staging system was effective prognostically. Most cases of CM presented in an advanced stage, and the rate of distant metastases was high.

The retrospective cohort included 83 patients with CM who were treated in China during the last two decades. The authors documented clinical and histologic findings for each patient and used Kaplan-Meier survival curves and Cox proportional-hazards models to analyze risk factors. Main outcome measures were disease-specific survival period, metastatic pattern and site, and time to nodal/distant metastasis.

At presentation, the tumors of five patients (6%) were staged as cT1 (clinical tumor 1), those of 34 patients (41%) were classified as cT2, and those of 44 patients (53%) were graded as cT3. Four patients (5%) had nodal metastasis.



## PPV Versus PPV Plus Scleral Buckle for RDs

July 2022

In an international study, Ong et al. set out to determine surgeons' preferences for treating giant retinal tear–related retinal detachments. They found that pars plana vitrectomy (PPV) and PPV plus scleral buckle (PPV+SB) are equally common and have comparable anatomic and visual outcomes among adults. Among children younger than age 18 years, however, PPV+SB was superior to PPV alone at the one-year mark.

For this retrospective cohort study, the researchers reviewed electronic medical records from seven medical institutions around the world. A total of 195 patients (200 eyes), 42 of whom were children, were included in the study. All told, 101 eyes underwent PPV alone, and 99 underwent PPV+SB. Baseline demographics and ocular characteristics studied did not differ between the two groups except for those patients with a history of developmental abnormalities or who had prior intraocular surgery and were phakic.

With regard to anatomic outcomes, the overall success rates were similar between the two groups at six and 12 months: 82.2% and 77.2% for PPV alone, respectively, and 87.9% and 85.7% for PPV+SB, respectively. However, when stratified by age, the 12-month success rate was higher for PPV+SB than for PPV alone for children younger than age 18 (88.5% versus 56.3%;  $p = .03$ ).

With regard to visual outcomes, the mean best-corrected visual acuity at baseline did not differ between PPV and PPV+SB groups. Once again, however, when stratified by age, children who underwent PPV+SB had better outcomes at 12-month follow-up than those who underwent PPV alone ( $p = .001$ ). No such difference was found for adults.

The mean time to first redetachment was 7.9 months in the PPV group and 5.5 months in the PPV+SB group, with proliferative vitreoretinopathy as the

sis at presentation, and none had distant metastasis. During the follow-up period, nodal metastasis was observed in 12 patients (14%), distant metastasis occurred in 29 (35%), and there were 26 (31%) disease-related deaths. Common sites of metastases were the brain, liver, and lungs. Patients with brain involvement had a poor prognosis, and their median survival time was only five months.

A high cT category carried greater risk of distant metastasis ( $p < .001$ ) and disease-specific death ( $p = .002$ ). A separate analysis that included primary and recurrent tumors showed that metastatic risk was highest for cT3 tumors. Ulceration, thicker tumors, and regression correlated with distant metastasis. Among the 29 patients who experienced distant metastasis, 11 (38%) had nodal metastasis before distant metastasis, and 18 (62%) had distant metastasis without previously known nodal metastasis. Grade cT3 tumors generally followed the latter pattern. Previously unreported mutations were detected in the tumor suppressor genes *FAT4* and *SYK*.

These findings indicate that patients who present with a cT3 tumor are more likely than those with lower-grade tumors to develop distant metastasis without previous nodal metastasis. The authors emphasized that histologic features such as thickness and ulceration may help to determine prognosis and optimal treatment. The results of this study will allow physicians to provide more accurate prognostic information for patients with CM.

## Enduring Effects of Microstent Use

July 2022

Randomized trials of the Hydrus Microstent (HMS) have found that it significantly reduces IOP and medication burden through two years following surgery for primary open-angle glaucoma (POAG). By year 3, recipients of the HMS were less likely to require additional incision surgery for glaucoma. Subsequently, Ahmed et al. looked at five-year outcomes of the HORIZON trial, in which cataract surgery alone

was compared with combined cataract/glaucoma surgery with the HMS. They found that the stent group had greater reductions in IOP, lower medication use, and less need for post-op incisional glaucoma-filtration surgery. Long-term presence of the implant did not adversely affect corneal endothelial cells.

HORIZON was a prospective, multicenter, randomized controlled trial. Participants included those with cataract and POAG who had received at least one glaucoma medication and had not undergone incisional surgery for glaucoma. Washed-out diurnal IOP ranged from 22 to 34 mm Hg. Eyes were assigned randomly (2:1) to receive either the HMS or no stent after successful cataract surgery. Main outcomes included IOP, use of glaucoma medication postoperatively, need for additional glaucoma surgery, visual acuity and visual field, procedure-related adverse events, and endothelial cell counts.

Of the original HORIZON cohort, five-year follow-up was complete for 83.5% of the HMS group and 71.7% of those who underwent cataract surgery alone. At five years, the HMS group had a higher proportion of eyes with IOP  $\leq 18$  mm Hg (49.5% vs. 33.8%;  $p = .003$ ) and greater likelihood of an IOP reduction of at least 20% (54.2% vs. 32.8%;  $p < .001$ ). The number of glaucoma medications used at the five-year mark was  $0.5 \pm 0.9$  in the HMS group and  $0.9 \pm 0.9$  in the cataract surgery–only group ( $p < .001$ ); no glaucoma medication was used in 66% of HMS eyes and 46% of cataract surgery–only eyes ( $p < .001$ ). Moreover, the cumulative risk of further incisional surgery was lower in the HMS group (2.4% vs. 6.2%;  $p = .027$ ). From three to 60 months post-op, no clinically or statistically significant differences were noted in the rate of endothelial cell loss.

The authors emphasized that by reducing medication burden and lowering risk of repeat glaucoma surgery, the HMS would likely have durable and meaningful effects on quality of life. The results suggest that HMS placement at time of cataract surgery offers long-term benefit for management of POAG.

—Summaries by Lynda Seminara

most common cause of redetachment. Postoperative complications were similar between the two groups.

Overall, these results support the use of PPV+SB in children and PPV alone in adults as an option for treating giant retinal tear–related retinal detachments, the authors said.

—*Summary by Jean Shaw*

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Thyroid Function and AMD Risk

July 2022

Although a link between thyroid hormones and risk of age-related macular degeneration (AMD) has been reported for animal models, findings of subsequent observational studies have been inconsistent, suggesting that hidden confounding factors could affect results. To eliminate potential confounders, Li et al. explored the relationship between thyroid hormone function and AMD using Mendelian randomization (MR). They found that genetic variants predisposing patients to free thyroxine (FT4) levels in the high-normal range were associated with greater AMD disease risk. However, there was no clear evidence of an independent causal relationship between AMD and levels of thyroid-stimulating hormone (TSH).

To enhance their study's statistical power, the authors used two separate population samples. In one, the single-nucleotide polymorphisms associated with FT4 and TSH were extracted from a genome-wide association study (GWAS) of 72,167 people of European descent. In the other, summary-level data for AMD were obtained from an International Age-Related Macular Degeneration Genomics Consortium GWAS that included 16,144 patients with AMD and 17,832 control subjects, recruited from 26 studies.

The results showed that each standard deviation (SD) increase in genetically predicted FT4 levels was significantly associated with an 18.9% increase in overall AMD risk ( $p = .005$ ). In the multivariable MR analysis that

was controlled for TSH level, the causal effect of FT4 level on the risk of AMD also was strong (odds ratio, 1.207;  $p = .004$ ). In contrast, a 1-SD increase in TSH levels coincided just nominally with a 10% reduction in overall AMD risk ( $p = .032$ ). Subsequent multivariable MR analysis adjusted for FT4 level did not show a direct causal relationship between TSH level and AMD risk ( $p = .582$ ).

Given the multiple sensitivity analyses for pleiotropic genes plus adequate statistical power to detect causal associations, the overall findings of this study suggest an intrinsic negative effect of thyroid hormone function on the development of AMD. The authors encourage investigation of the mechanism behind the apparent link between FT4 and AMD risk, which may be a basis for new risk-reduction strategies.

### COVID-19 Outcomes in Patients With AMD

July 2022

COVID-19 and age-related macular degeneration (AMD) each are linked to inflammaging, a term for human aging characterized by chronic low-grade systemic inflammation. Moreover, COVID-19 and AMD share an underlying mechanism—dysregulation of complement cascades—which may explain the observation that patients with AMD have a higher risk for severe COVID and poor outcomes. To further explore the relationship between AMD and SARS-CoV-2 susceptibility and outcomes, Yang et al. stratified AMD subtypes and used propensity-score matching to reduce confounder bias in a large study of patients with SARS-CoV-2. They found that the presence of exudative AMD increases the likelihood of testing positive for COVID and is a harbinger of poor outcome after infection.

For this two-sample nationwide cohort study in South Korea, the authors gathered data from COVID-19 registries and a national claims-related database on patients  $\geq 40$  years of age who had a SARS-CoV-2 test during the first 4½ months of 2020. Self-referrals were excluded. Outcome measures were

results of polymerase chain reaction testing for SARS-CoV-2 and related clinical outcomes. Confounders of interest included age, sex, and history of predesignated diseases (such as hypertension, diabetes, chronic kidney disease, and lung disease). Outcomes considered “severe” were ICU admission, mechanical ventilation, oxygen supplementation, and/or death.

The unmatched cohort comprised 135,435 patients who underwent SARS-CoV-2 testing. Of these, 4,531 (3.3%) had a positive COVID result, and 5,493 (4.1%) had AMD (mean age, 72.5 years). Patients with exudative AMD were older, more likely male, and more often had a history of comorbidity (all  $p < .001$ ). Matched groups had no significant difference in baseline characteristics.

Of those who tested positive for COVID, 150 also had AMD. After propensity score matching, exudative AMD was associated with an increased likelihood of susceptibility to SARS-CoV-2 infection (adjusted odds ratio [OR], 1.50; 95% confidence interval [CI], 1.03-2.25). In addition, exudative AMD was associated with a greater risk of severe COVID outcomes (OR, 2.26; 95% CI, 1.02-5.26).

To validate findings of this study, the authors urge research in large national, international, and multiethnic populations. —*Summaries by Lynda Seminara*

## JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

### Association of Topical Prostaglandins With Miscarriages

June 2022

Do topical prostaglandin analogues (PGAs) increase the risk of miscarriage in pregnant patients with glaucoma? Etmnan et al. examined this hypothesis and found no association between PGA use and spontaneous abortions.

For this case-series study, the researchers used the PharMetrics Plus database for health claims in the United States from 2006 to 2020. They quantified the percentage of spontaneous abortions among patients who took a

topical PGA and a control cohort of women in the database who did not take a PGA. All participants were between 15 and 45 years of age. The main outcome was billing codes for diagnosis and treatment of spontaneous abortion.

All told, the researchers identified 3,881 women of reproductive age who were prescribed a PGA. Of these, 261 were pregnant, and 26 had a spontaneous abortion code. In comparison, of the 3,881 women in the control group, 801 were pregnant, and 56 were identified as having experienced a spontaneous abortion. The researchers noted that both groups were comparable with respect to age, mood disorders, preeclampsia, and the use of drugs associated with spontaneous abortion (e.g., antiepileptics, selective serotonin reuptake inhibitors, and serotonin antagonists).

In their discussion, the authors noted that pharmacologic data indicate that oral PGAs may cause uterine contraction—and that systemic absorption has been reported with topical PGAs. In addition, they point out that topical PGAs are currently classified as pregnancy category C (teratogenic in animals), although the doses used in the relevant animal studies were up to 80 times higher than those used in humans.

Although the results of their study indicate no association between PGA use and the risk of spontaneous abortion, the authors recommend further exploration of the topic in epidemiologic studies that can better control for potential confounding variables. (*Also see related commentary by Thasarat Sutabutr Jajaranant, MD, MHA, in the same issue.*)

### **Missed Opportunities to Prevent Acute Angle-Closure**

June 2022

How often do clinicians miss opportunities to diagnose and treat acute angle-closure crisis (AACC)? **Wu et al.** set out to identify Medicare patients who presented with AACC and assess factors that may have raised their risk of developing it. They found that there appear to have been multiple opportu-

nities for interventions that may have averted AACC.

For this population-based retrospective cohort study, the researchers included a 20% nationwide sample of Medicare beneficiaries (n = 1,179). Patients aged 40 years or older with AACC were identified with billing codes. A two-year lookback period from the point of patients' initial presentation with AACC was used to identify those who had at last one eye care visit, received a diagnosis of open-angle glaucoma (OAG), or received at least one medication associated with risk of developing AACC (e.g., selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, antihistamines, carbonic anhydrase inhibitors, and topiramate). In addition, among patients who had at least one eye care visit, the researchers identified those who either had undergone gonioscopy or were diagnosed with an anatomic narrow angle before developing AACC.

The mean age of those with AACC was 66.7 years (range, 40-96 years), and 766 (65%) were women. With regard to race, the majority (n = 791; 67.1%) were White. A total of 464 individuals (39.4%) had OAG or suspected OAG, and 414 (35.3%) had received a medication associated with increased risk of AACC before they developed the condition.

With regard to eye care, 796 of the 1,179 patients (67.5%) had consulted an ophthalmologist or optometrist during the two-year lookback period; the remainder had received no eye care during this time. Of those who were examined, 264 (33.2%) underwent gonioscopy in the two years preceding their diagnosis with AACC. Of those who had gonioscopy, 113 (42.8%) received a diagnosis of an anatomic narrow angle.

In their discussion, the authors noted that the results highlight multiple missed opportunities for interventions to prevent AACC. They recommend addressing risk factors associated with the underuse of eye care as well as additional emphasis on correct gonioscopy technique, greater use of gonioscopy to identify patients with eyes at risk, and prophylactic laser peripheral iridotomy

when indicated. (*Also see related commentary by Alexander C. Day, PhD, and Gus Gazzard, MA, MD, MBBChir, in the same issue.*)

### **Residency Program Websites: Signs of Diversity and Inclusion**

June 2022

**Ledesma Vicioso et al.** evaluated U.S. ophthalmology program websites for information on diversity or inclusion. They found that this information is lacking on most program websites.

For this quality improvement study, the researchers included a cross-sectional review of ophthalmology program websites. The websites were reviewed for the presence of six predetermined diversity or inclusion information criteria, and the study was conducted in mid-2021.

The criteria, modeled after those implemented in previously published literature, were as follows: 1) evidence of commitment to, or value toward, diversity (i.e., in a message from the program director or department chair); 2) a separate diversity mission statement; 3) mention of rotations or fellowship opportunities for underrepresented minority medical students; 4) mention of diversity initiatives; 5) a web page or section on diversity; and 6) mention of diversity leadership positions.

Of the 121 U.S. program websites reviewed, 29 (24%) met at least one of the six criteria. Programs with more than 12 residents, as well as those programs ranked within the top 20 best hospitals for ophthalmology (as determined by the *US News & World Report*), were more likely to have at least one of the criteria on their website. Of note, 53 of the websites (44%) mentioned that their residency program offers trainees the opportunity to care for a diverse population.

In discussing the results, the authors noted that “these findings suggest that there is a gap in the information that prospective applicants can collect when evaluating ophthalmology residency program websites.” (*Also see related commentary by Russell S. Gonnering, MD, MMM, in the same issue.*)

—Summaries by Jean Shaw

## OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

### Prompt Open Globe Repair Is Crucial

*Clinical Ophthalmology*  
2022;16:1401-1411

Open globe injury from an intraocular foreign body (IOFB) can severely affect vision and lead to endophthalmitis. Although there is consensus on common risk factors and stratification schemes for these wounds, there is controversy about the type and timing of treatment. Keil et al. reviewed IOFB cases in an effort to define predictors of poor outcomes and explore management strategies. They found that poor visual acuity (VA) and severe injury at presentation were associated with poor visual outcomes. Prompt globe closure and antimicrobial prophylaxis were crucial to avoid infection.

For this study, the authors gathered details from medical records of 88 patients (88 eyes) who experienced IOFB-related injury and were seen at the University of Michigan Medical School from 2000 through 2019. Pertinent data were documented, including VA, injury characteristics, treatment modalities, and clinical outcomes. Multivariate logistic regression was employed to determine correlations between presenting factors and visual outcomes, which were classified as good (corrected VA of 20/40 or better) or poor (corrected VA of 20/200 or worse). Unpaired t tests and Fisher's exact tests were used to compare continuous and categorical variables, respectively.

The analyses showed that delayed presentation ( $p = .016$ ) and organic IOFB ( $p = .044$ ) correlated strongly with endophthalmitis. Retinal detachment ( $p = .012$ ), wound length  $>5$  mm ( $p = .041$ ), and reduced VA ( $p = .003$ ) were linked to poor final visual outcomes. All patients were given antibiotic prophylaxis, but the choice of specific agent and route of delivery varied. More than 80% of patients received antibiotics systemically, and

intravitreal administration was used in 50% of primary IOFB removals and in 86% of secondary removals. Endophthalmitis occurred in 4.9% of the eyes after initial management, and rates were similar for primary and secondary procedures.

Findings of this 20-year experience indicate that outcomes are optimized by prompt treatment, including globe closure and antimicrobial prophylaxis. The authors noted that if IOFB removal and globe closure cannot be done concurrently, aggressive antibiotic prophylaxis alone may be sufficient to prevent endophthalmitis.

### Intereye Correlation in Patients With Glaucoma

*Graefe's Archive for Clinical and Experimental Ophthalmology*  
Published online May 2, 2022

About 50% of patients diagnosed with open-angle glaucoma will eventually develop it in both eyes. In some countries, patients can be hospitalized for 24-hour monitoring of IOP to capture elevations that may occur outside of office hours. Previously, Dakroub et al. developed an extraction tool for manually charted IOP curves (HIOP-Reader), analyzed data for right eyes, and found that 24-hour monitoring is a poor tool for detecting glaucoma progression. In a subsequent study, they looked at data for left eyes to compare intereye IOP, ocular perfusion pressure, and progression parameters. They hypothesized that even though 24-hour IOP data may be flawed, both eyes are affected similarly, and thus intereye measurements may help to predict glaucoma in contralateral eyes. As in their previous study, they found that measuring IOP in one eye inadequately predicted progression, but intereye correlations were

meaningful for all parameters tested.

In this study, the authors gathered 24-hour data for left eyes using the HIOP-Reader software. They explored the relationship between mean ocular perfusion pressure (MOPP) and retinal nerve fiber layer (RNFL) thickness. They determined receiver operating characteristic (ROC) curves for peak IOP, average IOP, IOP variation, and historical IOP cutoff levels to assess glaucoma progression (i.e., rate of RNFL loss). They used bivariate analysis to look for intereye relationships.

The study included 217 eyes. Per the hospital's standard protocol, IOP measurements were obtained at 10 a.m., 2 p.m., 5 p.m., 9 p.m., and midnight. During the monitoring period, the average IOP was  $14.8 \pm 3.5$  mm Hg, and the mean variation was  $5.2 \pm 2.9$  mm Hg. RNFL data indicated glaucoma progression in 52% of eyes. There were no significant differences in peak IOP, average IOP, or IOP variation between those who progressed and those who did not. Except for average IOP in relation to temporal RNFL, disease progression in any quadrant was not found to correlate with peak IOP, average IOP, or IOP variation. In- and outpatient IOP readings were not sensitive or specific for detecting progression.

Moreover, the correlation of intereye parameters was moderate, and the relationship to disease progression was weak.

This research and previous work suggest that IOP data are unreliable diagnostically but that intereye findings may be clinically relevant. For most patients in this study, IOP and MOPP were similar for left and right eyes. Therefore, when substantive RNFL loss is observed in one eye, it is likely occurring in the contralateral eye as well.

—Summaries by Lynda Seminara

### Two IRIS Registry Research Grant Applications Due Aug. 2

Don't miss the Aug. 2 application deadline for two private research funds:

- The Knights Templar Eye Foundation (KTEF) Pediatric Ophthalmology Fund, which focuses on pediatric ophthalmic disease.
- The H. Dunbar Hoskins Jr., MD, Center for Quality Eye Care IRIS Registry Research Fund, which supports members in private practice.

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