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Big data to guide glaucoma treatment

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Abstract:

Ophthalmology has been at the forefront of the medical application of big data. Often harnessed with a machine learning approach, big data has demonstrated potential to transform ophthalmic care, as evidenced by prior success on clinical tasks such as the screening of ophthalmic diseases and lesions via retinal images. With the recent establishment of various large ophthalmic datasets, there has been greater interest in determining whether the benefits of big data may extend to the downstream process of ophthalmic disease management. An area of substantial investigation has been the use of big data to help guide or streamline management of glaucoma, which remains a leading cause of irreversible blindness worldwide. In this review, we summarize relevant studies utilizing big data and discuss the application of the findings in the risk assessment and treatment of glaucoma.

Keywords:

Big data, glaucoma, machine learning, treatment

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Introduction

The advancement in data and technologies has driven the 4th industrial revolution,[1] and the medical profession is amongst the groups that have benefitted the greatest from this revolution. In the past two decades, "big data," which describes a massive amount of data that requires more sophisticated measures to analyze, has garnered particular attention in ophthalmology due to the data-driven nature of this field.[2,3] In addition to expanding the breadth and depth of ophthalmic research, information unveiled through big data has also influenced the management of ophthalmic diseases from multiple aspects. With the maturation of machine learning (ML) techniques,[4] it is inevitable that big data will continue to transform ophthalmic practice.

Despite many decades of investigation, the exact pathophysiology of glaucoma, a leading cause of blindness worldwide, has yet to be fully elucidated.[5] Due to the irreversible nature of this disease,[5] consistent efforts have been made to optimize the clinical management of glaucoma, including searching for better ways to predict outcome and monitor progression, and developing more effective treatments. With the rapid accumulation of ophthalmic data and the establishment of various large, electronic datasets,[6] the findings from big data in ophthalmology may help to markedly improve glaucoma care. In this review, we discuss how big data may influence or guide future glaucoma management.

Methods: Literature Search

PubMed and Google Scholar were searched for relevant published studies through February 2023 using keywords relevant to this review. Major keywords used included: "big data," "information system," "big dataset," "nationwide data," "biobank," "IRIS Registry," "All of Us," "glaucoma," "glaucoma treatment," "glaucoma management," "glaucoma surgery," "glaucoma medication," "prediction," "outcome," "artificial intelligence," "machine learning," and "deep learning.". No filter for publication year, language, or study type was applied. The references of identified records were also checked for potential inclusion. Studies

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utilizing big data or discussing the application of big data in glaucoma management were considered relevant to the current review. Abstracts of non-English articles with relevant information were also included in the study.

Big Data in Ophthalmology

While primarily used to describe a large volume of data, the term "big data" encompasses more than just the size, but also many other characteristics, of the data. As described in prior literature, big data features other unique qualities such as "variety," "veracity (accuracy)," and "velocity (speed of accumulation/aggregation)."[1,7] Notably, the rise of big data in ophthalmology can be largely attributed to its variety,[6] which span across the different settings of data collections, sources, and formats of data (e.g., genetic information, clinical measurements, and ocular imaging), and the purposes of the application (e.g., research, clinical care, and administration). The development of computerized systems and electronic health records (EHR), which is now commonly used in ophthalmic clinics, has further improved the velocity and veracity of ophthalmic data. Together, these contribute to the most clinically important characteristic of big data, the "value."

Various ophthalmic studies have been performed using different types of big data. Briefly, the main types of big data most commonly utilized in ophthalmic research included:[1] (1) virtual biobanks (e.g., the UK biobank[8,9]), which collect, handle, and store genetic and phenotypic data acquired from human specimens and tissue samples; (2) data registries (e.g., the American Academy of Ophthalmology Intelligent Research in Sight [IRIS®] Registry[10,11]), which gather the patients' clinical and health-care utilization information by exporting them from the EHR; (3) research consortia (e.g., the European Eye Epidemiology consortium[12]), which aggregate data provided by parties from different countries and domains through a formalized collaboration to address a shared research goal;[13] (4) nationwide health insurance databases (e.g., the Taiwan National Health Insurance Research Database[14,15]), which are usually only available in countries with national health insurance programs; (5) digital health data programs (e.g., *All of Us* Research Program[16]), which include EHR and health questionnaire/survey data provided by volunteer participants; (6) ocular image databases (e.g., Kaggle dataset[17]), which are large-scale image databases often made public for research purposes; (7) population-based data (e.g., The Beaver Dam Eye Study[18]), which are data collected from a set of individuals with shared characteristics, often geographic or ethnic similarities, in prospective, longitudinal cohort studies.

The utilization of these big data resources has led to novel findings and achievements in ophthalmology. For example, multiple studies have discovered clinical predictors for surgical outcomes in various ophthalmic conditions (e.g., globe injuries, pterygia) using the IRIS Registry.[19-21] As precision medicine becomes the new goal in patient care, these sources of information may help clinicians to make treatment and follow-up plans on a patient-by-patient basis. Another example is the application of ML on ophthalmic big data. Trained on large-scale ocular image databases, ML techniques such as deep learning (DL) models have shown robust performance in automated diagnosis and staging of diabetic retinopathy (DR) using color fundus photographs,[22,23] which started the era of ML-based diagnosis of ophthalmic diseases.[24,25] Notably, the Food and Drug Administration (FDA) approval of IDx-DR,[26] a DL-based assistive DR screening system, was a ground-breaking example of big data improving and transforming ophthalmic care on a wider scale.

Big Data to Guide Glaucoma Treatment

To date, the use of big data in optimizing glaucoma practice has focused primarily on the upper-stream processes, which include disease screening, diagnosis, and staging.[24,27] It was only recently that the application of big data in glaucoma extends to the downstream processes, such as outcome prediction and treatment effect evaluation. In this section, we summarize studies presenting relevant findings that may guide or influence glaucoma treatment planning, organized based on the clinical aspects that are addressed.

Spatial pattern analysis of visual field change

The detection of functional progression is a crucial part of glaucoma management since patients with progressive visual field (VF) loss typically have impaired quality of life and higher risk of further functional deterioration that requires interventions.[28,29] In addition to conventional VF assessment based on scoring and global/point-wise indices, a more in-depth evaluation of VF change through spatial pattern analysis was made possible by big data and ML techniques.[30]

Using consortium data from the Glaucoma Research Network, Wang *et al*. were among the first to perform pattern analysis on VF data.[31] They identified a total of 16 VF archetypes from a training cohort of more than 10,000 eyes, and developed an ML-based "archetype method" that detects VF progression based on quantified information of VF pattern changes over time. As the archetype method outperformed conventional methods in detecting VF progression, the authors suggested it may be clinically beneficial to incorporate this method to more accurately assess glaucoma progression.[31] Additional studies have since performed ML-based VF pattern/archetypal analysis on glaucoma eyes, and in comparison to conventional methods, VF pattern/archetype-based methods have consistently shown superior performance in detecting and predicting VF progression, even for central VF progression.[17,32,33] By incorporating pattern analysis, a VF feature model developed on the same consortium data were even able to predict the reversal of false-alarming glaucoma hemifield test results to normal with high precision.[34]

To summarize, big data enables the discovery of these relevant hidden patterns in VF results, while ML algorithms help convert this information into clinically applicable strategies. Together, they contribute to a novel method for functional progression assessment and prediction, which may assist clinicians in providing more timely treatment.

Risk stratification based on genetic profiling

Characterized by heritability, chronicity, irreversibility, clinical heterogeneity, and treatability, glaucoma is considered an ideal candidate for genetic risk profiling.[35] Knowledge about genes relevant to the development and pathophysiology of glaucoma may aid in risk stratification and outcome prediction, both of which might facilitate a more personalized and risk-stratified means of glaucoma management.

A few studies have used the UK Biobank to perform genetic risk profiling for glaucoma, and have demonstrated the usefulness of monogenic or polygenic risk score (PRS) in the risk prediction of glaucoma.[36,37] The *MYOC* (myocilin) p. Gln368Ter variant is the most common disease-causing mutation in European decedents with primary open-angle glaucoma (POAG).[38] Zebardast *et al*. evaluated the disease penetrance and characteristics among individuals with p. Gln368Ter using UK Biobank.[39] They found one out of four in this population showed signs of glaucoma, including many who were undiagnosed.[39] Moreover, a higher POAG PRS was associated with increased glaucoma penetrance and severity in this particularly susceptible population.[39] Also using UK Biobank, Craig *et al*. conducted a large genome-wide association study that identified new risk loci for glaucoma.[35] In addition, they developed a new PRS through multi-trait analysis, which revealed individuals in the top PRS decile may not only develop glaucoma earlier but also are at a much higher risk of developing advanced glaucoma. Furthermore, the new PRS was able to predict progression in early-manifesting cases and the need of surgical intervention in advanced cases.[35] Similarly, Gao *et al*. used the UK Biobank data to construct a new intraocular pressure (IOP) PRS and found the IOP PRS to not only correlate with IOP but also predict POAG.[40]

These studies demonstrated how glaucoma PRS constructed based on big genetic data may help to identify high-risk individuals in glaucoma practice. In comparison to the lower-risk group, high-risk individuals may benefit from more intensive monitoring and treatment plans for glaucoma, particularly if administered at early time points of the disease.

Evaluation of surgical outcomes and predictors

The evaluation of surgical outcomes is essential in improving glaucoma treatment. It helps to provide guidance on the surgical options most effective for individual patients, as well as a better understanding of the risks for important adverse events at the time of surgery and during postoperative care. By exploring predictors of poor surgical outcomes, clinicians can also better identify patients more prone to surgical nonresponse/failure and adjust treatment plans accordingly. Although such evaluation can also be performed on regular datasets, analysis of big data may help to reach a more accurate, reliable, and generalizable conclusion. In addition, the amount of data from a single center may not always be sufficient when there are multiple surgical methods to compare, or when the ones assessed only recently became available.

Using a single-center dataset, Wang *et al*. were amongst the first to examine surgical outcomes of glaucoma eyes on a larger scale.[41] They included 7574 eyes with and without glaucoma to assess the long-term IOP change ($\geq$14 months) after cataract surgery.[41] They found that, in comparison to nonglaucomatous eyes, glaucomatous eyes were more likely to achieve sustained postoperative IOP reduction. Furthermore, cataract surgery is more likely to yield long-term IOP reduction in patients with higher baseline IOP.[41]

Numerous later studies have used the IRIS Registry to evaluate surgical outcomes and associated factors in glaucoma eyes. Rothman *et al*. examined IOP changes following stand-alone phacoemulsification in glaucoma eyes and found a significant IOP reduction during the 90-day postoperative period.[21] Chang *et al*., examined the outcomes of laser trabeculoplasty (LTP) in glaucoma eyes in two studies,[42,43] with a successful LTP response defined as an IOP reduction $\geq$20% without medication use. They reported the overall failure rate was 0.2%, 6.1%, 16.8%, 29.1%, and 40.8% at 0, 6, 12, 18, and 24 months, respectively.[42] Moreover, consistent with the finding by Wang *et al*.,[41] a longer response duration and lower risk of nonresponse were observed for eyes with higher baseline IOP, while lower baseline IOP, angle recession, uveitis, and aphakia were associated with increased odds of LTP nonresponse.[42,43] Investigating risk factors for the failure (revision or removal) of glaucoma drainage device (GDD), Hall *et al*. showed the presence of chronic angle-closure glaucoma and dry eye disease may increase the risk of GDD failure; furthermore, male sex, unknown race, and right-eye laterality are likely to reach GDD failure within a shorter period.[44]

Recently, several devices for microinvasive glaucoma surgery (MIGS), a novel surgical option for mild-moderate glaucoma, have been approved by the FDA. Due to the various advantages of MIGS as compared to conventional glaucoma surgeries, including faster visual recovery and fewer postoperative complications,[45] MIGS have been increasingly performed in glaucoma patients at earlier stages of the disease. A few studies have used big data to assess the practice pattern of MIGS in glaucoma (see below for additional discussion).[46-49] Among them, Yang *et al*. used the IRIS Registry to evaluate the reoperation rate in patients receiving MIGS with and without concurrent phacoemulsification.[49] They found overall low complication rates for MIGS (1%–2%), supporting the safety of this procedure. They also found a lower reoperation rate when MIGS was performed in combination with phacoemulsification. In addition, risk factors for higher odds of reoperation were identified, such as Black race, older age, higher baseline IOP, and moderate-severe glaucoma, suggesting more intensive postoperative follow-up should be considered in these patients.[49]

Emulation of randomized clinical trials

Although not yet widely performed in ophthalmology, big data has been used to emulate the results of randomized control trials (RCTs), especially those assessing treatment effectiveness or safety.[50] Emulation based on large, observational data provides several benefits. It can serve as the validation for RCTs results, given RCTs are usually conducted under ideal conditions, and the patient population in the real world may not mirror the study population in an RCT.[51] In addition, findings of the differences between RCTs and big data-based emulations may inform investigators on the future design of RCT and pitfalls in current clinical care. On the other hand, by serving as the control arm (or both experimental and control arms), the emulation may be an alternate method to answer clinical questions when an RCT is not feasible.[50]

An example of big data-based RCT emulation in glaucoma was the study by Vanner *et al*.[52] The authors emulated the tube versus trabeculectomy (TVT) RCT using the IRIS Registry and compared the 1-year outcome of TVT IRIS and TVT RCT.[52,53] Interestingly, they found noticeable differences in the results, with the failure rate being similar for tube and trabeculectomy in TVT IRIS.[52] The reasons associated with the higher tube failure rate in TVT IRIS, such as reoperation for glaucoma (not seen in TVT RCT), were also analyzed, providing insight into patient groups that may consider one surgical option over the other given the potential benefits and adverse events. By serving as real-world evidence,[54] big data-based emulation may guide glaucoma treatment decision-making by confirming the efficacy and safety of treatment options in a clinic population and clarifying the differences between RCT settings and real-world practice patterns, as well as informing us about how these differences may affect treatment outcomes.

Risk analysis of future surgical intervention

An advantage of EHR and health insurance claim big data is the easy access to information about the patients' sociodemographic characteristics, systemic health status, and healthcare utilization. Moreover, relevant clinical events such as surgical interventions are clearly recorded and can be used as surrogates for progressive disease in glaucoma research. There are some potential benefits of risk analysis for future surgical intervention:[55,56] Scientifically, knowledge about risk factors associated with progressive glaucoma may help to identify new therapeutic measures. Clinically, it may help the clinician to practice precision medicine from multiple aspects when making treatment plans.

Using the Korean National Health Insurance Service dataset, Lee *et al*. examined risk factors associated with the need for glaucoma surgeries within 5 years of POAG diagnosis.[57] They found older age, female sex, and more intensive IOP-lowering treatment to increase the likelihood of undergoing glaucoma surgery, while a lower socioeconomic status (SES) was associated with a lower rate of glaucoma surgery.[57] The latter finding indicates that, for patients with lower SES, the decision to receive surgeries might have been compromised due to barriers that may be mitigated by additional support and outreach. Although sociodemographic factors are often neglected in glaucoma, prior studies have shown they are predictive of the patients' health-care utilization and outcomes.[58,59] Therefore, the identification of relevant sociodemographic risk factors for progressive glaucoma requiring surgery, particularly modifiable ones, should be attended to in the era of big data.

On the other hand, other studies have demonstrated an improved performance of ML models in predicting future surgical intervention in glaucoma when trained based on big data, instead of a single dataset. Baxter *et al*. trained ML models to predict the need for surgical intervention in POAG based on both single-center EHR data and the *All of Us* database,[55,60] and found significantly superior performance of models trained on the latter.[55] Their findings demonstrated the variety and veracity of big data in comparison to smaller or individual dataset, which can be leveraged in ophthalmic research. Moreover, based on the best-performing All of Us-trained ML model, basic body measurements (e.g., weight and hip/waist circumference) and blood pressure measurements were amongst the most important predictors.[55] This supports further investigation into whether incorporating lifestyle modification (e.g., blood pressure reduction and weight loss) in glaucoma treatment may be beneficial for patients.

Characterization of practice patterns, barriers, and disparities

As previously mentioned, big data has been used to evaluate the practice patterns in glaucoma. Such analysis is mostly performed using EHR or insurance claim-based datasets, given that they provide more detailed information on the SES, healthcare utilization, and clinical events of the patients.

The practice pattern of MIGS was most studied using the IRIS Registry.[46-48] Yang *et al*. analyzed the trend and usage patterns of MIGS in the United States.[46] A significant increase in annual MIGS procedures was found from 2013 to 2018, while that of standard glaucoma procedures (GDD or trabeculectomy) decreased. Among different MIGS procedures, iStent accounts for the highest proportion, and iStent and endoscopic cyclophotocoagulation (ECP) were the most common concurrent procedures.[46] In their other study, they revealed the differing practice patterns among MIGS utilization among various types of glaucoma.[48] The iStent was most commonly performed in open-angle glaucoma or normal-tension glaucoma, while GDD was most common in secondary glaucoma or other glaucoma. After an initial standard procedure, ECP was the most common MIGS performed, particularly in secondary glaucoma and primary angle-closure glaucoma eyes.[48] These studies showed that MIGS has become one of the preferred surgical options in glaucoma, and the type of glaucoma and prior surgical history may influence the choice of surgical method. More importantly, the authors highlighted the need for more evidence on the long-term safety and efficacy of MIGS, which remains lacking despite the increased utilization in glaucoma patients.

In addition to changing practice patterns, big data may also help characterize existing barriers or disparities in glaucoma care. The study by Lee *et al*. (described previously), which utilized an insurance-claim dataset to examine factors predicting future surgical intervention in glaucoma, has shown a potential disparity among glaucoma patients in Korea due to financial barriers.[57] Using the *All of Us* dataset, Delavar *et al*. further examined the financial barriers to medication adherence among glaucoma patients in the United States and found non-Hispanic African Americans and Hispanic individuals (versus non-Hispanic White individuals) to have greater difficulty in affording glaucoma medications.[61] Similarly, Acuff *et al*. used the *All of Us* dataset to identify socioeconomic factors associated with visit nonadherence among glaucoma patients and found lower income and education levels to predict worse visit adherence.[62] In another study analyzing data from the 1996 to 2017 Medical Expenditure Panel Survey, glaucoma patients with a low health literacy had fewer outpatient visits, despite being prescribed more medications and having higher medication costs.[63] In general, these big data studies revealed the presence of racial/ethnic and socioeconomic disparities in glaucoma care on a systemic level. To improve the outcome and equity of glaucoma care on a wider scale, it is important that the clinicians and policy makers be aware of these barriers and take the initiatives to mitigate them.

Conclusion

Big data possesses the potential to guide and streamline future treatment for glaucoma. Current literature has shown its utilities in facilitating personalized treatment strategy through risk profiling and outcome prediction, as well as in improving glaucoma care on a wider scale through RCT emulation and practice pattern analysis. Although most prior studies have utilized single-modal ophthalmic data, particularly ocular images or EHR, it is expected that future research will explore the potential benefits of incorporating multi-modal data on the emergence of new data types (e.g., clinical notes)[56,64] and ML techniques.[65,66] As the application of big data in ophthalmology broadens, the ethical and societal challenges accompanying this advent should also be considered.[67] It remains to be seen how the aforementioned results can be incorporated clinically to improve glaucoma care.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

Prof. Shan Lin, an editorial board member at *Taiwan Journal of Ophthalmology*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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