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Title: Glaucoma Detection from Retinal Images Using Statistical and Textural Wavelet Features.

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Source: Journal of Digital Imaging (J DIGIT IMAGING), Feb2020; 33(1): 151-158. (8p)

Publication Type: Article - diagnostic images, equations & formulas, pictorial, research, tables/charts

Language: English

Major Subjects: Glaucoma -- Diagnosis
Retina
Health Screening
Image Processing, Computer Assisted -- Methods

Minor Subjects: Algorithms; Early Diagnosis; Early Intervention; Diagnostic Imaging; Human

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Journal Subset: Allied Health; Biomedical; Computer/Information Science; Double Blind Peer Reviewed; Peer Reviewed; USA

ISSN: 0897-1889

MEDLINE Info: *NLM UID:* 9100529

Entry Date: 20200317

Revision Date: 20210201

DOI: 10.1007/s10278-019-00189-0

Accession Number: 142164496

Database: CINAHL Complete

Glaucoma Detection from Retinal Images Using Statistical and Textural Wavelet Features

Glaucoma is a silent progressive eye disease that is among the leading causes of irreversible blindness. Early detection and proper treatment of glaucoma can limit severe vision impairments associated with advanced stages of the disease. Periodic automatic screening can help in the early detection of glaucoma while reducing the workload on expert ophthalmologists. In this work, a wavelet-based glaucoma detection algorithm is proposed for real-time screening systems. A combination of wavelet-based statistical and textural features computed from the detected optic disc region is used to determine whether a retinal image is healthy or glaucomatous. Two public datasets having different resolutions were considered in the performance analysis of the proposed algorithm. An accuracy of 96.7% and area under receiver operating curve (AUC) of 94.7% were achieved for the high-resolution dataset. Analysis of the wavelet-based statistical and textural features using three different methods showed their relevance for glaucoma detection. Furthermore, the proposed algorithm is shown to be suitable for real-time applications as it requires less than 3 s for processing the high-resolution retinal images.

Keywords: Glaucoma; Retinal images; Wavelet transform; Gray-level co-occurrence matrix; Statistical features; Classification

Introduction

According to the World Health Organization, glaucoma is a leading cause of blindness worldwide accounting for over 12% of global blindness [[1]]. In 2010, it was estimated that 60.5 million people suffered from glaucoma, a figure expected to increase to 80 million by the year 2020 [[2]]. Generally, glaucoma is more common in elderly individuals with African and Hispanic origins than in Caucasians, specifically those suffering from severe nearsightedness, diabetes, or high blood pressure. Glaucoma causes progressive impairment of the optic nerve responsible for sending image signals from the eye to the brain. At its early stages, glaucoma has absolutely no effect on vision hence usually passes unnoticed by patients. In more advanced stages, glaucoma causes loss of peripheral sight that can progress to irreversible blindness. However, early diagnosis and proper treatment can help control glaucoma progression thus avoiding vision loss.

Periodic eye examination of candidate glaucoma patients is thus essential to facilitate the early detection of the disease. In an eye examination, a patient's retinal image is captured then manually inspected by an ophthalmologist to determine whether or not glaucoma symptoms are present. Manual analysis of retinal images can be very time consuming [[3]]. In addition, the images should be inspected by highly trained ophthalmologists in order to assure accuracy of the performed diagnosis [[4]]. Periodic manual screening would hence cause a huge overload on expert ophthalmologists who would be required to examine a large number of patient images, most of which have no disease symptoms. Automatic screening systems have the potential to overcome these limitations by automatically capturing and processing retinal images, advising only patients with detected glaucoma symptoms to seek medical treatment.

In retinal images, the damage of the optic nerve associated with glaucoma can be depicted in the cupping of the optic disc, which is the increase of the cup size with respect to the optic disc, as well as in the change of its overall characteristics [[5]]. Automatic methods thus commonly rely on analysis of the optic disc region for glaucoma diagnosis. Generally, there are three types of glaucoma detection algorithms in literature: (1) structural, (2) generic, and (3) hybrid.

Structural glaucoma detection algorithms rely on the segmentation of both the optic disc and cup followed by the computation of structural measures to determine whether or not the disease is present. Common measures for glaucoma detection include the cup-to-disc ratio (CDR) [[6]–[8]], inferior superior nasal temporal (ISNT) rule [[9]], disk damage likelihood scale (DDLS) [[10]], and glaucoma risk index (GRI) [[11]], all which are computed using the vertical disc and cup heights [[12]]. The performance of structural glaucoma detection algorithms is thus highly dependent on the segmentation accuracy of the optic disc and cup from the retinal images. Consequently, the accurate detection of the boundaries of both the disc and cup is essential to ensure the efficiency of these methods [[13]]. However, in some cases, the cup and disc are hardly distinguishable which would make their accurate segmentation extremely challenging [[8], [14]]. Moreover, segmentation algorithms can be complex and time consuming making them unsuitable for real-time automatic retinal screening systems.

Generic methods are based on the intuition that the damage of the optic nerve associated with glaucoma affects the overall characteristics of the optic disc region. Generic methods thus rely on a combination of statistical and textural features, computed from either the spatial or wavelet domains of the image. Dua et al. [[15]] proposed using average wavelet energy computed from the retinal images' level 1 detail subbands for glaucoma classification. They reported an accuracy of 93% using tenfold cross validation with support machine vector (SVM) classifier for a dataset consisting of 30 normal and 30 glaucomatous images. In another work, Singh et al. [[16]] calculated the mean and energy of the optic disc region's first wavelet level detail subbands for differentiating between normal and glaucomatous images.For both *k* nearest neighbor (*k*NN) and SVM classifiers, an accuracy of 94.7% was achieved using a 63-image dataset, where 70% of the data was used for training and the rest for testing. In their work, Singh et al. concluded that wavelet features extracted from the optic disc region were more clinically significant than features computed from the whole retinal image. They also showed that their method gave higher results than several other approaches from literature. Dey et al. [[17]] implemented a glaucoma detection algorithm using spatial textural features calculated from the gray-level run and co-occurrence matrices. An overall accuracy of 94% was achieved using tenfold cross-validated SVM classifier tested with a private dataset.

Hybrid approaches combine both structural measures, requiring optic disc and cup segmentation, along with generic textural and statistical features for glaucoma detection. Hybrid methods hence share the limitation of the structural glaucoma detection methods in that they can be prone to segmentation errors as well as being computationally expensive. Akram et al. [[18]] integrate spatial and spectral features along with cup-to-disc and rim-to-disc ratios for glaucoma detection. Their method resulted in accuracies between 85 and 95% for several public and private datasets. Vijapur et al. [[19]] implemented several structural measures along with wavelet energy features for glaucoma classification. The best performance was achieved by combining both the structural and wavelet features resulting in an accuracy of 86.7% using the SVM classifier on a public dataset consisting of 30 retinal images. Khalil et al. [[20]] used a combination of textural and intensity features along with several structural features calculated from the segmented optic disc and cup in order to classify glaucomatous retinal images. Their algorithm resulted in accuracies of 94% and 83% for the textural and structural features, respectively, using a tenfold cross-validated SVM classifier. These results show the superiority of textural over structural features for glaucoma classification.

Generic glaucoma detection algorithms thus have the potential to overcome the limitations of structural methods by being computationally inexpensive while giving reliable results. In literature, generic features were most commonly computed from the images' spatial domain. Few researches have also computed generic features from the wavelet decomposition of the retinal images. However, wavelet-based generic glaucoma

detection algorithms introduced in literature mainly relied on only a limited number of statistical features such as the mean and energy [[15]].

In this work, a novel wavelet-based generic glaucoma detection algorithm is proposed that relies on a combination of both textural and statistical features. Wavelet transform is a multiresolution technique that has the advantage of being localized in both time and frequency [[21]]. Wavelet decomposition separates an image's edge and luminance information in its detail and approximation subbands, respectively. Detail subbands mainly include information related to the retinal vessels which are of low relevance to glaucoma detection. On the other hand, approximation subbands include the image's illumination and textural information. Consequently, only the retinal images' approximation subbands were considered in the proposed algorithm. Initially, the optic disc region was detected from the image's red channel approximation subband. Next, several statistical and textural features were computed from the detected optic disc region's green and blue approximation subbands. Feature selection was then employed to find the most relevant features and the reduced feature set was used to classify two publicly available retinal image datasets of different resolutions into healthy or glaucomatous. Finally, perfromance and timing analysis along with comparisons to other methods were perfromed demonstrating the superiority of the proposed glaucoma detection algorithm.

Materials

In this work, balanced subsets of two publicly available retinal image datasets were used to evaluate the performance of the proposed method.

- GlaucomaDB [[20]]: includes 33 healthy and 33 glaucomatous images taken with a TopCon TRC 50EX camera originally having a resolution of 1504 × 1000 pixels. However, images publicly provided within this dataset only include the optic disc and a small surrounding region. The cropped image sizes vary slightly among them but are generally less than 200 × 200 pixels.

- High-resolution fundus (HRF) image database [[22]]: consists of 15 healthy and 15 glaucomatous retinal images captured using a Canon CR-1 fundus camera at a resolution of 3504 × 2336 pixels. All images within the HRF dataset were taken at a 45° field of view (Fig. 1a). In order to increase the processing speed of the proposed algorithm, the HRF images were initially cropped to separate only the part including the optic disc and surrounding region. Images were cropped by first excluding the black image edges. Next, the retinal image was divided into three rows and three columns and only the block containing the optic disc was considered for further processing. The considered region thus had a resolution of 870 × 780 pixels (Fig. 1b).

Graph: Fig. 1 Retinal image from the HRF dataset a before and b after cropping

Methods

Glaucoma is associated with the damage of the optic disc resulting in the change of its overall characteristics within the retinal image [[5]]. Optic discs are generally characterized by their bright yellowish appearance as opposed to the reddish-orange retinal image. Figure 2 shows an example of the red, green, and blue channels of a cropped retinal image from the HRF dataset. The optic disc is seen to be most distinguishable in the retinal image's red channel. However, the green and blue channels demonstrate a larger contrast between the disc and cup. Consequently, in this work, the red channel was used for optic detection whereas the green and blue channels were used for the feature extraction. The proposed wavelet generic glaucoma detection algorithm is summarized in Fig. 3 and its details are given within this section.

Graph: Fig. 2 The a red, b green, and c blue channels of the optic disc region (for an image from the HRF dataset)

Graph: Fig. 3 Flowchart of the proposed glaucoma detection algorithm

Preprocessing

Several enhancement techniques were implemented to make the red channel more suitable for optic disc detection. Initially, the illumination of the red channel was normalized by subtracting its mean from all the channel pixels. Next, unsharp masking [[24]] and contrast-limited adaptive histogram equalization (CLAHE) [[25]] were performed in order to increase the overall contrast of the red channel hence enhancing the appearance of the optic disc with respect to the image background (Fig. 4c).

Graph: Fig. 4 a Cropped retinal color image from the HRF dataset. b Cropped image's red channel. c Preprocessed red channel. d Approximation subband of the preprocessed red channel. e Clean optic disc mask created by thresholding of the preprocessed red channel. f Detected optic disc identified on the green approximation subband

Wavelet Decomposition

Wavelet transform is a multiresolution technique that can separate the edge and illumination information of an image in its detail and approximation subbands, respectively. Wavelet detail subbands contain information conveying the sharpness of the retinal structures whereas the wavelet approximation subbands mainly include the luminance information of the structures [[26]]. In this work, we are interested in the illumination characteristics of the optic disc in order to determine whether the inspected retinal image is healthy or glaucomatous. Accordingly, retinal images were decomposed using Daubechies4 wavelet and only the approximation channel subbands were considered in all subsequent processing. Specifically, the second and fourth wavelet subbands were considered for the GlaucomaDB and cropped HRF images, respectively, in order to account for the size difference between the two datasets [[27]]. Accordingly, the resolution of the final processed images for both datasets was ~ 55 × 60 pixels.

Optic Disc Detection

Initially, image thresholding of the preprocessed red channel's approximation subband was performed to generate a binary image including the highest intensity pixels within the retinal image. The threshold was chosen to be the nth quantile of the approximation subband where n is dependent on image size, taken as 80 and 90 for the GlaucomaDB and HRF datasets, respectively. Next, the binary image was cleaned by removing regions whose area was less than 6% of the total image size representing high-intensity pixels within the background of the retinal image that are not part of the optic disc. The cleaned binary image hence only includes the optic disc mask (Fig. 4e). Finally, the BoundingBox function in MATLAB [[28]] was used to identify the center, radius, and rectangular borders of the optic disc from the cleaned binary image (Fig. 4f). The rectangular borders of the detected optic disc were then employed to crop the optic disc from both the green and blue approximation subbands to be used for feature extraction (Fig. 5). In this work, the approximation subbands were normalized prior to feature computation in order to account for the luminance variations within different retinal images [[29]].

Graph: Fig. 5 Final cropped optic disc region in the a green and b blue approximation subbands

Features Extraction

A healthy optic disc is typically orange to pink in appearance becoming paler in color for glaucomatous retinas whereas the optic cup, located in the center of the optic disc, is relatively brighter and more yellowish [[12]].

Generally, glaucomatous images are characterized by enlarged cup size with respect to the optic disc. Figure 6 shows examples of normal and glaucomatous images demonstrating the difference in size and color between healthy and abnormal optic discs.

Graph: Fig. 6 Examples of a healthy and b glaucomatous optic discs from the HRF dataset

In this work, a combination of wavelet-based textural and statistical features was computed from the green and blue normalized approximation subbands of the detected optic disc region (Fig. 5) in order to thoroughly characterize the optic disc for glaucoma classification. Feature selection was then used to remove the insignificant features in order to improve the overall classification performance.

Textural Features

Texture features are widely implemented in medical image analysis to give useful information about the characteristics of certain objects or regions of interest within an image. Gray-level co-occurrence matrices (GLCM) are among the most commonly used methods for texture feature computations. GLCM describes image texture by showing how often specific pixel pairs occur in an image, thus giving information about the pixel arrangement of color intensities in that image. In this work, preliminary ten textural features were implemented for specification of the optic disc characteristics: contrast, energy, entropy, dissimilarity, correlation, homogeneity, cluster shade, cluster prominence, difference variance, and information measure of correlation [[30]].

Contrast and difference variance were used to measure the image's contrast whereas the cluster shade and cluster prominence emulated human perception [[30]]. Furthermore, the information measure of correlation, energy, entropy, dissimilarity, homogeneity, and correlation measures were used to represent the image's homogeneity. All features were calculated from the gray-level co-occurrence matrices in four directions (0°, 45°, 90°, 135°), then averaged in order to efficiently describe the textural characteristics of the detected optic disc. The GLCM are specified as $p(i, j)$ where i and j indicate the row and column within a certain matrix. The GLCM textural features were calculated using the following equations:

$$\text{Contrast}=\sum i\sum j i-j2.pij$$

Graph

$$\text{Energy}=\sum i\sum j pij2$$

Graph

$$\text{Entropy}=-\sum i\sum j pij.\log pij$$

Graph

$$\text{Dissimilarity}=\sum i\sum j|i-j|.pij$$

Graph

$$\text{Correlation}=\sum i\sum j i-\mu xj-\mu ypij\sigma x\sigma y$$

Graph

$$\text{Homogeneity}=\sum i\sum j p(i,j)1+(i-j)2$$

Graph

$$\text{Cluster Shade}=\sum i\sum j i+j-\mu x-\mu y 3pij$$

Graph

$$\text{Cluster Prominence}=\sum i\sum j i+j-\mu x-\mu y 4pij$$

Graph

$$\text{Difference variance}=\text{variancepx}-y$$

Graph

$$\text{Info.MeasureofCorrelation}=(1-\exp(-2(HXY2-HXY))$$

Graph

where μ_x, μ_y, σ_x and σ_y are the means and standard deviations for the rows and columns of $p(i, j)$, whereas $p_x(i)$ and $p_y(j)$ are the i^{th} and j^{th} elements in the marginal x and y probability matrices of $p(i, j)$ and

$$px-yk=\sum i\sum jpij,\text{for}|i-j|=k$$

Graph

$$HXY=-\sum i\sum jpij\log pij$$

Graph

$$HXY2=-\sum i\sum jpxipyj\log pxipyj$$

Graph

Statistical Features

Glaucoma affects the overall illumination characteristics within the optic disc as a result of the associated optic cup enlargement [[32]]. Initially seven different statistical features were considered: mean, variance, skewness, kurtosis, energy, entropy, and super pixels. The mean and skewness described the overall intensity of the detected optic disc region whereas the variance and kurtosis measured its illumination discrepancy. The energy and wavelet Shannon entropy [[33]] evaluated the information content within the optic disc region. Super pixels refer to the highest intensity pixels within a specific region of interest, specifically the pixels whose value is larger than or equal to 0.9. The number of super pixels is thus associated with the increase in cup size characteristic of glaucoma.

Feature Selection

In order to study the relevance of the proposed wavelet textural and statistical features for glaucoma classification, three different analyses were performed: two-sample *t* test, Relief algorithm [[34]], and Information Gain [[35]]. The two-sample *t* test is a statistical test used to determine whether the average difference between two feature classes is significant or if it is mostly due to random chance. The Relief algorithm weights each of the different features according to its relevance to a specific class. Initially, all weights are set to zero and then weights are updated iteratively in accordance with their significance.

Information Gain is an entropy-based method that evaluates the discriminatory potential of features in different classes by measuring their information content.

Results

The proposed glaucoma classification algorithm was tested using two different retinal image datasets, GlaucomaDB and HRF. All features were computed using the MATLAB software (Mathworks, Inc., Natick, MA, USA). For feature selection, the two-sample *t* test was performed in MATLAB whereas Weka [[36]] implementations of the Relief and Information Gain algorithms were utilized.

The *k*NN classifier was chosen for classification as it is easy to tune and gives consistent results as well as being efficiently used for glaucoma classification in literature. In all experiments, the *k* parameter was varied over the range from 1 to 15 and best classification results were reported. All classifications were performed using fivefold cross-validation in Weka.

Reduced Feature Vector

All three feature selection methods were found to give highly consistent results for both the GlaucomaDB and the HRF datasets. Among the wavelet-based textural features, the correlation, information measure, and cluster prominence computed from the green approximation subband were generally found to be the most significant followed by the contrast, dissimilarity, difference variance, and cluster shade. As for the statistical features, the variance, entropy, and super pixels from both the green and blue approximation subbands were the most relevant for glaucoma detection. The rest of the features had negligible association with the glaucoma detection problem hence were removed from the final feature vector.

Classification Results

Performance analysis was made by calculating the sensitivity, specificity, accuracy, and area under the receiver operating characteristic curve (AUC). Sensitivity, specificity, and accuracy indicate the percentage of correctly classified images within the diseased class, the healthy class, and both classes, respectively, whereas the AUC shows how good a test can distinguish between the healthy and diseased classes. Tables 1 and 2 show the confusion matrices of the GlaucomaDB and HRF, respectively. Table 3 summarizes the performance metrics for the two datasets.

Confusion matrix of the GlaucomaDB

	Healthy	**Glaucoma**
Healthy	30	3
Glaucoma	4	29

Confusion matrix of the HRF dataset

	Healthy	**Glaucoma**
Healthy	15	0
Glaucoma	1	14

Summary of performance metrics for the GlaucomaDB and the HRF datasets

	Sensitivity (%)	**Specificity (%)**	**Accuracy (%)**	**AUC (%)**
GlaucomaDB	87.9	90.9	89.4	92.2
HRF	93.3	100	96.7	94.7

For the GlaucomaDB, the proposed glaucoma classification algorithm was able to correctly detect 29 out of 33 glaucoma cases and 30 out of 33 normal cases hence achieving a sensitivity of 87.9%, a specificity of 90.9%, and an overall accuracy of 89.4%. More superior results were achieved when using the HRF dataset where all

healthy images as well as all but one glaucomatous images were accurately classified. A sensitivity of 93.3%, specificity of 100%, and overall accuracy of 96.7% were hence achieved. Moreover, AUCs of 92.2% and 94.7% were attained for the GlaucomaDB and the HRF datasets, respectively.

Timing Analysis

The proposed glaucoma classification algorithm is intended for real-time systems; consequently, rapid processing times are very important. For the high-resolution HRF dataset in which images are of size 3504 × 2336 pixels, image cropping, preprocessing, wavelet decomposition and feature extraction all required less than 3 s per image. On the other hand, for the GlaucomaDB having a resolution of ~200 × 200 pixels, complete analysis and feature computation required less than 0.25 s per image.

Discussion

In this work, wavelet textural and statistical features computed from retinal images' approximation subbands were shown to be suitable for glaucoma detection.

Wavelet features were previously shown to be computationally inexpensive when used for retinal image processing [[37]] making them attractive for implementation within real-time systems. Wavelet decomposition involves subsequent image down sampling; hence, image resolution is halved with every wavelet decomposition resulting in much faster feature computation times for the lower wavelet levels. A strong merit of the proposed glaucoma detection algorithm is thus its fast processing speed resulting from adopting lower wavelet levels for feature computations. In this work, high-resolution retinal images of size 3504 × 2336 pixels required less than 3 s for preprocessing, optic disc detection, and feature extraction. Previous glaucoma classification methods have reported significantly larger run times. For example in [[16]], approximately 30 s were required for optic disc segmentation, blood vessel inpainting, and feature extraction for images of resolution 1696 × 2544 pixels which is approximately 10 times slower than the proposed algorithm, and for smaller images.

Glaucoma detection algorithms reported in literature commonly use private datasets for their evaluation. Moreover, a limited number of glaucoma classified datasets are publically available. Consequently, a comparison of different glaucoma detection algorithms is somewhat challenging [[38]]. Nevertheless, most related works report an accuracy that is usually within the range from 85 to 95% [[12]]. In this work, accuracies of 89.4% and 96.7% were achieved for the balanced subsets of the GlaucomaDB and HRF datasets, respectively, using fivefold cross-validated *k*NN classifier. In [[18]], a hybrid glaucoma detection algorithm resulted in accuracies of 90.8% and 91.1% for the complete GlaucomaDB and HRF datasets, respectively. Another approach in [[19]] reported accuracies of 80% and 86.7% when using the CDR and hybrid features, respectively, using the balanced HRF dataset. The proposed wavelet-based feature detection algorithm is thus shown to give superior results specifically for the high-resolution HRF dataset.

Wavelet features have the advantage of capturing both the spatial and frequency information of an image making them effective for glaucoma classification [[16], [39]]. Wavelet-based glaucoma detection algorithms in literature usually relied on only the detail subbands within the first wavelet level for feature computation. In this work, the wavelet textural and statistical features were computed from the retinal images' approximation subbands under the intuition that approximation subbands convey more information related to the optic disc's luminance and texture [[26]]. Furthermore, multilevel wavelet decomposition was used to reduce information related to the blood vessels, which are of minimal relevance to glaucoma detection.

In literature, structural methods are commonly employed for automatic glaucoma detection in retinal images. However, generic methods have been shown to give reliable results for glaucoma detection, at times

exceeding the performance of structural methods [[20]]. In this work, wavelet-based textural and statistical features were used for glaucoma diagnosis. Feature selection showed that wavelet statistical features were more significant for glaucoma classification than the wavelet textural features. Moreover, statistical features calculated from both the green and blue channels were found to be closely relevant. Overall, the five most significant features in both datasets were found to be the variance, super pixels along with the GLCM correlation, information measure, and cluster prominence. Consequently, feature ranking showed that although wavelet features computed from the approximation subbands have the potential to efficiently classify between healthy and glaucomatous retinal images, not all features were equally relevant. In order to enhance the performance of the glaucoma detection algorithm, future work involves exploring the significance of more wavelet-based textural and statistical features.

Conclusions

Early detection and treatment of glaucoma with the aid of automatic screening systems can limit the increasing number of irreversible blindness occurring in progressive stages of the disease. In this work, a wavelet-based generic glaucoma detection algorithm is implemented that is intended for automatic screening systems. A combination of statistical and textural wavelet features was computed from the green and blue approximation subbands of the optic disc segmented region. An accuracy of 96.7% was achieved by the proposed method using the *k*NN classifier. Several statistical analyses performed showed the relevance of wavelet-based statistical and textural features calculated from the approximation subbands for glaucoma classification. The proposed algorithm also has the advantage of being computationally inexpensive requiring less than 3 s for processing and analysis of high-resolution retinal images.

Compliance with Ethical Standards

Conflict of Interest

The author declares that there is no conflict of interest.

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References

1 World Health Organization: Blindness and vision impairment prevention. Available at: http://www.who.int/blindness/causes/priority/en/. Accessed May 2018.

2 Bright Focus Foundation: Glaucoma: facts & figures. Available at: https://www.brightfocus.org/glaucoma/article/glaucoma-facts-figures. Accessed May 2018.

3 Kumar BN, Chauhan RP, Dahiya N. Detection of glaucoma using image processing techniques: A critique. Semin Ophthalmol. 2018; 33; 2: 275-228

4 Almazroa A, Burman R, Raahemifar K, Lakshminarayanan V. Optic disc and optic cup segmentation methodologies for glaucoma image detection: A survey. Journal of ophthalmology. 2015; 2015: 1-28

5 Kavya N, Padmaja KV: Glaucoma detection using texture features extraction. Proceedings of the 51st IEEE Asilomar Conference on Signals, Systems, and Computers, 1471–1475, 2017.

6 Dey N et al.: Optical cup to disc ratio measurement for glaucoma diagnosis using harris corner. In: 3rd IEEE International Conference on Computing Communication & Networking Technologies (ICCCNT), pp. 1–5, 2012.

7 Dutta MK et al.: Glaucoma detection by segmenting the super pixels from fundus colour retinal images. In: International IEEE Conference on Medical Imaging, m-Health and Emerging Communication Systems (MedCom), pp. 86–90, 2014.

8 Nath MK, Dandapat S. Differential entropy in wavelet subband for assessment of glaucoma. Int J Imaging Syst Technol. 2012; 22; 3: 161-165

9 Nawaldgi S, Lalitha YS and Reddy M: A novel adaptive threshold and ISNT rule based automatic glaucoma detection from color fundus images. In: Satapathy S, Bhateja V, Raju K, Janakiramaiah B Eds. Data Engineering and Intelligent Computing. Advances in Intelligent Systems and Computing, vol 542. Singapore: Springer, 2018.

Spaeth GL. Systems for staging the amount of optic nerve damage in glaucoma: A critical review and new material. Surv Ophthalmol. 2006; 51; 4: 293-315

Bock R, Meier J, Nyúl LG, Hornegger J, Michelson G. Glaucoma risk index: Automated glaucoma detection from color fundus images. Med Image Anal. 2010; 14; 3: 471-481

Thakur N, Juneja M. Survey on segmentation and classification approaches of optic cup and optic disc for diagnosis of glaucoma. Biomed Signal Process Control. 2018; 42: 162-189

Youssif AA, Ghalwash AZ, Ghoneim AA. Optic disc detection from normalized digital fundus images by means of a vessels' direction matched filter. IEEE Trans Med Imaging. 2008; 27; 1: 11-18

Bechar ME. Semi-supervised superpixel classification for medical images segmentation: Application to detection of glaucoma disease. Multidim Syst Sign Process. 2018; 29; 3: 979-998

Dua S, Acharya UR, Chowriappa P, Sree SV. Wavelet-based energy features for glaucomatous image classification. IEEE Trans Inf Technol Biomed. 2012; 16; 1: 80-87

Singh A, Dutta MK, ParthaSarathi M, Uher V, Burget R. Image processing based automatic diagnosis of glaucoma using wavelet features of segmented optic disc from fundus image. Comput Methods Prog Biomed. 2016; 124: 108-120

Dey A, Dey KN: Automated glaucoma detection from fundus images of eye using statistical feature extraction methods and support vector machine classification. In: Bhattacharyya S, Sen S, Dutta M, Biswas P, Chattopadhyay H Eds. Industry Interactive Innovations in Science, Engineering and Technology. Lecture Notes in Networks and Systems, vol 11. Singapore: Springer, 2018.

Akram MU, Tariq A, Khalid S, Javed MY, Abbas S, Yasin UU. Glaucoma detection using novel optic disc localization, hybrid feature set and classification techniques. Australas Phys Eng Sci Med. 2015; 38; 4: 643-655

Vijapur NA, Kunte RSR. Sensitized glaucoma detection using a unique template based correlation filter and undecimated isotropic wavelet transform. J Med Biol Eng. 2017; 37; 3: 365-373

Khalil T, Usman Akram M, Khalid S, Jameel A. Improved automated detection of glaucoma from fundus image using hybrid structural and textural features. IET Image Process. 2017; 11; 9: 693-700

Mallat SG. A theory for multiresolution signal decomposition: The wavelet representation. IEEE Trans Pattern Anal Mach Intell. 1989; 11; 7: 674-693

Budai A, Bock R, Maier A, Hornegger J, Michelson G. Robust Vessel Segmentation in Fundus Images. Int J Biomed Imaging. 2013; 2013: 1-11

HRF Dataset website link: https://www..cs.fau.de/research/data/fundus-images/ Accessed March 2018.

Jain AK: Fundamentals of digital image processing. Upper Saddle River: Prentice-Hall, Inc., 1989.

Zuiderveld K: Contrast limited adaptive histogram equalization. Chapter VIII.5, Graphics Gems IV. Heckbert PS Eds. Cambridge: Academic Press, 1994, pp 474–485.

Abdel-Hamid L, el-Rafei A, el-Ramly S, Michelson G, Hornegger J. Retinal image quality assessment based on image clarity and content. J Biomed Opt. 2016; 21; 9

Abdel-Hamid L. Performance dependency of retinal image quality assessment algorithms on image resolution: Analyses and solutions. SIViP. 2017; 12; 1: 9-16

Maths Work: Regionprops. Available at http://www.math-works.com/help/images/ref/regionprops.html. Accessed May 2018.

Abdel-Hamid L, el-Rafei A, Michelson G. No-reference quality index for color retinal images. Computers in biology and medicine. 2017; 90: 68-75

Haralick RM, Shanmugam K. Textural features for image classification. IEEE Trans Syst Man Cybern. 1973; SMC-3; 6: 610-621

Conners RW. Segmentation of a high-resolution urban scene using texture operators. Comput Vision Graph Image Processing. 1984; 25: 273-310

*Abdel-Hamid L: Glaucoma detection using statistical features: comparative study in RGB, HSV and CIEL*a*b* color model. Proceeding of the 10th SPIE International Conference on Graphic and Image Processing (ICGIP2018), In Press.*

Coifman RR, Wickerhauser MV. Entropy-based algorithms for best basis selection. IEEE Trans. Inf. Theory. 1992; 38; 2: 713-718

Kira Kenji, Rendell Larry A.. A Practical Approach to Feature Selection. Machine Learning Proceedings 1992. 1992: 249-256

Quinlan JR: C4.5: Programs for machine learning. San Francisco: Morgan Kaufmann Publishers, 1993.

Hall M, Frank E, Holmes G, Pfahringer B, Reutemann P, Witten IH. The WEKA data mining software: An update. ACM SIGKDD Explor. Newsl.. 2009; 11; 1: 10-18

Hamid L, El-Rafei A, El-Ramly S, Michelson G, Hornegger J. No-reference wavelet based Retinal Image Quality Assessment. Computational Vision and Medical Image Processing V. 2015: 123-129

Salam AA et al.: Benchmark data set for glaucoma detection with annotated cup to disc ratio. Proceedings of IEEE International Conference Signals and Systems (ICSigSys), pp. 227–233, 2017.

Kausu TR, Gopi VP, Wahid KA, Doma W, Niwas SI. Combination of clinical and multiresolution features for glaucoma detection and its classification using fundus images. Bioprocess Biosyst Eng. 2018; 38; 2: 329-341

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Source: Journal of Digital Imaging
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Record: 1

Title: Risk of Glaucoma in Patients Receiving Hemodialysis and Peritoneal Dialysis: A Nationwide Population-Based Cohort Study.

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Source: International journal of environmental research and public health [Int J Environ Res Public Health] 2020 Sep 17; Vol. 17 (18). *Date of Electronic Publication:* 2020 Sep 17.

Publication Type: Journal Article

Language: English

Journal Info: *Publisher:* MDPI *Country of Publication:* Switzerland *NLM ID:* 101238455 *Publication Model:* Electronic *Cited Medium:* Internet *ISSN:* 1660-4601 (Electronic) *Linking ISSN:* 16604601 *NLM ISO Abbreviation:* Int J Environ Res Public Health *Subsets:* MEDLINE

Imprint Name(s): *Original Publication*: Basel : MDPI, c2004-

MeSH Terms: Glaucoma*/epidemiology
Peritoneal Dialysis*/adverse effects
Renal Dialysis*/adverse effects
Adult ; Aged ; Aged, 80 and over ; Case-Control Studies ; Cohort Studies ; Female ; Humans ; Incidence ; Male ; Middle Aged ; Population ; Retrospective Studies ; Risk Factors ; Taiwan/epidemiology ; Young Adult

Abstract: This paper investigated the incidence and risk of newly diagnosed glaucoma after the initiation of maintenance dialysis in Taiwan. A case-control study was conducted using the National Health Insurance Research Database (NHIRD) in Taiwan. There were 3949 patients with dialysis in the study group and 78,980 non-dialysis subjects matched by age and sex in the comparison group. The incidence of newly diagnosed glaucoma after the initiation of maintenance dialysis was

analyzed based on the diagnostic code for glaucoma. Patients with dialysis had a higher risk of glaucoma (adjusted hazard ratio (aHR): 1.270; 95% confidence interval (CI): 1.035-1.560) than patients without dialysis. The incidence rate of glaucoma was 8.18 per 10,000 person months in the dialysis group, which was higher than that in the non-dialysis group (5.01 per 10,000 person months). Patients with dialysis exhibited a significantly higher risk of angle-closure glaucoma (ACG) (aHR: 1.550; 95% CI: 1.074-2.239). In contrast, there was no significant risk of developing open-angle glaucoma or normal-tension glaucoma in dialysis patients. Our data suggest that dialysis patients are more susceptible to ACG. Regular ophthalmic examinations may be useful in patients with dialysis to identify high-risk individuals with glaucoma, and preventive measures can be applied to avoid permanent vision loss as soon as intraocular pressure (IOP) elevation is identified.

References:

Lancet. 2015 May 16;385(9981):1975-82. (PMID: 25777665)
Ren Fail. 1989;11(2-3):117-24. (PMID: 2623197)
Trans Am Soc Artif Intern Organs. 1962;8:300-8. (PMID: 13913503)
JAMA Ophthalmol. 2013 Dec;131(12):1525-31. (PMID: 24232671)
Arq Bras Oftalmol. 2017 Jun;80(3):176-180. (PMID: 28832743)
Curr Eye Res. 1998 Apr;17(4):339-47. (PMID: 9561825)
Mayo Clin Proc. 1969 Jun;44(6):406-29. (PMID: 4893701)
J Ophthalmol. 2019 Aug 14;2019:2406547. (PMID: 31485341)
Can J Ophthalmol. 1966 Oct;1(4):301-7. (PMID: 5977442)
Case Rep Ophthalmol. 2013 Apr 13;4(1):69-73. (PMID: 23687499)
Br J Ophthalmol. 2007 Aug;91(8):1091-3. (PMID: 17638826)
Arch Ophthalmol. 1964 Nov;72:626-31. (PMID: 14196745)
Nephron. 2002 Feb;90(2):181-7. (PMID: 11818703)
Nephrology (Carlton). 2018 Oct;23 Suppl 4:112-115. (PMID: 30298659)
Hemodial Int. 2019 Jul;23(3):E72-E77. (PMID: 30785657)
Am J Kidney Dis. 2000 Jul;36(1):197-8. (PMID: 10873891)
N Engl J Med. 1980 Sep 18;303(12):702. (PMID: 6772953)
Adv Chronic Kidney Dis. 2013 Jan;20(1):39-44. (PMID: 23265595)
Adv Clin Exp Med. 2018 Jan;27(1):105-110. (PMID: 29521050)
J Glob Health. 2017 Dec;7(2):020705. (PMID: 29302324)
Arch Ophthalmol. 2000 Aug;118(8):1105-11. (PMID: 10922206)
Clin Ophthalmol. 2013;7:1635-9. (PMID: 23976841)
Am J Ophthalmol. 2000 Apr;129(4):534-6. (PMID: 10764868)
Br J Ophthalmol. 2019 Mar;103(3):355-360. (PMID: 29777045)
Diabetes Care. 2012 Nov;35(11):2286-92. (PMID: 22912425)
Ren Fail. 1990;12(2):109-12. (PMID: 2236725)
Ann Ophthalmol. 1991 Jan;23(1):31-4. (PMID: 2012372)
Semin Dial. 2005 May-Jun;18(3):252-7. (PMID: 15934974)
Am J Kidney Dis. 2019 Mar;73(3 Suppl 1):A7-A8. (PMID: 30798791)
Am J Ophthalmol. 2006 Aug;142(2):337-9. (PMID: 16876525)
BMC Ophthalmol. 2018 Aug 23;18(1):208. (PMID: 30139333)
Eye Vis (Lond). 2020 Mar 10;7:15. (PMID: 32175441)

Osteoporos Int. 2013 Jun;24(6):1835-41. (PMID: 23052942)
Clin Ophthalmol. 2015 Jan 09;9:109-14. (PMID: 25657575)
Br J Ophthalmol. 1998 Nov;82(11):1342. (PMID: 9924350)
Eye (Lond). 2005 Dec;19(12):1249-56. (PMID: 15543171)
J Diabetes Complications. 2014 Sep-Oct;28(5):612-6. (PMID: 25037987)
BMC Ophthalmol. 2016 Mar 05;16:23. (PMID: 26944556)
Br J Ophthalmol. 1998 Jul;82(7):751-3. (PMID: 9924365)
Osteoporos Int. 2004 Dec;15(12):998-1002. (PMID: 15156304)

Contributed Indexing: *Keywords:* end-stage renal disease*; hemodialysis*; intraocular pressure*

Entry Date(s): *Date Created:* 20200922 *Date Completed:* 20201214 *Latest Revision:* 20201214

Update Code: 20210210

PubMed Central ID: PMC7559152

DOI: 10.3390/ijerph17186774

PMID: 32957502

Database: MEDLINE with Full Text

Risk of Glaucoma in Patients Receiving Hemodialysis and Peritoneal Dialysis: A Nationwide Population-Based Cohort Study

This paper investigated the incidence and risk of newly diagnosed glaucoma after the initiation of maintenance dialysis in Taiwan. A case–control study was conducted using the National Health Insurance Research Database (NHIRD) in Taiwan. There were 3949 patients with dialysis in the study group and 78,980 non-dialysis subjects matched by age and sex in the comparison group. The incidence of newly diagnosed glaucoma after the initiation of maintenance dialysis was analyzed based on the diagnostic code for glaucoma. Patients with dialysis had a higher risk of glaucoma (adjusted hazard ratio (aHR): 1.270; 95% confidence interval (CI): 1.035–1.560) than patients without dialysis. The incidence rate of glaucoma was 8.18 per 10,000 person months in the dialysis group, which was higher than that in the non-dialysis group (5.01 per 10,000 person months). Patients with dialysis exhibited a significantly higher risk of angle-closure glaucoma (ACG) (aHR: 1.550; 95% CI: 1.074–2.239). In contrast, there was no significant risk of developing open-angle glaucoma or normal-tension glaucoma in dialysis patients. Our data suggest that dialysis patients are more susceptible to ACG. Regular ophthalmic examinations may be useful in patients with dialysis to identify high-risk individuals with glaucoma, and preventive measures can be applied to avoid permanent vision loss as soon as intraocular pressure (IOP) elevation is identified.

Keywords: end-stage renal disease; hemodialysis; intraocular pressure

1. Introduction

End-stage renal disease (ESRD) is a chronic condition in which patients rely on either maintenance dialysis or a renal transplant, and it is also associated with a significant socioeconomic burden. Taiwan has been reported to have the highest incidence (493 per million) and prevalence (3392 per million) of treated ESRD in the world [[1]]; 87.5% of these patients receive hemodialysis (HD), while 8.5% receive peritoneal dialysis (PD) [[2]]. In 2010, it was estimated that 2.6 million individuals worldwide received renal replacement therapy, and the number is estimated to be more than 5.4 million by 2030 [[4]].

Several studies have discussed intraocular pressure (IOP) changes during HD since the first demonstration of an increase in IOP during dialysis in 1964 [[5]]. Some studies have revealed that IOP may be elevated [[6], [8], [10]], some have shown that IOP does not change [[11]], and some have demonstrated that IOP decreases [[13], [15], [17]]. However, these previous results were either limited by small patient numbers, a short follow-up period, or lack of a comparative group. Moreover, the relationship between IOP changes and the subsequent development of glaucoma is also not well studied. Doshiro et al. [[14]] showed that IOP decreased during HD possibly due to plasma colloid osmotic pressure increase; however, patients with HD for more than 12 years had a tendency for increased IOP.

It has become an accepted concept that eyes with impaired aqueous outflow facilities, such as shallow anterior chambers of angle closure, may have a significant increase in IOP during HD [[12]]. Because of the high prevalence of occludable angles in Taiwanese people [[18]], it is of clinical importance to investigate the development of glaucoma after the initiation of maintenance dialysis in Taiwan. Utilizing a nationwide population-based dataset in Taiwan, namely, the National Health Insurance Research Database (NHIRD), we designed a cohort study to investigate the incidence and risk of newly diagnosed glaucoma after the initiation of maintenance dialysis in Taiwan.

2. Materials and Methods

2.1. Data Source

This retrospective population-based cohort study was approved by the National Health Insurance Administration and the Institutional Review Board of Chung Shan Medical University (Registration Number: CSMUH CS2-15061). The claim data originated from the National Health Insurance Research Database (NHIRD) in Taiwan. National Health Insurance (NHI) in Taiwan is a nationwide healthcare program that was launched in 1995. NHI covers 99.82% of Taiwan residents, with a total of 23.948 million by the end of 2018 [[19]]. The NHIRD provides individuals' encrypted information—date of birth, sex, place of residence, inpatient and outpatient services, details of medications, intervention procedures, date of admission and discharge, and diagnosis records (based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)). We utilized the Longitudinal Health Insurance Database (LHID), a dataset released by the NHIRD, which contains all of the original claim data (from 1997 to 2013) of 1 million individuals who were randomly sampled from the NHIRD. Several high-quality studies have shown the accuracy of the NHIRD [[20], [22]].

2.2. Patient Selection

Our study cohort included individuals newly diagnosed with ESRD who had received HD or PD more than twice, and whose treatment period of HD or PD was more than three months during the study period from January 1997 to December 2013. The index date was defined as 90 days after the first dialysis. To evaluate the correlation between dialysis and new-onset glaucoma, the following exclusion criteria were defined: (1) Diagnosis of glaucoma before the index date; (2) legal blindness at any time; (3) an index date earlier than 2000; (4) age younger than 20 or older than 100; (5) deceased before the index date; (6) diagnosis of an ocular tumor before the index date; (7) absence of an eyeball or anophthalmos before the index date; (8) cataract surgery before the index date. After the exclusions, 3949 patients with dialysis remained in the study cohort. This study design compared the difference in the risk of glaucoma between dialysis and non-dialysis cohorts. Each dialysis patient was assigned to 20 controls matched by age and sex, and a total of 78,980 comparison cases were included in this study (Figure 1).

2.3. Main Outcome Measurement

The primary outcome was defined as newly diagnosed glaucoma after the initiation of maintenance dialysis based on the diagnostic code for glaucoma (ICD-9 codes: 365.1x, 365.2x, 365.7x, and 365.9; ICD-10 codes: H40.1x, H40.2x, H40.89, and H40.9) after the index date. The study period was from 1 January 2000 to 31 December 2013. Subgroups of glaucoma, including open-angle glaucoma (OAG) (ICD-9 code: 365.10, 365.11, 365.13, and 365.15; ICD-10: H40.10x, H40.11x, H40.13x, and H40.15x), angle-closure glaucoma (ACG) (ICD-9: 365.2x; ICD-10: H40.2x), and normal-tension glaucoma (NTG) (ICD-9: 365.12; ICD-10: H40.12x), were analyzed to identify their relationships with dialysis. To ensure accuracy, only patients with diagnostic codes of glaucoma made by ophthalmologists (department code: 10), ≥2 clinic visits, and prescribed with glaucoma medications (categorized using the Anatomical Therapeutic Chemical (ATC) drug code, including sympathomimetics in glaucoma therapy (S01EA), parasympathomimetics (S01EB), carbonic anhydrase inhibitors (S01EC), beta blocking agents (S01ED), and prostaglandin analogues (S01EE)) were included in this study. Moreover, glaucoma-related codes that indicate identifiable factors (e.g., pigment dispersion in pigmentary glaucoma, pseudoexfoliative material of pseudoexfoliation syndrome, and steroid-induced glaucoma), suspected glaucoma, ocular hypertension, steroid responders, anatomical narrow angle, and pre-glaucoma were excluded from the current study to avoid overestimation and confusion of the diagnosis.

2.4. Identification of Comorbidities

We identified the comorbidities of each participant to evaluate their health status and to investigate the correlation between glaucoma and comorbidities. Comorbidities included hypertension, diabetes mellitus, hyperlipidemia, ischemic heart diseases, congestive heart failure, cerebrovascular disease, dementia, liver disease, hemiplegia or paraplegia, uveitis, retinal vessel occlusion, non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy. Participants were confirmed to have these comorbidities if the relevant ICD codes were diagnosed once or more at the inpatient service or twice or more at the outpatient service with a minimal interval of more than 30 days within one year before enrollment.

2.5. Statistical Analysis

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). After 1:20 matching, the absolute standardized difference (ASD) was used to evaluate the balance between the study and control groups. Student's *t*-tests were used to compare continuous variables, while chi-square tests or Fisher's exact tests were used to compare the differences between categorical variables. Calculations of the incidence rate and the corresponding 95% confidence intervals were conducted using the Poisson assumption. Cumulative incidence rates were calculated according to analysis of the cumulative incidence of competing risks. Multiple Cox proportional hazards regressions were used to generate an adjusted hazard ratio (aHR) by integrating individuals' demographic information and comorbidities. The aHRs of the dialysis, demographics, and comorbidities were analyzed. Glaucoma was divided into three subgroups: OAG, NTG, and ACG. The incidence rates of each subgroup were computed. A p-value < 0.05 was regarded as statistically significant.

3. Results

3.1. Baseline Characteristics of the Study Cohort

A total of 3949 subjects under maintenance dialysis were included in the study group, and another 78,980 non-dialysis subjects served as the control group. The flow chart of subject selection is shown in Figure 1. Table 1 summarizes the differences in the baseline characteristics between the dialysis and non-dialysis groups. The number of people diagnosed with hypertension, diabetes mellitus, ischemic heart diseases, hyperlipidemia, congestive heart failure, cerebrovascular disease, dementia, non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy was significantly higher in the dialysis group than in the non-dialysis group. The frequency of visits to ophthalmologists of the two groups is shown below.

3.2. Comparison of the Incidence Rates and Cumulative Risk of Glaucoma between Dialysis and N...

The incidence rates for new glaucoma cases are presented in Table 2. The incidence rate of glaucoma per 10,000 person months was 8.18 (95% CI: 7.01–9.54) in the dialysis group, which was significantly higher than that in the non-dialysis group (5.01; 95% CI: 4.83–5.2). The cumulative incidence of glaucoma in the dialysis group after approximately 120 months of follow-up was significantly greater than that in the non-dialysis group ($p < 0.0001$, log-rank test; Figure 2), and the crude relative risk was 1.618 (95% CI: 1.38–1.897).

3.3. Adjusted Hazard Ratios of Glaucoma Related to Dialysis Based on Various Covariates

The risk of glaucoma development based on the multivariate Cox proportional hazards models is presented in Table 3. After adjustment for potential confounders, the dialysis group was associated with a significantly higher risk of glaucoma (adjusted HR: 1.270; 95% CI: 1.035–1.560). In addition, older age (older than 60 years old), hypertension, diabetes mellitus, ischemic heart disease, hyperlipidemia, uveitis, retinal vessel occlusion, and proliferative diabetic retinopathy were also associated with an increased risk of glaucoma.

3.4. Incidence Rate and Adjusted Hazard Ratios of Different Types of Glaucoma and Trabeculect...

After stratifying by different types of glaucoma, subevent analysis demonstrated that the dialysis group had a significantly higher incidence rate of ACG than the control group—2.28 (95% CI: 1.71–3.04) for the dialysis group, and 1.52 (95% CI: 1.43–1.63) for the non-dialysis group (Table 4). After adjusting for potential confounders, dialysis patients were associated with a significantly higher risk of ACG (adjusted HR: 1.550; 95% CI: 1.074–2.239). Furthermore, dialysis was also associated with trabeculectomy, which is a surgical treatment for severe glaucoma (adjusted HR: 3.666; 95% CI: 1.366–9.840). The incidence rate and adjusted HR of OAG and NTG showed no significant differences between the dialysis and non-dialysis groups (Table 4).

4. Discussion

To the best of our knowledge, this is the first study to investigate the role of dialysis in the cumulative risk of glaucoma using population-based claims big-data analysis. The large sample size of Taiwan's NHIRD allowed for a statistically powerful assessment of rare events. In this population-based follow-up study of 3949 patients first receiving HD or PD and 78,980 control cases, the incidence rate of new-onset glaucoma per 10,000 person months was 8.18 (95% CI: 7.01–9.54) in the dialysis group, with a relative risk of 1.618 (95% CI: 1.38–1.897) (Table 2). In subevent analysis, the adjusted hazard ratios for ACG and trabeculectomy for subjects who were undergoing dialysis were 1.550 (95% CI: 1.074–2.239) and 3.666 (95% CI: 1.366–9.840), respectively, compared with the control cases (Table 4). On the other hand, OAG and NTG showed no difference between the dialysis and control groups.

Ocular abnormalities are frequently associated with patients on chronic dialysis, including IOP fluctuation, corneal calcification, retinal hemorrhage, retinal toxicity related to desferrioxamine, anterior ischemic neuropathy, and uremic optic neuropathy [[24]]. Among them, the relationship between IOP changes and dialysis has been reported with various results [[6], [8], [10], [12], [14], [16], [25]]. Moreover, there has long been a debate regarding whether transient IOP changes during HD would result in the progression of glaucoma [[26]]. The present study utilized a population-based claims database, applied multivariate regression methods with adjustment of confounders, and proved that patients receiving dialysis were at a higher risk of developing glaucoma (Table 2 and Table 3).

Our study confirmed the hypothesis that HD has a greater impact on eyes with impaired aqueous outflow facilities, such as a shallow anterior chamber of the ACG. The mechanism of IOP changes during dialysis is still unknown, but the proposed mechanism is as follows: During HD, the dialysis procedure removes osmotically active substances by diffusion, which leads to a decrease in serum osmolality and loss of body

fluids. Rapid reduction in plasma osmolality results in disequilibrium between the intraocular fluid and plasma because of the rapid decrease in plasma osmolality and the unchanged ocular osmolality during HD [[6]]. The relatively high urea concentration in the intraocular fluid compartment during HD [[27]] might cause fluid shifting from blood plasma to the anterior chamber [[12], [26], [28], [30]]. For eyes with normal outflow facilities, water movement on this scale might not influence the IOP. In contrast, for eyes with impaired aqueous outflow facilities, the increment of IOP is more prominent [[12], [31]]. The decrease in anterior chamber depth during HD further compromises outflow facilities [[32], [34]]. Therefore, detailed ophthalmic examination should be conducted among patients receiving dialysis to screen high-risk individuals who have the potential to develop ACG.

Because IOP elevation usually occurs during dialysis, and patients receiving maintenance dialysis have a greater risk of glaucoma, preventive measures during dialysis should be taken with high-risk patients to avoid irreversible vision loss. Conventional HD protocols consist of three sessions per week, and each session lasts approximately three to four hours. For those individuals susceptible to experiencing IOP elevation during HD, chronic elevation in IOP might result in optic nerve damage. Some approaches have been reported to hinder a symptomatic rise in IOP during dialysis, including intravenous mannitol [[35]], hypertonic sodium dialysis or use of hyperosmotic agents [[12]], slower urea removal [[36]], modified dialysis parameters with colloid infusion [[30]], and intravenous glucose administration [[37]].

Acute primary angle closure (APAC) is a medical emergency and remains a therapeutic challenge, particularly in ESRD patients. Conventional management of APAC includes medical therapy and laser periphery iridotomy (LPI). However, LPI is extremely difficult to perform due to severe corneal edema during APAC. Patients with APAC frequently present with ocular pain, nausea, and vomiting. Oral medications (including acetazolamide, glycerol, and isosorbide) are often contraindicated in ESRD patients and are unable to be administered when patients are experiencing nausea and vomiting. The iris sphincter may be unresponsive to topical miotic agents at high IOP due to pressure-induced ischemic paralysis of the iris. Rapid IOP reduction is important for relieving ocular symptoms and clearing the cornea for a more definitive procedure, such as LPI or cataract extraction. Intravenous hyperosmotic agents (e.g., mannitol) are the first drugs of choice for APAC. Nevertheless, in ESRD patients, intravenous administration of mannitol should be followed by dialysis to avoid fluid overload [[38]]. To avoid this challenging conundrum, prophylactic LPI or cataract extraction may be considered a preventive measure in patients with ESRD who are at risk of APAC. Trabeculectomy and Ahmed valve implantation [[39]] are surgical options for medically uncontrolled IOP. The Xen Gel Stent, an ab interno minimally invasive glaucoma surgery, offers an alternative option for mild to moderate OAG with the advantage of lower ocular surface inflammation compared to topical therapy and trabeculectomy [[40]].

There are still some limitations to our study. First, identification of the demographic information and associated comorbidities of these patients depended on the accuracy of the ICD-9-CM codes, so coding errors might exist, and the disease codes might be less accurate. Second, the observational cohort study design may not have elucidated causal inference, and the findings of this study should be interpreted with discretion. Third, the prevalence of open-angle glaucoma and normal tension glaucoma is underestimated in the Asian population [[41]] and most of the insurants of Taiwan are Chinese; therefore, it is unclear whether these results can be generalized to other racial/ethnic groups. Fourth, the diagnosis of glaucoma relies only on diagnostic codes made by ophthalmologists without supporting evidence, such as optic disc and visual field analysis, so the results should be interpreted with caution. Fifth, the prevalence of glaucoma in the non-dialysis group may have been underestimated due to limited clinic visits compared to the dialysis group. Sixth, the inclusion and exclusion criteria in our study may have excluded some cases of mild glaucoma under observation without

treatment, thus reducing the number of participants; however, this could have enhanced the accuracy of the diagnosis of glaucoma and precluded cases of suspected glaucoma.

5. Conclusions

The presented results support the hypothesis that patients with dialysis are at an increased risk of glaucoma compared with non-dialysis individuals. Furthermore, our data suggest that dialysis patients are more susceptible to ACG, which is possibly due to decreased ACD and, subsequently, increased IOP during dialysis. As a consequence, regular ophthalmic examinations may be useful in patients with dialysis to identify high-risk individuals with glaucoma, and preventive measures should be applied to avoid permanent vision loss as soon as IOP elevation is identified.

Figures and Tables

Graph: Figure 1 Flow diagram showing the selection of the study participants with and without dialysis. Index date: For dialysis patients, the index date was 90 days after the first dialysis. For non-dialysis individuals, the index date nested with the paired dialysis patients. All study participants were at risk on the index date.

Graph: Figure 2 Kaplan–Meier curves of the cumulative probability of glaucoma.

Table 1 Baseline characteristics.

	Non-Dialysisn = 78,980	Dialysisn = 3949	ASD
Sex			0.000
Female	37,440 (47.40%)	1872 (47.40%)	
Male	41,540 (52.60%)	2077 (52.60%)	
Age			0.003
20–39	5968 (7.56%)	295 (7.47%)	
40–59	30,032 (38.02%)	1504 (38.09%)	
60–79	35,310 (44.71%)	1767 (44.75%)	
80–100	7670 (9.71%)	383 (9.70%)	
Urbanization			0.031
Urban	45,437 (57.53%)	2256 (57.13%)	
Suburban	23,815 (30.15%)	1197 (30.31%)	
Rural	9728 (12.32%)	496 (12.56%)	
Low income	504 (0.64%)	35 (0.89%)	0.029
Length of hospital stay *			3.081
0 days	69,845 (88.43%)	251 (6.36%)	
1–6 days	4371 (5.53%)	365 (9.24%)	
≥7 days	4764 (6.03%)	3333 (84.40%)	
Comorbidity *			
Hypertension	24,337 (30.81%)	3438 (87.06%)	1.393
Diabetes mellitus	10,574 (13.39%)	1985 (50.27%)	0.862
Ischemic heart disease	8239 (10.43%)	1180 (29.88%)	0.500
Hyperlipidemia	10,546 (13.35%)	1017 (25.75%)	0.317
Congestive heart failure	2650 (3.36%)	1282 (32.46%)	0.821
Cerebrovascular disease	5580 (7.07%)	728 (18.44%)	0.346
Dementia	915 (1.16%)	90 (2.28%)	0.086
Uveitis	116 (0.15%)	12 (0.30%)	0.033

	Non-Dialysisn = 78,980	Dialysisn = 3949	ASD
Retinal vessel occlusion	94 (0.12%)	29 (0.73%)	0.095
NPDR	440 (0.56%)	241 (6.10%)	0.313
PDRFrequency of visits to ophthalmologists after index date01≥2	153 (0.19%)57,165 (72.38%)8938 (11.32%)12,877 (16.30%)	375 (9.50%)2632 (66.65%)433 (10.96)884 (22.39%)	0.4440.128

* The length of hospital stay and comorbidities were identified within one year before the index date. ASD, absolute standardized difference; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2 Incidence of glaucoma in the non-dialysis and dialysis groups.

	Non-Dialysisn = 78,980	Dialysisn = 3949
Follow-up person months	5,737,499	196,905
New glaucoma cases	2877	161
Incidence rate * (95% CI)	5.01 (4.83–5.2)	8.18 (7.01–9.54)
Crude relative risk (95% CI)	Reference	1.618 (1.38–1.897)

* Incidence rate, per 10,000 person months. CI, confidence interval.

Table 3 Multiple Cox proportional hazards regressions for the estimation of adjusted hazard ratios for glaucoma.

Variable	aHR (95% CI)
Dialysis (ref: Control)	1.270 (1.035–1.560)
Sex (ref: Female)	
Male	0.898 (0.836–0.965)
Age (ref: 40–59)	
20–39	0.445 (0.353–0.561)
60–79	2.069 (1.902–2.251)
80–100	1.399 (1.185–1.652)
Low income	0.968 (0.592–1.582)
Co-morbidity *	
Hypertension	1.133 (1.041–1.233)
Diabetes mellitus	1.524 (1.383–1.678)
Ischemic heart diseases	1.151 (1.035–1.279)
Hyperlipidemia	1.155 (1.046–1.276)
Uveitis	3.555 (2.203–5.737)
Retinal vessel occlusion	2.330 (1.315–4.128)

* Co-morbidity was identified within one year before index date. aHR, adjusted hazard ratio; CI, confidence interval.

Table 4 Subevent analysis in age- and sex-matched population.

	Incidence Rate * (95% CI)		
Sub-Event	Control	Dialysis	aHR + (95% CI)
OAG	0.94 (0.86–1.02)	1.53 (1.08–2.17)	1.008 (0.637–1.595)
NTG	0.18 (0.15–0.22)	0.29 (0.13–0.66)	0.901 (0.327–2.483)
ACG	1.52 (1.43–1.63)	2.28 (1.71–3.04)	1.550 (1.074–2.239)
Trabeculectomy	0.11 (0.08–0.14)	0.44 (0.23–0.85)	3.666 (1.366–9.840)

* Per 10000 person years; + adjusted for demographic variables, length of hospital stay, and comorbidities at baseline. ACG, angle-closure glaucoma; aHR, adjusted hazard ratio; CI, confidence interval; NTG, normal-tension glaucoma; OAG, open-angle glaucoma.

Author Contributions

Conceptualization, C.-C.L., J.-H.H., and S.-F.Y.; methodology, C.-C.L., J.-H.H., C.-Y.L., and S.-F.Y.; validation, C.-Y.L., F.-C.H., and J.-Y.H.; formal analysis, C.-Y.L., F.-C.H., and J.-Y.H.; investigation, C.-Y.L.; writing—original draft preparation, C.-C.L., J.-H.H., and S.-F.Y.; writing—review and editing, C.-C.L., J.-H.H., and S.-F.Y.; supervision, S.-F.Y. All authors have read and agreed to the published version of the manuscript.

Funding
This research received no external funding.

Conflicts of Interest
The authors declare no conflict of interest.

References
1 Saran R., Robinson B., Abbott K.C., Agodoa L.Y.C., Bragg-Gresham J., Balkrishnan R., Bhave N., Dietrich X., Ding Z., Eggers P.W. US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am. J. Kidney Dis. 2019; 73(Suppl. S1): A7-A8. 10.1053/j.ajkd.2019.01.001. 30798791

2 Wu M.Y., Wu M.S. Taiwan renal care system: A learning health-care system. Nephrology. 2018; 23: 112-115. 10.1111/nep.13460. 30298659

3 United States Renal Data System. 2017 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States; National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, USA. 2017

4 Liyanage T., Ninomiya T., Jha V., Neal B., Patrice H.M., Okpechi I., Zhao M.H., Lv J., Garg A.X., Knight J. Worldwide access to treatment for end-stage kidney disease: A systematic review. Lancet. 2015; 385: 1975-1982. 10.1016/S0140-6736(14)61601-9

5 Sitprija V., Holmes J. Preliminary observations on the change in intracranial pressure and intraocular pressure during hemodialysis. ASAIO J. 1962; 8: 300-308. 10.1097/00002480-196204000-00061. 13913503

6 Sitprija V., Holmes J.H., Ellis P.P. Intraocular pressure changes during artificial kidney therapy. Arch. Ophthalmol. 1964; 72: 626-631. 10.1001/archopht.1964.00970020626008. 14196745

7 Austin J., Klein M., Mishell J., Contiguglia S., Levy J., Chan L., Shapiro J. Intraocular pressures during high-flux hemodialysis. Ren. Fail. 1990; 12: 109-112. 10.3109/08860229009087127

8 Choong Y., Menage M. Symptomatic acute raised IOP following haemodialysis in a patient with end stage renal failure. Br. J. Ophthalmol. 1998; 82: 1339. 10.1136/bjo.82.11.1339d

9 Masuda H., Shibuya Y., Ohira A. Markedly increased unilateral intraocular pressure during hemodialysis in a patient with ipsilateral exfoliative glaucoma. Am. J. Ophthalmol. 2000; 129: 534-536. 10.1016/S0002-9394(99)00438-9

Fischer M.D., Fleischhauer J., Keusch G., Abegg M.H. Rise in intraocular pressure during haemodialysis in a patient with reduced outflow facility. Br. J. Ophthalmol. 2007; 91: 1091-1093. 10.1136/bjo.2006.110072

Costagliola C., Mastropasqua L. The influence of hemodialysis on intraocular pressure: III. Aqueous humor dynamics and tissue hydration. Ann. Ophthalmol. 1991; 23: 31-34

Tawara A., Kobata H., Fujisawa K., Abe T., Ohnishi Y. Mechanism of intraocular pressure elevation during hemodialysis. Curr. Eye Res. 1998; 17: 339-347. 10.1080/02713689808951214. 9561825

Tokuyama T., Ikeda T., Sato K. Effect of plasma colloid osmotic pressure on intraocular pressure during haemodialysis. Br. J. Ophthalmol. 1998; 82: 751-753. 10.1136/bjo.82.7.751. 9924365

Doshiro A., Ban Y., Kobayashi L., Yoshida Y., Uchiyama H. Intraocular pressure change during hemodialysis. Am. J. Ophthalmol. 2006; 142: 337-339. 10.1016/j.ajo.2006.03.017

Caglayan M., Kosekahya P., Takmaz T., Altunoglu A., Ayan B., Atilgan C.U., Uysal B.S. Effects of hemodialysis on corneal and anterior chamber morphometry and intraocular pressure in patients with end-stage renal disease. Arq. Bras. Oftalmol. 2017; 80: 176-180. 10.5935/0004-2749.20170043. 28832743

Chelala E., Dirani A., Fadlallah A., Slim E., Abdelmassih Y., Fakhoury H., Baz P., Bejjani R. Effect of hemodialysis on visual acuity, intraocular pressure, and macular thickness in patients with chronic kidney disease. Clin. Ophthalmol. 2015; 9: 109-114

Kilavuzoglu A.E.B., Yurteri G., Guven N., Marsap S., Celebi A.R.C., Cosar C.B. The effect of hemodialysis on intraocular pressure. Adv. Clin. Exp. Med. 2018; 27: 105-110. 10.17219/acem/68234

Wang L., Huang W., Huang S., Zhang J., Guo X., Friedman D.S., Foster P.J., He M. Ten-year incidence of primary angle closure in elderly Chinese: The Liwan Eye Study. Br. J. Ophthalmol. 2019; 103: 355-360. 10.1136/bjophthalmol-2017-311808

Ministry of Health and Welfare, R.O.C. (Taiwan) 2019 Taiwan Health and Welfare ReportAvailable online: https://www.mohw.gov.tw/cp-137-52878-2.html(accessed on 15 June 2020)

Chie W., Yang R., Liu J., Tsai K. High incidence rate of hip fracture in Taiwan: Estimated from a nationwide health insurance database. Osteoporos. Int. 2004; 15: 998-1002. 10.1007/s00198-004-1651-0

Hsu C.C., Lee C.H., Wahlqvist M.L., Huang H.L., Chang H.Y., Chen L., Shih S.F., Shin S.J., Tsai W.C., Chen T. Poverty increases type 2 diabetes incidence and inequality of care despite universal health coverage. Diabetes Care. 2012; 35: 2286-2292. 10.2337/dc11-2052

Chen H.L., Hsiao F.Y. Risk of hospitalization and healthcare cost associated with diabetes complication severity index in Taiwan's national health insurance research database. J. Diabetes Its Complicat. 2014; 28: 612-616. 10.1016/j.jdiacomp.2014.05.011

Keller J., Kang J.H., Lin H.C. Association between osteoporosis and psoriasis: Results from the Longitudinal Health Insurance Database in Taiwan. Osteoporos. Int. 2013; 24: 1835-1841. 10.1007/s00198-012-2185-5. 23052942

Evans R.D., Rosner M. Fellows' Forum: Ocular Abnormalities Associated with Advanced Kidney Disease and Hemodialysis. Semin. Dial. 2005; 18: 252-257. 10.1111/j.1525-139X.2005.18322.x

Levy J., Tovbin D., Lifshitz T., Zlotnik M., Tessler Z. Intraocular pressure during haemodialysis: A review. Eye. 2005; 19: 1249-1256. 10.1038/sj.eye.6701755. 15543171

Hu J., Bui K.M., Patel K.H., Kim H., Arruda J.A.L., Wilensky J.T., Vajaranant T.S. Effect of Hemodialysis on Intraocular Pressure and Ocular Perfusion Pressure. JAMA Ophthalmol. 2013; 131: 1525-1531.

10.1001/jamaophthalmol.2013.5599. 24232671

Watson A.G., Greenwood W.R. Studies on the intraocular pressure during hemodialysis. Can. J. Ophthalmol. 1966; 1: 301-307

Wakim K. In The pathophysiology of the dialysis disequilibrium syndrome. Mayo Clin. Proc. 1969; 44: 406-429

Lippold C.L., Kalarn S.P., Swamy R.N., Patel A.M. Ocular dialysis disequilibrium—Management of intraocular pressure during hemodialysis of open angle glaucoma: A case report and review of the literature. Hemodial. Int. 2019; 23: E72-E77. 10.1111/hdi.12718

Minguela I., Andonegui J., Aurrekoetxea B., de Gauna R.R. Prevention of intraocular pressure elevations during hemodialysis. Am. J. Kidney Dis. 2000; 36: 197-198. 10.1053/ajkd.2000.8294

De Marchi S., Cecchin E., Tesio F. Intraocular Pressure Changes During Hemodialysis: Prevention of Excessive Dialytic Rise and Development of Severe Metabolic Acidosis Following Acetazolamide Therapy. Ren. Fail. 1989; 11: 117-124. 10.3109/08860228909066953

Chen H., Zhang X., Shen X. Ocular changes during hemodialysis in patients with end-stage renal disease. BMC Ophthalmol. 2018; 18208. 10.1186/s12886-018-0885-0

Shin Y.U., Kim J.H., Cho H., Kim D.S., Yi J.H., Han S.W., Seong M. Effect of Hemodialysis on Anterior Chamber Angle Measured by Anterior Segment Optical Coherence Tomography. J. Ophthalmol. 2019; 2019. 10.1155/2019/2406547. 31485341

Gracitelli C.P.B., Stefanini F.R., Penha F., Góes M.Â., Draibe S.A., Canziani M.E., Paranhos A. Jr. Anterior chamber depth during hemodialysis. Clin. Ophthalmol. 2013; 7: 1635-1639. 10.2147/OPTH.S45952. 23976841

Jaeger P. Prevention of glaucoma during hemodialysis by mannitol and acetazolamide. N. Eng. J. Med. 1980; 303: 702

Tovbin D., Belfair N., Shapira S., Rosenthal G., Friger M., Feldman L., Lifshitz T., Tessler Z. High postdialysis urea rebound can predict intradialytic increase in intraocular pressure in dialysis patients with lowered intradialytic hemoconcentration. Nephron. 2002; 90: 181-187. 10.1159/000049040. 11818703

Frezzotti P., Menicacci C., Bagaglia S., Mittica P., Toto F., Motolese I. Management of intraocular pressure elevation during hemodialysis of neovascular glaucoma: A case report. BMC Ophthalmol. 2016; 1623. 10.1186/s12886-016-0199-z

Hirsch K.G., Josephson S.A. An update on neurocritical care for the patient with kidney disease. Adv. Chronic Kidney Dis. 2013; 20: 39-44. 10.1053/j.ackd.2012.09.003

Pichi F., Morara M., Lembo A., Ciardella A.P., Meduri A., Nucci P. Neovascular glaucoma induced by peripheral retinal ischemia in neurofibromatosis39 type 1: Management and imaging features. Case Rep. Ophthalmol. 2013; 4: 69-73. 10.1159/000350956

Baiocchi S., Mazzotta C., Sgheri A., Di Maggio A., Bagaglia S.A., Posarelli M., Ciompi L., Meduri A., Tosi G.M. In vivo confocal microscopy: Qualitative investigation of the conjunctival and corneal surface in open angle glaucomatous patients undergoing the XEN-Gel implant, trabeculectomy or medical therapy. Eye Vis. 2020; 7: 1-14. 10.1186/s40662-020-00181-8

Song P., Wang J., Bucan K., Theodoratou E., Rudan I., Chan K.Y. National and subnational prevalence and burden of glaucoma in China: A systematic analysis. J. Glob. Health. 2017; 7: 20705. 10.7189/jogh.07.020705

Foster P.J., Oen F.T., Machin D., Ng T.P., Devereux J.G., Johnson G.J., Khaw P.T., Seah S.K. The prevalence of glaucoma in Chinese residents of Singapore: A cross-sectional population survey of the Tanjong Pagar district. Arch. Ophthalmol. 2000; 118: 1105-1111. 10.1001/archopht.118.8.1105

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Reported by Author; Author; Author; Author; Author; Author

Source: International journal of environmental research and public health, 2020 Sep 17, Vol. 17 Issue 18
Item: 32957502
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