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Detecting diabetic retinopathy using an artificial intelligence-based software platform: a pilot study

A. O. Nevska [1], O. A. Pohosian [1], K. O. Goncharuk [2], D. F. Sofyna [2], O. O. Chernenko [3], K. M. Tronko [4], N. Ie. Kozhan [5], A. R. Korol [1]

[1] SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine"
Odesa (Ukraine)

[2] CheckEye LLC

[3] MedCapitalGroup Private Enterprise

[4] The State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the NAMS of Ukraine»

[5] Shupyk National Healthcare University of Ukraine
Kyiv (Ukraine)

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Purpose: *To examine the potential for the detection of diabetic retinopathy (DR) using the artificial intelligence (AI)-based software platform Retina-AI CheckEye©.*

Material and Methods: *This was an open-label, prospective, pilot observational case-control study for the detection of DR using an AI-based software platform. The study was conducted at the sites of healthcare facilities in Chernivtsi oblast. Four hundred and eight diabetics and 256 non-diabetic controls were involved in the study. All fundus images were analyzed using the artificial intelligence (AI)-based software platform Retina-AI CheckEye©. Receiver operating characteristic (ROC) curve analysis was performed to determine the sensitivity and specificity of the DR diagnosis method.*

Results: Using the AI-based software platform, signs of DR in at least one eye were detected in 143 diabetics (22% of total study subjects (664 individuals; 1328 eyes) or 35% of the diabetics (408 patients)). No DR signs were detected in 322 individuals (48% of total study subjects). In 199 individuals (30% of total study subjects), the results were not obtained due to the features of the optical media and presence of certain eye diseases (in most cases, unilateral cataract or corneal opacity). This trial found 93% sensitivity and 86% specificity for the Retina-AI CheckEye-assisted detection of DR.

Conclusion: *An AI-based software platform, Retina-AI CheckEye©, has been for the first time developed in Ukraine. The platform was demonstrated to have a high accuracy (93% sensitivity and 86% specificity) in diagnosing DR in diabetic patients and can be used for large-scale DR screening.*

Introduction

The global diabetes prevalence in 20–79 year olds in 2021 was estimated to be 10.5% (536.6 million) people. The number of individuals with diabetes significantly increases every 10 to 15 years [1]. Therefore, diabetes has become a social problem. It is noteworthy that diabetes prevalence varies widely by geographic region and by race/ethnicity. Type 2 diabetes mellitus (T2DM) is most prevalent among the Asians. In the UK, 20% of individuals of Asian origin older than 40 years and 17% of individuals of African origin older than 40 years have T2DM, but the disease is less common among Caucasians of the same age. The increasing prevalence of diabetes in Ukraine is a pressing issue, too. According to the International Diabetes Federation Atlas, there were about 2,325,000 inhabitants with T2DM in Ukraine in 2021, representing a prevalence of 7.1% [2].

Because diabetic retinopathy (DR) is a common diabetic complication and a major cause of vision loss [3], there is an urgent need to develop new methods for early diagnosis of DR.

Artificial intelligence (AI) may be defined as a branch of computer science that deals with the study and development of programs capable of performing tasks that usually require skilled human intelligence. AI systems are developed for self-learning based on experience, identifying regularities and patterns, and making decision on the basis of input data. The term “artificial intelligence” was coined by Professor John McCarthy at Dartmouth College in 1956 and “refers to hardware or software that exhibits behavior which appears intelligent” [4].

Machine learning (ML) is a specific subset of AI; it is focused on teaching computers to learn from data and to improve from experience – instead of being explicitly programmed to do so.

Deep learning (DL) is a more sophisticated ML that uses neural networks to learn from unstructured or unlabeled data [5, 6, 7].

In recent years, AI has been increasingly used in medicine for diagnosis of diseases. Studies have demonstrated that AI facilitated histological analysis of breast cancer [8], classification of skin cancer [9], cardiovascular risk prediction [10] and detection or lung cancer [11].

There are many AI applications for early diagnosis of eye diseases like cataract [12], glaucoma [13], age-related macular degeneration (AMD) [14], and DR [15, 16, 17]. Hansen and colleagues [7] and Abràmoff and colleagues [18] reported on the results of the use of AI for the diagnosis of DR. Li and colleagues [19] compared the performance of seven automated AI-based DR screening algorithms against human graders when analyzing real-world imaging data [19]. Rahimy [20] described the emerging applications of DL in ophthalmology.

The purpose of this study was to examine the potential for the detection of diabetic retinopathy using the AI-based software platform Retina-AI CheckEye©.

Material and Methods

This was an open-label, prospective, pilot observational case-control study for the detection of DR using an AI-based software platform. The study was conducted at the sites of healthcare facilities in Chernivtsi oblast (Regional Community Interest Company "Chernivtsi Regional Endocrinological Center"; Community Interest Company "City Polyclinic No.1"; Community Interest Company "City Polyclinic No.2"; Koroviia Community Outpatient Clinic for General Practice and Family Medicine; Community Healthcare Facility "City Hospital No.4"; Community Interest Company "City Polyclinic No.1, Outpatient Department;" Community Interest Company "City Polyclinic No.1", Preventive Health Check-Up Department; Community Interest Company "Kitsman Multispecialty Intensive Care Hospital"; Community Interest Company "Khotyn Multispecialty Hospital"; Community Interest Company "Storozhynets Multispecialty Intensive Care Hospital"; and Community Interest Company "Novoselytsia Hospital").

Patients with diabetes and non-diabetic controls (totally, 664 individuals, 1328 eyes) were involved in the study. Patients were selected by general practitioners.

This clinical trial was approved by the local bioethics committee and informed consent was obtained from subjects. All procedures performed in the study were in accordance with the ethical standards of the Helsinki Declaration. The clinical trial was registered at ClinicalTrials.gov under identifier IDNCT06112691.

Inclusive criteria for patients with DM:

1. A clinically verified diagnosis of DM;
2. Understanding the study purpose, procedures, risks and benefits, and readiness to provide informed consent;
3. Individuals of at least 18 years of age;
4. Being diagnosed with (a) T1DM for ≥ 5 years or (b) T2DM for any period (408 patients totally).

Inclusive criteria for non-diabetic controls (256 individuals)

1. Individuals of at least 18 years of age
2. Understanding the study purpose, procedures, risks and benefits, and readiness to provide informed consent
3. No diabetes

Exclusion criteria:

1. Age younger than 18 years
2. Inability to provide informed consent due to ophthalmological reasons
3. Ocular comorbidities like inflammation of the eye or ocular adnexa, abnormal intraocular pressure regulation, hereditary dystrophy, degeneration, congenital defects, or vascular disorders
4. History of surgery (including laser intervention) for any retinal disease (AMD, retinal vascular occlusion, etc)

The first phase of the study included several steps; in this phase, a proprietary neural network was trained on a training set of 12,000 color fundus images from CheckEye© database. In the step of validation of fundus images, the latter were divided into two groups (valid and invalid). That is, an annotator made a decision based on whether the image was acceptable for further processing and whether fundus details and diabetic changes were visualized on the image. The next step was the annotation of fundus images, with any diabetic manifestations (like hemorrhages, exudation, intraretinal macroaneurysms, neovascularization, partial vitreous hemorrhage, and etc.) annotated with labels. Image annotation was performed by a research group of ophthalmologists (annotators). An annotator used the VGG Image Annotator (VIA) tool for manual annotation of fundus images. In this way, the neural network was trained to recognize diabetic changes. Subsequently, annotators performed the determination of the stage and form of DR, and the neural network was trained to determine the stage and form of DR on the basis of the examples of data processed by annotators. Annotators checked whether the stage and form of DR determined by the neural network were correct (this was repeated several times to finalize neural network training).

The second phase included screening of diabetics and non-diabetic controls using an AI-based cloud storage. Fundus images were analyzed by the AI software platform Retina-AI CheckEye©. At this phase, after written informed consent, eligible subjects were enrolled at the places where operators (nurse, medical receptionist, intern physician) worked and were taking ophthalmic photographs. These operators had no previous professional experience in ophthalmic photography, but had a four-hour training session on the subject. Operator took fundus images with a non-mydriatic fundus camera (FundusScope, Rodenstock, Munich, Germany) as per the Retina-AI CheckEye© imaging protocol (an optic disc centered image and a fovea centered image for each eye). Thereafter, operator uploaded fundus images in the AI system for processing by the neural network. The neural network evaluated images for validity. Whenever the system indicated image validity (sufficient image quality), the neural network determined whether DR was present. Research ophthalmologists verified the acquired fundus images by comparing diagnostics results with a unique diagnosis by the neural network, and, in this way, checked the quality and performed further network training for DR diagnosis technology. Whenever the system indicated image invalidity (insufficient image quality possibly due to cloudy media), the patient was informed about the need to visit his ophthalmologist for additional evaluation for corneal, lenticular or vitreal disease.

Receiver operating characteristic (ROC) curve analysis was performed using the Python language and Matplotlib to determine the sensitivity and specificity of the method.

Results

The results of screening using the AI-based software platform Retina-AI CheckEye were as follows. Using the AI-based software platform, signs of DR in at least one eye were detected in 143 diabetics (22% of total study subjects (664 individuals; 1328 eyes) or 35% of the diabetics (408 patients)). No DR signs were detected in 322 individuals (48% of total study subjects). In 199 individuals (30% of total study subjects), the results were not obtained due to the features of the optical media and presence of certain eye diseases (unilateral cataract or corneal opacity in most cases).

This trial found 93% sensitivity and 86% specificity, with an area under curve (AUC) of 0.97 (Fig. 1), for the Retina-AI CheckEye-assisted detection of DR.

Therefore, the AI-based software platform Retina-AI CheckEye can be used for the diagnosis of DR in patients with DM with a high accuracy of the method.

Discussion

Ophthalmic applications of AI are not new. The CASNET-based glaucoma consultation program in 1976 demonstrated the feasibility of applying the ML aspect of AI in clinical practice [21]. Hansen and colleagues [7] and Abràmoff and colleagues [18] reported on the results of the use of AI for the diagnosis of DR [22, 18]. Caixinha and Nunes [17] and Hashimoto and colleagues [23, 24] reviewed applications of traditional ML methods for the diagnosis and monitoring of general diseases (histological analysis of breast cancer, classification of skin cancer, cardiovascular risk prediction detection or lung cancer and etc.). Lee and colleagues [16] and Lee and colleagues [19] presented the results of a multicenter validation study of seven DL systems for DR screening. Rahimy [20] described the emerging applications of DL in ophthalmology, too. Each innovator used a particular AI mechanism or subsets of these mechanisms for application in the area of his/her interest.

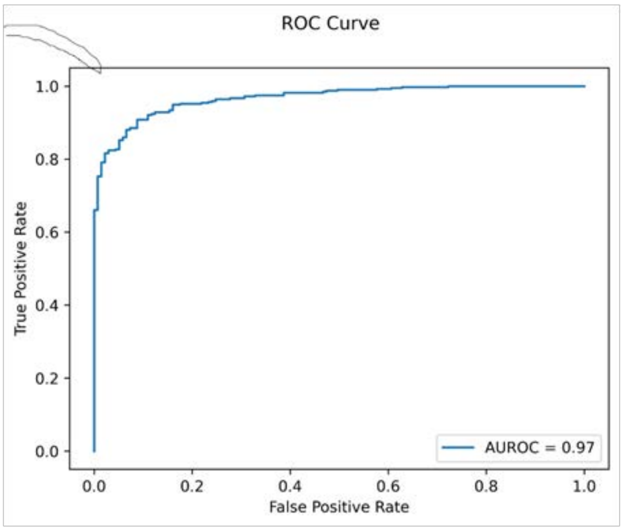

Fig. 1. Receiver operating characteristic (ROC) curve for determining the accuracy of diabetic retinopathy detection with the artificial intelligence (AI)-based software platform (93% sensitivity and 86% specificity, with an area under curve of 0.97)

Many DL models for automatic DR detection have been developed in recent years [25, 26]. DL facilitated improved diagnosis of proliferative DR, which is more difficult for AI-aided diagnosis than non-proliferative DR. Most studies have used one-field fundus images for this purpose. Advanced AI systems like Iowa Detection Program (IDP), EyeArt, and Google's Automated Retinal Disease Assessment (ARDA) (with EyePACS and Messidor datasets) [27, 28, 29, 30] used DL of a proprietary network with a preliminary validation of fundus images and annotation of artifacts and signs of different stages and forms of DR in 10,000-700,000 images. An optic disc centered image and a fovea centered image for each eye were uploaded and processed within 2-3 seconds depending on the severity of diabetic manifestations.

Validation of the IDP on the Messidor-2 dataset achieved a sensitivity of 96.8% and specificity of 59.4% in detecting referable DR. EyeArt has used images obtained from the EyePACS telescreening system to train AI algorithms to screen for DR with a 90% sensitivity at 63.2% specificity. Google's AI system (automated retinal disease assessment – ARDA) was evaluated with the help of two test runs using fundus photos from pre-diagnosed DR patients by expert physicians (The EyePACS-1 data set and MESSIDOR-2 data set). These tests resulted in high sensitivity values of 97.5% and 96.1% in each practice set and specificity values of 98.1% and 98.5%.

In the current study, we used a machine learning/computer vision approach, and a proprietary neural network was trained on a training set of more than 12,000 fundus images from CheckEye© database, with a preliminary validation and annotation of artifacts and signs of different stages and forms of DR. This trial found 93% sensitivity and 86% specificity for the Retina-AI

CheckEye-assisted detection of DR, and these results are close to those reported by others.

Unlike other AI-based diagnostic systems developed for detecting retinal diseases in Ukraine, Retina-AI CheckEye© is a solution focused on large-scale DR screening in primary healthcare settings (other tools are aimed at providing care in eye clinic settings). This has become possible due to the following: 1) a diagnosis may be made not only by an ophthalmologist; 2) the examination takes little time, and 3) operator takes images with a nonmydriatic fundus camera. CheckEye is already capable for detecting DR and determining the stage of DR (no DR, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, proliferative DR). We are going to begin training the platform to determine the form and severity of the disease, which will make the methodology unique. Achieving 93% sensitivity for the Retina-AI CheckEye-assisted detection of DR is sufficient for using the system in large-scale screening.

The work is underway to advance the system performance to make additional advantages of the system convenient for use by primary healthcare specialists. In addition, due to the continuing war, increasing numbers of Ukrainian individuals become internally displaced people and lose connections with their general physician or postpone their visits to their ophthalmologist, which results in late diagnostic evaluation for diabetic complications, e.g., DR. Therefore, the introduction of Retina-AI CheckEye-assisted large-scale DR screening will aid earlier detection of reduced visual function, avoidance of severe ophthalmic sequelae, and reduction in the rate of disability among individuals with diabetes.

Conclusion

An AI-based software platform, Retina-AI CheckEye©, has been for the first time developed in Ukraine. The platform was demonstrated to have a high accuracy (93% sensitivity and 86% specificity) in diagnosing DR in diabetic patients and can be used for large-scale DR screening.

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Disclosures

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Corresponding author: *Alla O. Nevska, Ophthalmologist, Laser Eye Microsurgery Department, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine", Odesa, E-mail: esbarena@gmail.com*

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Abbreviations: *AI, artificial intelligence; DL, deep learning; DM, diabetes mellitus; ML, machine learning*