Ultra-wide-field fundus photography compared to ophthalmoscopy in diagnosing and classifying major retinal diseases

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To analyze the performance of ultra-wide-field (UWF) fundus photography compared with ophthalmoscopy in identifying and classifying retinal diseases. Patients examined for presumed major retinal disorders were consecutively enrolled. Each patient underwent indirect ophthalmoscopic evaluation, with scleral depression and/or fundus biomicroscopy, when clinically indicated, and mydriatic UWF fundus imaging by means of CLARUS 500™ fundus camera. Each eye was classified by a clinical grader and two image graders in the following groups: normal retina, diabetic retinopathy, vascular abnormalities, macular degenerations and dystrophies, retinal and choroidal tumors, peripheral degenerative lesions and retinal detachment and myopic alterations. 7024 eyes of new patients were included. The inter-grader agreement for images classification was perfect (kappa = 0.998, 95% Confidence Interval (95%CI) = 0.997–0.999), as the two methods concordance for retinal diseases diagnosis (kappa = 0.997, 95%CI = 0.996–0.999) without statistically significant difference. UWF fundus imaging might be an alternative to ophthalmoscopy, since it allows to accurately classify major retinal diseases, widening the range of disorders possibly diagnosed with teleophthalmology. Although the clinician should be aware of the possibility that a minority of the most peripheral lesions may be not entirely visualized, it might be considered a first line diagnostic modality, in the context of a full ophthalmological examination.

The recent coronavirus disease 2019 (COVID-19) pandemic has forced the medical community to revise and reorganize the methods of clinical evaluation, particularly in ophthalmology: despite being the current gold standard for the examination of retinal periphery, indirect ophthalmoscopy, as well as central fundus biomicroscopy for macular disorders, require a close contact with the patient and need adequate time of evaluation1–3. The broad use of ultra-wide-field (UWF) fundus cameras has helped to partly overcome these obstacles, allowing: the clinician to analyze fundus images even at distance, namely in a different location than the clinic, to reduce the time of evaluation for the patient and the clinician; to perform screening for retinal disorders, such as diabetic retinopathy4–6 and peripheral retinal lesions7–9. Fundus imaging can be considered UWF when covering a field of retina equal to 100° or more4,7,10–12, showing, in a single shot, retinal features anterior to vortex vein ampullae in all four quadrants13. Conversely, the term “wide field” should be used for images showing retinal features beyond the posterior pole but posterior to vortex vein ampulla, in all four quadrants13.

The most widespread UWF fundus imaging systems currently in use are: Clarus™ (CLARUS 500™, Carl Zeiss Meditec AG, Jena, Germany) and Optos® (Optos California®, Optos PLC, Dunfermline, United Kingdom). Clarus™ is a fundus camera providing a real color photograph of retina and covering up to 133° of field in a single image, reaching over 200° of field with the auto-montage function. Eyelashes and eyelids artifacts are reduced or abolished thanks to the partially confocal optics of Clarus™. Some tools intrinsic to the system allow the clinician to compare images1. Conversely, Optos® is a scanning laser ophthalmoscope able to capture in a single image up to 200° of the retina. The combination of monochromatic red and green scanning laser leads to a semi-realistic

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two-tone fundus image which may show some differences with a real color picture. These two cameras have shown similar effectiveness in grading the severity of diabetic retinopathy, while it is still debated their role in localizing peripheral lesions. Another fundus camera recently developed is Eidon (Centervue S.P.A., Padova, Italy), which is a confocal scanning laser ophthalmoscope, arranging a real fundus color image, encompassing a field of 90° in single exposure and up to 160° with mosaic function.

The aim of this study was to assess the performance of one UWF fundus camera, namely Clarus, compared to indirect ophthalmoscopy, plus central fundus biomicroscopy when macular involvement is suspected or present, in identifying and classifying major retinal disorders.

Methods

Population and procedures. This was a non-interventional cross-sectional study with prospective enrollment, compliant with the tenets of the Declaration of Helsinki and approved by the local Institutional Review Board (“Comitato Etico per la Sperimentazione Clinica della Provincia di Padova”—Prot. N. 11,870-2022). Informed consent was obtained from each patient. All new patients addressed to our Department and evaluated between February 2020 and December 2021 were consecutively included and examined for major retinal diseases. Each patient underwent indirect ophthalmoscopic evaluation, with scleral depression, when clinically indicated according to the examiner’s judgment, and/or central fundus biomicroscopy, when macular involvement was suspected or present, performed by a retinal (blinded to patient’s clinical records) expert and mydriatic UWF fundus imaging by means of Clarus fundus camera, performed by a specialized technician. Images were obtained for each gaze position (superior, inferior, right, left), auto-mounted by the system and exported for analysis as JPG files of 6604 × 4274 pixels. Pictures were then independently reviewed and classified by two masked retinal specialists, in order to calculate the intergrader agreement. The examiners were masked to each other evaluations and patients’ characteristics, including visual symptoms.

Thus, each eye received three independent classifications by: one clinical grader (CG) and two clinical image graders (IG1, IG2), in the following groups: normal retina (NR), diabetic retinopathy (DR), vascular abnormalities (VA), macular degenerations and dystrophies (MD), retinal and choroidal tumors (T), peripheral degenerative lesions and retinal detachment (PLD) and myopic alterations (MY). Graders were specifically trained to choose only one diagnosis, applying the most appropriate to each case. Poor quality images, patients with significant media opacities (corneal opacities, cataract or vitreous hemorrhage) were excluded. See Fig. 1 for the flow chart of the study.

Statistical analysis. The sensitivity for identifying major retinal diseases with Clarus imaging system was calculated for each individual disorder as follows: number of eyes accurately classified by UWF imaging divided by number of eyes correctly labeled by ophthalmoscopy. Specificity was calculated for each disorder as follows: number of eyes accurately classified on UWF imaging divided by number of not affected eyes identified by UWF imaging method, showing a sensibility and specificity of almost 100% for each disease group. See Table 3 for sensibility and specificity results in individual groups.

Results

A total of 7250 eyes of 3625 patients were consecutively enrolled. 226 eyes were excluded due to significant media opacities (172) and/or poor quality images (54). 7024 eyes were finally examined. The clinical features (CG) of the eyes examined were the following: diabetic retinopathy, from mild to proliferative, occurred in 1819 eyes (26% of the total) (Fig. 2A); vascular abnormalities, such as vascular occlusions, Coats disease or hemangiomas, affected 380 eyes (5%); macular degenerations and dystrophies (MD), retinal and choroidal tumors (T), peripheral degenerative lesions and retinal detachment (PLD) and myopic alterations (MY). The results of clinical and imaging classifications are reported in Table 1. The time required for each clinical evaluation was of 8.5 ± 3.0 min, 3.0 ± 1.5 for each auto-montage imaging acquisition, 3.5 ± 1.0 for imaging analysis.

The inter-grader agreement between clinical imaging graders was substantial (k = 0.998, 95%CI = 0.997–0.999). The analysis among clinical (CG) and imaging diagnosis (IG1, IG2) of retinal disorders showed an excellent concordance of the two methods, both in the overall results, with k = 0.997 (95%CI = 0.996–0.999), and in each individual disorder (k ≥ 0.994). PABAK and Gwet’s first-order agreement coefficient did not show any significant difference with k coefficient. Compared classifications and k index (standard and adjusted) with the 95% confidence interval assessed for each disorder are reported in Table 2.

No significant difference appeared in retinal evaluation between the two procedures. An overall of 5316 of 5321 eyes were correctly classified by UWF imaging method, showing a sensibility and specificity of almost 100% for each disease group. See Table 3 for sensibility and specificity results in individual groups.
Discussion

Although indirect ophthalmoscopy, particularly associated to scleral depression, and posterior biomicroscopy still remain the gold standard for fundus examination\(^1\), over the last ten years the use of fundus photography system has extensively increased\(^1\), as an adjunct to clinical evaluation\(^7\) and as a screening tool for many retinal diseases, in particular diabetic retinopathy\(^4\), peripheral retinal lesions\(^6\), and other retinal disorders\(^16\), also by means of deep learning technologies\(^3\). This is due to the progressive improvement of retinal fundus cameras, involving both the extent of retinal field evaluated and the quality of images: from the earliest cameras...
encompassing a retinal field of 20–30° in a single image, we have now systems capable of acquiring real color fundus images covering up to 200° of retinal field with a pixel definition of 6604 × 4274 (Clarus™), or providing a two-tone fundus image of 200° of field with a 3900 × 3072 pixel definition (Optos®). The COVID-19 pandemic has exacerbated this trend due to the need for reducing close contacts and the burden on health-care systems: besides safety, eye tele-screening reduces the time of the examination both in adults and in children.

Recent studies evaluated UWF imaging for individual disorders, most of which performed on diabetic retinopathy, peripheral retinal lesions or other retinal disorders. Some reports have shown that UWF fundus imaging is an effective useful tool for the assessment of diabetic retinopathy, focusing on the higher accuracy of Clarus™ in detecting microaneurysm and retinal hemorrhages: by providing real color images and reducing lids and lashes artifacts, it allows a slightly more precise staging of diabetic retinopathy and maculopathy than Optos® camera. Conversely, studies assessing the effectiveness of UWF imaging in detecting peripheral retinal lesions, such as retinal degenerations, retinal breaks, rhegmatogenous retinal detachment, have been conducted primarily with Optos®: despite considering UWF imaging a useful adjunct to medical evaluation, some authors do not agree it may represent substitute of clinical ophthalmoscopy due to the possible missing of some peripheral retinal lesions. Other authors observed consistent findings between clinical and UWF imaging examination, and consider the two methods interchangeable.

Moreover, even if the effective fields of views between Clarus™ and Optos® seem different depending on the specific retinal quadrant, a recent study found a similar ability to detect treatment-requiring retinal breaks between the two systems. UWF imaging appeared to be useful also for screening of ocular Toxoplasmosis and even superior to dilated fundus examination for the screening of sickle cell retinopathy, because of the higher accuracy in detecting capillary occlusion or anastomosis, and in inherited retinal dystrophies, providing previously unavailable information about retinal periphery.

Our study was planned to compare retinal UWF imaging versus clinical evaluation and to validate the technique of clinical analysis of retinal UWF imaging, obtained by means of Clarus™, performed without a deep learning system. We enrolled patients evaluated in daily clinics for presumed major retinal disorders in a period of about two years, without differentiating for individual disorder, thus collecting a very large unselected population (7024 eyes).

Table 1. Clinical grading versus Imaging grading.

| Retinal disorders                      | Clinical Grading | Imaging grading 1 | Imaging grading 2 |
|----------------------------------------|------------------|-------------------|-------------------|
| Diabetic Retinopathy                   | 1819             | 1816              | 1820              |
| Vascular Abnormalities                 | 380              | 383               | 379               |
| Peripheral lesions and retinal detachment | 369             | 370               | 372               |
| Choroidal and retinal tumours          | 1426             | 1429              | 1428              |
| Macular degenerations and dystrophies  | 777              | 769               | 772               |
| Myopic alterations                     | 550              | 548               | 547               |
| Normal retina                          | 1703             | 1709              | 1706              |
| Total                                  | 7024             | 7024              | 7024              |

Figure 2. Examples of missed diagnosis with clinical examination: (a) Mild diabetic retinopathy; (b) small, flat nevus.
In accordance with another analysis, the missing diagnosis we reported were very limited in the temporal periphery (4 cases). The classification and diagnosis achieved with UWF imaging allowed to capture images of the extreme temporal periphery, since most of the missed lesions were located in the upper quadrant by the limitation induced by the patient's nose when trying to see the macula appears to be involved. For major retinal diseases these evaluation systems have similar sensitivity and specificity (almost 100%) and no statistically significant difference was found in fundus assessment between the two procedures (k = 0.997, 95%CI = 0.996–1.000). These findings differ from some previous reports, but it must be underlined that the other study populations were small and mostly limited to peripheral retinal degenerations. Moreover, these last reports used Optos® system, whose limitations, mainly concerning true color, have already been reported. On the other hand, our results are consistent with some recent studies, even if these studies were also performed on small populations, for selected diagnosis. Clinical grader classification; IMG1 Image grader 1 classification; IMG2 Image grader 2 classification; + + = eyes classified correctly by both examiners; + − / − + = eyes classified correctly by one examiner; − − = eyes classified without the specific disorder by both examiner; Pp = observed agreement; BI = bias index; PI = prevalence index; k (95%IC) = kappa coefficient with the corresponding 95% confidence interval calculated for each disease; PABAK (95%IC) = Prevalence-adjusted and bias-adjusted kappa with the corresponding 95% confidence interval calculated for each disease.

Our results demonstrated that UWF imaging, by means of Clarus™ fundus color images, is comparable to ophthalmoscopic examination performed with indirect ophthalmoscopy plus macular biomicroscopy, when the macula appears to be involved. For major retinal diseases these evaluation systems have similar sensitivity and specificity (almost 100%) and no statistically significant difference was found in fundus assessment between the two procedures (k = 0.997, 95%CI = 0.996–0.999). These findings differ from some previous reports, but it must be underlined that the other study populations were small and mostly limited to peripheral retinal degenerations. Moreover, these last reports used Optos® system, whose limitations, mainly concerning true color, have already been reported. On the other hand, our results are consistent with some recent studies, even if these studies were also performed on small populations, for selected diagnosis (diabetic retinopathy, peripheral lesions, rhegmatogenous retinal detachment, ocular Toxoplasmosis, sickle cell retinopathy). In accordance with another analysis, the missing diagnosis we reported were very limited in the temporal periphery (4 cases). The classification and diagnosis achieved with UWF imaging allowed to capture images of the extreme temporal periphery, since most of the missed lesions were located in the upper temporal periphery (4 cases). The classification and diagnosis achieved with UWF imaging allowed to capture images of the extreme temporal periphery, since most of the missed lesions were located in the upper temporal periphery (4 cases). The classification and diagnosis achieved with UWF imaging allowed to capture images of the extreme temporal periphery, since most of the missed lesions were located in the upper temporal periphery (4 cases). The classification and diagnosis achieved with UWF imaging allowed to capture images of the extreme temporal periphery, since most of the missed lesions were located in the upper temporal periphery (4 cases). The classification and diagnosis achieved with UWF imaging allowed to capture images of the extreme temporal periphery, since most of the missed lesions were located in the upper temporal periphery (4 cases).

The relevance of this clinical study also lies in analyzing UWF fundus photographs of such a broad population, both in terms of numbers and disorders. Moreover, the use of Clarus™ system, providing real color fundus imaging, allows realistic and accurate evaluation, comparable to the clinical one with ophthalmoscopy, except for some rare cases. However, according to patients’ symptoms and clinical features and/or to UWF photos characteristics, the examination also with indirect ophthalmoscopy may be necessary for an accurate diagnosis. In fact, at present, the approach to patients affected by retinal diseases should always be multimodal, and UWF fundus photo might be the first diagnostic modality in this approach, followed by the other, eventually
clinically-indicated, diagnostic procedures, including ophthalmoscopy. Therefore, the perspective might be a shift from a "photo-assisted ophthalmoscopy" to an "ophthalmoscopy-assisted UWF fundus photography" approach.

A possible limitation of our study may be the use of this system without a deep learning tool, which may offer a more standardized classification.

In conclusion, we reported a substantial agreement in the classification of major retinal diseases using UWF imaging. This assessment highlights the interchangeability of UWF imaging and ophthalmoscopy by validating the technique of UWF imaging analysis in diagnosing major retinal diseases in daily clinical practice and should encourage the use of UWF imaging for fundus examination both in clinical and telehealth contexts. UWF imaging may improve the quality of clinical evaluation, allowing to compare images of the same eye acquired in different moments thus helping to monitor chronic diseases, such as diabetic retinopathy, and easily detect recurrences (i.e. choroidal and retinal tumors), also by using some tools intrinsic to the system. Moreover, it allows an accurate assessment of specific retinal areas, such as the macula or very peripheral sectors, without increasing the discomfort of the patient, as may happen during a prolonged ophthalmoscopic evaluation. The validation of UWF imaging for retinal evaluation also widens the possible uses of teleophthalmology: it allows to examine images at a different location than the clinic, possibly applying a deep learning algorithm, to reduce the time of evaluation and to perform screening for major retinal diseases thus rapidly directing the patient to a specific clinical care pathway if needed.

**Data availability**
The data presented in this study are available in the article. Eventual additional data are available on request from the corresponding author.

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| Classifications                          | ++ | +− | −+ | −  | SS  | SP  |
|-----------------------------------------|----|----|----|----|-----|-----|
| **CG vs IMG1**                          |    |    |    |    |     |     |
| Diabetic retinopathy                    | 1816 | 3  | 0  | 5205 | 100.00 | 99.94 |
| Vascular abnormalities                  | 380  | 0  | 3  | 6641 | 99.22  | 100.00 |
| Peripheral alterations and retinal detachment | 369  | 0  | 1  | 6654 | 99.73  | 100.00 |
| Tumors                                  | 1426 | 0  | 3  | 5595 | 99.79  | 100.00 |
| Macular degenerations and dystrophies   | 769  | 8  | 0  | 6247 | 100.00 | 99.87 |
| Myopic alterations                      | 548  | 2  | 0  | 8474 | 100.00 | 99.97 |
| Normal                                  | 1703 | 0  | 6  | 5315 | 99.65  | 100.00 |
| **CG vs IMG2**                          |    |    |    |    |     |     |
| Diabetic retinopathy                    | 1819 | 1  | 0  | 5204 | 100.00 | 99.98 |
| Vascular abnormalities                  | 379  | 1  | 0  | 6644 | 100.00 | 99.98 |
| Peripheral alterations and retinal detachment | 369  | 0  | 3  | 6652 | 99.19  | 100.00 |
| Tumors                                  | 1426 | 0  | 2  | 6247 | 100.00 | 99.92 |
| Macular degenerations and dystrophies   | 772  | 5  | 0  | 6247 | 100.00 | 99.92 |
| Myopic alterations                      | 547  | 3  | 0  | 8474 | 100.00 | 99.95 |
| Normal                                  | 1703 | 0  | 3  | 5318 | 99.82  | 100.00 |

Table 3. Sensibility and specificity in individual diseases. *CG Clinical grader classification; IMG1 Image grader 1 classification; IMG2 Image grader classification; ++ = eyes classified with a specific disorder correctly by both examiners; +− / −+ = eyes classified correctly by one examiner; − = eyes classified without the specific disorder by both examiner; SS sensibility; SP specificity.*
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Author contributions
E.M. and G.M.: study conception, design, interpretation of data, drafting and revising; final approval and agreement to be accountable for all aspects of the work. S.D.G., G.R., E.L., L.F., E.P., R.P. and G.M.: data acquisition/analysis/interpretation, drafting and revising of work, final approval and agreement to be accountable for all aspects of the work.

Competing interests
The authors declare no competing interests.

Additional information
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