Original Article

Potential impact of fluorescein angiography as a primary imaging modality in the management of diabetic retinopathy

Mohamed Ashraf, Walaa Wagdy[1], Mohamed A Tawfik[2], Islam Shereen Hamdy Ahmed[3], Ahmed Souka[3]

Purpose: To evaluate current practice patterns for Egyptian ophthalmologists in the diagnosis of diabetic retinopathy (DR) and explore potential implications of these approaches on management. **Methods:** Cross-sectional survey conducted in Egypt amongst practicing ophthalmologists. **Results:** The study had 203 responses (~6% of all Egyptian ophthalmologists). A majority of respondents were general ophthalmologists (78.2%), practicing for five to ten years (41.9%). In patients with DR and no diabetic macular edema (DME), 33.0% of respondents would use FA in patients with mild DR, 44.3% in patients with moderate DR and 51.2% in patients with severe non-proliferative diabetic retinopathy (NPDR). Color imaging (CI) was used by less than 1% as the sole imaging modality for any level of DR. Approximately 70% of respondents used fluorescein angiography (FA) to grade and base treatment decisions for DR, either alone or in conjunction with dilated eye exams and/or CI. Given the known more severe appearance of DR on FA than on standard color imaging upon which treatment guidelines are based, use of FA as the primary modality over a one-year period could result in PRP that would otherwise not be suggested in approximately 78,820 eyes at an additional cost of $10.1 million US dollars. These numbers are projected to double by 2045. **Conclusion:** Given that FA detects significantly greater pathology than CI, and that treatment and follow-up recommendations are based on CI, its use as the primary imaging modality in DR grading may result in apparently significantly higher DR severity, with subsequently increased procedures and associated costs.

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Diabetes mellitus (DM) is a major public health problem worldwide.[1] Diabetic retinopathy (DR) is the most common microvascular complication of diabetes.[2] It is the leading cause of visual loss in the working age population.[3] The current gold standard for the diagnosis and classification of DR is color fundus photography.[4] The Early Treatment Diabetic Retinopathy Study (ETDRS) classification was developed based on color fundus images (CI). Progression rates for different DR severity levels and suggested follow-up intervals are hence based on CI grading.[4,5]

Recent data has suggested that fluorescein angiography (FA) can detect significantly more pathology compared to CI.[6] Microaneurysm (MA) counts were 3.2 fold higher in the ETDRS fields on FA compared to CI.[6] This resulted in 1.6 to 3.5 more fields with Mas ≥20, the cut off used by the international classification to grade more advanced levels of DR (moderate non-proliferative DR (NPDR): 1–3 fields; and severe NPDR: 4 fields).[6,7] The increased pathology detected on FA causes a 26.5% one-step increase in DR severity and a 7.34% two-step increase in DR severity.[8] The current 2019 American Academy of Ophthalmology preferred practice patterns (AAO-PPP) recommends FA mainly to guide focal laser treatment for diabetic macular edema (DME) and to identify suspected but clinically undetectable neovascularization. Current preferred practice patterns do not recommend FA to screen for DR or to assess its severity level. Furthermore, there is no widely adopted FA grading scale for DR severity that has been validated in multicenter prospective trials.

In 2019, Egypt ranked ninth among countries with the highest numbers of adults (aged 20–79) with diabetes mellitus (DM). By 2030, Egypt will rank eight with 11.0 million patients and by 2045, seventh with 16.9 million patients. This represents a 100% increase in the number of adults with DM by 2045 compared to current numbers.[1] The largest population-based prevalence study conducted in Egypt of over 4000 patients estimated that the prevalence of DR was 17.9%, with 5.2% having sight-threatening DR.[9] Smaller studies estimated that the prevalence of DR ranged between 34% and 50% in known diabetics compared to 10% and 13% in newly diagnosed ones.[10,11] It was estimated that 5%–14% of patients had vision-threatening DR that required treatment.[9,11]

There is significant use of FA in the real-world practice that exceeds current practice patterns and recommendations.[12] It

Harvard Medical School, 1 Joslin Place, Boston, USA, [1]Alexandria Faculty of Medicine, Champilion Street, Azarita, Raml Station, Alexandria, [2]Memorial Institute, Cairo, [3]Alexandria Faculty of Medicine, Champilion Street, Azarita, Raml Station, Alexandria, Egypt

Correspondence to: Dr. Mohamed Ashraf, Harvard Medical School, 1 Joslin Place, Boston, USA. E-mail: mohamed.elmasry@joslin.harvard.edu

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is unclear what the preferred diagnostic modality is amongst Egyptian ophthalmologists and whether their approaches may significantly affect treatment decisions and associated costs. This is particularly important given that despite having public health care and insurance in Egypt, most patients prefer to receive treatment in private institutes and tend to pay out of pocket. Therefore, the impact of over- or under-treatment may have significant socioeconomic implications.

The purpose of the current study was to evaluate the current practice patterns of Egyptian ophthalmologists with regards to the diagnosis of DR and to examine the potential implications these approaches may have on treatment and long-term follow-up.

Methods

This study was a cross-sectional, non-probability survey. Data was collected from 1 September 2021 to 15 October 2021. The study sampled both retinal specialists as well as general ophthalmologists. The survey explored practice patterns in the management of diabetic retinopathy (DR) with particular attention to diagnostics and DR grading. Given that this was a survey amongst practicing ophthalmologists and not involving human subjects, the University of Alexandria Human Research Ethics Committee approval was waived.

Using data from the International Council of Ophthalmology website (http://www.icoph.org/ophthalmologists-worldwide.html), the estimated number of ophthalmologists in Egypt in 2020 was 3780, based on a recorded number of 2,400 practicing ophthalmologists in 2012, with approximately 150 entering practice and 12 leaving practice every year. Initially, a sample size of 145 was calculated to achieve a margin of error of ± 8% at 95% confidence level (https://www.qualtrics.com/blog/calculating-sample-size). However, given that the final count was 203 responses (estimated to represent 6% of all Egyptian ophthalmologists), the final margin of error was recalculated to be ± 6.5%. The survey was modeled after the American Society of Retina Specialists (ASRS) preferences and trends (PAT) survey (https://www.asrs.org/asrs-community/pat-survey). A version of the survey can be found online (https://forms.gle/YEytrJCVQMDeW9GB8), however new responses have been disabled.

A link to the Google Form website with the survey was posted on Facebook groups frequently visited by Egyptian ophthalmologists. To ensure that only ophthalmologists currently practicing in Egypt were included in the final analysis, a question was included in the survey as to where they were currently practicing. In addition, the survey was disseminated on WhatsApp groups exclusive for ophthalmology departments across Egypt. Ophthalmologists were encouraged to fill the survey voluntarily and it is unknown how many deferred. The survey was posted online on 9 September 2021 and new survey responses were collected until 4 October 2021.

Results

In total, 223 people submitted their responses, among which 8 were empty and 12 were completed by ophthalmologists practicing outside Egypt, yielding a final count of 203 responses in the final analysis. Of the total respondents, 78.2% were general ophthalmologists, 7.9% were retinal specialists and 13.9% were specialized in a sub-specialty other than the retina with 46.8% practicing only in a public hospital setting, 44.3% in both a private hospital and in private practice and only 8.9% in a private clinic alone. The duration of their clinical experience varied with 32.5% having practiced less five years, 41.9% for five to ten years and 25.6% for more than ten years.

In patients with DR and no DME, 2% of respondents would order an fluorescein angiography (FA) for eyes with no DR, 33.0% for mild NPDR, 44.3% for moderate NPDR, 51.2% for severe NPDR and 47.8% for PDR [Fig. 1]. Additionally, 1.5% of respondents stated that they would never order FA for a patient with DR and no DME. When asked about which modality they would use to grade the level of retinopathy, only 21.7% stated they would use color photography, while approximately three-quarters of those surveyed stated that they would use dilated fundus exams (DFEs) (67.5%) or FA (70.4%) [Fig. 2]. Of those respondents who said that they would use FA to grade DR, approximately 37.1% (53/143) said they would use FA alone, while a similar number would use a combination of FA and dilated eye exam (59/143) [Fig. 2]. A breakdown of imaging modality used by years of experience is shown in Supplementary Fig. 1 showing no substantial differences between the groups. Use of CI varied with 53.2% of respondents saying they would never order CI alone without FA, while 38.4% said they might do it occasionally and only 7.9% responding that they would do so often [Supplementary Fig. 2]. When planning treatment for patients with DR without DME, 18.2% said that they would use CI, 53.2% said they use DFE and approximately three-quarters responded with FA (74.4%) [Fig. 3].

For levels of retinopathy less than PDR, 52.2% respondents said they would perform panretinal photocoagulation (PRP) in eyes with severe NPDR and 21.2% said they would do so in eyes with moderate NPDR [Fig. 4]. For the first line management of PDR, 93.5% of respondents used some form of laser therapy whether it be full PRP (30.5%), one or more anti-VEGF followed by full PRP (45.3%) or FA-guided targeted PRP to ischemic areas (17.7%) [Supplementary Fig. 3]. Very few respondents used anti-VEGF alone to manage PDR (6.4%) [Fig. 5]. Post-PRP, most ophthalmologists determined the need for further management based on FA either occasionally (23.8%) or often (32.2%) or almost always (42.6%) [Supplementary Fig. 4].

It is estimated that 8.9 million Egyptians had DM in 2019 and based on data from a large DR screening program, it is

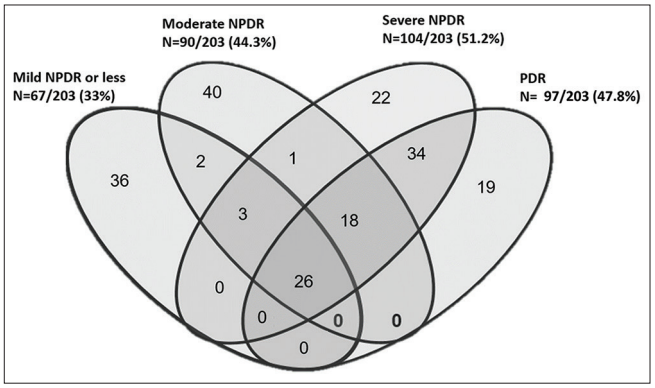

Figure 1: Level of diabetic retinopathy without edema for which respondents (n = 203) would order a fluorescein angiography (FA)

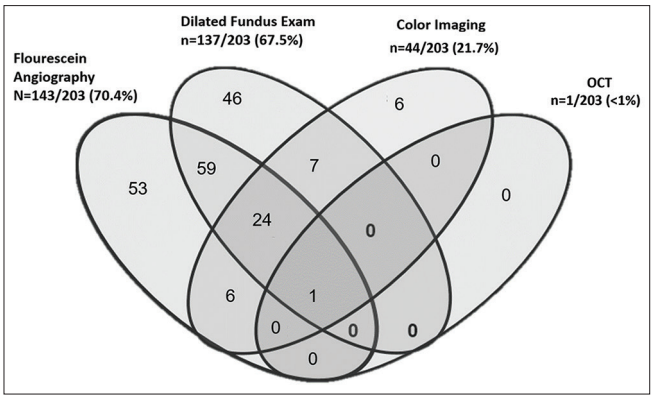

Figure 2: Imaging modality respondents ($n = 203$) would use to grade diabetic retinopathy in eyes without edema

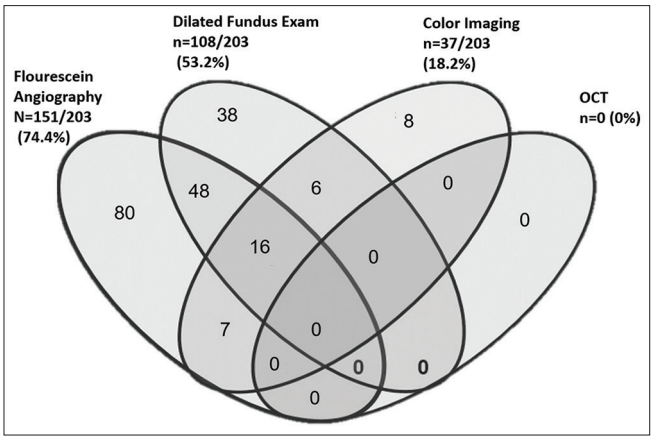

Figure 3: Imaging modality respondents ($n = 203$) indicated they would use to treat diabetic retinopathy (DR) without edema

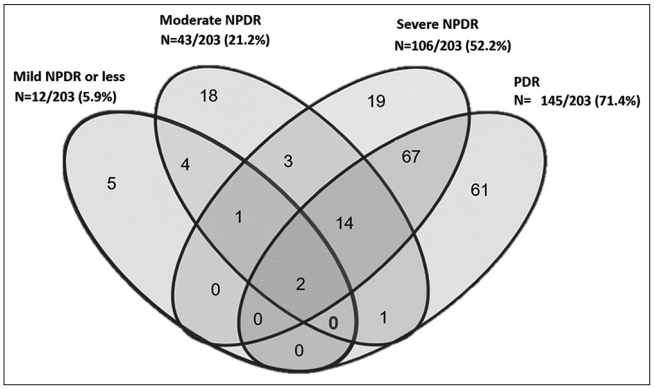

Figure 4: DR severity levels for which pan-retinal photocoagulation is performed per respondent responses

estimated that 4.4% would have moderate NPDR and 8.1% would have mild NPDR on CI.[1,13] An analysis of data from respondents who would order an FA for moderate NPDR or less, use FA to grade retinopathy and treat patients with moderate or severe NPDR was conducted [Fig. 5]. Additionally, data from a recent study was used which suggested that 21% of eyes with mild NPDR when graded on FA would be moderate and 41% of eyes with moderate NPDR on FA would be graded as severe NPDR.[8] Calculation of the total additional eyes that would appear to require PRP due to FA usage was estimated to be 78,820. Based on the current estimated cost of a single PRP session of 1000 EGP or 64 USD, it is estimated that an additional cost of 156,640,000 EGP or 10,105,128 USD would be needed. In addition, given that the number of diabetics is expected to double by 2045, the projected estimated increased cost would be 313,280,000 EGP or 20,210,256 USD by that date.

Discussion

The responses of this Egyptian ophthalmologist survey highlight the use of FA as the primary imaging modality for grading and management of DR without DME. This is clinically relevant given that FA is not intended to be used as a tool for screening and follow-up of DR. This approach hypothetically results in an additional 300,000 FAs in patients with mild and moderate NPDR, and a projected additional 78,820 PRPs that would not have been performed if using standard color imaging. The projected financial burden for these procedures is estimated to be 10.1 million USD in 2019, doubling to 20.2 million USD by 2045. The landmark ETDRS study demonstrated the benefits of PRP in eyes with high-risk PDR in reducing severe vision loss.[4,5] In a separate analysis, patients with type 2 DM (but not type 1 DM) and severe NPDR benefited from having early scatter PRP.[14] The vast majority of patients with DM in Egypt have type 2 DM, and thus may benefit from PRP in those eyes with severe NPDR.[15] However, this determination is based on CI analysis and not FA. The results of this study highlight the reliance of Egyptian ophthalmologists on FA to grade retinopathy and the subsequent overestimation of DR severity. In eyes with moderate NPDR, use of FA rather than CI may result in over 100,000 eyes receiving a worse DR severity grade and may lead to PRP being performed in a quarter of them. PRP in itself is not a complication-free procedure and can have several side effects including the development of macular edema, visual field loss, reduced night vision, loss of color vision and reduction in contrast sensitivity.[16] The ETDRS study reported no significant benefit in receiving PRP in eyes with moderate NPDR as graded using CI. Thus, FA use may place patients at unnecessary risks without substantive benefits.[17] Furthermore, the five-year rate of development of high-risk PDR for eyes with moderate NPDR was 26.5%; meaning that three-quarters of those eyes may not need treatment within five years.

The primary choice of treatment for PDR amongst Egyptian doctors is laser therapy with most ophthalmologists either using PRP alone (17.7% targeted PRP and 30.5% full PRP) or a combination of PRP and anti-VEGF (45.3). This is not surprising given the cost-effectiveness of PRP compared to anti-VEGF over five years and the high costs associated with repeated injections, which many Egyptian patients are unable to incur.[18] Furthermore, the poor compliance of many patients in Egypt and the high risk of associated loss of vision amongst patients noncompliant with anti-VEGF appointments, makes PRP a more desirable option for many.[19] Given these results, it is unlikely that many ophthalmologists will recommend anti-VEGF therapy for less severe levels of retinopathy (moderate-severe or severe NPDR), as suggested by the PANORAMA study and the DRCR Retina Network Protocol W.[20,21] Interestingly, most Egyptian respondent MDs follow the outcome of their PRP using FA to determine the need for further therapy, with 42.6% using it always and the remaining either occasionally (23.8%) or often (32.2%). Given

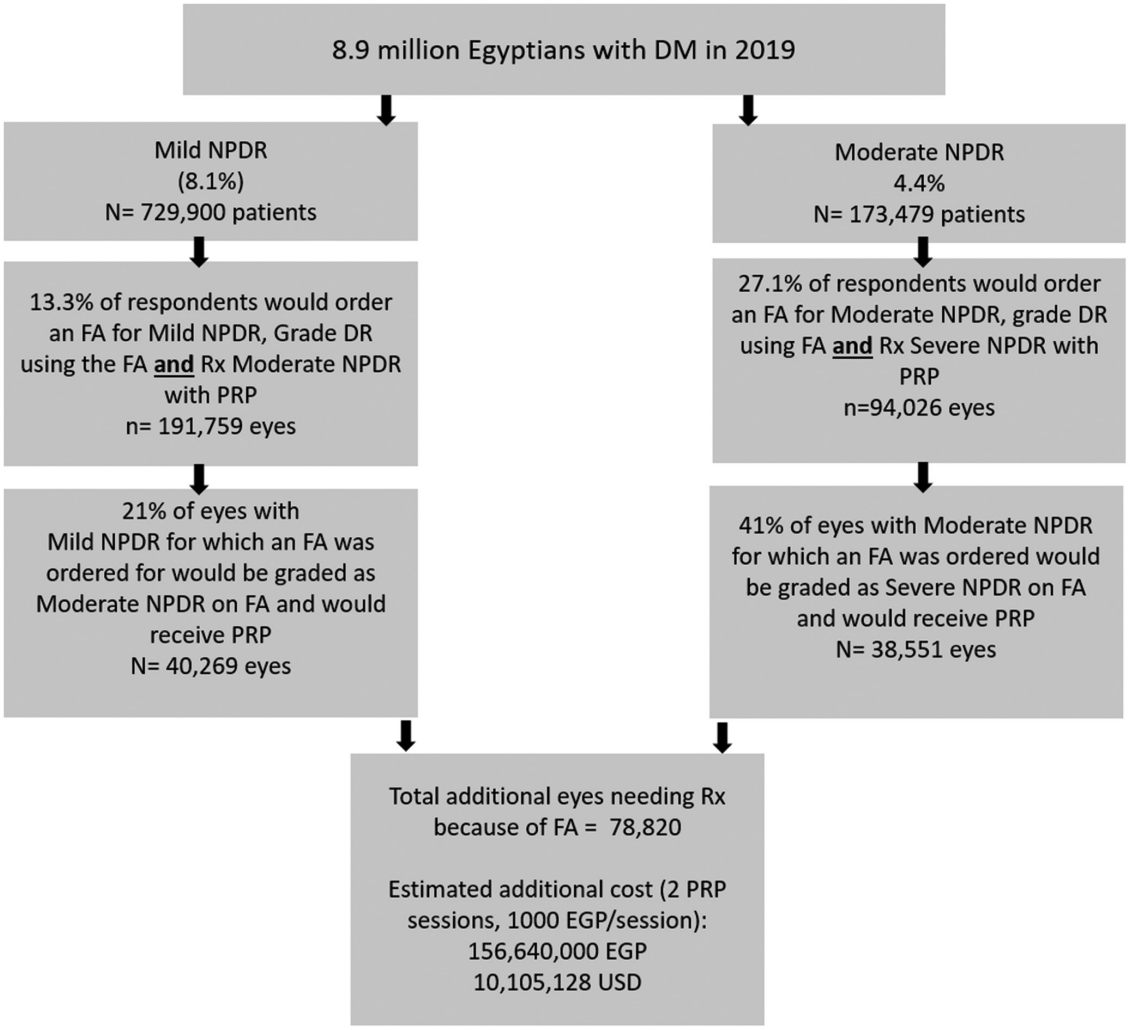

Figure 5: Estimation of additional costs incurred due to PRP resulting from DR grading of FA images, Abbreviations: NPDR=non-proliferative diabetic retinopathy; FA=fluorescein angiography; PRP=panretinal photocoagulation; Rx=treatment

that it is sometimes difficult to differentiate active leakage from staining, especially in larger neovascular membranes and fibrovascular proliferation, this approach may inadvertently result in the risk of over-treatment and the increased likelihood for PRP complications including severe visual field loss.

There remain several unanswered questions regarding the use of FA. It is unclear how baseline non -erfusion measurements may affect progression rates in different DR severity levels. It is also unclear whether the progression rates differ depending on which modality is used to grade the level of retinopathy. Furthermore, the DRCR Retina Network is currently exploring the use of ultrawide field imaging, both color and FA, in the detection of predominantly peripheral lesions and how they may impact progression rates.[22] Currently, there are no ultrawide field cameras in Egypt and the result of the current survey reflect only the use of narrower field cameras that are not as adept at imaging the far periphery. It is also unclear what the exact reason is for over-reliance on FA amongst Egyptian ophthalmologists. Possible reasons could be the lack of training on how to read and interpret color images, the false misconception that grading FA is more accurate than color since you can visualize more DR lesions and the relative ease at detecting neovascularization and differentiating them from intraretinal microvascular abnormalities (IRMA) as compared to color imaging. Another possible reason could be that 78% of respondents were general ophthalmologists with limited training in the management of DR.

Limitations of the current study include the relatively small sample size and, while we calculated the margin of error as ± 6%, the total number of respondents represents only 6% of all ophthalmologists in Egypt. It is possible that patterns will differ in areas with less access to health care and more remote areas in Egypt. However, the clear trend for predominant FA use suggests that the overall trend is likely to remain. Another limitation was that the survey was posted online and response was voluntarily. This limits the ability to know how many deferred participation and whether those that agreed to participate were somehow different in their care paradigms than those who did not respond. Furthermore, this methodology limits our analysis to only physicians with access to internet and social media. Of note, most younger and less experienced MDs usually either consult or communicate with more experienced

practitioners regarding their medical retina cases. Finally, the cost projections incorporate several broad assumptions including that all patients with DM would be screened, that the percentages of DR would resemble those of larger screening programs in developed countries such as the US and the UK and that all those identified for treatment would receive the necessary therapy. No adjustments were made for poor patient compliance and the lack of a national screening program.

Conclusion

In conclusion, the current study highlights how reliance on FA rather than standard color images for DR assessment may be affecting treatment and costs in Egypt. The study also highlights the lack of utilization amongst ophthalmologists in Egypt of color fundus photography. This may impact the development of a national screening program, given the general worldwide use of CI for such endeavors and the poor feasibility of FA for mass screening efforts. Furthermore, if FA were to be used in such a national program, it might be associated with unnecessary referrals which may overwhelm the health care system. With artificial intelligence expected to be widely used in future DR screening programs, it is possible that adoption of AI approaches based on CI may be met with significant resistance in Egypt. Increased formal training in the management of vitreoretinal disorders and education regarding the use of CI as opposed to FA amongst practicing ophthalmologists may be needed to increase their confidence in that modality and help the establishment of successful screening initiatives. Finally, results of the upcoming DRCR Retina Network Protocol AA may provide further guidance as to when FA may be applicable in a clinical setting.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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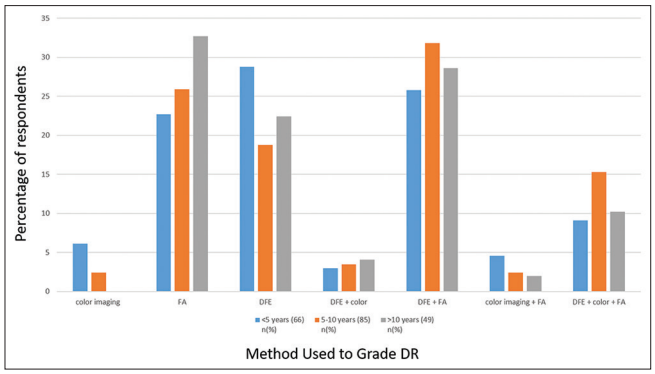
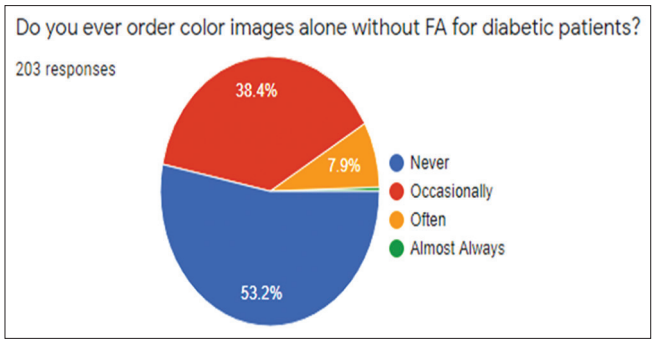
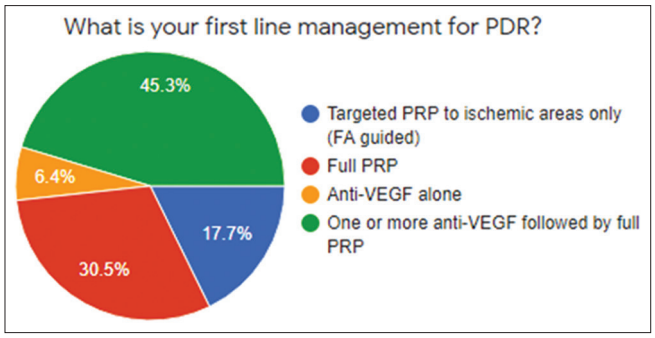


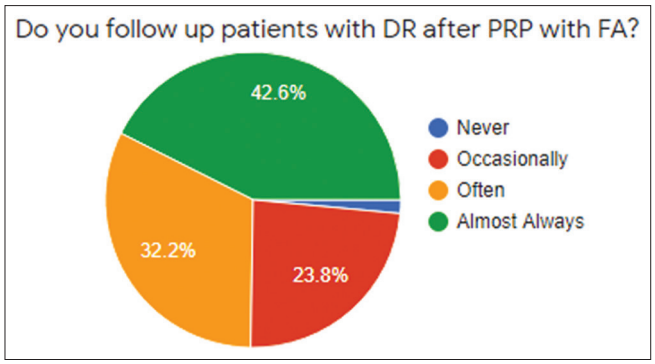
Supplementary Figure 1: Method used to grade DR severity stratified by years in practice



Supplementary Figure 2: Percentage of respondents ordering FA alone for diabetic patients



Supplementary Figure 3: Respondent responses for their choice of first-line management for PDR



Supplementary Figure 4: Percentage of respondents who follow DR after PRP with FA