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Original Article

Ophthalmology Section

Progression of Diabetic Retinopathy during COVID-19 Pandemic: A Retrospective Study

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ABSTRACT

Introduction: Emergence and subsequent exponential spread of Coronavirus Disease-2019 (COVID-19) infection during 2020 forced the Government to issue countrywide lockdown from March 2020. Diabetic Retinopathy (DR) is one of the debilitating diseases of the eye which requires regular follow-ups and timely intervention to prevent permanent vision loss. The impact of countrywide lockdown on prevalence and progression of DR needs to be evaluated.

Aim: To assess the effect of COVID-19 pandemic situation on the prevalence and progression of DR and analyse the possible risk factors for progression of DR in the ongoing pandemic period by comparing retrospective data from immediate prepandemic quarter with post lockdown quarter.

Materials and Methods: This retrospective study was conducted in the Department of Opthalmology at Regional Institute of Ophthalmology, Kolkata, West Bengal, India. The study was done during the prepandemic period, from November 2019 to February 2020. In the present study, a cohort of 83 diabetic patients with pre-existing DR was selected from past medical records and compared with post lockdown period during November 2020 to February 2021. Data regarding prevalence of various types of DR, mean Central Macular Thickness (CMT), mean Visual Acuity (VA), proportion of patients requiring >3 doses of monthly anti-Vascular Endothelial Growth Factors (VEGF) and additional laser therapy or vitrectomy, VA improvement and reduction of mean CMT were gathered and compared between those two quarters. The data was analysed using Statistical Package for Social Sciences (SPSS) version 25.0.

Results: The prevalence of moderate Non Proliferative Diabetic Retinopathy (NPDR) (13% vs 25%), severe NPDR (19% vs 8%), Proliferative DR (PDR) (18% vs 7%), Advanced Diabetic Eye Disease (ADED) (4.8% vs 1%) and Diabetic Macular Oedema (DME) (62% vs 28%) increased several folds during post lockdown quarter in comparison to prepandemic quarter. There was a statistically significant difference (p-value<0.05) in baseline mean LogMar Best Corrected Visual Acuity (BCVA) (0.4±0.08 vs 0.9±0.07), mean CMT (386.4±26.8 to 421.8±21.6) positive correlations of some of the possible risk factors for poor visual outcome among the same cohort of patients in the post lockdown period: poor socioeconomic status (35%; Odds Ratio (OR):3.59, Relative Risk (RR):2.68), irregular diabetic medication (52%; OR:3.56, RR:2.23), residence more than 100 km from the hospital (38%; OR:3.03, RR:2.26).

Conclusion: The present study, concludes that, the status of DR stage among study subjects in the post lockdown period has deteriorated when compared with the prepandemic period.

Keywords: Coronavirus disease-2019, Eye disease, Risk factors, Visual outcome

INTRODUCTION

The DR is a chronic disorder of the microvasculature of the retina [1] affecting roughly 93 million patients worldwide [2]. Although, the sequelae of untreated DR can be debilitating, repeated studies have shown that, timely treatment can significantly reduce visual loss in patients with DR [3,4]. Despite this, patient compliance with timely follow-up remains a significant barrier to prevent severe vision loss in the diabetic population [3,4]. DR is expected to become an increasingly common cause for morbidity in the developing world, over the coming decades. There has been a well documented rise in the cases of diabetes in the developing world. Prevalence of DR in India is expected to increase 3-fold by the 2025 [5,6]. The overall prevalence rates of DR in India, have been seen to vary between 3%-5% in urban populations [7] and approximately 1.1% in rural populations [8]. The DR is classified as: very mild NPDR, mild NPDR, moderate NPDR, severe NPDR, ADED and DME, based on internationally accepted Early Treatment Diabetic Retinopathy Study (ETDRS) classification of DR [9].

The advent of Intravitreal Injections (IVIs) of anti-VEGF has revolutionised the management of DR. Studies regarding the efficacy of IVIs of anti-VEGF have shown comparable and potentially superior outcomes to Pan Retinal Photocoagulation (PRP) therapy [10,11]. However, both PRP and IVIs of anti-VEGF require regular patient follow-up to evaluate the response to therapy and the need for further drug intervention to prevent disease progression. As the COVID-19 pandemic emerged and was increasing at an exponential rate during 2020, the Government issued a countrywide lockdown from March, 2020 (order No.40-3/2020-DM-I(A) dated (24.03.2020) [12]. This situation affected almost every aspect of the lives up to a great extent. Even after extensive search, similar studies involving DR who compared the progression of disease between the prepandemic period with the post lockdown period, could not be accessed.

Hence, the present study was conducted to assess the effect of COVID-19 pandemic situation on the prevalence and progression of DR patients. The retrospective data from immediate prepandemic quarter regarding prevalence of DR has been compared with post lockdown quarter on a cohort of DR patients. The study has also analysed the possible risk factors for progression of DR in the ongoing pandemic period among the same cohort of study subjects.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Opthalmology at Regional Institute of Ophthalmology, Kolkata, West Bengal, India. The study was done during the prepandemic period, from November 2019 to February 2020. The study was approved by the Institutional Review Board (IEC no. EC/RIO-62/2021). The data analysis was done after February, 2021. The same cohort of patients was compared for four months in the immediate pre lockdown period and post lockdown period.

Inclusion criteria: Patient's who were diagnosed with DR during prepandemic quarter.

Exclusion criteria: Patients with co-existing systemic diseases like hypothyroid, hypertension, dyslipidaemia were excluded from the study. Patients who did not turn up in the post lockdown quarter or whose follow-up was not regular or who developed systemic complications related or unrelated to diabetes mellitus were also excluded from the study. Patients with co-existing non diabetic ocular diseases (retinal pathology in addition to DR e.g., co-existent retinal vein occlusion, macular degeneration, etc.,) and the patients, whose complete clinical data and history could not be retrieved from past records in the prepandemic quarter were excluded too.

Study Procedure

In this retrospective study, first a cohort of 83 diabetic patients with pre-existing DR was selected from past medical records who attended the eye clinic during the study quarter of November 2019 to February 2020 (hence, forth referred as prepandemic quarter) after doing simple random sampling. These same cohorts were again examined and treated as and when necessary, between November 2020 to February 2021 (hence, forth referred as post lockdown quarter).

Baseline characteristics e.g., serum Fasting Blood Sugar (FBS)/ Postprandial Blood Sugar (PPBS) HbA1c and ocular data including VA; intraocular pressure; presence of DME, Neovascularisation of the Disc (NVD), Neovascularisation Elsewhere (NVE), and Vitreous Haemorrhage (VH); Tractional Retinal Detachment (TRD), Neovascularisation of the Iris (NVI), and Neovascular Glaucoma (NVG) were gathered at the visit during prepandemic quarter and the return visit after ending of lockdown period. VA was recorded using the best available Snellen VA and was converted to the logarithm of the minimum angle of resolution (LogMar) for analysis. These parameters were evaluated by slit lamp biomicroscopic examination augmented with stereoscopic +90 D evaluation of posterior segment of eye ball. Fundus photography and fluorescein angiography were also performed at enrolment and when indicated for confirmation when doubted. In the prepandemic quarter, the clinical data and relevant history was extracted from the hospital records section and from patients' personal medical records. In the post lockdown quarter, valid informed written consent for inclusion in the study was obtained from every study subject included in the same cohort of 83 patients and were comprehensively examined, investigated and treated {IVI of anti-VEGF/laser/positive predictive value (PPV)} and followed-up for four months.

STATISTICAL ANALYSIS

The data obtained from prepandemic quarter was compared with that of the post lockdown quarter and analysed using SPSS version 25.0. Paired t-test was performed for comparison and correlation of probable risk factors with the outcome was assessed by calculating odds ratio. Statistical significance was set at p-value<0.05.

RESULTS

A cohort of 83 patients with DR, who satisfied the inclusion criteria was included in the study. Progression of DR status during the delayed follow-up period (the patients were advised to follow-up between 4-5 months) is summarised in [Table/Fig-1]. The prevalence of different stages of DR was compared between the prepandemic quarter and the post lockdown quarter among the same cohort of patients: prevalence of moderate NPDR (13% vs 25%), severe NPDR (19% vs 8%), PDR (18% vs 7%), ADED (4.8% vs 1%) and DME (62% vs 28%) increased several folds during post lockdown quarter in comparison to prepandemic quarter whereas, prevalence of very mild NPDR (34% vs 19%) and mild NPDR (29% vs 14%) decreased; these differences were statistically significant (p-value <0.05) except ADED group (p-value=0.2, Z-value is -1.4) [Table/Fig-1]. There was a statistically significant difference (p-value <0.001) in baseline mean LogMar BCVA (0.4±0.08 vs 0.9±0.07) and mean CMT (386.4±26.8 to 421.8±21.6) between prepandemic quarter and post lockdown quarter [Table/Fig-2].

Category of DR patients presented in OPD	November 2019-February 2020 (Prepandemic quarter)	November 2020-February 2021 (Post lockdown quarter)	p-value	Z-value
Very mild NPDR	34 (41%)	16 (19%)	<0.01	3.0
Mild NPDR	24 (29%)	11 (14%)	0.01	2.5
Moderate NPDR	11 (13%)	21 (25%)	0.04	-2.0
Severe NPDR	7 (8%)	16 (19%)	0.04	-2.0
PDR	6 (7%)	15 (18%)	0.03	-2.1
ADED	1 (1%)	4 (4.8%)	0.2	-1.4
Any stage of DR with DME	24 (28%)	52 (62%)	<0.01	-4.3
Total no. of patients	(N=83)	(N=83)		

[Table/Fig-1]: Number (%) of various types of DR patients before and after lockdown.
'n' represent cohort sample size. DR: Diabetic retinopathy; NPDR: Non proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; ADED: Advanced diabetic eye disease; DME: Diabetic macular oedema; Paired t-test, level of significant p-value <0.05

Parameters	November 2019-February 2020 (Prepandemic quarter)	November 2020-February 2021 (Post lockdown quarter)	p-value
Mean CMT of patients with DME (μ)	386.4±26.8 (n=24)	421.8±21.6 (n=52)	<0.001
Mean BCVA (LogMar) among NPDR patients	0.4±0.08 (n=76)	0.9±0.07 (n=64)	<0.001

[Table/Fig-2]: Change in mean CMT value and mean BCVA (LogMar) before and after lockdown period.
'n' represent total number of patients at each point of time.
Paired t-test, level of significant p-value <0.05

The post lockdown quarter and prepandemic quarter values of mean FBS (136.4±12.4 vs 121.6±10.6; p<0.001), PPBS (189.3±9.2 vs 176.4±9.8; p<0.001), and HbA1c (7.8±1.2 vs 7.4±1.1; p-value=0.02) were also significantly high [Table/Fig-3].

Parameters	November 2019-February 2020 (Prepandemic quarter)	November 2020-February 2021 (Post lockdown quarter)	p-value
Mean FBS (mg/dL)	121±10.6	136±12.4	<0.001
Mean PPBS (mg/dL)	176±9.8	189±9.2	<0.001
Mean HbA1c (%)	7.4±1.2	7.8±1.1	0.02

[Table/Fig-3]: Change in the mean values of FBS, PPBS, HbA1c before and after lockdown. FBS: Fasting Blood Sugar; PPBS: Post Prandial Blood Sugar.
Paired t-test, level of significant p-value <0.05

A total of 46 (55%) out of 83 patients needed >3 doses of monthly IVI of anti-VEGF, when they resumed follow-up after lockdown in comparison to 16 (19%) out of 83 in the prepandemic quarter. The difference was found to be statistically significant (p<0.001). There was significantly greater number of patients who required either additional laser treatment or PPV during post lockdown quarter (42% vs 13%; 22% vs 8%; respectively; p-value=0.04). However, a statistically significant decrease in proportion of patients having BCVA improvement by >0.2 LogMar scale (45% vs 75%) and >10% reduction in mean CMT (39% vs 68%) among patients who received >3 doses of anti-VEGF during post lockdown quarter (n=46) in respect to prepandemic quarter (n=16) [Table/Fig-4]. Statistical analyses revealed significant and positive correlations of some of the possible risk factors for poor visual outcome among the same cohort of patients in the post lockdown period: poor socioeconomic status, irregular diabetic medication, residence more than 100 km from the hospital; however, past history of COVID-19 infection and obesity (Body Mass Index (BMI) >30 kg/m^2) did not have any positive correlation with the poor visual outcome among the study subjects [Table/Fig-5].

Various types of treatment required	November 2019-February 2020 (Prepandemic quarter)	November 2020-February 2021 (Post lockdown quarter)	p-value	Z-value
>3 monthly dose of IVI of anti-VEGF	16 (19%) (n=83)	46 (55%) (n=83)	<0.001	-4.8
>0.2 LogMar V/A improvement (after monthly 3 doses of IVI of anti-VEGF)	12 (75%) (n=16)	21 (45%) (n=46)	0.04	2.0
>10% reduction in mean CMT value (after monthly three doses of IVI of anti-VEGF)	11 (68%) (n=16)	18 (39%) (n=46)	0.04	2.0
Additional laser treatment	11 (13%) (n=83)	35 (42%) (n=83)	<0.001	-4.2
PPV	7 (8%) (n=83)	19 (22%) (n=83)	0.01	-2.6

[Table/Fig-4]: Comparison of various types of treatment required and response to treatment (reduction of mean CMT or BCVA improvement after three doses of anti-VEGF injection) at previous and current visit after lockdown is summarised.
'n' represents total number of patients at each point of time.
Paired t-test, level of significant p-value <0.05

Risk factors	% of risk	OR	RR	Inference
Lower middle or less socioeconomic status as per modified kuppuswamy scale	35% vs 13%	3.59	2.68	More than twice risk present
Residence >100 km away from hospital	38% vs 17%	3.03	2.26	More than twice risk present
Irregular diabetic medication	52% vs 23%	3.56	2.23	More than twice risk present
History of COVID-19 infection	24% vs 23%	1.07	1.05	Comparable risk
BMI >30 kg/m^2	13% vs 14%	0.9	0.88	Comparable risk

[Table/Fig-5]: Association of various risk factors with poor visual outcome among Diabetic Retinopathy (DR) patients during COVID-19 pandemic. Correlation of risk factors is expressed as Odds Ratio (OR) and Relative Risk (RR).

Regarding the change of residence or socioeconomic status, these alterations might have happened because of the pandemic. For the same reason, many of them could not avail public transport to reach hospital and the distance from the hospital became a major factor. During post lockdown check-up, patients specifically mentioned that, they could not avail the medications locally. The regularity of medications was ascertained by checking their physician's prescriptions, clinical history and blood reports. COVID-19 infection was ascertained based on history checking the treating physician's prescriptions, discharge certificate and laboratory reports.

DISCUSSION

The present study has shown that, among a cohort of DR patients the prevalence of the stages of DR has worsened significantly when compared between the prepandemic quarter and the post lockdown quarter. Abdelmotaal H et al., conducted a study, among 467 PDR patients as study subjects who received prior PRP and or intravitreal anti-VEGF therapy with an aim to find out the causes for loss of follow-up among the study subjects [13]. The authors reported that, the baseline means LogMar BCVA during inclusion of patients who were followed-up was 0.22±0.07 (20/33) and the final mean BCVA was 0.31±0.28 (20/40). In the present study, the mean BCVA deteriorated from 0.4±0.08 to 0.9±0.07. A 9.9% of PDR patients who were followed up required PPV with respect to the 8% in the present study required PPV. Loss of timely follow-up is an important attribute in deterioration of visual outcome among DR patients. In the present study, the effect of lockdown in pandemic period negatively impacted on the visual outcome the cohort patients. Abdelmotaal H et al., also found positive correlation between loss of follow-up among PDR patients and treatment unaffordability, increasing age, lack of social support and increasing number of IVIs [13]. In the present study, too poor visual outcome among the study cohort of DR patients was found to be positively correlated with poorer socioeconomic status, increased distance of residence from hospital and irregular diabetic medication.

Vengadesan N et al., conducted a questionnaire-based study among 500 DR patients with an aim to identify social factors influencing delayed follow-up among study subjects [14]. The authors found that, lack of awareness of visual symptoms, inability to find an attendant to accompany and financial liability had significant positive correlation with delayed follow-up among the study subjects. However, the present study was conducted way before the COVID-19 pandemic. The present study has shown that, increased distance of residence from the hospital and poor socioeconomic status had a significant negative impact on the treatment outcome among the study cohort after the lockdown period. In a multicentre retrospective study by Khan R et al., among DR patients in the Indian subcontinent has identified that, lack of awareness among diabetic patients for visual symptoms as a major factor for increased prevalence and poor visual outcome [15]. The present study also identified PRP as an effective treatment modality for PDR patients. The lacunae of awareness for retinopathy and visual symptoms among patients that was already pre-existing in the subcontinent has been an additional factor in the lockdown period which has further worsened the visual outcome among the study cohort in the present study.

In an African cross-sectional study by Mtuya C et al., to identify the reasons for poor follow-up among DR patient's financial factor was highlighted as the principal factor [16]. The lockdown period has negatively impacted the global economy in more than one way. The present study also echoes the same findings by showing poorer socioeconomic status as an important factor in poorer visual outcome among DR patients in the post lockdown quarter.

In another retrospective cohort study among PDR patients to analyse the outcome of more than 6 months of loss of follow-up with the visual outcome among the cohort by Obeid A et al., it was shown that, the patients, who received combined therapy with intravitreal anti-VEGF and laser had a better visual outcome than patients, who received only intravitreal injections after more than six months of loss of follow-up [17]. The present study has also shown that, in the post lockdown period due to lack of regular follow-up previously during the lockdown period, the visual outcome and reduction of mean CMT was poorer even with three consecutive doses of anti-VEGF injection and additional laser therapy among the study cohort.

Limitation(s)

For risk factor assessment, multivariate analysis was not done. Also, blinding was not done during case selection.

CONCLUSION(S)

The present study concluded that, prevalence, progression among the DR study subjects in the post lockdown has increased when compared with the prepandemic period. The possible risk factors for such outcome, have been attributed to poorer socioeconomic status, irregular antidiabetic therapy and increased distance of residence from the hospital. The COVID-19 pandemic has negatively impacted in the visual outcome of DR patients which may increase the burden of non preventable blindness in the society. However, the present study needs to be followed-up with a community based prospective analysis to investigate the clinical and social outcome of the COVID-19 pandemic among the DR patients in the subcontinent.

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