Original Article

Impact of Coronavirus Disease 2019 Pandemic on the Epidemiology of Intravitreal Injections

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Abstract

Purpose: To evaluate the epidemiologic pattern of intravitreal injections (IVIs) during Coronavirus Disease 2019 (COVID-19) pandemic.

Methods: The records of patients receiving IVIs in two 12-month periods immediately before and after the beginning of the COVID-19 epidemic were included. Age, province of residency, indication, number of injections, and number of operating room (OR) visits were analyzed.

Results: Compared to pre-COVID period, a 37.6% decrease in the number of patients receiving IVI in COVID period was seen (10518 vs. 6569). There was a parallel decrease in the number of OR visits (25590 vs. 15010: 41.4%) and injections (34508 vs. 19879: 42.4%). Regarding IVI indication, age-related macular degeneration (AMD) showed the highest decrease in IVI rate (46.3%) which was significantly higher than decrease in other indications ($P < 0.001$). Retinopathy of prematurity (ROP) patients showed no change after epidemic. Mean overall age in AMD group was the highest (67.7 ± 13.2 years) compared to other indication groups (excluding ROP) ($P < 0.001$); while the mean age of the other indications was not significantly different from each other (excluding ROP).

Conclusions: COVID pandemic decreased the number of IVIs significantly. While previous studies suggested that the AMD patients had the highest risk of visual loss due to failure to receive IVIs in a timely manner, this very same group showed the highest decrease in the IVI number after pandemic. The health systems should devise strategies to protect this most vulnerable group of patients in future similar crises.

Keywords: Age-related macular degeneration, Coronavirus disease, Intravitreal injection

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Introduction

The coronavirus disease 2019 (COVID-19) epidemic changed many practices and even halted elective medical care during its peaks. In March 2020, the American Academy of Ophthalmology recommended that ophthalmologists cease providing nonurgent care during epidemic waves.[1] Gradually, more information became available regarding the efficacy of facial masks as an effective prevention method.[2] Introduction of vaccines is the most promising measure in the fighting against the pandemic, and mass vaccination has led to the relative control of COVID-19.[3]

Intravitreal injections (IVIs) are now considered the standard of care in many retinal disorders. Prior to the COVID-19 pandemic, we reported an average monthly number of 1734 operation room visits for IVIs in our tertiary referral center (Farabi Eye Hospital, Tehran, Iran).[4] On a national scale, the number of injections is staggering; it is estimated that 5.9 million injections were performed in the US in 2016.[5] As IVIs are considered an elective medical measure in most cases, their number as well as the referral pattern of patients receiving them are expected to be influenced by the pandemic.

We conducted this study to evaluate the epidemiologic impact of the pandemic on IVI procedures performed in our center in terms of changes in IVI numbers, IVI indications, and referral patterns of patients. We hope that such studies provide some

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insights into patient-health system behavior during future health crises.

Methods

This retrospective comparative cohort study was conducted at a tertiary referral center (Farabi Eye Hospital, Tehran, Iran). All procedures performed in this study were in accordance with the ethical standards of the Institutional Review Board of Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran (ethical registration code of IR.TUMS.FARABIH.REC.1400.044) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study at the time of injection according to hospital protocols.

Data were retrieved from the hospital electronic registry of patients receiving IVIs between 20 February 2019 and 20 February 2021, covering the 12 months before the official beginning of the COVID-19 epidemic in Iran (20 February 2020) and the 12 months after that. The electronic registry included the names and surnames of all patients, reception number (unique to each patient), birth date, address, injection date, and the diagnostic code. The gender of patients was not recorded. According to the diagnostic code, patients were categorized into 5 groups: (1) Diabetic macular edema (DME)-related indications, (2) choroidal neovascularization (CNV)/age-related macular degeneration (AMD)-related indications, (3) retinal venous occlusion (RVO)-related indications, (4) retinopathy of prematurity (ROP), and (5) miscellaneous indications. Patients were also classified as 1) residents of Tehran province (capital province) and 2) residents of other provinces. National COVID-19 data including daily new infection, mortality cases and periods of quarantine was obtained from Iran Health Ministry databases.

The IVIs of either bevacizumab or triamcinolone acetonide or both together were performed following a defined protocol in a modified operating room (OR) setting that is previously described.[6] ROP injections were conducted following a different protocol which has also been described previously.[7] In cases where both eyes needed to be injected, bilateral injections were performed with separate surgical sets and vials. Hence, the number of injections and the number of OR visits were both extracted from the electronic health registry system.

All statistical analyses were performed using the SPSS software version 24 for Windows (SPSS Inc., Chicago, Illinois, USA). The primary outcomes of this study were the change in total number of injections and the change in various IVIs indications, whereas the secondary outcome was the change in referral pattern of patients. For categorical variables, Pearson Chi-square test was used. The continuous variables were explored for the normality of data using Kolmogorov − Smirnov test, and significant differences between groups were analyzed using Mann-Whitney *U*-test or one-way analysis of variance as appropriate. Correlation between injections and COVID-19 confirmed cases or deaths was assessed by Pearson correlation. Statistical significance was set at $P = 0.05$. In any analyses involving age variable, ROP patients were excluded.

Results

The emergence of COVID-19 epidemic in Iran was officially declared on 20 February 2020.[8] One month after the initial report, the government policy was self-isolation and physical distancing. The National Health Ministry provided a color-coded map of Iranian cities and applied travel restrictions to and from red-coded cities.[8] These policies are generally called "Quarantine" compared to "Lockdown" strategy which is termination of all public events.[9] During the 12-month study period between 20 February 2020 and 20 February 2021, the epidemic had three waves in spring, summer, and autumn of 2020. The first and third waves were approached by national quarantine, and the second wave was controlled by national lockdown.[8]

A total number of 40600 OR visits were recorded during the study period: 25,590 (34,508 injections) in pre-COVID and 15010 (19,879 injections) in COVID periods; a 41.4% decrease in the number of OR visits after epidemic with a parallel decrease in the number of injections (42.4%). Ten-thousand five-hundred and eighteen patients received at least one IVI in pre-COVID as compared to 6569 patients in the COVID period (37.6% decrease). Number of OR visits for corresponding months in the pre-COVID and COVID periods, the associated monthly decrease, and time-point COVID infection and mortality rates are shown in Figure 1 and Table 1. The maximum decrease rate in the number of injections was seen at months 1 and 12 (71% and 69%, respectively).

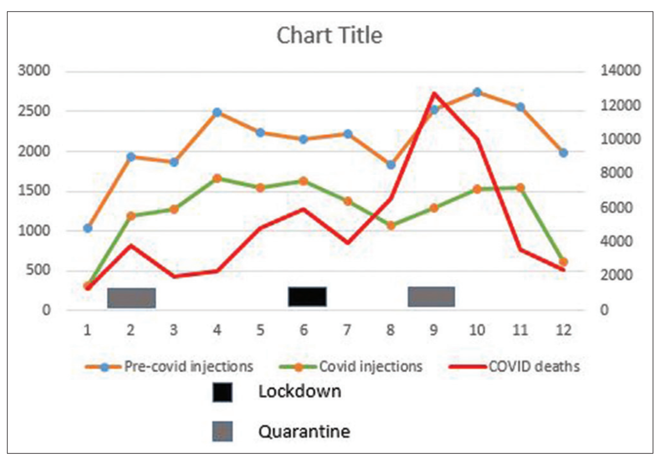

Figure 1: The course of intravitreal injections in 12-month pre-Coronavirus disease (pre-COVID) and COVID periods. The red line represents monthly number of new COVID-deaths; the three deadly peaks were controlled by quarantine and lockdown. The number of injections shows a decrease of 41.4% in COVID period compared to the pre-COVID period. However, the general pattern of monthly changes in the number of injections is quite similar between two periods

No correlation was found between the number of reported national confirmed cases or COVID‑related deaths and IVI numbers ($P = 0.71$ and 0.45, respectively). Number of OR visits for patients during two studied periods is shown in Figure 2.

The mean number of OR visits per patient was 2.43 ± 1.58 and 2.28 ± 1.56 in pre‑COVID and COVID periods, respectively ($P < 0.001$). The mean number of injections per eye was 2.33 ± 1.53 and 2.18 ± 1.49, in the two periods, respectively ($P < 0.001$).

The total number of bilateral injection visits was 8919 (34.8%) and 4869 (32.4%) in pre‑COVID and COVID periods, respectively ($P < 0.001$). The highest rate of bilateral injection in a 2‑year study period was seen in ROP patients (213/247; 86.2%) followed by DME (11195/27928; 40.1%) and AMD (1024/4479; 22.9%). The lowest was seen in RVO (590/4588; 12.9%).

The most prevalent indication in both periods was DME related OR visits; 68.6% (17,542) and 69.2% (10,386) in pre‑COVID and COVID, respectively [Figure 3]. In the pre‑COVID period, AMD was the second prevalent indication of IVI visits with 11.9% (3054) followed by RVO with 11.1%, (2838) while in the COVID period, RVO was the second prevalent indication with 11.7% (1750), and AMD was the third with 9.5% (1425) of all indications. This change was statistically significant ($P < 0.001$). The decreased rate of OR visits between the two periods was 39.4% in RVO, 40.8% in DME, and 53.4% in AMD. The AMD group had a significantly higher decrease in OR visit rate compared to the other two groups ($P < 0.001$). Although the number of ROP OR visits was reduced (127 versus 120 in pre‑COVID and COVID periods, respectively, the corresponding percentage in total OR visits was increased significantly (0.5% to 0.8%, $P \leq 0.01$).

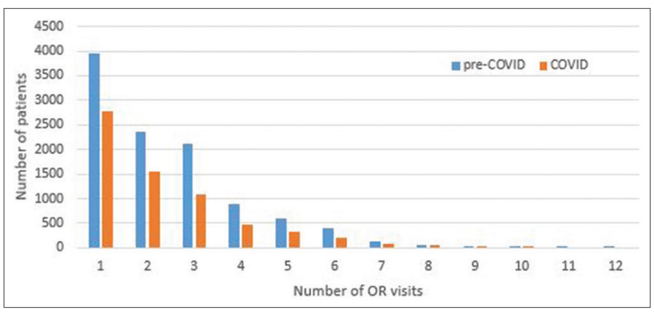

Figure 2: Comparison of the number of patients having specified number of operating‑room visits during pre‑Coronavirus disease (pre‑COVID) and COVID study periods

Parallel to the change in the number of injections, a similar pattern in the number of patients receiving IVIs was observed [Table 2]. AMD patients showed the highest decrease in the number of IVI patients (46.3%) while the number of ROP patients showed no decrease (0%).

The age and residence of patients in each category are summarized in Tables 3 and S1. The mean age of patients (excluding ROP patients) was 61.6 ± 11.3 years. The mean age of COVID subgroups (excluding ROP patients) were statistically lower from pre‑COVID subgroups [Table 3]. The mean age of ROP patients was not statistically different between the two time periods (55.7 ± 23.7 days vs. 54.4 ± 26.5 days; $P = 0.9$).

In the pre‑COVID period, the percentage of patients from outside of Tehran province ranged from 34.6% to 38.9% in different categories, quite similar to each other, with the exception of ROP patients; ROP patients were mostly from non‑Tehran provinces either in pre‑COVID (55.1%) or COVID (60.8%) periods. Compared to pre‑COVID period, no significant change was seen in referral pattern in any indication subgroup in the COVID period, $P = 0.62$ [Table S1].

Table 1: Number of intravitreal injections during pre‑Coronavirus disease (pre‑COVID) and COVID study periods and corresponding monthly decrease, national monthly COVID cases, and national monthly COVID deaths

Months	1	2	3	4	5	6	7	8	9	10	11	12	Total
Pre‑COVID injections	1042	1926	1863	2499	2234	2160	2224	1828	2531	2753	2554	1976	25,590
COVID injections	298	1192	1271	1669	1540	1624	1370	1075	1289	1529	1544	609	15,010
Decrease rate	0.71	0.38	0.32	0.33	0.31	0.25	0.38	0.41	0.49	0.44	0.40	0.69	0.41
COVID deaths	1284	3834	2001	2273	4796	5937	3993	6594	12,705	10,031	3525	2368	59,341
COVID infections	18,407	63,804	42,392	75,659	73,526	76,491	68,764	115,588	280,486	336,955	190,062	216,025	1,558,159

COVID: Coronavirus disease

Table 2: Distribution of number of intravitreal injections patients among different indications in pre‑Coronavirus disease (pre‑COVID) and COVID periods

	DME	AMD	RVO	Others	ROP	Total	*P**
Pre‑COVID	6877	1205	1140	1180	116	10,518	$P<0.001^{\S}$
COVID	4359	646	701	747	116	6569	
Decrease rate (%)	36.6	46.3	38.5	36.6	0	37.6	

*Chi square analysis, §*Post hoc* test after Chi‑square test (adjusted *Z* value) revealed that changes in “AMD” (P=0.001) and “ROP” (P<0.001) intravitreal injections account for this statistical significance. COVID: Coronavirus disease, DME: Diabetic macular edema, RVO: Retinal venous occlusion, ROP: Retinopathy of prematurity, AMD: Age‑related macular degeneration

Table 3: Overall and per-indication age description in pre-Coronavirus disease (pre-COVID) and COVID periods

Age	DME	AMD	RVO	Others	Overall	*P**	ROP (days)
Pre-COVID	61.4±10.1	67.7±13.2	61.7±11.8	59.6±11.0	62.1±11.1	<0.001§	55.7±23.7
COVID	60.6±10.8	65.5±14.8	60.7±11.8	58.7±11.3	60.8±11.7	<0.001§	54.4±26.5
P¥	<0.001	<0.001	0.001	0.01	<0.001		0.9
Total	61.1±10.4	67±13.8	61.3±11.8	59.2±11.1	61.6±11.3	<0.001§	55.0±25.0

*Comparison of mean age among different indications (analysis of variance; ROP cases were excluded), §A significant difference existed in the mean age of AMD subgroup compared to the others in subgroup analysis ($P<0.001$), ¥Comparison of mean age in each indication among pre-COVID and COVID periods (Mann-Whitney test). COVID: Coronavirus disease, DME: Diabetic macular edema, RVO: Retinal venous occlusion, ROP: Retinopathy of prematurity, AMD: Age-related macular degeneration

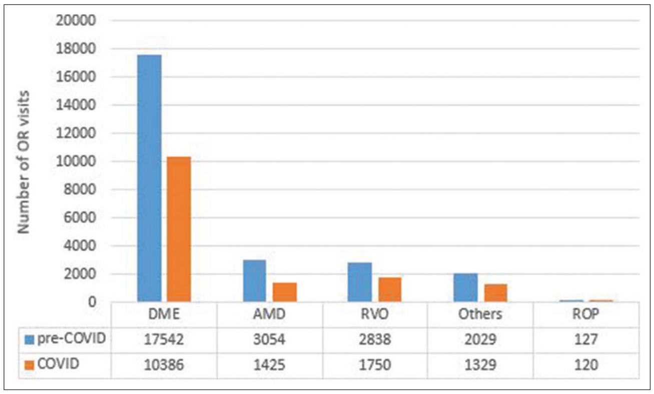

Figure 3: Distribution of intravitreal injection operating room visits for various indications in pre-Coronavirus disease (pre-COVID) and COVID periods. Diabetic macular edema (DME) was the most prevalent indication in both studied periods. The second and third prevalent indications in the pre-COVID period were age-related macular degeneration (AMD) and retinal venous occlusion (RVO), respectively. However, their ranks were switched with each other in the COVID period; AMD patients experienced more decrease in the rate of intravitreal injections (53.4%) compared to RVO or DME patients (39.4% and 40.8% respectively, $P < 0.001$)

Discussion

In this retrospective study, we evaluated the changes in epidemiologic pattern of IVIs in the COVID period compared to the pre-COVID period. The number of IVI-OR visits showed a decrease of 41.4%, and the mean number of IVI-OR visits per patient was reduced from 2.43 ± 1.58–2.28 ± 1.56 after emergence of the epidemic. Similar to the pre-COVID period, DME remained the most frequent cause of IVI in the COVID period while the second most prevalent indication was changed from AMD to RVO. Considering the ratio of non-Tehran-resident patients to Tehran-resident patients, we found no significant change in referral pattern after the beginning of the epidemic.

In a previous report, we described the epidemiology of IVIs in our tertiary referral hospital between September 2014 and November 2016; DM-indications (mostly DME) consisted 62.9%, AMD 15.8%, RVO 14.7%, ROP 1.1%, and miscellaneous indications 5.4% of the total 38165 IVI-OR visits.[4] In the current study, the pattern of IVI indications during the immediate 12-month pre-COVID period was largely in line with our previous report (DME: 68.6%, AMD: 11.9%, RVO: 11.1%, and ROP: 0.5%).

With the emergence of the COVID pandemic, some authors proposed guidelines for ophthalmic care.[10,11] Viola *et al*., from Milan, Italy, suggested a classification of IVI candidate patients into three priority groups: emergent, urgent, and nonurgent.[11] They suggested to perform IVI for emergent patients immediately, and for urgent and nonurgent patients with a possible delay of 2–4 weeks and more than 4 weeks, respectively. Similarly, Carnevali *et al*., categorized their patients into three groups of high, moderate, and low priority with time to act of 3–7 days, 10–15 days, and 30–40 days, respectively.[10] Borrelli *et al*. proposed a rebound effect of postponing treatment during quarantine periods.[12] In our center, although on a nonofficial basis, a similar triage process was followed at the managing ophthalmologists' discretion. We found a 41.4% decrease in IVIs in the COVID period compared to the pre-COVID period, which can be understood as a consequence of decreased number of patients seeking for ophthalmic care [Table 2] as well as decreased IVIs administered by ophthalmologists. Both of these factors are most probably a consequence of concerns regarding the presumed high chance for acquisition of COVID-19 infection in a crowded tertiary hospital setting. Although this study did not evaluate the longitudinal records of patients referring to the clinic to calculate the loss to follow-up rates, Table 2 implies that loss to follow-up was a major event during the epidemic. As Figure 3 depicted, we found that the most prominent decrease of IVIs in the COVID period was among the patients with AMD (53.4%); this decrease was 40.8% for DME IVIs and 39.4% for RVO-related IVIs. The greater decrease in AMD-related IVIs was more than enough to make the AMD the third most prevalent IVI indication in the COVID period, while it was the second most prevalent IVI indication in the pre-COVID period. This finding is also confirmed by the number of patients' decrease rates [Table 2].

In a previous study, it was found that in our center, patients receiving IVI for AMD are almost 10 years older than patients receiving IVI for DM or RVO-related indications.[4] Similarly, in the present study, we found that patients with AMD were older than patients from other subgroups [Table 3]. In pre-COVID period, the mean age of AMD patients was 6.44 (95% confidence interval [CI] of 6.03–6.86) years higher than the mean age of other subgroups (excluding ROP). In COVID period, mean age of AMD patients was 5.06 (95% CI of 4.42–5.70) higher than mean age of other subgroups (excluding

ROP). Considering the fact that very early in the beginning of the pandemic, it was revealed that older age is a major risk factor for the severity of COVID-19 disease, it can be hypothesized that the concerns about COVID-19 infection had its greatest effect on AMD patients compared to the younger groups of patients with other IVI-indications. It is also noteworthy that older people are probably more dependent on their family members for seeking health care services, and this may further compromise the chance for receiving IVIs. This disproportionate decrease of IVIs in AMD patients is especially worrisome, because in most of the proposed triage recommendations for IVIs in the COVID era, AMD-related CNVs were considered an indication with the highest priority.[10,11] It is not unexpected that this decrease in IVIs for AMD patients may have resulted in more loss of vision in this group of patients, a subject that should be addressed in future studies. Previous studies showed that DME patients treated with anti-vascular endothelial growth factor (anti-VEGF) who has been lost to follow-up for a prolonged period of time experienced a modest decline in visual acuity (VA) which could be recovered after restarting the IVI treatment.[13] In contrast, eyes with AMD-related CNVs under treatment with anti-VEGF IVIs who were lost to follow-up, experienced a significant VA decline at the return visit that persisted on the final follow-up despite normalization of macular thickness.[14] In other words, while AMD patients had the highest risk of visual loss after follow-up failure, our study showed that, unfortunately, this senile group had the highest decrease in IVI rates compared to other indications. This finding urges authorities to urgently reform the health care system in ways to protect this vulnerable age/disease group in future similar health crises. On the other hand, the fact that ROP-IVIs, which are usually considered to be an emergent indication, showed no decreased rate during the pandemic is promising and may hint to the relative stability and reliability of national ROP screening and referring system despite considerable stress imposed by COVID pandemic.

In contrast with our study, in a recent study from Houston, Texas, authors compared 7 months of the COVID era (March to September 2020) with averaged 7 months across the past 3 years (2017–2019) and reported 2% increase in IVIs (21,940 vs. 22,418).[15] However, results from other studies are more similar to ours. In Italy (one of the most severely inflicted countries at the beginning of the pandemic), Carnevali *et al*. reported a decrease of 91.7% in (Catanzaro city),[10] and Borrelli *et al*. reported a decrease of 53.6% (Milan city)[12] in number of injections during the quarantine period compared to the same period in 2019. Viola *et al*. from Milan reported that the patients' adherence rate for intravitreal treatment during the quarantine period was 37% as compared to 90% in the same period in 2019.[11] It should be noted that the time periods studied in these reports are different from our study in Tehran or Naguib *et al*. in Texas.[15] Our study is the only one that compared two consecutive 12-month periods before and after the emergence of the COVID epidemic.

We found no significant correlation between the decreased rate of IVIs and the reported confirmed COVID cases or COVID-related deaths. In fact, the most decrease in the IVI rate was seen at months 1 and 12 after epidemic; we cannot explain this finding for now. Figure 1 shows that from month 3 to month 6, COVID cases and deaths were rising as well as IVI rates. However, concurrent with the deadly third wave of COVID outbreak in months 8 and 9, IVI injections were reduced. Finding a comprehensive explanation for this poor correlation pattern needs more in-depth studies on the behavior and dynamism of health systems and individual persons in reaction to an epidemiologic crisis. However, factors like lack of reliable COVID-related statistics, poor agility, and slow reaction of health system to crises, or lack of reliable information and guideline, especially in the early months of the pandemic, may be considered.

The age of patients in different subgroups of DME, AMD, and RVO IVIs was significantly lower in the COVID period as compared to the pre-COVID period. The most obvious hypothesis for this finding is the concern of patients, family members, and physicians regarding the higher chance of severe COVID infection in the elderly patients. Again, this finding points to vulnerability of elderly patients in such epidemiologic settings and emphasize the need to reform the health-care system to be capable of providing elderly patient with health services while protecting them from infection risks.

We found no change in the ratio of IVI patients referred from outside of Tehran province to Tehran province residents in the COVID period compared to the pre-COVID period, which was an unexpected finding. An explanation is that despite efforts to convince people from unnecessary traveling, the closure of ophthalmic care facilities in small cities has left patients with no choice other than to seek care in the remaining active referral centers in large cities. This is an area that needs further research and attention from a health management and service distribution perspective.

As our previous report showed, the majority of ROP-IVI patients were referred from the outside of Tehran province which represents a different pattern compared to other indications of IVIs. The reasons behind this referral pattern and its practical implications have been extensively covered elsewhere and are beyond the scope of the present study.[4] This pattern remained largely unchanged throughout the 24 months of the current study, which probably means that the referral system of ROP patients has not been disrupted by the pandemic to a magnitude that can affect the referral pattern significantly. This hypothesis is supported by the fact that the mean age of ROP-IVI patients remained the same in the COVID period as compared with the pre-COVID period. However, expansion and empowerment of local facilities for ROP care have obvious advantages, especially in the events of infectious epidemics.

The main limitations of this study are its retrospective nature, which was inevitable and possible clerical errors in data entry. A relatively large number of injections and the feasibility of comparison between similar periods in pre-COVID and

COVID eras make our results useful, especially for authorities in health-care systems. We also studied the changes in epidemiologic pattern for each IVI indication separately. This provided us with the opportunity to detect failure to treat rate for each indication separately. It should be noted that in this study, we did not perform an age-adjusted analysis regarding the observed differences in pre-COVID and COVID numbers of injections between the subgroups. Therefore, we cannot evaluate the potential role of factors other than age in the observed difference with certainty. The records of the patients did not include their gender. We also could not differentiate between new patients and patients with previous injections. Therefore, the study of the potential effect of these two factors was not feasible. Further studies may address these issues.

In conclusion, the number of IVI decreased during the epidemic; however, the decrease rate was significantly higher among AMD patients which were older comparing to the other indications. Considering the evidence of significant risk of visual loss after loss to follow-up in AMD patients,[14] health systems should program and run strategies to minimize "the system failure to treat" during epidemics.

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Conflicts of interest

There are no conflicts of interest.

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Table S1: Non-Tehran residents to Tehran residents odds ratio-visit ratio in precoronavirus disease and coronavirus disease periods

Non-Tehran resident's OR-visits	DME, *n* (%)	AMD, *n* (%)	RVO, *n* (%)	Others, *n* (%)	ROP, *n* (%)	Overall, *n* (%)	*P**
Pre-COVID	6062 (34.6)	1068 (35)	1048 (36.9)	790 (38.9)	70 (55.1)	9038 (35.3)	<0.001[§]
COVID	3571 (34.4)	492 (34.5)	602 (34.4)	527 (39.7)	73 (60.8)	5265 (35.1)	<0.001[§]
P[¥]	0.77	0.77	0.08	0.69	0.37	0.62	
Total	9633 (34.5)	1560 (34.8)	1650 (36)	1317 (39.2)	143 (57.9)	14303 (35.2)	<0.001[§]

*Comparison among different indication subgroups (Chi square), [§]*Post hoc* test after Chi square test (adjusted *Z* value) showed the ratio of OR-visit of non-Tehran resident ROP patients was significantly different to other subgroups (*P*<0.001 for pre-COVID, COVID and in overall 24 month study periods, [¥]Comparison between pre-COVID and COVID ratio of non-Tehran residents to Tehran residents OR-visits in each indication subgroup (Chi square). DME: Diabetic macular edema, AMD: Age-related macular degeneration, RVO: Retinal venous occlusion, ROP: Retinopathy of prematurity, COVID: Coronavirus disease, OR: Odd's ratio