Ther Adv Chronic Dis
2021, Vol. 12: 1–15
DOI: 10.1177/20406223211026389

The influence of delayed treatment due to COVID-19 on patients with neovascular age-related macular degeneration and polypoidal choroidal vasculopathy

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Abstract

Purpose: To explore the impact of coronavirus disease 2019 (COVID-19) on the prognosis of patients with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV), and share the experience in managing them during pandemics.

Method: This is a retrospective study of nAMD and PCV patients treated at Peking Union Medical College Hospital from 31 December 2019 to 1 August 2020. Baseline demographic and clinical characteristics, best corrected visual acuity (BCVA), optical coherence tomography (OCT) features, duration of delayed treatment and number of anti-vascular endothelial growth factor (VEGF) injections were analyzed.

Results: A total of 130 nAMD patients (155 eyes) and 76 PCV patients (89 eyes) were identified. Compared to the conditions before COVID-19, the BCVA of delayed cases decreased significantly, and the proportion of patients presenting with sub-macular scar was significantly greater in the delayed treatment group ($p < 0.05$). The BCVA of non-delayed cases remained stable, with the percentage of patients with disease activity sub-retinal fluid and hemorrhage at the fovea decreasing significantly ($p < 0.05$). The stable cases who did not require anti-VEGF treatment had significantly worse baseline and final BCVA, these patients were likely to be chronic and 'burnt out' cases with significantly worse anatomical structures ($p < 0.05$).

Conclusions: The delayed cases due to the pandemic suffered compromised visual function and a higher rate of sub-macular scar formation, while the visual function of non-delayed cases remained stable with favorable anatomical outcomes, suggesting the importance of regular follow-up for nAMD and PCV patients. Besides, effective measures of hospitals during pandemics are crucial to provide timely treatment for chronic disease.

Keywords: COVID-19, neovascular age-related macular degeneration, polypoidal choroidal vasculopathy, prognosis

Received: 10 November 2020; revised manuscript accepted: 1 June 2021.

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Introduction

The novel coronavirus disease 2019 (COVID-19) broke out in December of 2019 and then spread all over the world, with over 100 million confirmed diagnosed cases and one million deaths as of 29 January 2021. The rapid spread of COVID-19, the exhaustion of medical resources, along with different levels of lockdown and quarantine, had a huge impact on patients with chronic diseases, such as cancer, neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV).[1–8] Fortunately, the painful memories and previous experience in handling the severe acute respiratory syndrome (SARS) pandemic in 2003 had prepared China for this pandemic, especially in Beijing.[9–11] During

the COVID-19 pandemic, Peking Union Medical College Hospital (PUMCH) continued to offer routine medical services to patients with chronic diseases.[12,13] We accumulated previous experience in dealing with COVID-19 and managing chronic diseases, such as nAMD and PCV.

At present, nAMD is the leading cause of severe visual impairment in elderly patients and the third cause of legal blindness worldwide, and PCV is regarded as an important subtype of nAMD.[14–16] Fortunately, proper administration of intravitreal injection of anti-vascular endothelial growth factor (VEGF) treatment effectively blocks angiogenesis, and induces the regression of abnormal new blood vessels, leading to stable or even improved vision.[17] However, the delay of anti-VEGF treatment has been shown to lead to significant visual loss and potentially blinding complications, such as sub-retinal hemorrhage (SRH), sub-retinal fibrosis, macular atrophy, and even vitreous hemorrhage (VH).[18–21] Despite our department consistently offering routine medical services during the pandemic, many nAMD and PCV patients could not visit clinics because of the lockdown and quarantine restrictions. This unprecedented situation gave us an unprecedented opportunity to analyze the impact of enforced delay in receiving anti-VEGF treatment for these conditions. Firstly, we could objectively compare the visual outcome of patients who missed their regular follow-up and treatment with those who continued to attend clinics during this outbreak. Secondly, we identified risk factors and disease characteristics for patients who lost vision due to delayed hospital visits, which could help us distinguish those patients who cannot afford to have delayed treatment. In addition, we are glad to share our experience in managing active nAMD and PCV during the COVID-19 pandemic, hopefully to provide a reference for ophthalmologists worldwide, and also better to prepare us for the next crisis.

Methods

Study design

This study was a retrospective review of nAMD and PCV patients continually examined and treated from 31 December 2019 to 1 August 2020 at the Ophthalmology Department of Peking Union Medical College Hospital. This retrospective study was approved by the Institutional Review Board/Ethics Committee of Peking Union Medical College Hospital and conducted following the tenets of the Declaration of Helsinki (no. S-K1632). Written informed consent was provided by each patient before treatment.

Participants

The following inclusion criteria were used: (a) This study included the patients who had had nAMD or PCV before the outbreak of COVID-19, and were followed up at the Ophthalmology Department of Peking Union Medical College Hospital during the research period; (b) Patients with nAMD were confirmed by the presence of active leakage of choroidal neovascularization (CNV) detected by fluorescein angiography (FA) or optical coherence tomography angiography (OCTA); confirmation of PCV was based on the detection of hyperfluorescent dilated polyps with or without branching vascular networks (BVNs) on indocyanine green angiography (ICGA); (c) Patients with detailed medical records underwent necessary ophthalmological examination including at least best corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp examination, optical coherence tomography (OCT) and OCTA. The exclusion criteria were: (a) The presence of CNV related to other etiologies, such as myopia, uveitis or central serous chorioretinopathy; (b) Coexisting ocular disorders, such as retinal vascular occlusion, diabetic retinopathy, retinal vasculitis or neovascular glaucoma; (c) Patients with incomplete medical records, such as the patients who were mainly treated and followed up at other hospitals, the measurement of OCT and the detailed medical records were not achievable; the data of BCVA, IOP, OCT or OCTA data could not be achieved and analyzed for any reason; after diagnosis and developing a treatment plan at PUMCH, the patient decided to go back to their local or nearest hospital to get further treatment and follow-up, the later medical records and follow-up detail were not achievable. The inclusion of those patients was evaluated independently by two experienced researchers (XYZ, LHM) according to the aforementioned criteria. Disagreements were adjudicated by a discussion with the senior corresponding author (YXC). Cases in which the diagnosis could not be made with certainty were also excluded from this study.

Therapy strategy

Our current treatment regimen for nAMD and PCV is 3+pro re nata (PRN): a loading dose of three

intravitreal anti-VEGF injections (0.5 mg/0.05 mL, Lucentis, Genentech Inc.; or 0.5 mg/0.05 mL, Conbercept, Chengdu Kanghong Biotech, Inc.; 2 mg/0.05 mL, Eylea, Regeneron Pharmaceuticals Inc.;) followed by additional injections on an 'as-needed' basis based on any of the following criteria: (a) Visual deterioration of more than two lines (>0.2 logarithm of the minimum angel of resolution, logMAR); (b) OCT evidence of sub-retinal fluid (SRF), intra-retinal fluid (IRF), or SRH; (c) Central retinal thickness (CRT) increasing more than 100 μm on OCT images; (d) Leakage detected on FA and ICGA examination.[22] The follow-up intervals after anti-VEGF injections were ranging from 4 to 6 weeks. Pars plana vitrectomy (PPV) would be performed for patients with unresolved VH.

Statistical analyses

This study was a real-world retrospective analysis. The sample size depended mainly on the number of patients who had nAMD/PCV and visited PUMCH during the research period. Subgroup analysis categorized patients into two groups: the delayed group who missed their regular follow-up visits more than 3 months due to COVID-19, and the non-delayed group who continued to be reviewed and treated as scheduled.

As described in our previous study, pigment epithelial detachment (PED) was classified into fibrovascular PED, serous vascularized PED and hemorrhagic PED.[23] Parameters such as sub-foveal choroidal thickness (SFCT) and CRT were manually measured. All the clinical characteristics and imaging parameters such as the presence of SRF, IRF were collected and evaluated by two retinal specialists (XYZ and LHM). Three measurements were taken by each investigator for each visit and averaged for analysis. For the classification data and descriptive data, evaluation was made separately and the Kappa test was used to assess the inter-rater agreement. The Snellen best corrected visual acuity (BCVA) was converted to the logMAR equivalent for statistical analysis,[24] no light perception (NLP) was set at 2.9 logMAR, light perception (LP) at 2.6 logMAR, hand movements (HM) at 2.3 logMAR, and counting fingers (CF) at 1.85 logMAR.[25] The continuous variables were summarized using mean ± standard deviation (SD) and the categorical variables were analyzed in terms of counts and percentages. The one-sample *t*-test, independent *t*-test and samples paired *t*-test were used to evaluate comparative statistical analyses. The chi-squared test or Fisher's exact test was used to examine categorical variables. Statistical analyses were performed using StataSE 12.0 software (StataCorp, College Station, TX, USA), and a p value less than 0.05 was considered statistically significant.

Results

General data

In total, the Ophthalmology Department of PUMCH had 29,251 outpatient visits (13,921 patients) from 31 December 2019 to 1 August 2020. Among them, 623 patients were diagnosed with nAMD or PCV. After excluding 249 patients who were regularly treated and followed up at other hospitals, 74 patients whose OCT images were unachievable or unmeasurable, 46 patients who were newly diagnosed during the research period, 48 patients demanding further treatment at a local hospital and thus lost to follow-up, 206 patients were finally included in our study, including 130 nAMD patients (155 eyes) and 76 PCV patients (89 eyes) (Figure 1). Their baseline demographics and clinical characteristics are summarized in Table 1. There was no significant difference in baseline characteristics recorded at the last visit before the outbreak of COVID-19 between the two groups ($p > 0.05$). The mean duration of delay was (4.12 ± 0.79) months in the delayed nAMD group and (4.24 ± 0.88) months in the delayed PCV group. The non-delayed nAMD group received significantly more anti-VEGF injections than the delayed nAMD group ($p < 0.001$).

In the delayed nAMD group, the final BCVA became significantly worse than that at the last follow-up before the outbreak of COVID-19 ($p = 0.013$). The final BCVA in the non-delayed group was relatively stable ($p = 0.431$) and significantly better than that of the delayed nAMD group ($p = 0.013$). In addition, the percentage of final SRF, SRH, fluid and hemorrhage at macular fovea decreased significantly in the non-delayed nAMD group ($p < 0.05$), while the proportion of sub-macular scar increased significantly in the delayed group ($p = 0.043$).

There was no significant difference in final BCVA between the delayed and non-delayed PCV group ($p = 0.13$), while the final BCVA of the delayed group became significantly worse than that before

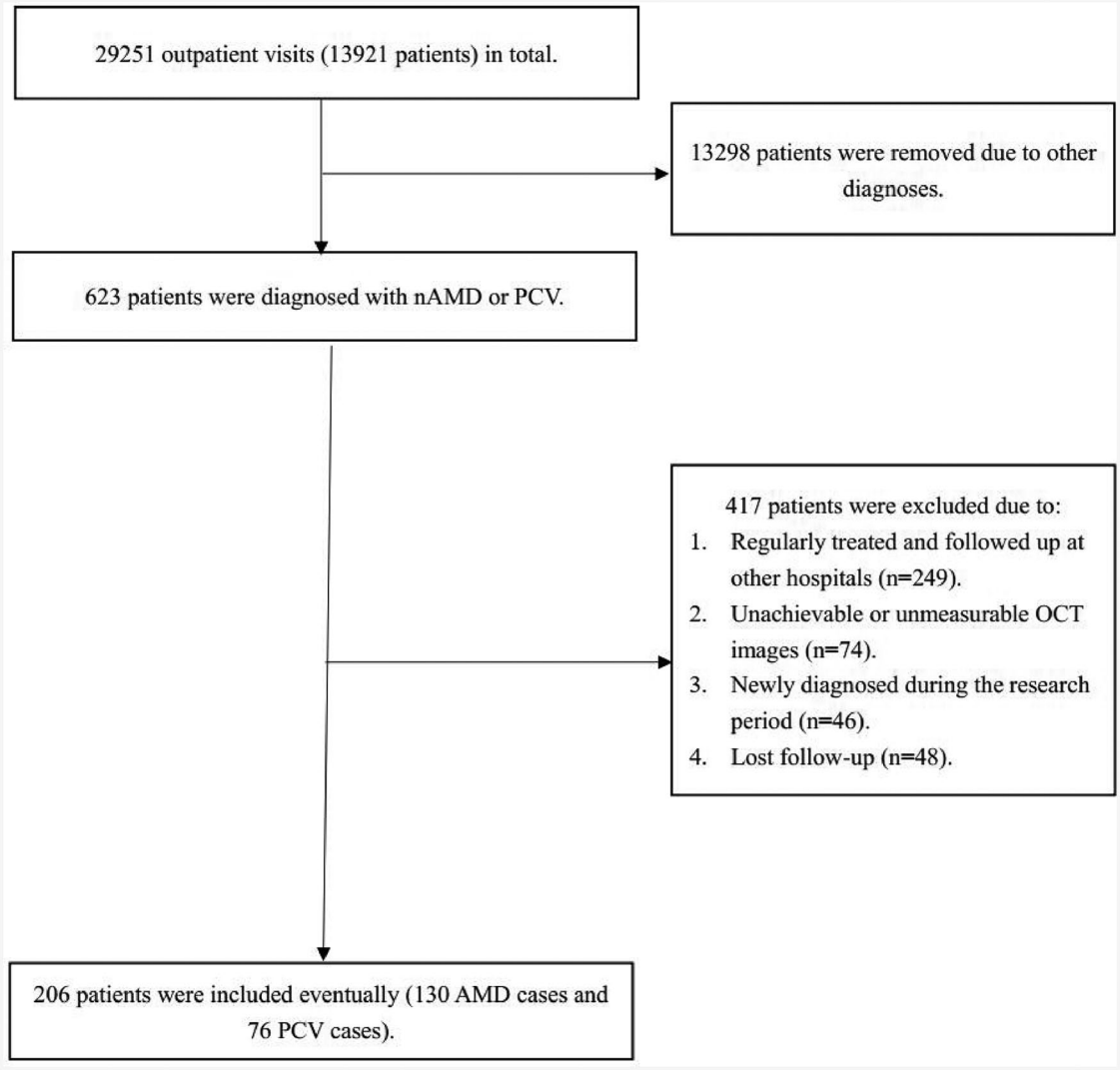

Figure 1. The flow chart of data collection.

the outbreak of COVID-19 ($p=0.044$). The percentage of SRF decreased significantly in both these two groups ($p<0.05$). The proportion of sub-macular scar increased significantly in the delayed group ($p<0.041$), whereas the proportion of fluid at macular fovea significantly decreased ($p<0.025$). In addition, the proportion of hemorrhage at macular fovea decreased significantly in the non-delayed PCV group ($p<0.024$).

Patients receiving anti-VEGF treatment during the COVID-19 pandemic

The clinical characteristics of active nAMD and PCV patients who underwent anti-VEGF treatment during the outbreak of COVID-19 are summarized in Table 2. The non-delayed group received significantly more anti-VEGF injections than the delayed group ($p<0.001$ and $p=0.026$, respectively). The BCVA was relatively stable in the non-delayed group ($p=0.430$ and $p=0.709$, respectively), and significantly better than that of the delayed group ($p=0.027$ and $p=0.043$, respectively).

The percentage of final SRF, IRF, SRH, fluid and hemorrhage at macular fovea decreased significantly in the non-delayed nAMD group ($p<0.05$), while the percentage of sub-macular scar increased significantly in the delayed nAMD group ($p=0.025$). The final CRT, percentage of final IRF and fluid at the macular fovea of the non-delayed group were significantly lower than that of the delayed group ($p<0.05$).

Table 1. Demographics, clinical characteristics and prognosis of delayed/non-delayed nAMD/PCV patients during COVID-19 pandemic.

Characteristics	Delayed nAMD	Non-delayed nAMD	*p*-Value	Delayed PCV	Non-delayed PCV	*p*-Value
Patients (eyes)	82 (96)	48 (59)	NA	44 (49)	32 (40)	NA
Age (years)	74.39 ± 11.37	72.83 ± 10.91	0.401	68.48 ± 8.62	67.81 ± 8.85	0.719
Female (%)	42 (51.22)	22 (45.8)	0.428	23 (52.27)	17 (53.13)	0.675
Pre-BCVA	0.80 ± 0.46	0.82 ± 0.55	0.808	0.87 ± 0.66	0.99 ± 0.46	0.333
No. of previous anti-VEGF injections	6.13 ± 3.77	7.10 ± 3.28	0.105	5.90 ± 3.36	7.17 ± 3.49	0.085
IVR	3.28 ± 1.44	3.66 ± 1.66	NA	3.05 ± 1.38	3.77 ± 1.89	NA
IVC	1.71 ± 1.65	2.05 ± 1.73	NA	1.69 ± 1.86	2.01 ± 1.92	NA
IVA	1.14 ± 2.86	1.39 ± 2.48	NA	1.16 ± 2.57	1.39 ± 2.66	NA
Duration of the disease (months)	43.4 ± 24.17	44.32 ± 24.47	0.819	41.21 ± 36.26	45.05 ± 28.91	0.588
Interval between last injection (months)	4.37 ± 6.72	4.28 ± 8.37	0.941	5.57 ± 9.22	5.64 ± 6.68	0.968
Pre-CRT (μm)	279.81 ± 139.78	281.88 ± 147.21	0.930	228.62 ± 99.65	228.34 ± 125.11	0.991
Pre-SFCT (μm)	173.35 ± 52.93	185.06 ± 81.37	0.279	292.26 ± 88.25	294.27 ± 73.79	0.909
Pre-SRF (%)	33 (34.3)	26 (44.0)	0.228	20 (40.81)	14 (35.0)	0.574
Pre-IRF (%)	27 (28.1)	20 (33.9)	0.448	14 (28.57)	9 (22.50)	0.515
Pre-SRH (%)	10 (10.4)	9 (15.25)	0.373	7 (14.29)	6 (15.00)	0.924
Pre-massive SRH (%)	0 (0)	0 (0)	NA	0 (0)	1 (2.50)	0.919
Pre-VH (%)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Pre-foveal involvement, *n* (%)						
CVN, polyps or BVN	91 (94.8)	55 (93.2)	0.685	46 (93.88)	40 (100)	0.317
Fluid	32 (33.3)	26 (44.1)	0.180	19 (38.78)	13 (32.50)	0.539
Hemorrhage	10 (10.4)	9 (15.25)	0.373	7 (14.29)	6 (15.00)	0.924
Atrophy	24 (25.0)	20 (33.9)	0.233	18 (36.73)	12 (30.00)	0.504
Sub-macular scar	42 (43.75)	31 (52.54)	0.287	23 (46.94)	25 (62.50)	0.143
Types of PED						
Fibrovascular PED (%)	87 (90.6)	51 (86.4)	0.418	42 (85.71)	37 (92.5)	0.313

(Continued)

Table 1. (Continued)

Characteristics	Delayed nAMD	Non-delayed nAMD	*p*-Value	Delayed PCV	Non-delayed PCV	*p*-Value
Serous vascularized PED (%)	10 (10.4)	5 (8.5)	0.691	8 (16.32)	1 (2.50)	0.072
Hemorrhagic PED (%)	1 (1)	0 (0)	0.805	2 (4.08)	1 (2.50)	0.858
Delayed time (months)	4.12 ± 0.79	NA	NA	4.24 ± 0.88	NA	NA
Final CRT (μm)	270.86 ± 112.58	244.46 ± 115.06	0.162	244.64 ± 96.32	221.87 ± 132.31	0.351
Final SFCT (μm)	182.52 ± 64.49	183.14 ± 79.54	0.958	293.96 ± 68.61	296.38 ± 86.22	0.883
Final SRF (%)	28 (29.2)	11 (18.64)*	0.143	10 (20.41)*	6 (15.0)*	0.509
Final IRF (%)	36 (37.5)	12 (20.34)	0.025*	11 (22.45)	9 (22.50)	0.995
Final SRH (%)	4 (4.2)	1 (1.7)*	0.706	6 (12.24)	2 (5.0)	0.414
Final massive SRH (%)	0 (0)	0 (0)	NA	3 (6.12)	2 (5.0)	0.815
Final VH (%)	0 (0)	0 (0)	NA	2 (4.08)	2 (5.0)	0.759
Final foveal center involvement, *n* (%)						
CNV, polyps or BVN	89 (92.7)	55 (93.22)	0.904	46 (93.88)	40 (100.0)	0.317
Fluid	26 (27.1)	6 (10.17)*	0.012*	9 (18.37)*	6 (15.0)	0.673
Hemorrhage	4 (4.2)	1 (1.7)*	0.706	4 (8.16)	0 (0)*	0.182
Atrophy	28 (29.2)	21 (35.59)	0.403	20 (40.82)	13 (32.5)	0.419
Sub-macular scar	56 (58.3)*	33 (55.93)	0.769	33 (67.35)*	27 (67.5)	0.988
Types of PED						
Fibrovascular PED (%)	89 (92.7)	51 (86.44)	0.200	46 (93.88)	38 (95.0)	0.815
Serous vascularized PED (%)	9 (9.4)	3 (5.08)	0.509	9 (18.37)	2 (5.0)	0.114
Hemorrhagic PED (%)	2 (2.1)	0 (0)	0.702	4 (8.16)	3 (7.5)	0.779
No. of anti-VEGF injecion during COVID-19 outbreak	1.10 ± 0.98	1.98 ± 1.31	<0.001*	1.51 ± 1.10	1.47 ± 1.63	0.891
Final BCVA	0.95 ± 0.52*	0.75 ± 0.40	0.013*	1.13 ± 0.60*	0.93 ± 0.63	0.130

*Means $p < 0.05$ in the comparison between pre and final items.
AMD, age-related macular degeneration; BCVA, best corrected visual acuity; BVN, branching vascular networks; CRT, central retinal thickness; CNV, choroidal neovascularization; COVID, corona virus disease; IRF, intraretinal fluid; IVA, intravitreal aflibercept; IVC, intravitreal conbercept; IVR, intravitreal ranibizumab; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; SFCT, sub-foveal choroidal thickness, SRF, sub-retinal fluid; SRH, sub-retinal hemorrhage; VEGF, vascular endothelial growth factor; VH, vitreous hemorrhage.

Table 2. Subgroup analysis of active nAMD/PCV patients who underwent anti-VEGF treatment during COVID-19 pandemic.

Characteristics	Delayed nAMD	Non-delayed nAMD	*p*-Value	Delayed PCV	Non-delayed PCV	*p*-Value
Patients (eyes)	69 (79)	36 (45)	NA	31 (35)	17 (22)	NA
Age (years)	74.55 ± 9.80	73.56 ± 8.76	0.575	69.84 ± 8.03	70.82 ± 8.57	0.664
Female (%)	34 (49.28)	17 (47.22)	0.567	19 (61.29)	10 (58.82)	0.802
Pre-BCVA	0.71 ± 0.46	0.77 ± 0.53	0.510	0.70 ± 0.52	0.81 ± 0.51	0.437
No. of previous anti-VEGF injections	6.64 ± 3.54	7.4 ± 3.07	0.231	5.91 ± 3.43	6.54 ± 3.31	0.497
Duration of the disease (months)	49.97 ± 21.68	46.87 ± 23.7	0.461	39.66 ± 37.92	39.18 ± 22.86	0.958
Interval between last injection (months)	2.42 ± 2.37	2.64 ± 3.33	0.670	2.77 ± 3.70	2.18 ± 2.59	0.516
Pre-CRT (μm)	300.2 ± 142.07	295.35 ± 160.91	0.862	244.90 ± 80.28	253.07 ± 98.04	0.733
Pre-SFCT (μm)	185.24 ± 50.23	193.19 ± 81.68	0.503	312.83 ± 90.24	329.01 ± 59.83	0.461
Pre-SRF (%)	33 (41.77)	26 (57.78)	0.086	20 (57.14)	14 (63.64)	0.627
Pre-IRF (%)	25 (31.65)	19 (42.22)	0.237	11 (31.43)	7 (31.82)	0.975
Pre-SRH (%)	10 (12.66)	9 (20.00)	0.275	7 (20)	6 (27.3)	0.524
Pre-massive SRH (%)	0 (0)	0 (0)	NA	0 (0)	1 (4.55)	0.813
Pre-VH (%)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Pre-foveal center involvement, *n* (%)						
CVN, polyps or BVN	76 (96.2)	44 (97.78)	0.959	35 (100)	22 (100)	NA
Fluid	32 (40.51)	26 (57.78)	0.064	19 (54.29)	13 (59.09)	0.722
Hemorrhage	10 (12.66)	9 (20.00)	0.275	7 (20)	6 (27.3)	0.524
Atrophy	16 (20.25)	12 (26.67)	0.411	10 (28.57)	3 (13.64)	0.191
Sub-macular scar	32 (40.51)	21 (46.67)	0.505	13 (37.14)	13 (59.09)	0.105
Types of PED						
Fibrovascular PED (%)	71 (89.87)	38 (84.44)	0.373	30 (85.71)	22 (100)	0.169
Serous vascularized PED (%)	8 (10.13)	4 (8.89)	0.927	8 (22.86)	1 (4.55)	0.141
Hemorrhagic PED (%)	1 (1.27)	0	0.775	2 (5.71)	1 (4.55)	0.677
Delayed time (months)	4.15 ± 0.85	NA	NA	4.19 ± 0.83	NA	NA
Final CRT (μm)	294.96 ± 114.54	251.3 ± 119.18	0.047*	263.65 ± 89.01	256.22 ± 125.18	0.795
Final SFCT (μm)	193.03 ± 51.89	188.77 ± 72.88	0.706	305.63 ± 59.49	317.88 ± 79.42	0.509
Final SRF (%)	28 (35.44)	11 (24.44)*	0.205	10 (28.57)*	6 (27.27)*	0.915

(Continued)

Table 2. (Continued)

Characteristics	Delayed nAMD	Non-delayed nAMD	*p*-Value	Delayed PCV	Non-delayed PCV	*p*-Value
Final IRF (%)	33 (41.77)	10 (22.22)*	0.028*	8 (22.86)	6 (27.27)	0.706
Final SRH (%)	4 (5.06)	1 (2.22)*	0.765	6 (17.14)	2 (9.1)	0.645
Final massive SRH (%)	0 (0)	0 (0)	NA	3 (8.6)	2 (9.1)	0.679
Final VH (%)	0 (0)	0 (0)	NA	2 (5.7)	2 (9.1)	0.963
Final foveal involvement, *n* (%)						
CNV, polyps or BVN	74 (93.67)	44 (97.78)	0.555	35 (100)	22 (100)	NA
Fluid	26 (36.91)	6 (13.33)*	0.017*	9 (25.71)*	6 (27.27)*	0.897
Hemorrhage	4 (5.06)	1 (2.22)*	0.765	4 (11.43)	0 (0)*	0.266
Atrophy	18 (22.78)	12 (26.67)	0.627	11 (31.43)	3 (13.64)	0.129
Sub-macular scar	45 (56.96)*	23 (51.11)	0.529	22 (62.9)*	15 (68.2)	0.682
Types of PED						
Fibrovascular PED (%)	72 (91.14)	38 (84.44)	0.257	32 (91.43)	22 (100)	0.423
Serous vascularized PED (%)	8 (10.13)	1 (2.22)	0.204	8 (22.86)	1 (4.55)	0.141
Hemorrhagic PED (%)	2 (2.53)	0 (0)	0.738	4 (11.4)	3 (13.6)	0.867
No. of anti-VEGF injection during COVID-19 outbreak	1.78 ± 0.57	2.6 ± 0.78	<0.001*	2.11 ± 0.63	2.68 ± 1.25	0.026*
Final BCVA	0.89 ± 0.51*	0.69 ± 0.42	0.027*	1.04 ± 0.49*	0.75 ± 0.55	0.043*

*Means $p < 0.05$ in the comparison between pre and final items.
AMD, age-related macular degeneration; BCVA, best corrected visual acuity; BVN, branching vascular networks; COVID, corona virus disease; CRT, central retinal thickness; CNV, choroidal neovascularization; IRF, intraretinal fluid; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; SFCT, sub-foveal choroidal thickness, SRF, sub-retinal fluid; SRH, sub-retinal hemorrhage; VEGF, vascular endothelial growth factor; VH, vitreous hemorrhage.

The percentage of final SRF, fluid and hemorrhage at macular fovea decreased significantly in the non-delayed PCV group ($p < 0.05$). The percentage of final SRF and fluid at macular fovea also decreased significantly in the delayed PCV group ($p = 0.016$ and $p = 0.015$, respectively), while the percentage of sub-macular scar increased significantly ($p = 0.031$).

Stable cases and cases required anti-VEGF treatment

We then compared the clinical characteristics of stable cases that did not require anti-VEGF treatment with those required and got anti-VEGF treatment (Table 3). The proportion of stable cases was significantly higher in PCV patients than nAMD patients (20% *versus* 36%, $p = 0.006$).

For nAMD patients, compared to those patients who required anti-VEGF treatment, the pre and final BCVA of stable nAMD were significantly worse, accompanied by a shorter duration of disease, longer intervals between the last injection, thinner CRT and SFCT, and lower percentage of SRF, IRF and SRH ($p < 0.05$). With regard to the foveal involvement, stable cases had a lower percentage of CNV, fluid or hemorrhage, but a higher percentage of atrophy and sub-macular scar ($p < 0.05$).

For PCV patients, the pre and final BCVA of stable PCV also significantly worsened, with longer

Table 3. Subgroup comparison of the clinical characteristics between stable nAMD/PCV cases and active cases required anti-VEGF treatment.

Characteristics	Stable nAMD	nAMD required anti-VEGF injection	*p*-Value	Stable PCV	PCV required anti-VEGF injection	*p*-Value
Patients (eyes)	25 (31)	105 (124)	NA	28 (32)	48 (57)	NA
Age (years)	72.16 ± 16.86	74.21 ± 9.43	0.369	66.52 ± 9.03	70.19 ± 8.15	0.053
Female (%)	13 (52.00)	51 (48.57)	0.935	11 (39.28)	29 (60.42)	0.133
Pre-BCVA	0.96 ± 0.51	0.73 ± 0.49	0.022*	1.25 ± 0.55	0.74 ± 0.51	<0.001*
No. of previous anti-VEGF injections	5.67 ± 3.90	6.92 ± 3.38	0.076	7.03 ± 3.60	6.15 ± 3.37	0.201
Duration of the disease (months)	34.26 ± 24.75	48.85 ± 22.39	0.002*	49.09 ± 33.24	39.47 ± 29.62	0.117
Interval between last injection (months)	8.45 ± 12.39	2.50 ± 2.75	<0.001*	11.05 ± 10.97	2.54 ± 3.30	<0.001*
CRT (μm)	243.00 ± 90.91	298.44 ± 148.55	0.048*	193.65 ± 139.65	248.05 ± 86.80	0.012*
SFCT (μm)	156.22 ± 63.55	188.13 ± 63.26	0.014*	247.01 ± 63.31	319.07 ± 79.68	<0.001*
SRF (%)	0 (0)	59 (47.58)	<0.001*	0 (0)	34 (59.65)	<0.001*
IRF (%)	3 (9.68)	44 (35.48)	0.005*	5 (15.63)	18 (31.58)	0.099
SRH (%)	0 (0)	19 (14.52)	0.043*	0 (0)	13 (22.81)	0.009*
Massive SRH (%)	0 (0)	0 (0)	NA	0 (0)	1 (1.75)	0.768
VH (%)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA

(Continued)

Table 3. (Continued)

Characteristics	Stable nAMD	nAMD required anti-VEGF injection	*p*-Value	Stable PCV	PCV required anti-VEGF injection	*p*-Value
Foveal involvement, *n* (%)						
CNV, polyps or BVN	26 (83.87)	120 (96.77)	0.020*	29 (90.63)	57 (100)	0.082
Fluid	0 (0)	58 (46.77)	<0.001*	0 (0)	32 (56.14)	<0.001*
Hemorrhage	0 (0)	19 (14.52)	0.043*	0 (0)	13 (22.81)	0.009*
Atrophy	16 (51.61)	28 (22.58)	0.001*	17 (53.13)	13 (22.81)	0.004*
Sub-macular scar	20 (64.52)	53 (42.74)	0.030*	22 (68.75)	26 (45.61)	0.036*
Types of PED						
Fibrovascular PED (%)	29 (93.55)	109 (87.90)	0.563	27 (84.38)	52 (91.22)	0.527
Serous vascularized PED (%)	3 (9.68)	12 (9.68)	0.734	0 (0)	9 (15.79)	0.045*
Hemorrhagic PED (%)	0 (0)	1 (0.81)	0.452	0 (0)	3 (5.26)	0.479
Final BCVA	1.01 ± 0.41	0.82 ± 0.49	0.048*	1.24 ± 0.72	0.93 ± 0.53	0.008*

*Means $p \leftarrow 0.05$ in the comparison between stable and active cases.

AMD, age-related macular degeneration; BCVA, best corrected visual acuity; BVN, branching vascular networks; COVID, corona virus disease; CRT, central retinal thickness; CNV, choroidal neovascularization; IRF, intraretinal fluid; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; SFCT, sub-foveal choroidal thickness; SRF, sub-retinal fluid; SRH, sub-retinal hemorrhage; VEGF, vascular endothelial growth factor; VH, vitreous hemorrhage.

intervals between last injections, thinner CRT and SFCT, and a lower percentage of SRF and SRH ($p < 0.05$). For the foveal involvement, stable PCV had a lower percentage of fluid, hemorrhage, while a higher percentage of atrophy and sub-macular scar ($p < 0.05$). In addition, stable cases had a higher percentage of serous vascularized PED ($p = 0.045$).

Discussion

From January to May 2020 in China, many nAMD and PCV patients could not visit clinics because of lockdown and quarantine. When the domestic epidemic improved in May, quarantine and lockdown policies were gradually withdrawn. As PUMCH consistently offered routine medical services and necessary anti-VEGF treatment during the COVID-19 pandemic, we were allowed to compare the visual outcomes of patients with and without regular treatment. The first observation was that BCVA of patients in the delayed treatment group was significantly worse than that of those who continued regular scheduled follow-up; the percentage of sub-macular scar also increased significantly in the delayed treatment group, while the BCVA of non-delayed cases could remain stable, the percentage of SRF and hemorrhage at the fovea decreased significantly. These findings confirmed the importance of regular follow-up and timely anti-VEGF treatment for the management of patients with nAMD and PCV. The proportion of stable cases was significantly higher in PCV patients than nAMD patients. Numerous differences existed when the clinical characteristics were compared between stable cases and cases requiring anti-VEGF treatment. The stable cases had significantly worse baseline and final BCVA, with a longer interval between the last injection, thinner CRT and SFCT, and a significantly higher percentage of macular atrophy and sub-macular scar ($p < 0.05$). These results indicated that the patients who were in a stable condition and not requiring anti-VEGF treatment during the study period were likely to be chronic and 'burnt out' cases with significant macular atrophy.

There was no significant difference in final BCVA between the delayed and non-delayed PCV group ($p > 0.05$), while the final BCVA of the delayed group became significantly worse than that before the outbreak of COVID-19 ($p < 0.05$). The BCVA was relatively stable in the non-delayed group ($p > 0.05$), and significantly better than that of the delayed group ($p < 0.05$). For stable nAMD and PCV patients, the interval between the last injection was significantly longer [(8.45 ± 12.39) months and (11.05 ± 10.97) months], which means these patients were generally stable and dry, they only missed their regular follow-up visits, thus the influence of COVID-19 on them should be minimal. While for active cases requiring anti-VEGF injection, the interval between the last injection was significantly shorter [(2.50 ± 2.75) months and (2.54 ± 3.3) months], so the 3 months delay of regular follow-up visits and the missing of required anti-VEGF treatments could greatly jeopardize the visual function of these patients.

Based on the results of our study and the experience we accumulated during the COVID-19 pandemic, we propose several recommendations for the management of nAMD and PCV patient in similar crises in the future: (a) The follow-up of patients with poor baseline visual function (such as a sub-macular scar with refractory IRF) could be delayed until the crisis is resolved. (b) For patients combined with SRH, regular follow-up is essential. Timely anti-VEGF injection should be applied, as SRH tends to transfer to sub-macular scar without appropriate anti-VEGF treatment, leading to severe and irreversible vision loss.[23] (c) For the delayed patients who have previous SRH, the anti-VEGF treatment must be continued, preferably at a 4-week interval to prevent possible vision loss. (d) The follow-up of patients with macular atrophy and sub-macular scar can likely be extended. (e) For PCV patients who had previous VH, underwent PPV with or without silicone oil tamponade, most of the lesions were relatively stable, the follow-up could be prolonged.

In our hospital, many active measures were taken to deliver the best possible care for patients while minimizing the risk of infection (Figure 2),[26–29] which we would like to share with the ophthalmologists worldwide. Firstly, countless efforts have been made in increasing the screening capacity of COVID-19 since the outbreak. For example, independent mobile cabins for nasopharyngeal swabs were built in less than 2 weeks, namely the Nucleic Acid Clinic, boosting the capacity of nucleic acid testing per day from hundreds to thousands. Doctors and nurses volunteered to rotate in the Nucleic Acid Clinic, taking samples

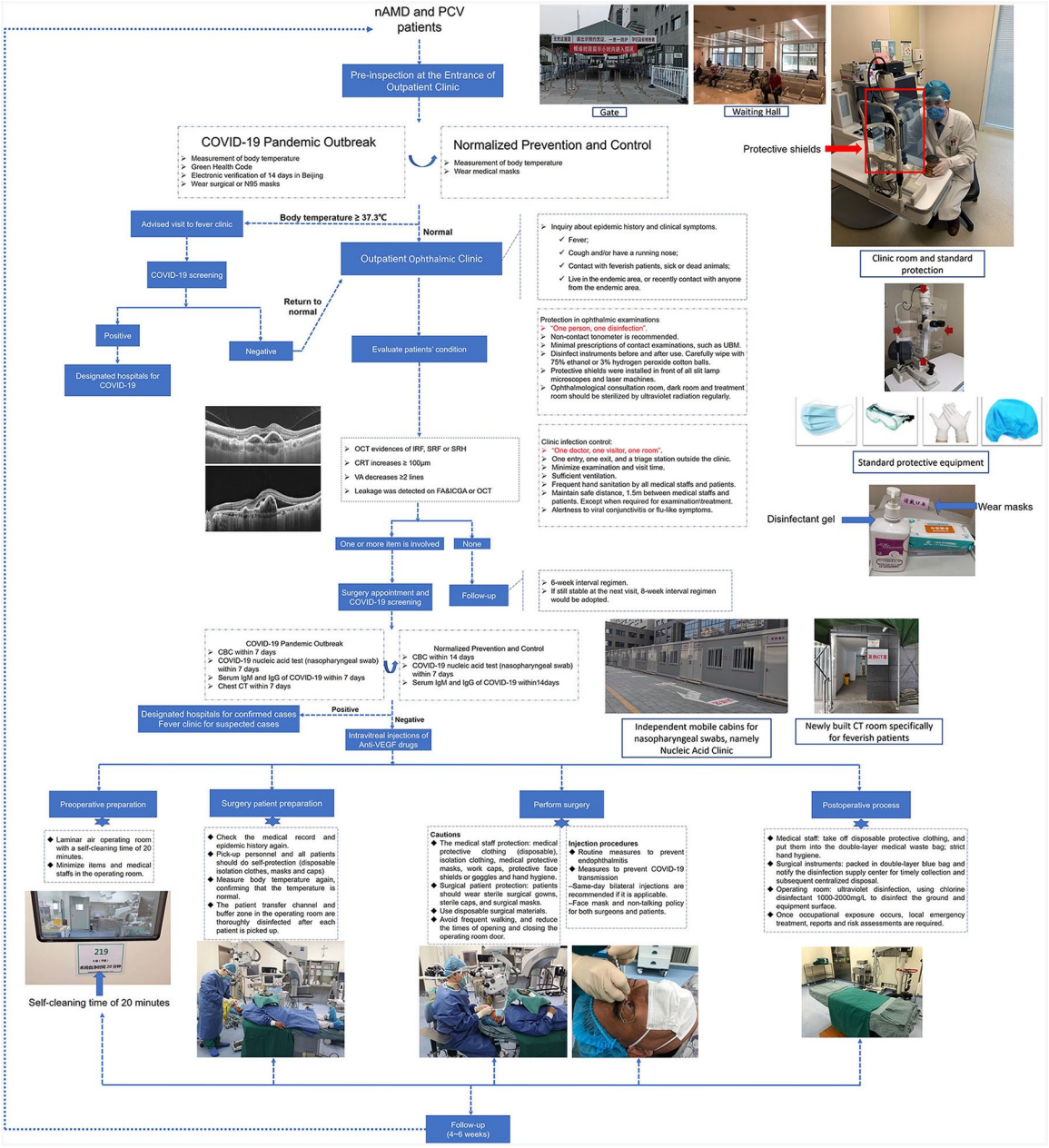

Figure 2. Schematic illustration of our experiences in dealing with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) during the coronavirus disease 2019 (COVID-19) pandemic.

in isolation gowns for consecutively 4–6 h under intense heat, and staff of clinical laboratory counted every minute to report the results. New computed tomography (CT) rooms specifically for feverish patients were built in less than 1 week (Figure 2). Secondly, the criteria to enter the outpatient clinic and operating room (OR) evolved with the severity of the pandemic over time. For example, normal body temperature, a green health code (shown in WeChat, meaning the user had not been to the epidemic area in the last 14 days), electronic verification of 14 days in Beijing and wearing preventive masks were strictly required during the pandemic outbreak. If intravitreal injections were needed then COVID-19 screening was an essential step to exclude asymptomatic infections, including complete blood counting (CBC), nucleic acid test, serum IgM and IgG of

COVID-19 and chest CT within 7 days. When the epidemic eased and it came to regular epidemic prevention and control period, only normal body temperature and medical masks were needed to enter the outpatient clinic, and CT was no longer needed before the surgery. In the meantime, typical prevention measures, such as standard protection of staff, a triage station outside the department, minimizing visit time, disinfection of examination equipment between patients, were also strictly implemented (Figure 2). Thirdly, anti-VEGF treatment regimens were adjusted best to extend visit and treatment intervals. If there were no signs of active lesions (such as IRF, SRF and hemorrhage), or obvious changes of CRT and VA, we advised the patients to re-visit in 6 weeks. If the lesions were still stable at the next visit, an 8-week follow-up regimen would be adopted. Fourthly, the intravitreal injections were strictly implemented according to the protective guidelines. The COVID-19 screening tests must all be negative and patients receiving anti-VEGF injections should come to the hospital at the appointed time. The surgery must be performed in ORs with laminar air flow and only necessary items and medical staff. After the surgery, the OR was required to be disinfected by ultraviolet, then chlorine disinfectant 1000–2000 mg/L to disinfect the ground and equipment surface (see the details in Figure 2).

Several limitations of this study need to be considered: (a) As this is a single center study with a relatively small sample size, the results might not be extrapolated to other populations; (b) The preventive measures in PUMCH might not be suitable for other hospitals, because their locations (PUMCH is located in the center of Beijing), medical resources and capability of medical staffs may not be comparable to PUMCH; (c) Disadvantages are inherent in a retrospective study, different anti-VEGF agents and the different individual conditions might also add to the bias and confounding factors; (d) Due to the quarantine and lockdown policies, some patients from remote areas and cities could not achieve treatment and follow-up at PUMCH. Besides, some elderly patients in Beijing would prefer not to go to the hospital to avoid the risk of cross-infection and exposure to COVID-19, they preferred to delay their routine treatment and follow-up until the end of the pandemic. All these might truly cause some bias to the demographics of our study. However, there were no significant differences in the demographics and clinical characteristics of the included delayed and non-delayed patients in our study, this means the results and conclusion of our study were generally reasonable.

Conclusions

The outbreak of COVID-19 adversely influenced the prognosis of nAMD and PCV patients by causing a delay of diagnosis and anti-VEGF treatment for active disease. Patients who were in the delayed treatment group had significantly compromised visual function and a higher rate of sub-macular scar formation, while the visual function of non-delayed cases remained stable with a favorable anatomical outcome. These findings confirm the importance of regular follow-up and timely anti-VEGF treatment for the management of patients with nAMD and PCV. Of course, rigorous measures of preventing cross-infection and contamination are essential in delivering the best possible care for these patients.

Authors' note

No portion of the contents of this paper have been published previously.

Acknowledgements

The authors would also like to thank Shengzhi Liu for revising the manuscript.

Author contributions

Xinyu Zhao and Lihui Meng carried out the entire procedure including the collection of medical records, image evaluation, statistical analysis and manuscript drafting. Luoming Yue, Weihong Yu and Adrian Koh contributed in drafting and revising the manuscript. Hanyi Min and Rongping Dai helped in data collection. Youxin Chen conceived of the study, coordinated and participated in the entire process of drafting and revising the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship,

and/or publication of this article: This work was supported by The Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2018PT32029).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was provided by each patient before treatment.

Informed consent

Written informed consent was obtained from all individual participants included in the study.

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