



Drop in well-being of ARMD patients under treatment with anti-VEGF injections during the COVID-19 pandemic

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Abstract

Purpose Patients with age-related macular degeneration (ARMD) are required to follow a treatment protocol that requires regular follow-ups. The COVID-19 pandemic has created an additional burden for patients with ARMD under treatment with anti-vascular endothelial growth factor (anti-VEGF) injections, since patients face a congestion of the health system and closing of the outpatient services. This study examines the impact of the uncertainty regarding patients' treatment on their sense of well-being.

Methods This is a longitudinal cohort study of eighty patients who were followed during the year following the outbreak of the COVID pandemic. Patients reported their sense of well-being with the WHO-5 questionnaire and their perception and fears

for the impact of the pandemic on their ongoing ARMD treatment.

Results There was a significant drop in mental well-being during the pandemic that paralleled the self-reported impact of the pandemic on ARMD treatment. Patients who reported a higher impact of COVID-19 on their treatment had experienced a higher drop in mental wellbeing compared to those who hadn't, with female gender being an additional risk factor. Objective measurements of visual acuity did not factor in the drop of sense of well-being.

Conclusions The high initial level of uncertainty regarding ARMD patients' long-term course was further exacerbated when exposed to additional uncertainties during the pandemic regarding their standard of care. Planning ahead for continuation of services and close contact with patients during similar health emergencies is of paramount importance.

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Introduction

Age-related macular degeneration (ARMD) is a degenerative disorder of the macula characterized by a combination of accumulation of both non-neovascular pathology (drusen and changes of the retinal pigment epithelium) and neovascular pathology (choroidal neovascular membrane formation). It results in serious vision impairment characterized by a decline

in sharp, central vision. This decline affects the clarity of focus and greatly impacts common tasks of daily living such as reading and driving. However, ARMD causes no pain and advances very slowly with patients noticing little day-to-day change until late in the disease course, although there are instances with rapid loss of vision in both eyes. The diagnosis of ARMD is based on visual dysfunction and characteristic macular findings [1]. ARMD has been conventionally divided into two main types, dry (non-exudative, non-neovascular) and wet (exudative, neovascular). Modern treatments for wet ARMD are intravitreal injections with anti-vascular endothelial growth factors (anti-VEGF) with a similar effect in improving vision. Unfortunately, the recurrence rate with vision loss after treatment is high and a long-term prognosis is uncertain [2]. Patients are required to keep a scheduled program of regular clinical examinations and subsequent administration of injections, if deemed appropriate, in order to preserve and improve their vision, with a possibility for extending the between-treatment interval should the clinical examination permits. With elderly patients facing other comorbid health issues and uncertainties, it is not uncommon that scheduled appointments are missed. A recent study on the regularity of follow-ups in 109 patients with ARMD concluded that 22% of them had at least one absence of more than 100 days, while only 50% were always on schedule [3]. The more common reasons given for absences were related to the burden of comorbid diseases, issues with the clinic or a change of the attending physician and insurance issues.

The COVID-19 pandemic spread throughout the world during 2019 showing a higher risk of morbidity and mortality in elderly patients [4], who are also the most frequently affected by ARMD. It is thus not surprising that the pandemic has been found to have a detrimental effect on the course of ARMD patients. While outpatient care for all ophthalmic disease has been negatively affected, a recent study showed that ARMD patients were the most impacted, with a 79% drop in outpatient visits and a 53.6% drop in received anti-VEGF injections [5]. The authors speculated that there would be significant repercussions on the visual outcome of patients and this hypothesis was supported by a recent comparative study of ARMD patients diagnosed during the COVID-19 pandemic to patient cohorts from 2018 and 2019; this study concluded that patients with newly diagnosed

treatment-naïve exudative neovascular ARMD referred during the COVID-19 pandemic had worse clinical characteristics at presentation and short-term visual outcomes [6]. COVID-19 pandemic-related postponement in patient care was significantly associated with worse short-term outcomes in ARMD patients in a related study [7].

Methods

Patients were recruited from the outpatient services of the General Hospital of Serres and they were required to be diagnosed with wet ARMD and to be included in a therapeutic protocol with anti-VEGF intravitreal injections with at least three injections in the past. The first wave of measurements took place during June to September 2020, before mass disruption of health provision due to the second wave of COVID-19. The follow-up measurements took place during June to August 2021 following the end of the third wave of COVID-19 locally. Mean duration of follow-up period was 12.6 months ($SE \pm 0.3$ months) the institutional ethics' committee of the General Hospital of Serres has approved the research and all procedures adhered to the Declaration of Helsinki. Exclusion criteria included inability to offer informed consent and the existence of other comorbid eye pathology that could affect visual acuity.

A convenience sample of eighty consecutive patients offered their written informed consent after being informed on the aims of the study and concluded the study while five patients who were approached declined to participate. This included all patients that were followed in the outpatient services. There were no dropouts. A power analysis was conducted where we assumed a moderate correlation coefficient r of 0.4 between the difference in well-being and the impact of COVID-19. This translated to an effect size (d) equal to 0.645. The required sample size for a significance level (alpha) equal to 0.05 and a power index (beta) equal to 0.8 equals 39 patients (or more) [8]. Post hoc we confirmed the correlation coefficient as 0.41.

The patients were handed the research material for completion in paper-pen format. It included a short demographics questionnaire reporting gender, educational status and family status, the World Health Organization Five Well-Being Index (WHO-5) and

five items on the specific impact of the COVID-19 pandemic on the subject's regularity of appointments and subjective fears on the outcome of the underlying disease ("Appendix 1"). There was an effort to address other potential reasons for missing or rescheduling appointments as described above. The patients were followed in the same clinic by the same attending physician and the provision of treatment is equal for all patients in the Greek National Health Service (National Health System—E.S.Y). The items of the questionnaire were worded to specifically address COVID-19 related problems with the appointments.

The WHO-5 is a short, self-report measure of current mental wellbeing, with five items measured on a six-point Likert scale. It has been found to have adequate validity in screening for depression and in measuring outcomes in clinical trials, with good construct validity as a unidimensional scale measuring well-being in both young and elderly populations [9]. The items on the impact of the pandemic were answered in simple yes/no format. These were five items questioning whether the pandemic affected the regularity of the appointments, whether the treatment protocol was applied as planned and fears that their vision has worsened or will worsen during the pandemic and feelings of helplessness related to their vision. Data were collected in two waves, the WHO-5 was recorded twice, once in the beginning of the study and once in the end while the five items on the impact of the pandemic were recorded only in the end. Visual acuity was measured in the Early Treatment Diabetic Retinopathy Study (EDTRS) scale charts. A total result for the five items on the impact of COVID-19 was computed with each item contributing a single point for a 'Yes' response. All data were collected in live interviews during a follow-up in the hospital. Five patients contracted COVID-19 in between the two waves of measurement but their total was too low to be accounted for with a separate variable in the analysis. These five patients survived and kept their scheduled appointments.

All statistical analyses were conducted with the SPSS statistical package, version 25.

All continuous variables were examined for meeting the normality assumption with the Kolmogorov–Smirnov test statistic, and a choice between parametric and nonparametric statistics was made accordingly. Differences between different levels

of demographic (nominal) variables on the measured continuous variables (WHO-5 total score and items related to COVID-19) were assessed with the Kruskal–Wallis test for non-normally distributed variables. Differences in normally distributed continuous variables between the two waves of measurement were assessed with the *t*-test for paired samples while differences in non-normally distributed variables were assessed with the Wilcoxon Signed Ranks test. Correlations between normally distributed variables were assessed with the Pearson's *r* statistic and between non-normal variables with the Spearman r_s statistic. A stepwise regression was employed to assess the more prominent variables in a linear combination to predict the difference in mental wellbeing (difference in WHO-5 scores) between the two waves of measurement. An alpha level of 0.05 was accepted as the threshold for statistical significance. Effect sizes for the differences were calculated and assessed according to accepted guidelines [8].

Results

Patients were nearly equally split on gender, 38 were male (47.5%) and 42 female (52.5%). 25 patients (32.13%) had primary education, 35 patients (43.8%) secondary education while 20 patients (25%) had higher education. Sample demographics and scores on the measured variables are presented in Table 1.

Five patients contracted COVID-19 in between the two waves of measurement but their total number was too low to be accounted for with a separate variable in the analysis.

Comparative results from the two applications of the WHO-5 questionnaire showed a significant decline in all items when comparing results from 2020 to results from 2021, marking a reduced sense of well-being (Table 2). Effect sizes for the differences range from 0.5 to 0.7 denoting moderate clinical significance.

There were no differences between patients of different educational levels with regards to their decrease in WHO-5 well-being scores between 2020 and 2021 (Kruskal–Wallis $H=1.427$, $d.f=2$, $p=0.49$) or their scores in the items related to COVID-19 (Kruskal–Wallis $H=2.542$, $d.f=2$, $p=0.28$). Likewise, there were no differences between patients of different family status with regards to their decrease

Table 1 Sample demographics and results on the measured variables pre- and post-pandemic

Variable		
Gender	Male	38 (47.5%)
	Female	42 (52.5%)
Family status	Living alone	21 (26.3%)
	Live with partner	31 (38.8%)
	Live with children	28 (35%)
Educational status	Primary school	25 (22.7%)
	High school	35 (31.8%)
	Higher education	20 (25%)
Variable	Year	Mean (SD)
Age	2020	73.87 (6.69)
Visual acuity	2020	0.49 (0.29)
	2021	0.52 (0.33)
WHO-5 total score	2020	15.11 (4.07)
	2021	12.91 (4.37)
Total score of items on impact of COVID-19	2021	2.287 (1.72)

Table 2 Paired samples comparison on each individual's responses on the WHO-5 pre- and post-pandemic

WHO-5 item (over the past 2 weeks)	Year	Mean	SD	Mean difference	SD of the mean difference	<i>t</i>	<i>p</i>	<i>d</i>
I have felt cheerful and in good spirits	2020	3.19	1.020	0.500	0.729	6.133	<0.001	0.685
	2021	2.69	0.988					
I have felt calm and relaxed	2020	3.14	0.938	0.538	0.745	6.450	<0.001	0.721
	2021	2.60	0.949					
I have felt active and vigorous	2020	2.90	0.936	0.400	0.722	4.954	<0.001	0.553
	2021	2.50	0.968					
I woke up feeling fresh and rested	2020	3.08	1.077	0.375	0.582	5.764	<0.001	0.644
	2021	2.70	1.107					
My daily life has been filled with things that interest me	2020	2.81	1.032	0.388	0.738	4.698	<0.001	0.525
	2021	2.42	1.111					
Total	2020	15,112	4.07	2.2	2.5	7.863	<0.001	0.88
	2021	12,912	4.37					

(*n* = 80 patients)

in WHO-5 well-being scores between 2020 and 2021 (Kruskal–Wallis $H=0.649$, $df=2$, $p=0.72$) or their scores in the items related to COVID-19 (Kruskal–Wallis $H=4.739$, $df=2$, $p=0.09$).

The difference in visual acuity pre and post COVID-19 did not correlate with the difference in WHO-5 scores between 2020 and 2021 (Spearman $r_s=0.044$, $p=0.69$) or the score of the items related to COVID-19 (Spearman $r_s=0.061$, $p=0.59$).

Responses on the five items related to COVID-19 were compared according to their mean difference on WHO-5 total score 2020–2021, in order to assess whether those patients who reported a negative impact of the pandemic differed in their well-being compared to those who weren't affected (Table 3). Results indicated that in four out of five items (with the exception of item 2 'Has the protocol for your treatment been applied as planned?') those

Table 3 Comparison of the answers on each item of the COVID-19 impact on the total WHO-5 score

COVID-19 impact	Response	<i>N</i>	Mean on total WHO-5 score	SD	<i>t</i>	<i>df</i>	<i>p</i>	<i>d</i>
Has the pandemic affected the regularity of your appointments?	Yes	59	2.559	2.692	2.851	63.272	0.006	0.724
	No	21	1.190	1.503				
Has the protocol for your treatment been applied as planned?	Yes	47	2.319	2.423	0.506	78	0.614	0.115
	No	33	2.03	2.639				
Do you believe that your vision has worsened during the pandemic?	Yes	36	3.111	2.905	2.970	56.670	0.004	0.667
	No	44	1.454	1.835				
Did you fear that your vision may worsen during the pandemic?	Yes	50	2.88	2.73	3.805	77.733	<0.001	0.878
	No	30	1.066	1.529				
Did you feel helpless/despair with regards to your vision problems?	Yes	25	4.2	2.901	4.681	31.292	<0.001	1.129
	No	55	1.29	1.651				

patients who reported a negative impact of the pandemic had a higher drop in the WHO-5 score than those who did not report a negative impact. Patients who believed that their vision had worsened during the pandemic (item 3) did not actually fare worse in visual acuity compared to those who believed that it hadn't (Mann–Whitney $Z=0.412$, $p=0.68$). A stepwise regression analysis with the mean difference on WHO-5 total score 2020–21 as the dependent variable included initially gender, age, visual acuity difference between the two measurements and the total of the five items on the impact of COVID-19 as the independent variables. The final model included only the mean score in the items related to the impact of COVID-19 and gender as important predictors $F(2, 77)=11.695$, $p<0.001$, effect size adjusted $r^2=0.233$ (Table 4). Age and difference in visual acuity were dropped by the analysis. These results denote those females who reported a higher impact of COVID-19 on their treatment experience had a higher drop in mental wellbeing between 2020 and 2021. Objective measurements of visual acuity did not factor in the

drop of sense of well-being. Table 4 presents parameter estimates for all predictor variables.

Discussion

These results indicate that the COVID-19 pandemic was associated with a significant deterioration in the mental well-being of ARMD patients undergoing anti-VEGF treatment. Furthermore, this negative outcome was associated with the treatment setbacks and health-related stress that the patients experienced, while controlling for gender effects. These findings complete the knowledge base on the detrimental effects of the COVID-19 pandemic on the ARMD patients, directly linking the subjective perception of insecurity regarding their treatment to their sense of well-being.

Living with a chronic health condition during the pandemic has added challenges compared to the ones posed by the direct impact on bodily health of the epidemic itself, as shown in a study in France [10].

Table 4 Parameter estimates for a stepwise regression with the difference in mental health status between 2020 and 2021 as the dependent variable

	Unstandardized coefficients		Standardized coefficients	<i>t</i>	<i>p</i>	95% Confidence interval for B	
	<i>B</i>	Std. error				Beta	Lower bound
(Constant)	1.793	0.873		2.054	0.043	0.054	3.531
Total impact of COVID-19	−0.602	0.145	−0.415	−4.152	<0.001	−0.891	−0.313
Gender	1.170	0.497	0.235	2.354	0.021	0.180	2.161

Patients who may not face higher odds of dire circumstances due to their underlying condition itself, will nonetheless face a congestion of the health system and closing of the outpatient services, leading to prolonged stress which may have lasting consequences on their well-being [11]. ARMD patients face an uncertain future, since there is no treatment option that provides a lasting cure. ARMD patients were found to have less hope for the future and higher rates of depression compared to age-related cataract patients with comparable initial loss of eyesight [12]. The high initial level of uncertainty regarding their long-term course can only be further exacerbated when exposed to additional uncertainties during the pandemic. In this study, actual change in visual acuity did not correlate to the drop in well-being and it did not correlate to the patient's own subjective feeling that his/her vision had worsened. This demonstrates the significant impact of the perception of health risk on well-being regardless of the objective negative outcome of the underlying disease. These results agree with earlier findings that patient-reported outcomes in ARMD treatment did not necessarily correlate with changes in visual acuity [13].

While the significance of treatment continuity for the ARMD patients is obvious, there is precious little to do in order to improve it during a pandemic. A recent review on the use of telemedicine in ARMD and its possible roles in the COVID-19 pandemic suggested that smartphone fundus photography images may be sent to a centralized teleophthalmology service to increase access and provider flexibility [14]. However, administering ARMD treatment invariably requires contact with the patient and this is a task outside the scope of telemedicine. Nonetheless, telemedicine may be employed in providing a complete general health status check immediately before a scheduled appointment so as to minimize chances for exposure to infection.

Invariably, compromises between an optimum level of care and patient and provider safety need to be determined beforehand. Sim et al. [15] have detailed an implemented treatment strategy in China designed to minimize contact time with patients and congestion of services, with a downside for stable patients who will not have their treatment intervals extended depending on their course. This choice was also reported in a study by Colantuano et al. in France [16]. A naturalistic study on the effect of temporary treatment extension to reduce

the number of visits during the COVID-19 pandemic found a significant short-term risk to vision when retreatment interval was extended beyond 12 weeks [17], hence clinicians may be forced to prioritize access to treatment with this time limit.

A limitation of this study is the convenience sample; however, it included the vast majority of the patients that were followed in the department and there was no reason to assume that it differed in a non-random manner from the population of patients at large. All material was filled-in during the follow-up which ensured validity but could have perceptibly made the patients more reluctant to come forward with more severe complaints or feelings of distress. However, the relationship between the patient and his/her ophthalmologist is a long-term one in this particular disease and method of treatment, so there is no reason to assume that the patients would be less forthcoming. A further limitation is the lack of a comparable control group since the pandemic affected all patients equal, and it is impossible to ascertain the degree to which the decline in visual acuity can be conclusively linked to an effect of the pandemic, while there are no relevant published data from Greece. However, our results with regards to the progression of the disease were empirically comparable to previous experience.

In conclusion, planning ahead for continuation of ARMD treatment services and close contact with patients during similar health emergencies is of paramount importance for the well-being of the patient. A clear pathway for patients may alleviate their fears and subjective sense of disease.

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Declarations

Conflict of interest No potential conflicts of interest were disclosed by the authors.

Ethical approval All participant offered their informed consent, after being briefed on the study goals. The research was approved by the scientific committee of the General Hospital of Serres.

Appendix 1

See Table 5.

Table 5 Items on the impact of the pandemic

1.	Has the pandemic affected the regularity of your appointments?
2.	Has the protocol for your treatment been applied as planned?
3.	Do you believe that your vision has worsened during the pandemic?
4.	Did you fear that your vision may worsen during the pandemic?
5.	Did you feel helpless/despair with regards to your vision problems?

References

- Bhutto I, Luty G (2012) Understanding age-related macular degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. *Mol Asp Med* 33:295–317. <https://doi.org/10.1016/j.mam.2012.04.005>
- Elshout M, Webers CA, van der Reis MI, Schouten JS (2018) A systematic review on the quality, validity and usefulness of current cost-effectiveness studies for treatments of neovascular age-related macular degeneration. *Acta Ophthalmol* 96:770–778
- Weiss M, Sim DA, Herold T, Schumann RG, Liegl R, Kern C, Kreutzer T, Schiefelbein J, Rottmann M, Priglinger S (2018) Compliance and adherence of patients with diabetic macular edema to intravitreal anti-vascular endothelial growth factor therapy in daily practice. *Retina* 38:2293–2300
- Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, Agha R (2020) World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). *Int J Surg* 76:71–76. <https://doi.org/10.1016/j.ijsu.2020.02.034>
- Borrelli E, Grosso D, Vella G, Sacconi R, Querques L, Zucchiatti I, Prascina F, Bandello F, Querques G (2020) Impact of COVID-19 on outpatient visits and intravitreal treatments in a referral retina unit: let's be ready for a plausible "rebound effect." *Graefes Arch Clin Exp Ophthalmol* 258:2655–2660. <https://doi.org/10.1007/s00417-020-04858-7>
- Borrelli E, Battista M, Vella G, Grosso D, Sacconi R, Querques L, Zucchiatti I, Prascina F, Bandello F, Querques G (2021) The COVID-19 pandemic has had negative effects on baseline clinical presentation and outcomes of patients with newly diagnosed treatment-naïve exudative AMD. *J Clin Med* 10:1265
- Borrelli E, Grosso D, Vella G, Sacconi R, Battista M, Querques L, Zucchiatti I, Prascina F, Bandello F, Querques G (2020) Short-term outcomes of patients with neovascular exudative AMD: the effect of COVID-19 pandemic. *Graefes Arch Clin Exp Ophthalmol* 258:2621–2628. <https://doi.org/10.1007/s00417-020-04955-7>
- Cohen J (1988) Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates, Hillsdale
- Topp CW, Østergaard SD, Søndergaard S, Bech P (2015) The WHO-5 Well-Being Index: a systematic review of the literature. *Psychother Psychosom* 84:167–176
- Mazza C, Ricci E, Biondi S, Colasanti M, Ferracuti S, Napoli C, Roma P (2020) A nationwide survey of psychological distress among Italian people during the COVID-19 pandemic: immediate psychological responses and associated factors. *Int J Environ Res Public Health* 17:3165
- Rapelli G, Lopez G, Donato S, Pagani AF, Parise M, Bertoni A, Iafrate R (2020) A postcard from Italy: challenges and psychosocial resources of partners living with and without a chronic disease during COVID-19 epidemic. *Front Psychol* 11:3559. <https://doi.org/10.3389/fpsyg.2020.567522>
- Mylona I, Floros G, Dermenoudi M, Ziakas N, Tsinopoulos I (2020) A comparative study of depressive symptomatology among cataract and age-related macular degeneration patients with impaired vision. *Psychol Health Med* 25:1130–1136
- Jelin E, Wisløff T, Jørstad ØK, Heiberg T, Moe MC (2019) Patient-reported outcome measures in the management of neovascular age-related macular degeneration: a 1-year prospective study. *BMJ Open Ophthalmol* 4:e000353. <https://doi.org/10.1136/bmjophth-2019-000353>
- Mintz J, Labiste C, DiCaro MV, McElroy E, Alizadeh R, Xu K (2020) Teleophthalmology for age-related macular degeneration during the COVID-19 pandemic and beyond. *J Telemed Telecare*. <https://doi.org/10.1177/1357633X20960636>
- Sim SS, Yip MYT, Wang Z, Tan ACS, Tan GSW, Cheung CMG, Chakravarthy U, Wong TY, Teo KYC, Ting DSW (2021) Digital technology for AMD management in the post-COVID-19 new normal. *Asia Pac J Ophthalmol (Phila)* 10:39–48. <https://doi.org/10.1097/APO.0000000000000363>
- Colantuono D, Miere A, Semoun O, Amoroso F, Souied EH (2020) AMD management during the COVID-19 pandemic. *Acta Ophthalmol* 98:e925–e925. <https://doi.org/10.1111/aos.14469>
- Teo KYC, Nguyen V, Barthelmes D, Arnold JJ, Gillies MC, Cheung CMG (2020) Extended intervals for wet AMD patients with high retreatment needs: informing the risk during COVID-19, data from real-world evidence. *Eye* 35:1–9. <https://doi.org/10.1038/s41433-020-01315-x>

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