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Evaluation of a calculation model to estimate the impact of the COVID-19 pandemic lockdown on visual acuity in neovascular AMD

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Abstract

Purpose: A model was calculated during the first Austrian coronavirus disease-2019 (COVID-19) pandemic lockdown to estimate the effect of a short-term treatment interruption due to healthcare restrictions on visual acuity (VA) in neovascular age-related macular degeneration (nAMD). The model was compared to the real-life outcomes before treatment re-started.

Methods: Retrospective data-collection of 142 eyes in 142 patients receiving repeated intravitreal injections with anti-VEGF at a retina unit in Vienna in a personalized pro-re-nata regimen prior to the COVID-19 associated lockdown, when treatment was deferred between March 16 and May 4, 2020. During the lockdown, the preliminary data was integrated into pre-existing formulae based on the natural course of the disease in untreated eyes in the long term. Patients were re-scheduled and treated after gradually opening operating rooms. The calculation model was compared to the effective VA change.

Results: The model calculated an overall VA loss of 3.5 ± 0.8 letters early treatment diabetes retinopathy study (ETDRS) ($p < 0.001$ [95% CI:3.3;3.6]) on average compared to 2.5 ± 6 letters ETDRS ($p < 0.001$ [95% CI:1.5;3.5]) as measured with a mean treatment delay of 61 ± 14 days after previously scheduled appointments. The total difference between the model exercise and the real-life outcomes accounted for 1 ± 5.9 letters ETDRS ($p = 0.051$ [95% CI: 0.1;1.9]).

Conclusion: The herein presented calculation model might not be suitable to estimate the effective VA loss correctly over time, although untreated eyes and eyes under therapy show similarities after short-term treatment interruption. However, this study demonstrated the potentially negative impact of the COVID-19 pandemic lockdown on patients compromised by nAMD.

Keywords

Anti-vascular endothelial growth factor, calculation model, coronavirus disease 2019, exudative neovascular age-related macular degeneration, intravitreal injection, visual acuity

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Introduction

In December 2019, a novel coronavirus (CoV) causing the severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2) emerged from China.[1] Meanwhile, the global impact of the pandemic named coronavirus disease 2019 (COVID-19) by the World Health Organization in February 2020 has encountered all aspects of daily life.[2] Restrictions were announced as of March 16, 2020 and maintained until declared otherwise in Austria.[3] As one of the first measures, the government gathered health care resources and medical competence. Hospitals were advised to lower all out-patient visits by keeping routine care to a minimum while preparing for worst-case scenarios. Ophthalmologic societies declared recommendations for patient care including the routine administration of intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF).[4–6] The highly frequented Medical Retina Unit of the Department of Ophthalmology at the Rudolf Foundation Hospital, Vienna, Austria was considered a spreading source of the disease in elderly with co-morbidities. COVID-19 has become an emerging situation and required quick adaptation. As an initial consequence and in accordance with the guidelines of the vision academy, patients with only one eye affected by the exudative neovascular type of age-related macular degeneration (nAMD) and scheduled appointments for follow-up and therapy were excluded from ongoing treatment between March 16 and May 4, 2020.[7] Some patients suspended therapy by choice out of fear of SARS-CoV-2. It was unknown whether eyes would recover once treatment was reinitiated and if their recovery was to the fullest or partially. These regulations implicated a bias on patient selection regarding disease activity and visual acuity (VA). Meanwhile, a calculation model based on the patient's data was performed to estimate the effect of the treatment deferral raised by the Austrian COVID-19 pandemic lockdown. The calculation originally derived from long-term data of untreated eyes as no comparable model was available at the time.

The purpose of this study was to evaluate the calculation model by quantifying the effective VA change in eyes under therapy after a short-term treatment interruption.

Methods

A retrospective data analysis was performed comparing a calculated predictive model to real-life results. The study protocol adhered to the tenets of the Declaration of Helsinki.

Patients

The data originated from the pool of patients who were originally under investigation for the calculation model and included eyes with previously diagnosed subtypes of macular neovascularization (MNV) secondary to exudative nAMD under current treatment with serial IVI of different anti-VEGF agents (Avastin®, Eylea®) at the tertiary eye care center. In daily routine before the lockdown, patients underwent an ophthalmic examination including best-corrected VA using the Early Treatment Diabetic Retinopathy Study chart at 4 m (ETDRS) - counting every correctly read letter - converted to Snellen, indirect slit-lamp biomicroscopy (Haag-Streit AG, Bern, Switzerland) with dilated pupils using 0.5% tropicamide and spectral domain-optical coherence tomography (SD-OCT; Zeiss Cirrus HD 4000, Carl Zeiss Meditec AG, Jena, Germany) imaging. The decision for ongoing treatment and its respective interval was made after the loading dose of 3 monthly IVI.[8,9] Patients continued a pro-re-nata regimen with individual visits and treatment as needed based on the previously elaborated personal interval (supplementary material). Only patients with a VA of 40 letters ETDRS (20/160 Snellen) or better in the affected eye at last follow-up of the pre-lockdown era were enclosed in the study, who had an appointment within the time period of the first COVID-19 associated restrictions and who came back for a follow-up and treatment. Exclusion criteria were eyes of patients with scheduled appointments without treatment over the past 6 months prior to the lockdown or without the necessity of ongoing treatment thereafter. Patients with a sudden onset of VA deterioration in the affected eye and a subsequent urgent intervention (3 patients with subretinal hemorrhage and straight forward surgery) were also excluded from further analysis to minimize the statistical bias in the VA change. For the initial model, 173 eyes in 173 patients were eligible for enrollment. After the last patient was brought in on July 2, 10 patients did not return for the scheduled appointment or ended therapy by choice and 1 patient died. Disease worsening due to a considerable amount of subretinal hemorrhage led to an urgent intervention in 3 patients. In another 14 patients, treatment was not indicated after re-opening. As the data of 3 more patients was missing, the VA of 142 eyes in 142 patients could be further analyzed.

Calculation model

The data of patients were collected via charts, who had a scheduled appointment between March 16 and May 4, 2020. The data were integrated into the equations from Elshout et al.,[10] a modified method originally published by Shah and Del Priore.[11] They assumed that VA loss followed a reciprocal course, which fitted the perception in nAMD that VA loss progressed more severely after the beginning of exudation and plateaued to an end-stage VA level over time. Elshout et al. described a double reciprocal general formula based on a literature review with a meta-analysis of published studies including non- or placebo-treated nAMD patients in 2 steps: First, the VA data of all included studies were combined into one plot. The VA data for each lesion type (occult,

minimally and predominantly classic) was separated into three more plots. Second, they automatically translated "months of enrolment" to "months of exudative disease" to extract the correct stage of the disease. In our model, the distribution of VA loss was calculated for the actual treatment delay of 9 weeks although the original model derived from untreated nAMD for up to 80 months. The combined model was applied to the overall patient cohort (n = 142), type 1 MNV (n = 107) was considered as the occult type of nAMD, mixed type MNV (n = 11) as minimally classic and type 2 (n = 8) as predominantly classic nAMD.[12]

Clinical management

Additional measures were installed to guarantee the best possible safety profile for both, patients and the staff. Eligible patients were contacted by phone and interrogated for respiratory symptoms via questionnaire.[13] After consenting, 2 patients at a time were scheduled in 15-min intervals in order to avoid overlaps with a maximum of 40 patients per day starting on May 4 and finishing on July 2. Trained operators with personal protective equipment including filtering face piece 2 or 3 masks conducted SD-OCT B-scans of both eyes.[14] Noncontact tonometry and VA testing were performed according to the hygiene standards to avoid a possible spread of the viral load.[15] Two medical retina specialists surveyed the images and checked the retina for hemorrhage by slit lamps with handcrafted manufactured 29,7 × 42 cm acrylate safety covers. If eligible, the affected eyes were prepared with 0.5% tropicamide, 2.5% phenylephrine and 5% polyvidone iodine. A resident or fellow together with the nurse staff promptly handled the process of intravitreal anti-VEGF administration. Patients were discharged immediately after the IVI.

Table 1. Demographic data including mean intervals in days for all eyes and separated into MNV subtypes.

	Overall	Type 1	Type 2	Mixed type	Type 3	Others[a]
n (%)	142 (100)	107 (75)	8 (6)	11 (8)	9 (6)	7(5)
Mean age in years	78.1 ± 8.5	77.9 ± 7.6	78.6 ± 9	77.6 ± 12	84.6 ± 8.4	71.4 ± 11.7
Sex m/f	62/80	50/57	3/5	3/8	3/6	3/4
Laterality r/l	78/64	56/51	5/3	4/7	8/1	5/2
Drug (A/E)	85/57	65/42	5/3	7/4	6/3	2/5
Total interval ± SD	1190 ± 1006	1164 ± 989	1313 ± 934	1452 ± 1231	590 ± 684	1802 ± 1106
Last interval ± SD	57 ± 29	56 ± 28	68 ± 28	58 ± 30	63 ± 43	43 ± 13
Planned Interval ± SD	59 ± 28	58 ± 27	62 ± 26	59 ± 41	68 ± 33	62 ± 29
Actual Interval ± SD	120 ± 31	120 ± 29	109 ± 31	117 ± 39	130 ± 43	121 ± 33
Delay ± SD	61 ± 14	62 ± 14	48 ± 20	57 ± 5	63 ± 15	60 ± 8

MNV = macular neovascularization; [a]polypoidal lesion or not classified; m = male; f = female; r = right; l = left; A = Avastin®; E = Eylea®

Table 2. Mean VA development in letters ETDRS (snellen) for all eyes and separated into MNV subtypes.

Before COVID-19 lockdown						
	Overall	Type 1	Type 2	Mixed type	Type 3	Others[a]
Baseline VA	70 ± 10.8 (20/40)	70.2 ± 10.5 (20/40)	67 ± 8 (20/50 + 2)	68.7 ± 14 (20/40 − 1)	68.1 ± 13.3 (20/40 − 2)	76.4 ± 9.3 (20/32 + 1)
Last VA	67.8 ± 12.4 (20/40 − 2)	67.4 ± 13 (20/50 + 2)	67.1 ± 12.2 (20/50 + 2)	67.9 ± 10 (20/40 − 2)	70 ± 9.4 (20/40)	71.1 ± 10.4 (20/40 + 1)
VA change	− 2.3 ± 11.8	− 2.8 ± 11.9	0.1 ± 7.9	− 0.8 ± 15.4	1.9 ± 10.5	− 5.3 ± 11
After COVID-19 lockdown						
Effective VA as measured	65.3 ± 13.5 (20/50)	65.3 ± 13.8 (20/50)	62.5 ± 18 (20/50 − 2)	61.2 ± 11.2 (20/63 + 1)	69.4 ± 8.8 (20/40 − 1)	69.9 ± 10.6 (20/40)
Effective VA change	− 2.5 ± 6 ($p < 0.001$)	− 2.2 ± 5.6 ($p < 0.001$)	− 4.6 ± 10.3 ($p = 0.246$)	− 6.7 ± 6.8 ($p = 0.008$)	− 0.6 ± 3.2 ($p = 0.621$)	− 1.3 ± 3.6 ($p = 0.380$)
Estimated VA as calculated	64.3 ± 12.4 (20/50 − 1)	63.3 ± 13.1 (20/50 − 2)	51.6 ± 14.2 (20/100 + 2)	52.2 ± 9.6 (20/100 + 2)		
Estimated VA change	− 3.5 ± 0.8 ($p < 0.001$)	− 4.1 ± 0.9 ($p < 0.001$)	− 15.5 ± 5.9 ($p < 0.001$)	− 15.7 ± 1 ($p < 0.001$)		
Difference effective vs estimated VA change	1 ± 5.9 ($p = 0.051$)	2 ± 5.6 ($p < 0.001$)	10.9 ± 9.1 ($p = 0.011$)	9 ± 6.8 ($p < 0.001$)		

VA = visual acuity; ETDRS = early treatment diabetic retinopathy study; MNV = macular neovascularization; COVID-19 = coronavirus disease 2019; [a]polypoidal lesion or not classified.

Statistical analysis

For the real-life outcomes, first the VA of the last treatment was compared to the VA after the COVID-19 pandemic lockdown using paired t-tests, and mean values with corresponding 95% confidence intervals (95% CI) were calculated. Univariable linear regression models were performed to investigate the following potentially influencing factors on the VA loss since the last treatment: age, sex, drug, total treatment interval, last interval, planned interval, delay, baseline VA and last measured VA. No multivariable regression

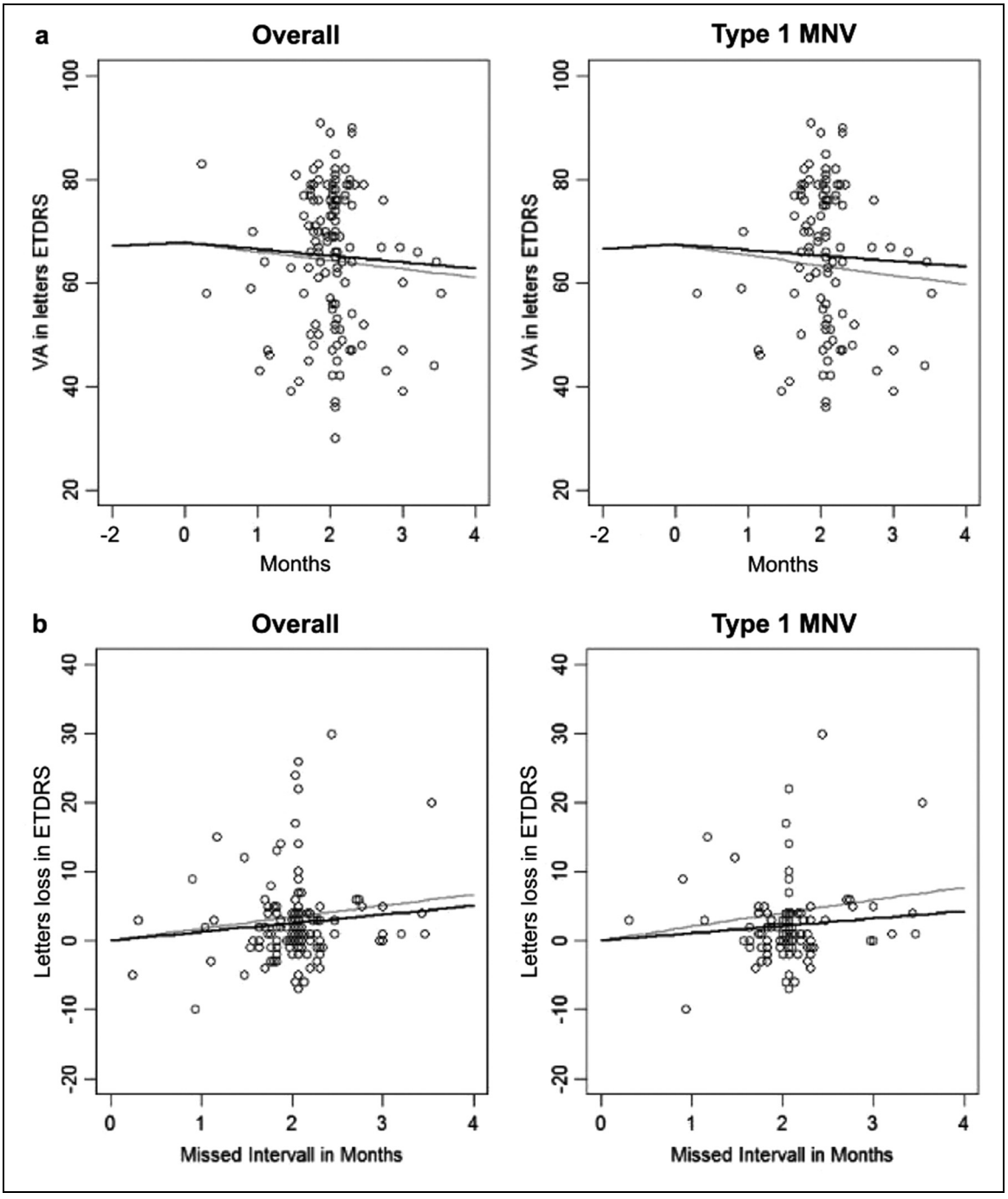

Figure 1. (a) change of visual acuity (VA) in letters early treatment diabetic retinopathy study (ETDRS) before the COVID-19 pandemic lockdown using the penultimate and last VA and development of effective VA as measured in real-life (black line) versus as estimated based on a calculation model (grey line) for the overall cohort and type 1 macular neovascularization (MNV) over time after the lockdown **(b)** effective letters loss in ETDRS (black line) versus estimated letters loss based on the calculation model (grey line) for the overall cohort and type 1 MNV dependent on the missed interval in months after the lockdown.

model was performed, as only one parameter (subtype) showed a significant result. The allocated interval between the 2 last consultations of each patient resulting in IVI treatment was opposed to the re-scheduled appointment and its delay. Continuous variables were summarized using mean and standard deviation. Categorical variables were summarized using absolute and percent values. Descriptive statistics were used for all eyes as well as separately for the MNV subtypes. The predicted values based on the models were compared to the real-life outcomes using paired t-tests. All analyses were performed using R, release 3.3.3.

Results

For this retrospective data analysis, 142 patients were brought in between May 4 and July 2, 2020. The demographic data was listed in Table 1. In the calculation model, the overall VA loss was estimated as 3.5 ± 0.8 letters ETDRS and hence showed a significant decrease when compared to the last VA before the lockdown ($p < 0.001$ [95% CI: 3.3;3.6]). The effective VA loss in all eyes accounted for 2.5 ± 6 letters ETDRS on average, which also showed a significant decrease in comparison to the last VA ($p < 0.001$ [95% CI:1.5;3.5]). The difference between the estimated and the effective VA loss in all eyes was 1 ± 5.6 letters ETDRS ($p = 0.51$ [95% CI: 0.1;1.9]) on average, which was borderline significant. The effective VA loss in type 1 MNV showed statistical significance ($p < 0.001$ [95% CI: 1.1;3.2]) as well as the mixed type MNV ($p = 0.008$ [95% CI: 2.2;11.2]) in contrast to type 2 MNV, type 3 MNV, polypoidal lesions and not classified MNV. Eyes compromised by the mixed type MNV demonstrated a more profound VA loss when compared to type 1 MNV ($p = 0.015$ [95% CI: 0.9;8.2]). VA development in all eyes and separated into MNV subtypes before and after the lockdown as measured and as calculated including significance levels were presented in Table 2. No significant influence of age ($p = 0.701$), sex ($p = 0.294$), drug ($p = 0.176$), total interval ($p = 0.238$), missed interval ($p = 0.125$), last interval ($p = 0.627$), baseline VA ($p = 0.404$) or last measured VA ($p = 0.650$) on the VA loss was observed. The comparison of VA loss in all eyes and type 1 MNV as the most representative subtype were illustrated in Figure 1.

Discussion

In this comparative analysis, the calculation model performed during the Austrian COVID-19 pandemic lockdown showed a borderline significantly higher VA loss than the real-life outcomes. All compared subtypes were investigated independently with a significant decrease in VA, but not all of them were representative owed to their low numbers (Table 2). A tendency towards greater disparity between the estimated and the effective VA loss was likely over time as the data were measured 9 weeks after the previously scheduled appointments. Predictions of a long-term treatment interruption due to the COVID-19 pandemic and its impact on VA behavior in exudative nAMD could not be evaluated. Most investigated eyes and type 1 MNV in particular showed a homogenous VA decline when compared to the estimated VA loss of the model exercise within the time period (Figure 1). This was interesting as the model was originally based on regression formulae for long-term progression of untreated eyes.[16–19] It would be conclusive that eyes under previous therapy maintained vision for some time and declined in the latter course of the disease. Our data confirm an effective VA loss of 2.5 letters on average when treatment was withheld for 61 days, considerably similar to untreated eyes. Thus said, this study demonstrated the potentially negative effect of the Austrian COVID-19 pandemic lockdown on care for patients with exudative nAMD and its increasing burden in the near future.[20]

Data on the natural course of nAMD revealed a progressive VA deterioration in every controlled trial. The era of repeated anti-VEGF therapy led to a stabilization of VA in eyes compromised by this disease as long as the treatment was sustained, independent of the investigated drug.[21–24] Real-life data and clinical trials predicted a VA decline once the therapeutic effect of anti-VEGF faded.[25,26] Soares et al. recently published data on eyes under anti-VEGF injections that were lost to follow-up for a mean of 12 months and concluded that the recovery would only be partially after re-treatment.[27] The herein presented data were different in the way they were acquired. Both, the calculation model as well as the real-life outcomes illustrated the consequences of the COVID-19 pandemic and its associated lockdown on the VA course of eyes which were successfully treated for more than 3 years on average and then had their care suspended for only 9 weeks not self-inflicted by choice but regulated. We were facing a tremendous backlog of patient visits and IVI treatments when we gradually re-opened operating rooms. The forced break of a continuous treatment as shown in this study might not be generalizable. Other countries suggested different regulations on patient care during the COVID-19 pandemic crisis.[28–32] Nevertheless, our findings correspond to international outcomes in respect of a VA response to delayed anti-VEGF therapy in nAMD.[33–35] The foreseeable future might hold on to reduced schedule volumes compared to pre-COVID-19 levels independent of the underlying coping mechanisms. Better strategies are needed by all involved parties including regulatory authorities, health care providers and medical societies to look ahead and adapt to the era of COVID-19.

This study has several limitations. The analyzed data was collected in challenging times of uncertainty. The general lockdown raised by the Austrian government and

the stoppage of care at the Rudolf Foundation Hospital was implemented once and for only 7 weeks, while the re-treatment took not more than 9 weeks. The extrapolation of the model did not involve short-term end points of the natural course of the disease and hence the comparison could be inadequate. Patients affected by the restrictive measures may have missed one treatment on average and could very well recover after ongoing treatment. The study did not pursue VA behavior after treatment was reinitiated. Applied protocols before the lockdown were not based on fixed treatment regimen as executed in pivotal trials but reflected real-life data. Therefore, this study did not differentiate between treatment intervals for the respective drugs.

In conclusion, the herein presented calculation model might not be suitable to estimate the effective VA loss due to a treatment interruption correctly over time. However, visual loss was evident and comparable to untreated eyes after a treatment deferral of 9 weeks. The concept of calculating the damage done by decisions when patients are forced to forego their treatment remains important as it poses questions for future regulations that could be partially answered by this comparative study. Long-term data on real-life outcomes are needed to confirm the herein demonstrated negative effect.

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Declaration of conflicting interests

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Ethics approval for retrospective studies

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Federal Hospitals Act §15a Abs. 3a states that a vote from the Viennese ethics committee is not obligatory for this study design.

Consent to participate

Informed consent was obtained from all participants.

Consent for publication

The paper has not been published previously and is not under consideration elsewhere. The authors have not published or submitted any related papers from this study. Neither was the paper presented at a meeting. Publication is approved by all authors as well as the responsible authorities. The statistical analysis was carried out by Alexandra Graf, an independent professional without affiliations to our department or the institute.

Availability of data and material

MS and SAS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The datasets used and/or analyzed to support the findings of this study are available from the corresponding author on reasonable request

Author contributions

MS is the lead author and guarantor: conceptualization, design, data acquisition, interpretation of data, draft of the article. AMH and DA: data acquisition, analysis and interpretation of data, draft of the article, review and editing. AG: statistical analysis and interpretation of data, draft of the article, review and editing. KK: interpretation of data and thorough revision of the article. SAS: Conception, methodology, supervision, critical revision. All authors read and approved the final version of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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