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ARTICLE

Relationship between visual acuity and visual field and its reproducibility in patients with retinitis pigmentosa

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BACKGROUND/OBJECTIVES: To investigate the association between visual acuity (VA) and visual field (VF) and its reproducibility in patients with retinitis pigmentosa (RP).
SUBJECTS/METHODS: The study cohort comprised 227 eyes of 227 patients with RP. The reproducibility of two Humphrey VF tests (10-2 Swedish Interactive Threshold Algorithm [SITA] tests) performed within a period of 3 months was calculated using the root mean squared error (RMSE) of each VF test point's sensitivity. The association between the logarithm of the minimum angle of resolution (logMAR) VA and VF sensitivity was investigated. Additionally, the relationship between RMSE and age, fixation loss, false positives, false negatives, and logMAR VA was determined.
RESULTS: The association between visual sensitivity and VA was most tight at the fovea, and it became weak toward the peripheral region in an eccentric manner. VF reproducibility appreciably increased as VA decreased. In particular, reproducibility was significantly decreased when logMAR VA was >0.5 compared with logMAR VA ≤ 0.
CONCLUSION: Reproducibility of VF tests decreases with a decrease in VA. Careful consideration is necessary when a patient's logMAR VA is >0.5.

INTRODUCTION

Retinitis pigmentosa (RP) is a hereditary retinal disease characterized by the progressive loss of photoreceptors [1, 2]. The symptoms include nyctalopia and constriction of the visual field (VF), which sometimes progresses to legal blindness. Precise VF measurement is crucial to assess RP and can be performed using a static automated perimeter, such as the Humphrey Field Analyzer (HFA) (Carl Zeiss Meditec Inc., Dublin, CA) [3, 4]. In particular, the central VF can be quantitatively measured using the HFA 10-2 test [5–7]. However, the sensitivity of the measured VF fluctuates [8, 9], which is problematic when detecting progression using either event-type or trend-type analysis for the clinical settings because the detectability of progression is markedly reduced in a series of VFs with poor reproducibility [10]. This is also important when interpreting the results of clinical studies because VF measurements are often the primary endpoint in clinical research studies, including clinical trials evaluating the effect of pharmacologic agents [11–15] and other variables [6, 7]. An ideal method to estimate the reliability of measured VF may be repeating the VF measurement and calculating the test-retest reproducibility, but it is unrealistic to adopt this approach in all patients. Instead, the reliability of VF measurements is usually estimated using fixation loss (FL), false-positive (FP), and false-negative (FN) rates [16, 17].

However, recent studies have highlighted limitations of these measurements [18–22].

Generally, VF reproducibility worsens as the VF deteriorates [23]. Visual acuity (VA) is closely correlated with sensitivities in the central area of the VF, and it is usually unaffected until late-stage RP. Indubitably, VA is essential to accurately measure VF because stable fixation cannot be ensured otherwise, implying that VA is closely related to VF reproducibility. Nonetheless, VA has not been included in the inclusion criteria in previous studies in general [6, 7, 11–14], which would make the assessment of VF progression inaccurate, and as a result, the difference of VF progression between two groups, such as between treated and placebo groups, may be masked. Thus, the primary objective of this study was to comprehensively investigate the association between visual sensitivity in the central VF and VA in eyes with RP. Subsequently, the association between VF reproducibility and VA was analysed.

METHOD

This study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at the University of Tokyo and Kyoto University. The study complied with the tenets of the

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Declaration of Helsinki. Written informed consent was given by patients for their information to be stored in the hospital database and used for research. Otherwise, based on the regulations of the Japanese Guidelines for Epidemiologic Study 2008 (issued by the Japanese Government), the study protocols did not require that each patient provide written informed consent. Instead, the protocol was posted at the outpatient clinic and/or website of the department to notify study participants.

Subjects

We retrospectively examined 238 eyes of 227 patients with RP (96 males and 131 females). All patients underwent 10-2 HFA VF tests (Humphrey Field Analyzer II; Carl Zeiss Meditec Inc.) twice within 3 months between June 2007 and September 2019. Only one eye per patient was included, and if both eyes satisfied the inclusion criteria, the right eye was automatically chosen.

RP was diagnosed when the following findings were present: (1) typical fundus findings of RP, such as bone spicule pigmentation, arteriolar attenuation, and waxy pallor of the optic disc; (2) reduction in a- and b-wave amplitudes or nondetectable full-field electroretinogram; and (3) RP was the only disease causing VF damage. VF measurements were performed using the HFA with the 10-2 program and the Swedish Interactive Threshold Algorithm (SITA) Standard. Other inclusion criteria were as follows: (1) no previous ocular surgery except for cataract extraction and intraocular lens implantation; (2) no other diseases of the anterior and posterior segments of the eye that could affect VF, including cataracts, except for clinically insignificant senile cataracts; (3) logarithm of the minimum angle of resolution (logMAR) VA ≤ 2.0, and (4) age ≥20 years. Those with intraocular surgery, including cataract surgery, during the observation period were excluded. Reliability criteria for VFs were applied, including FLs of <20% and false-positive responses of <15%. Based on a previous report [22], FN rate was not applied as a reliability criterion, as suggested in the recommendation by the manufacturer. The VF of the left eye was mirror-imaged to that of the right eye for statistical analyses.

Visual acuity

All participants underwent measurements of subjective refraction and corneal dioptric power with an autokeratorefractometer without cycloplegia within 3 months of the VF measurement. VA was measured using a Landolt ring chart at a distance of 5 m from the illuminated target; each ring was presented one at a time. If the VA was not 20/20 or better, refractive correction was performed beginning with the results of autokeratorefractometry, and the corrective lenses were adjusted manually. The refractive error was measured in −0.25 D steps, and the cylindrical power was measured and recorded in negative form. The refractive error was determined according to the results of corrective lenses that provided the best-corrected VA [24]. VA was estimated as logMAR VA, and the examined eyes were divided into five subgroups according to logMAR VA (group 1: ≤0, group 2: >0 and ≤0.15, group 3: >0.15 and ≤0.35, group 4: >0.35 and ≤0.5, and group 5: >0.5).

Visual field

VF tests were undertaken using the HFA II (Carl Zeiss Meditec Inc.) with a Goldmann size III stimulus under standard perimetric conditions (background, 10 candela/m^2) and the SITA Standard strategy.

Statistical analysis

VF sensitivities and VA. The Spearman rank test analysed the correlation between VA and different VF sensitivity measures, using the first VF of each patient: (1) the sensitivity of all 69 test points including foveal sensitivity in the HFA 10-2 VF, (2) the point with highest sensitivity from the fovea and central four points around the fovea in the HFA 10-2 VF (R_2), (3) the point with highest sensitivity from the fovea and central 17 points in the 10-2VF (R_3), and (4) the point with highest sensitivity from the fovea and central 37 points in the 10-2VF (R_4). Thus, VF sensitivity measures (2)–(4) were chosen to gradually expand outward from the fovea. Correlation coefficients were compared using the Meng–Rosenthal–Rubin method [25], which tests the difference between two overlapping (having a variable in common) correlation coefficients, using a z-test.

VF reproducibility and VA. VF reproducibility was assessed using the root mean squared error (RMSE) of the measured threshold at each test point,

as follows:

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^{68}(\text{threshold of the ith test point}(1st\ VF) - \text{threshold of the ith test point}(2nd\ VF))^2}{52}}$$

Then, the relationship between RMSE and FP, FN, FL, MD (mean deviation of the 1st and 2nd VFs), VA, and age, was analysed using linear modelling. All analyses were performed using the statistical programming language R (v2.15.1; The Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The demographics of the study subjects are summarized in Table 1. The mean age ± standard deviation [SD](range) of the study cohort was 51.0 ± 14.1 years (21–84). The MD value in the initial VF was −17.8 ± 9.0 (−35.2 to 0.1) and −17.7 ± 8.8 (−35.5 to −0.03) in the second VF. The pattern standard deviation (PSD) in the initial VF and second VF was 6.8 ± 2.7 (0.86 to 14.1) and 6.9 ± 2.7 (0.99 to 13.6), respectively. There were no significant differences in MD and PSD between paired VF tests (paired *t* test, $p = 0.43$ and 0.66, respectively).

Spearman correlation coefficients between VA and each test point on the HFA 10-2 VF are illustrated in S1. R_1, R_2, R_3, and R_4 were −0.7200 ($p < 0.01$), −0.7274 ($p < 0.01$), −0.7220 ($p < 0.01$), and −0.7272 ($p < 0.01$), respectively (Fig. 1A–D), but these values were not significantly different (Meng–Rosenthal–Rubin method, $p > 0.05$).

There was a significant relationship between RMSE and logMAR VA (RMSE = 3.7 + 1.63 × logMAR VA, $R^2 = 0.089$, $p < 0.001$). The RMSE distribution in each VA group is shown in Fig. 2; the mean ± SD (range) was 3.6 ± 1.7 (1.2–13.1) in group 1 (logMAR VA ≤ 0), 4.1 ± 1.7 (1.5–11.6) in group 2 (logMAR VA > 0 and ≤0.15), 4.1 ± 1.3 (1.5–9.5) in group 3 (logMAR VA > 0.15 and ≤0.35), 3.9 ± 1.7 (1.0–6.8) in group 4 (logMAR VA > 0.35 and ≤0.5), and 4.8 ± 2.1 [2.0–10.6] in group 5 (logMAR VA > 0.5). The group 4 RMSE was significantly larger than that of group 1 (Tukey multiple comparison test: $P < 0.001$). However, there was no significant difference between the RMSE in group 1 versus groups 2, 3, and 4 ($P = 0.52$, 0.38, and 0.98, respectively), and in group 5 versus groups 2, 3, and 4 ($P = 0.32$, 0.25 and 0.43, respectively). The demographic characteristics of each VA group are shown in S2. Significant differences were observed between group 4 versus group 1 for age ($P = 0.019$) and groups 4, 3, and 2 versus group 1 for MD in the initial and second VF ($p < 0.001$).

The average rates of FL, FP, and FN are presented in Table 1. The average FN rate and logMAR VA were significantly associated with RMSE (both $P < 0.001$, multiple linear regression analysis, Table 2), but the average FL, FP, and age were not. This analysis was conducted in 191 eyes because FN was estimated as not

Table 1. Subjects' demographics.

Characteristic	Value
Age, mean ± SD (range)	51.0 ± 14.0 (21 to 84)
Sex (male:female)	96:131
VA (logMAR)	0.21 ± 0.32 (−0.18 to 1.5)
MD in the initial VF, dB, mean ± SD (range)	−17.8 ± 9.0 (−35.2 to 0.1)
MD in the second VF, dB, mean ± SD (range)	−17.7 ± 8.8 (−35.5 to −0.03)
FL (%), mean ± SD (range)	2.1 ± 3.3 (0 to 15.4)
FP (%), mean ± SD (range)	1.0 ± 1.6 (0 to 10.5)
FN (%), mean ± SD (range)†	3.1 ± 5.2 (0 to 33.0)

VA visual acuity, *MD* mean deviation, *SD* standard deviation, *VF* visual field, *FL* fixation loss, *FP* false positive, *FN* false negative.
†FN rate was calculated in 191 eyes, because FN was estimated as not applicable in 36 eyes (FN was not used as an exclusion criterion, as recommended by the manufacturer: see Method section).
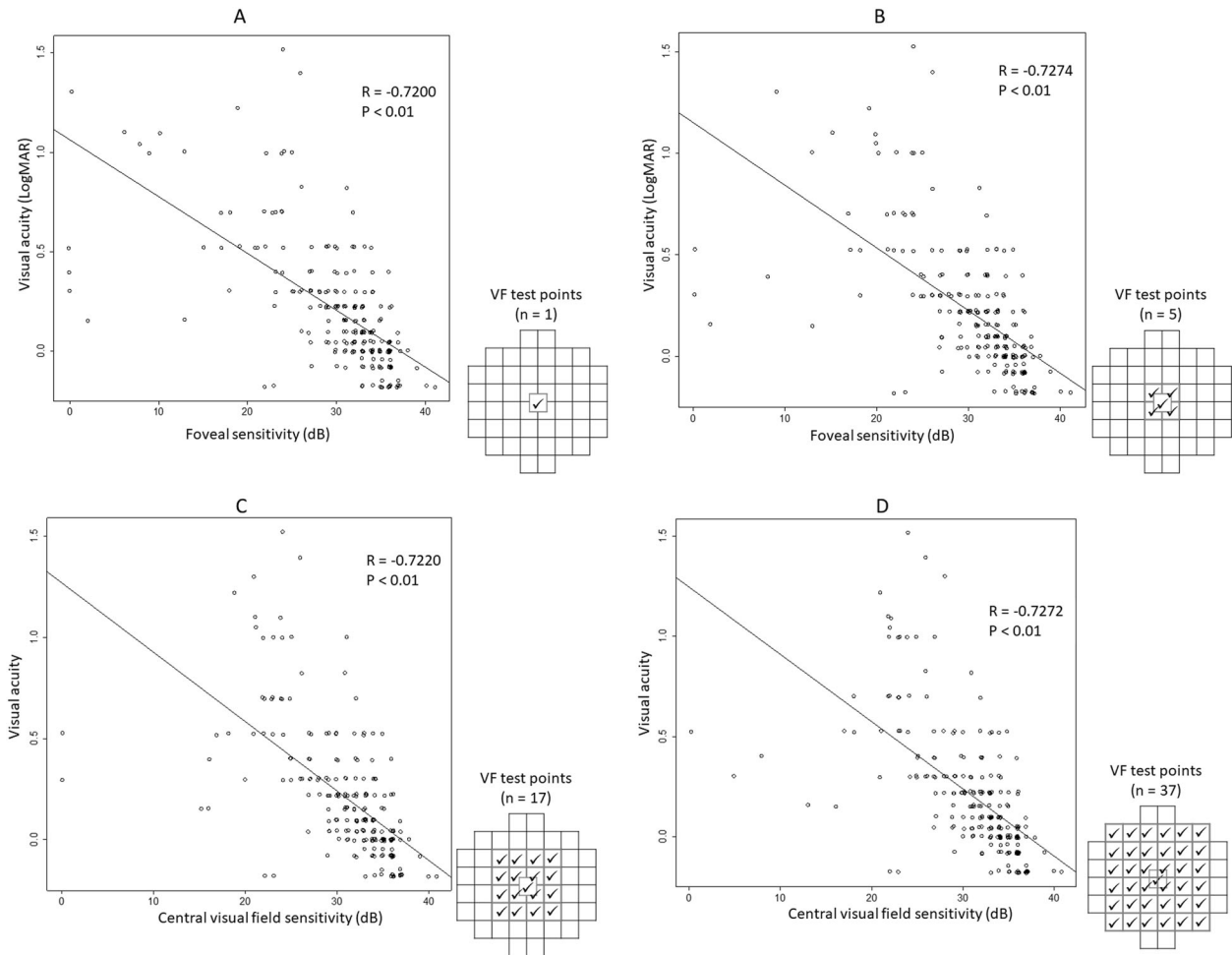
Fig. 1 Relationship between visual acuity and visual field (VF) sensitivity in central areas of the 10-2 VF. A Sensitivity of foveal test point. **B** Test point with the highest sensitivity from the central five points in the 10-2 VF. **C** Test point with the highest sensitivity from the central 17 points in the 10-2 VF. **D** Test point with the highest sensitivity from the central 37 points in the 10-2 VF. There were no significant differences among the Spearman correlation coefficient values (Meng–Rosenthal–Rubin method, *p* > 0.05) VF visual field.

applicable in 36 eyes (FN was not used as an as exclusion criterion, as recommended by the manufacturer: see Method section).

DISCUSSION

Our study first investigated the relationships between visual sensitivity and VA. The association between visual sensitivity and VA was most tight at the fovea, becoming weak toward the peripheral region in an eccentric manner. Additionally, the association between visual sensitivity at the fovea and VA was not significantly improved by replacing the foveal sensitivity with the higher visual sensitivity around the fovea. Subsequently, we investigated the association between VF reproducibility and VA, revealing that the VF reproducibility appreciably increases as VA decreases, as shown in the significant relationship between RMSE and logMAR VA. Notably, reproducibility significantly decreased when logMAR VA was >1.0 compared with eyes with logMAR VA ≤ 0. (see Fig. 1), implying that a recommended cut-off value of logMAR VA > 0.5 be used as an inclusion criterion when using VF outcomes in research, not only in studies evaluating structure-function, progression prediction, and progression detection but also when defining the outcome of any observation/intervention. This is because, as Jansonius previously reported, the detection of disease progression is delayed in VFs with large variability [10, 26]. For instance, the time to detect progression with 80% power for an

MD slope of −1.0 dB/year was 3 years when the SD of the MD was 0.5 dB (when VF was measured twice a year); however, this estimated duration rocketed to more than double (6.5 years) when the SD of the MD was 2.0 dB [10]. This duration was almost identical to when VF was measured annually, and the SD of the MD was 0.5 dB (6.0 years). Thus, careful consideration should be given when interpreting VF progression in eyes with logMAR VA > 0.5.

The clinical implications of the current results are as follows. The assessment of visual function is conducted using VF in RP. However, our results suggested clinicians can be warned that VF measurements are not reliable when logMAR VA was >1.0. This was in particular obvious when visual sensitivity around fovea is damaged, because it is directly associated with the deterioration of VA.

In this study, FN rate was significantly associated with the reproducibility of VFs, but FP and FL were not (Table 2). We previously analysed the relationship between VF (HFA 10-2 test) reproducibility and VF reliability indices, revealing that the FN, FL, and FP rates were useful in assessing VF reproducibility [27]. The reason for these contradicting results is unclear, but could be due to the wider range of FN rate in the current study (0–33.0%) compared with the previous study (0–19.5%) as well as the differences in sample size (227 and 42 eyes in the current and previous studies, respectively). An FN occurs when a patient fails to respond to a much more intense stimulus than they had
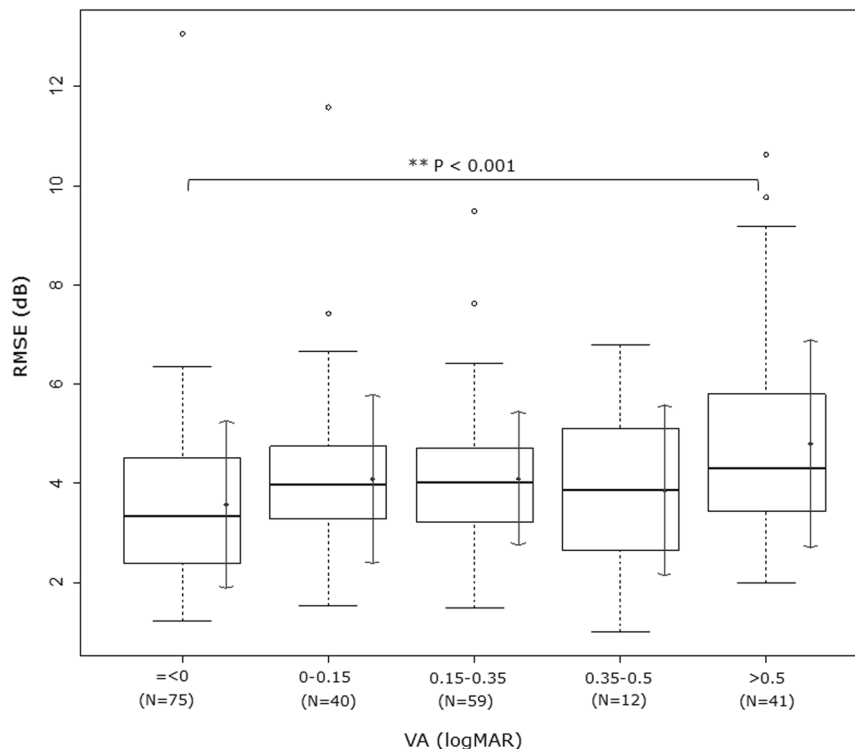
Fig. 2 Boxplot of RMSE in each VA group. The RMSE in eyes with logMAR VA > 1.0 was significantly different compared with eyes with logMAR VA ≤ 0 ($p < 0.001$, Tukey multiple comparison test). Blue arrows represent the mean and SD. RMSE root mean squared error, VA visual acuity.

Table 2. Association between age, FL, FP, FN rates and LogMAR VA, and RMSE.

Variable	Coefficient	SE	P value
Age	0.013	0.0082	0.13
FL	7.5	4.1	0.07
FP	−14.6	8.4	0.09
FN	13.9	2.2	<0.001
LogMAR VA	1.54	0.36	<0.001

FL fixation loss, *FP* false positive, *FN* false negative, *VA* visual acuity, *RMSE* root mean squared error, *SE* standard error.

This analysis was conducted in 191 eyes because FN was estimated as not applicable in 36 eyes (FN was not used as an exclusion criterion, as recommended by the manufacturer: see Method section).

responded to previously, and FNs are thought to represent inattention during the examination [28–30]. Although FN is no longer recommended for HFA by the manufacturers because it simply increases in accordance with VF deterioration [22], the results from this study suggest the usefulness of this parameter. Our recent studies suggested the usefulness of this index in estimating the accuracy of VF trend analysis [27] and VF reproducibility with the HFA 24-2 test [31], which further supports this standpoint.

FL and FP rates are considered indications of test reliability and vision fixation and "trigger-happy" patients, respectively [28–30]. However, some studies have suggested that the usefulness of these indices is limited [19–21], which agrees with the findings of our current study, where the rates were not significantly associated with VF reproducibility. Nonetheless, this does not totally negate the usefulness of these indices because we have previously reported their usefulness for estimating different

purposes, such as over- or underestimation of VF in trend analysis [32] or structure-function relationships [33].

In contrast, logMAR VA was a significant parameter for VF reproducibility; reproducibility significantly decreased when logMAR VA was >0.5. This finding was very similar to the result in our previous study with the HFA 24-2 test in eyes with glaucoma [34], and the same cut-off level (logMAR >0.5) was suggested. Notably, this finding was observed despite some differences between these studies. VA was most strongly associated with foveal sensitivity in eyes with both glaucoma and RP, but the association was not improved by including the surrounding VF test points in eyes with RP, whereas it was significantly improved by including the 16 innermost VF test points in eyes with glaucoma. Thus, logMAR VA is more directly associated with foveal sensitivity in eyes with RP than in eyes with glaucoma. Additionally, the area with high association between logMAR VA and visual sensitivity expands more peripherally in the direction of the papillomacular bundle in eyes with glaucoma compared with eyes with RP. Eye fixation including such a region would have a poor VF reproducibility, regardless of the logMAR VA level.

In both RP and glaucoma, central visual function is usually preserved until late-stage disease. Reflecting this, a close relationship was observed between VA and foveal sensitivity in the current study ($R = -0.72$; Fig. 1A), similar to the previous study in glaucoma ($R = -0.64$) [35]. However, a considerable difference was observed in the association of the VF test points surrounding the fovea; it became weak toward the peripheral region in an eccentric manner. Additionally, the association between visual sensitivity at the fovea in the current study was in contrast to a strong correlation in the temporal paracentral area in eyes with glaucoma. This difference is probably because retinal nerve fibre layers in this area penetrate the optic disc margin at the temporal angle, which usually is less likely to be affected in cases of early to moderate glaucoma [36–40]. Indeed, we have proposed the clinical usefulness of VF clusters derived from the intercorrelation

across VF test points in both RP and glaucoma. The mapping was concentric around the fovea in eyes with RP [41], whereas it reflected the mapping of the retinal nerve fibre distribution in eyes with glaucoma [42–44].

A limitation of the current study is that the results were not investigated using the HFA 24-2 test, and future studies using the HFA 24-2 should be undertaken. It would also be interesting to analyse the effect of parameters of optical coherence tomography, such as photoreceptor layer thickness, on VF reproducibility.

In conclusion, VA should be considered when assessing VF reproducibility. Specifically, careful consideration is necessary when logMAR VA is >0.5 because the reproducibility significantly increased beyond this level.

SUMMARY

What was known before

- The association between the reproducibility of the visual field and visual acuity has not been investigated in detail.

What this study adds

- Reproducibility of visual field becomes poor with a decrease in visual acuity, in particular less than 0.5 logMAR in eyes with retinitis pigmentosa.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are not publicly available due to the regulation at the ethics committees, but are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

RA contributed the conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing – original draft, and writing – review & editing. MM, AO, YF, HM, KA, RO and TA contributed methodology and the resources and writing – review & editing.

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COMPETING INTERESTS

The authors declare no competing interests.

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