



Foveal avascular zone area measurement in diabetic patients: Superficial, deep or combined retinal vascular complex?

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ABSTRACT

Purpose: To compare differences in the foveal avascular zone (FAZ) area, measured in the Superficial Vascular Complex (SVC), Deep Vascular Complex (DVC) and a combined analysis of both (SDVC), using two Spectral Domain OCT angiography (OCT-A) protocols, High Speed (HS) and High Resolution (HR).

Methods: A total of 26 eyes of diabetic patients, with and without macular oedema, were examined with two different fovea centered OCT-A volume scans. The two protocols were HS and HR volume scans, and the foveal avascular zone was manually measured in the SVC, DVC, and SDVC slabs by two masked investigators. Inter and intraoperator variability was analysed using Intraclass Correlation Coefficient (ICC) and differences were compared between the HR and HS acquisitions throughout the different vascular slabs.

Results: Intraoperator variability was low in all slabs (ICC > 0.9) and interoperator variability was lower for HR (ICC 0.835–0.911) compared to HS (ICC between 0.604 and 0.865). Comparing HS and HR measurements for the same slab, the correlation was only moderate in SVC and DVC (ICC was 0.640 and 0.568 respectively) but was good in the SDVC (ICC = 0.823). FAZ area measurement in SDVC also showed the smallest bias (mean difference 0.009 mm²) and the narrowest limits of agreement (−0.175 to 0.193 mm²).

Conclusions: Even in cases of diabetic macular oedema, when measuring the FAZ area, the reproducibility was better between HS and HR protocols when using the SDVC slab, compared to the SVC or DVC slabs alone. Further studies should evaluate the use of the combined SDVC slab for the FAZ assessment, compared to the SVC and DVC slabs alone, in the detection and progression of different retinal diseases.

1. Introduction

Diabetic Retinopathy (DR) is the ocular manifestation of diabetes which is characterized by a gradual and progressive change in retinal microcirculation, increased vascular permeability, areas of retinal ischemia and proliferation of abnormal retinal vessels. DR can be divided into two main stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) (Wang and Lo, 2018). The most frequent ophthalmologic changes that occur are diabetic macular oedema and neovascularization. Endothelial damage seems to be the main cause of these lesions, and together with microvascular complications, produce the clinical presentation of diabetic

retinopathy (Kusuhara et al., 2018).

The foveal capillary network forms a ring at the margin of the fovea, producing a capillary-free region called the foveal avascular zone (FAZ). The shape of the FAZ on the image obtained by OCT-A has shown to be a good indicator for detection of retinal pathologies (Shiuhara et al., 2018). Recent studies have shown that changes in retinal microcirculation might be detected before clinical onset of DR using Optical Coherence Tomography Angiography (OCTA), like a decreased parafoveal vascular density (VD) and an increased FAZ area when compared to healthy controls (Cao et al., 2018; Marques et al., 2020; Palma and Camacho, 2021; Sabaner et al., 2021). One study showed that individuals with diabetes had significantly larger FAZ areas in the SVC and

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DVC compared to age and sex matched individuals without diabetes and also that the FAZ area in the SVC is smaller than that in the DVC (Aitchison et al., 2022).

However, despite the high sensitivity of OCTA compared to physician examination (Palma and Camacho, 2021), and the expectation that it will be a promising tool in the study of vascular alterations in DM patients (Cheung et al., 2021), there is still no agreement on the best way to assess FAZ (Waheed et al., 2023).

OCT-HRA Spectralis® (Spectralis; Heidelberg Engineering, Heidelberg, Germany) allows the customization of many attributes of the OCT-A acquisition, such as the number of A-scans, B-scans, and spacing between scans. It is possible to select acquisition scan modes that select between two different lateral resolutions, with high speed (HS), the acquisition speed is faster and the OCT B-Scan has a lateral resolution of 11 μm , whereas with high resolution (HR), the acquisition speed is slower but the B-Scan has a lateral resolution of 6 μm (Corvi et al., 2020). In a previous study, manual measurements were performed independently by two investigators comparing manual measurements of the FAZ area between High Speed (HS) and High Resolution (HR) protocols, as measured in the SVC and DVC and it was concluded that there was good to excellent correlation for intra and interoperator measurements, but there was only a moderate to good correlation between HS and HR protocols within same vascular complex (Anacleto et al., 2023).

However, some authors suggest that there is a higher likelihood of segmentation errors, particularly at the foveal pit, occurring when using the SVC and DVC slabs individually, and the analysis of the combined SVC and DVC instead of an individual analysis will provide more reliable results, because this analysis takes into consideration all the layers of the inner retina (Hormel et al., 2021; Lu et al., 2018). Moreover, in diabetic patients with intraretinal fluid and disorganization of the retinal inner layers, it is important to find more precise ways of assessing and monitoring the FAZ (Han et al., 2022; Nassar et al., 2023).

With this study, we aim to compare the manual measurement of the FAZ area between High Speed (HS) and High Resolution (HR) protocols, as measured in the Superficial Vascular Complex (SVC), Deep Vascular Complex (DVC) and a combination of both (SDVC).

2. Methods

This is an observational analytical cross-sectional study based on the database of the study (IPL/2021/DiffMeDiME_ESTeSL) that previously characterized the differences in DNA methyltransferase gene expression in patients with different diabetic macular oedema responses that performed OCTA exams with HR and HS protocols (Camacho et al., 2023). The study was carried out at Lisbon School of Health Technology (ESTeSL), Instituto de Retina de Lisboa (IRL) and Associação Protectora dos Diabéticos de Portugal (APDP) after approval from each Institutional Ethical Review Board and according to the principles of the Declaration of Helsinki. After a complete explanation to each study participant of the purposes and contribution of the study, a free written informed consent was obtained.

The patients included in this study, aged 18 or above, had an established diagnosis of type 2 DM (T2DM) for at least 5 years. The exclusion criteria included the presence of glaucoma, Age-related Macular Degeneration, vitreomacular diseases (study eye), uncontrolled systemic diseases, intraocular pressure > 21 mmHg, high ametropia, systemic diseases with ophthalmic involvement, and patients with a history of ischemic heart disease. A total of 26 eyes from 26 patients were included in this analysis.

The equipment used was the Spectralis® HRA + OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) and the evaluation of the patients consisted of two OCTA scans of 512×512 pixels, one acquired using the HR protocol, covering an area of $10^\circ \times 10^\circ$ with a lateral resolution of 6 μm , and another with HS protocol, covering an area of $20^\circ \times 20^\circ$ with a lateral resolution of 11 μm (Fig. 1).

The analysis of the data was performed at Lisbon's Superior School of Health and Technology (ESTeSL) by two masked operators, an experienced orthoptist and a final-year student. In a first phase (Anacleto et al., 2023), manual measurements were performed independently by two masked investigators, O1 and O2, using the HEYEX® software (Heidelberg Engineering, Heidelberg, Germany) (Fig. 1). Before FAZ area measurements, if major segmentation errors were detected, they were corrected using “edit layer segmentation” option within the area of

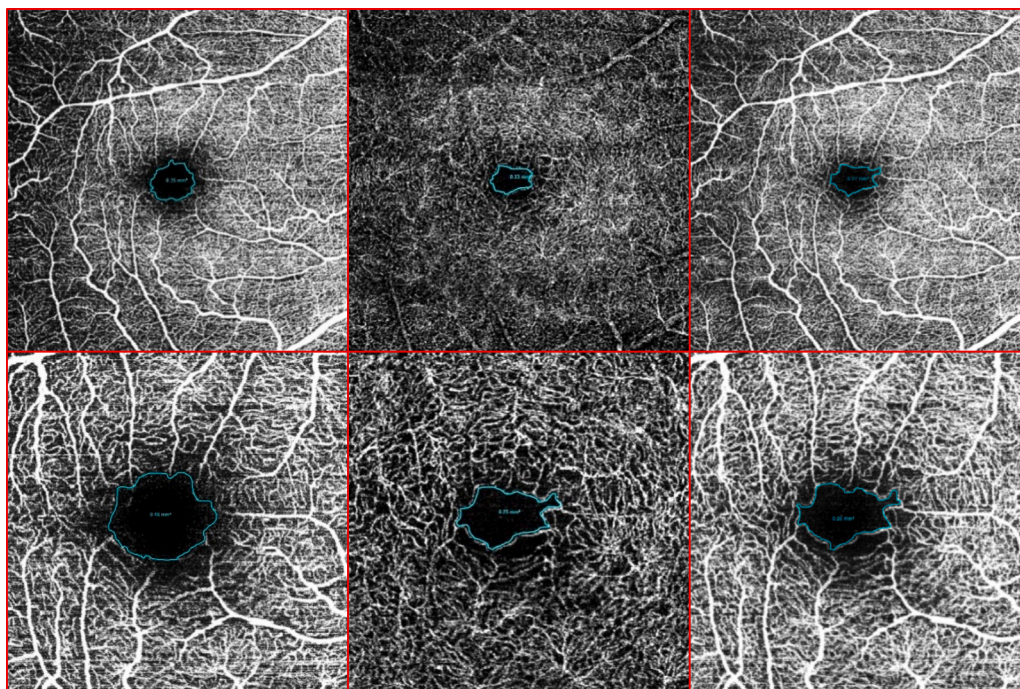


Fig. 1. Example of the manual FAZ area measurement in different retinal slabs and resolutions.

First column: Superficial Vascular Complex (SVC); Second column: Deep Vascular Complex DVC; Third column: Superficial and Deep Vascular Complex (SDVC). Top row: High Speed (HS); Bottom row - High Resolution (HR).

segmentation error (Deussen et al., 2024). For all 26 participants, the two operators measured the FAZ area twice using both protocols (HS & HR), in both SVC and DVC slabs. Taking this into account, in this current study, the O1 performed a single measurement of the FAZ area in a vascular slab combining SVC and DVC, which we called Superficial and Deep Vascular Complex (SDVC) in both HS and HR protocols, whereas the second investigator (O2) performed two measurements in each protocol, as he was not the same investigator who performed the previous measurements in the SVC and DVC slabs. The FAZ measurements were manually performed within the HEYEX® software (Heidelberg Engineering, Heidelberg, Germany) (Fig. 1) in a masked and non-consecutive manner, and subsequently exported as JPG files for further analysis (Fig. 1).

For the statistical analysis, IBM® SPSS® Statistics v27.0 software (IBM Corporation Armonk, NY, USA) was used. To assess intra and interoperator variability and differences between the two acquisition protocols, Wilcoxon test was used and a p -value <0.05 was considered statistically significant. The ICC (Intraclass Correlation Coefficient) was also calculated, with values below 0.5 showing poor correlation, values between 0.5 and 0.75 showing moderate reliability, values between 0.75 and 0.9 showing good reliability and any value above 0.9 showing excellent reliability (Bobak et al., 2018). Bland-Altman plots were constructed to assess the agreement between the measurements by the HS and HR protocols, one for each vascular slab (SVC, DVC and SDVC) (Fig. 2).

3. Results

A total of 26 eyes of 26 patients were included in the study, 11 participants were male (42.3 %), and 15 participants were female (57.7 %). Their age ranged from 61 to 90 years, with a mean age of 72 ± 7.61 years. Regarding DR severity, 11 eyes showed no DR (ETDRS level 10) and 15 eyes moderate to moderately severe Non-Proliferative DR (ETDRS level 43–47). Intraretinal fluid was present in 14 eyes and DRIL was present in 12 eyes.

Analysing the intraoperator variability (Supplementary Table 1), it is possible to confirm that all the FAZ area measurements showed an excellent intraoperator repeatability as all ICC values were over 0.911. Although there were no statistically significant differences, the largest measurement differences were in the SVC slab ($0.037 \pm 0.098 \text{ mm}^2$) using HS protocol for O1 and the DVC slab ($-0.013 \pm 0.045 \text{ mm}^2$) using HS protocol for O2. Regarding the smallest measurement differences, they were observed in the DVC slab ($0.004 \pm 0.102 \text{ mm}^2$) using HS protocol for O1, and in the DVC slab ($0.000 \pm 0.064 \text{ mm}^2$) using HR protocol for O2.

For the interoperator variability analysis (resumed in Table 1, detailed interoperator variability analysis can be found in Supplementary Table 2), the mean value of FAZ area measurement was considered when an operator has made two measurements. In most cases there were

no statistically significant differences between the measurements by O1 and O2 in the various slabs and protocols. However, there is an exception for the FAZ area measured in the SVC slab using HR protocol, where there was a $0.101 \pm 0.119 \text{ mm}^2$ significant difference (p -value = 0.004). On the other hand, the smallest measurement difference between operators was found in the HR protocol, in the SDVC slab ($-0.004 \pm 0.068 \text{ mm}^2$). It is also possible to observe that the interoperator measurements showed, in most cases, a strong correlation, whilst the lowest ICC values were found in the HS protocols for the DVC and SDVC slabs (ICC was 0.604 and 0.659 respectively).

The final value for each FAZ area in different retinal slabs and acquisition protocols was determined by averaging the measurements obtained from both operators. Independently of the acquisition protocol, the mean FAZ area was higher in the SVC ($0.614 \pm 0.385 \text{ mm}^2$ in HS and $0.502 \pm 0.224 \text{ mm}^2$ in HR) than the DVC ($0.555 \pm 0.316 \text{ mm}^2$ in HS and $0.438 \pm 0.212 \text{ mm}^2$ in HR), being the area measured in the SDVC the smallest one ($0.351 \pm 0.158 \text{ mm}^2$ in HS and $0.342 \pm 0.157 \text{ mm}^2$ in HR).

Comparing the measurements in the same vascular complex between HS and HR acquisition protocols (Table 1), there was a moderate correlation in the SVC and DVC measurements (ICC of 0.640 and 0.568, respectively), whereas there was a good correlation in the SDVC measurements (ICC of 0.823). If we consider the mean FAZ area differences between HS and HR, we can observe that the SDVC slab shows the smallest difference ($0.009 \pm 0.094 \text{ mm}^2$) when compared to the SVC ($0.112 \pm 0.268 \text{ mm}^2$) and DVC ($0.117 \pm 0.250 \text{ mm}^2$).

These results are confirmed by analysing the Bland-Altman plots (Fig. 2), as the FAZ area measurement in SDVC showed the smallest bias (mean difference 0.009 mm^2) and the narrowest limits of agreement (-0.175 to 0.193 mm^2) compared to SVC (mean difference 0.112 mm^2 , limits of agreement -0.413 to 0.637 mm^2) and DVC (mean difference 0.117 mm^2 , limits of agreement -0.374 to 0.607 mm^2).

4. Discussion

Based on the analysis of the mean values of the intraoperator differences, there are no statistically significant differences. However, we can still observe the largest mean measurement difference for each operator and protocol. In the case of O1, the largest mean measurement difference was found in the HS protocol, specifically in the SVC slab ($0.037 \pm 0.098 \text{ mm}^2$). On the other hand, in the case of O2, the largest mean measurement difference was observed in the DVC slab, also using the HS protocol ($-0.013 \pm 0.045 \text{ mm}^2$). Upon analysing Supplementary Table 1, it is evident that, for O1 and O2, all slabs and protocols demonstrate excellent correlation in their respective measurements.

Although these differences are not statistically significant, they still provide insights into the variations between measurements performed by these two operators. Studies confirm that the variations in the SVC slab may be attributed to factors such as non-perfusion areas. Conversely, within the DVC slab, variations may arise due to artifacts

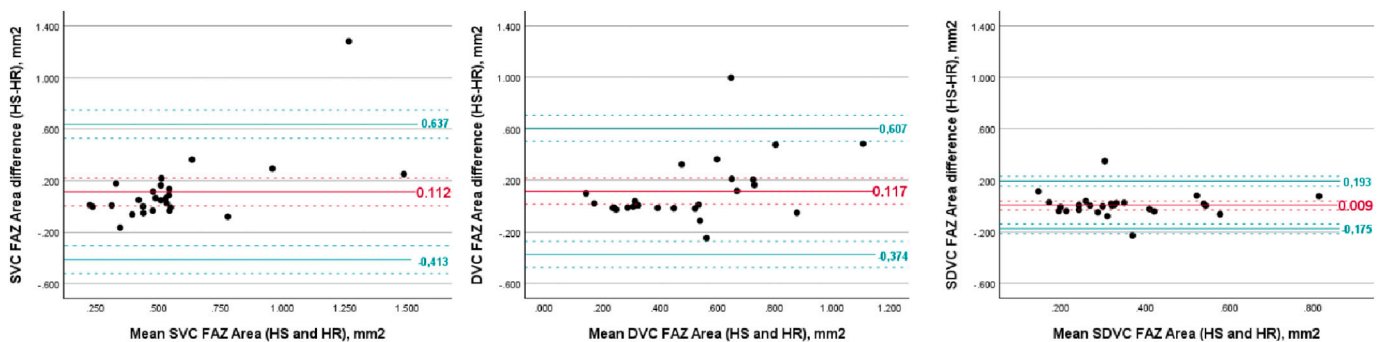


Fig. 2. Bland-Altman plots of the FAZ area in different slabs comparing HS and HR protocols.

Red lines indicate the average mean of the difference between the two protocols; Red dotted lines indicate the confidence intervals of the mean of the differences between the two protocols; Green lines indicate agreement limits for 95 %; Green dotted lines indicate the confidence intervals for the agreement limits.

Table 1

Interoperator variability and comparison between HS and HR protocols - statistical analysis.

Slab		HS	HR	(HS – HR)		ICC	P value
		$\bar{x} \pm \text{SD (mm}^2\text{)}$ CI 95 %	$\bar{x} \pm \text{SD (mm}^2\text{)}$ CI 95 %	$\bar{x} \pm \text{SD (mm}^2\text{)}$ CI 95 %	Median (mm ²) (IQ range)		
SVC	O1	0.623 ± 0.436 [0.447; 0.799]	0.543 ± 0.253 [0.441; 0.646]	0.080 ± 0.307 [−0.044; 0.204]	0,008 (−0,075; 0,100)	0.628 ^a	0,461
	O2	0.606 ± 0.358 [0.461; 0.750]	0.461 ± 0.213 [0.375; 0.548]	0.144 ± 0.249 [0.043; 0.245]	0,060 (0,010; 0,200)	0.642 ^a	<0,001
	ICC* (p-value) ^b	0.865 (0.545)	0.835 (0.004)	–	–	–	–
	Global	0.614 ± 0.385 [0.459; 0.770]	0.502 ± 0.224 [0.412; 0.593]	0.112 ± 0.268 [−0.165; 1.280]	0,049 (−0,007; 0,163)	0.640 ^a	0.014 ^b
	O1	0.581 ± 0.362 [0.434; 0.727]	0.459 ± 0.227 [0.368; 0.551]	0.121 ± 0.295 [0.002; 0.240]	0,020 (−0,020; 0,120)	0.524 ^a	0,035
DVC	O2	0.529 ± 0.344 [0.390; 0.668]	0.417 ± 0.215 [0.330; 0.504]	0.112 ± 0.301 [−0.010; 0.234]	0,020 (0,000; 0,180)	0.447 ^a	0,022
	ICC* (p-value) ^b	0.604 (0.615)	0.840 (0.253)	–	–	–	–
	Global	0.555 ± 0.316 [0.427; 0.683]	0.438 ± 0.212 [0.353; 0.524]	0.117 ± 0.250 [0.016; 0.218]	0,011 (−0,012; 0,208)	0.568 ^a	0.073 ^b
	O1	0.345 ± 0.169 [0.277; 0.414]	0.344 ± 0.161 [0.279; 0.409]	0.001 ± 0.087 [−0.034; 0.036]	0,015 (−0,020; 0,030)	0.861 ^a	0,396
	O2	0.357 ± 0.178 [0.285; 0.429]	0.340 ± 0.161 [0.275; 0.405]	0.017 ± 0.148 [−0.042; 0.076]	0,000 (−0,035; 0,025)	0.621 ^a	0,974
SDVC	ICC* (p-value) ^b	0.659 (0.587)	0.911 (0.303)	–	–	–	–
	Global	0.351 ± 0.158 [0.177; 0.852]	0.342 ± 0.157 [0.278; 0.406]	0.009 ± 0.094 [−0.029; 0.047]	0,005 (−0,037; 0,028)	0.823 ^a	0.736 ^b

$\bar{x}$ – Mean; SD – Standard Deviation; mm² – Square Millimetres; CI – Confidence Interval; ICC – Intraclass Coefficient Correlation; O1 – Operator 1; O2 – Operator 2; HS – High Speed; HR – High Resolution; SVC – Superior Vascular Complex; DVC – Deep Vascular Complex; SDVC – Superior and Deep Vascular Complex.

^a The estimator is the same, whether the interaction effect is present or not.

^b The P Value was obtained through the Wilcoxon Test.

observed in that slab but projected by the SVC slab (segmentation errors) (Hormel et al., 2021).

Based on the interoperator analysis in the various slabs and protocols, it appears that there are generally no statistically significant differences between the two operators. However, there is an exception found in the SVC slab in the HR protocol. This is indicated by a *p*-value of 0.004, which is below the threshold of 0.05 typically used for significance.

Regarding the interoperator measurements, it can be established through the ICC values that there is a strong correlation in most cases. It can be observed through the analysis of Supplementary Table 2 that in the HS protocol, the DVC and SDVC slabs present a moderate correlation (0.604 and 0.659 respectively). On the contrary, in the SDVC slab in the HR protocol there is an excellent correlation (0.911).

Through the analysis of the intra and interoperator variability, it is possible to see that the ICC values revealed a good correlation between the different measurements. Even in cases with diabetic macular oedema, OCTA showed to be an important and reliable scientific tool with no statistical differences found in the intra or interoperator variability analysis except for the interoperator variability in the SVC using HR protocol.

Although there are no statistically significant differences between the global FAZ area measurements when both HS and HR protocols are compared, the ICC for the SDVC slab indicates a good reliability (0.823), when compared to the moderate reliability for the SVC and DVC slabs alone (ICC of 0.640 and 0.568, respectively). This is also evident by the analysis of the Bland-Altman plots (Fig. 2), where the measurements in SDVC showed the smallest bias (mean difference 0.009 mm²) and the narrowest limits of agreement (−0.175 to 0.193 mm²) indicating the highest level of consistency and minimal bias. Therefore, FAZ area measurement within SDVC can be considered more reliable and precise compared to SVC (mean difference 0.112 mm², limits of agreement −0.413 to 0.637 mm²) and DVC (mean difference 0.117 mm², limits of agreement −0.374 to 0.607 mm²). This result suggests that if the analysis of the FAZ is performed by analysing the SVC and DVC slabs

individually, there would be a higher likelihood of encountering segmentation errors (Hormel et al., 2021; Lu et al., 2018). In general, when measuring the FAZ area, there is greater reproducibility (comparing HR and HR acquisitions) when using the SDVC slab than using the SVC or DVC slabs alone, which confirms the suggestion that the analysis of the combined SDVC plexus instead of an individual analysis provides more reliable results (Hormel et al., 2021; Lu et al., 2018).

The present study has some limitations, with a notable one being the small sample size. It is important to emphasize the significance of this study, as this topic is underexplored in terms of research. Other limitation was the assessment of FAZ area only, not assessing other FAZ metrics like shape or perimeter, however this is justified by the fact that we wanted to assess one of the most reported OCTA metrics in a real-world context. The ability of the operator to adjust image contrast and magnification during measurements may also contribute to discrepancies in the obtained measurements, but one more time, our goal was to assess the FAZ area measurement in a real-world context.

Future studies should evaluate the use of the combined SDVC slab for the FAZ assessment, not only FAZ area but other metrics like FAZ shape or perimeter, compared to SVC and DVC slabs alone, in the detection and progression of different retinal diseases.

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CRediT authorship contribution statement

Bruno Pereira: Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Ross Faria:** Writing – original draft, Methodology, Investigation, Formal analysis. **Cátia Domingues:** Writing – original draft, Methodology, Formal analysis. **Ana Barros:** Writing – original draft, Methodology, Formal analysis. **Teresa Varandas:** Resources. **José Henriques:** Validation, Resources. **João**

Nascimento: Writing – review & editing, Validation, Resources. **Eli-sabete Carolino:** Validation, Formal analysis. **Pedro Camacho:** Writing – review & editing, Project administration.

Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mvr.2024.104743>.

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