Preliminary Study of the Significance of Reverberation by IVUS Detection for Patients With Severe Calcified Lesions

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Research Article

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Abstract

Objectives—To explore the potential significance of the reverberation of calcification by comparing both intravascular ultrasound (IVUS) and optical coherence tomography (OCT) measurement post manual coregistration.

Background—The reverberation phenomenon is often detected by IVUS for severe calcified lesions post rotational atherectomy (RA), which is thought to be due to the glassy and smooth inner surfaces of calcifications. Because of the poor penetration of IVUS, it is impossible to measure the thickness of calcifications, and the relationship between multiple reverberations and the thickness of calcification lesions has not been reported before.

Methods—A total of forty-nine patients with severe calcified coronary lesions that were detected by IVUS and OCT simultaneously were enrolled in our retrospective study. If reverberation phenomena were detected by IVUS, intravascular imaging (IVI) data (including distance between the IVUS catheter center and the inner surface of the reverberation signal, the intervals between all adjacent reverberation signals, the number of layers of reverberation in IVUS, and the thickness of the calcification in OCT) were measured at the same position and same direction (each cross-section had 4 mutually perpendicular directions) at 1-mm intervals. If the observational point (direction) had a reverberation signal, it was an effective observational point that would be enrolled in our study; otherwise, it would be regarded as an invalid observational point and excluded from this study. The correlation between each reverberation observational value and OCT data was the primary target in this retrospective study.

Results—Four hundred twenty-eight valid observational points were analyzed simultaneously by IVUS and OCT; among them, 300 points had a single layer of reverberation, 83 had double layers of reverberation and 42 had multiple layers (≥3 layers) of reverberation by IVUS detection post-RA. Multivariate logistic regression analysis showed that the number of layers of reverberation by IVUS was significantly related to the thickness of calcifications by OCT at the same point and in the same direction ($p<0.001$). Single, double, and multiple layers of reverberation in IVUS correspond to median calcification thicknesses (interquartile ranges (IQRs)) of 0.620 mm (0.520–0.720), 0.950 mm (0.840–1.040) and 1.185 mm (1.068–1.373), respectively, by OCT detection. No correlation was found between the distance between the IVI catheter center and the inner surface of the reverberation signal or the interval between every adjacent reverberation signal and the thickness of the calcification.

Conclusions—The number of layers of reverberation signal detected by IVUS is positively correlated with the thickness of calcifications measured by OCT post-RA.

Condensed Abstract

We investigated the relationship between reverberation and the thickness of calcification by comparing both intravascular ultrasound (IVUS) and optical coherence tomography (OCT) measurement post manual coregistration by fiduciary side branch. The number of layers of reverberation by IVUS detection

was significantly related to the thickness of calcification by OCT measurement by multivariate logistic regression analysis (p,0.001). Single, double, and multiple layers of reverberation in IVUS correspond to median calcification thicknesses (interquartile ranges (IQRs)) of 0.620 mm (0.520–0.720), 0.950 mm (0.840–1.040) and 1.185 mm (1.068–1.373), respectively, by OCT detection.

Introduction

Although we have known for a long time that coronary calcification lesions are significantly related to the rate of future cardiac events, especially moderate to severe calcification lesions, which also significantly affect the outcome of percutaneous coronary intervention (PCI), with the development of intravascular imaging (IVI) technology in the field of PCI, (1–3) the cognition and treatment effects of calcified lesions are becoming increasingly optimized compared with the previous application of angiography only.(4–6) Even IVI techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), have significant advantages over coronary angiography in the diagnosis and guidance of PCI of calcification. Not every IVI imaging sign of calcification is well known, among which the reverberation of calcification detected by IVUS is one.(7, 8) Reverberation is regarded as a unique imaging sign of calcification that presents as multiple reflections from the oscillation of ultrasound between the transducer and calcium, which causes concentric arcs at reproducible distances and is often detected post rotational atherectomy (RA) treatment or orbital atherectomy but cannot be detected by angiography and OCT.(7, 9) Currently, its clinical meaning is only considered to be a manifestation of the smooth (glassy) inner surface of the calcification, and its further significance has not been deeply explored.(5, 7, 9) The goal of our retrospective study was to investigate the deep significance of reverberation signals by comparing imaging data point-by-point between IVUS and OCT.

Methods

Study design—This was a retrospective, single-center and observational study to compare the cross-sectional data measured by IVUS and OCT at the same observational point of the reverberation signal for patients with calcification in Nanjing First Hospital. From Apr 2014 to Oct 2020, reverberation phenomena were found by IVUS imaging detection in a total of fifty lesions in forty-nine patients with severe calcifications, and OCT detection in the corresponding segment was also performed at the same time. Patients were excluded if they did not receive both IVUS and OCT detection at the same time, IVUS did not find a reverberation phenomenon, or the OCT imaging quality was not high enough for measurement of the calcification thickness at the corresponding segment. If both IVUS and OCT imaging met the requirements simultaneously (IVUS found reverberation and OCT could measure the thickness of the calcification precisely), reverberation measurements were repeated every 1 mm, and the calcification thickness at the same level and direction was measured at the same site. Ultimately, 428 valid points with reverberation in 49 patients met the criteria of our study and were enrolled in the analysis. The study was approved by the institutional review board, and written informed consent was obtained from all patients.

IVUS and OCT images acquisition—Both IVUS and OCT images were acquired after nitroglycerin intracoronary injection for the same target vessel. IVUS (iLAB, Boston Scientific Corporation, Marlborough, Massachusetts) detection was performed by pulling back automatically at a speed of 0.5 mm/sec with a 40-MHz, 2.6F imaging catheter (Atlantis™ SR Pro, Galaxy®, Boston Scientific, Natick, MA). For OCT image checking, both ILUMIEN OPTIS and C7-XR (Lightlab Imaging Incorporated, Westford, MA) could be applied by a 2.7F (Dragonfly OPTIS or Dragonfly Duo imaging catheter, Westford, MA) catheter automatic pullback at a speed of 36 mm/sec with continuous contrast injection (3–4 ml/s).

IVUS and OCT images analysis—Off-line IVUS image data were analyzed by planimetry EchoPlaque 4.0 software (Index Medical Systems, Santa Clara, CA). Coronary calcification in IVUS was defined as a region with a hyperechoic leading edge compared to the adventitia with acoustic shadowing, which was categorized as superficial calcification when the leading edge appeared near the intima of the lumen or deep calcification appeared near the adventitia or mixed calcification, which included superficial and deep calcifications.(5, 10) Reverberation in IVUS imaging is considered one type of artifact represented by secondary, false echoes of the same structure and caused by a smooth leading edge of calcification,(5, 10, 11) which is usually found post RA. Off-line OCT images were analyzed using Lightlab OPTIS, E. 4 software (Lightlab Imaging Incorporated, Westford, MA). Calcification in OCT was defined as a signal-poor and heterogeneous region with sharply delineated near and far boundaries. (4, 7, 12, 13) The calcification thickness of each observational point was measured in the case of consistent OCT and IVUS observational points.

IVUS and OCT images were analyzed after manual coregistration by fiduciary side branch (position and direction as the marker of calibration) and known pullback speeds (the observational point was calculated by counting the slice number by the frame interval to the marker of calibration).(5, 7) Valid observational points were defined as follows: Radial positioning of observation points: in accordance with the direction indicated by the marker of calibration (referring to the direction of the side branch emission), the other three observation points in the same plane (i.e., there might be four observation points in each plane) were defined in the clockwise direction of the cross every 90 degrees. If there was a reverberation signal at this point, the observational point was enrolled in the study; otherwise, the point was excluded. Longitudinal positioning of the observation point was performed according to the calibration indicator point (with the center point of the side branch ostium as reference), accurately positioning the observation point of IVUS and OCT by the frame-counting method (Fig. 1).

The measurement indices of IVUS for each enrolled point were defined as follows: the number of layers of reverberation signal at each observational point: counting the number of layers of the radial reverberation signal; the interval between two adjacent reverberation signals in the radial direction ($interval_1$: the distance between the inner reverberation signal and the second reverberation signal; $interval_2$: the distance between the second reverberation signal and the third reverberation signal; $interval_3$: the distance between the third reverberation signal and the fourth reverberation signal; and $interval_4$, $interval_5$ and so on in a similar fashion, Fig. 1); and D_i: the distance between the IVUS catheter center and the inner surface of the calcification (inner reverberation signal, Fig. 1). The measurement index of OCT for each enrolled point was the thickness of the calcification in the corresponding site.

All imaging data (IVUS and OCT measurement indices post manual coregistration) that met the requirements were analyzed offline by two independent professional technicians who were blinded to the clinical information. If these two technicians' judgments diverged, another experienced technician worked with them until a consensus was reached. Intra- and interobserver variabilities of the image analysis were assessed by measuring 40 enrolled points randomly for both IVUS and OCT data. The intra- and interobserver reproducibilities of image analyses were assessed by Kappa statistics for categorical variables or intraclass correlation coefficients (ICCs) for continuous variables. There was very good intra- and interobserver consistency for the number of layers of reverberation by IVUS detection (Kappa: 0.992, 0.996), the distance between two layers of reverberation signals (ICC: 0.993, 0.998), the distance between the IVUS catheter center and the inner reverberation signal (ICC: 0.924, 0.997) and the calcification thickness by OCT measurement at the same point and the direction relative to the IVUS data (ICC: 0.990, 0.927). Finally, IVUS and OCT data were compared point-by-point to confirm the correlation between the reverberation signal and the calcification thickness.

Statistical analysis—Categorical variables are expressed as frequencies and counts, whereas continuous variables are expressed as means ± standard deviations or as medians with interquartile ranges (IQR), as appropriate. Categorical variables were compared by the chi-square test, and the normality of continuous variables was analyzed by the Shapiro–Wilk test. Nonnormally distributed continuous variables are shown as medians and first and third quartiles and were compared by the Mann–Whitney U or Kruskal–Wallis test with post hoc analysis by the Dunn-Bonferroni test. To study the correlation between reverberation and calcification thickness, a univariable Cox regression was performed for all variables, including the number of layers of reverberation signal, the interval between two adjacent reverberation signals and D_i. The independent association of several variables with reverberation was evaluated using forward stepwise Cox regression analysis if possible. All statistical tests were 2-tailed, and a p value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed with SPSS software, version 18.0 (SPSS 18, Inc., Chicago, Illinois) and Windows version R 4.0.5 software (https://www.r-project.org/).

Results

Patients' clinical characteristics and basic coronary disease description—The baseline clinical characteristics, such as clinical risk factors, clinical diagnosis and angiographic data, are summarized in Table 1. The patients' average age was 66±10.59 years old, and 75.5% were men. The prevalence of diabetes mellitus was 24.5% and that of chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/1.73 m^2) was 2.0%. A total of 1440 observational points in 360 layers of IVUS and OCT were initially analyzed at 1-mm intervals in 49 patients with 50 severe coronary calcified lesions post-RA. Ultimately, 428 effective observational points with high-quality OCT images and reverberation signals of IVUS images simultaneously were entered into the next step of measurement, with statistical analysis post radial and longitudinal manual coregistration by the fiduciary side branch. The study flow chart is shown in Fig. 2.

Table 1
Baseline clinical characteristics of the patients

Characteristics	**n = 49**
Age, years	66±10.59
Male, *n* (%)	37,(74)
Body mass index, kg/m^2	24.86±3.28
Diabetes mellitus, *n* (%)	12,(24.5)
Hypertension, *n* (%)	37,(75.5)
Hyperlipidemia, *n* (%)	39,(79.6)
Current smoking, *n* (%)	13,(26.5)
Chronic kidney disease, *n* (%)	1,(2)
Previous myocardial infarction, *n* (%)	6,(12.2)
Clinical presentation	
STEMI, *n* (%)	2,(4.1)
Non-STEMI, *n* (%)	2,(4.1)
Unstable angina, *n* (%)	34,(69.4)
Clinical examination	
Left ventricular ejection fraction, %	61.86±7.61
Total cholesterol, mmol/L	3.67±0.83
Low-density lipoprotein, mmol/L	2.06±0.67
High-density lipoprotein, mmol/L	0.94±0.25
eGFR, ml/min/1.73 m^2	85.90±36.56
Target vessel	
LAD (%)	37,(75.5)
RCA (%)	10,(20.4)
LCx (%)	2,(4.1)

Categorical variables are shown as number (%) and continuous variables are shown as mean ± standard deviation after confirming that the distribution is normal. CSA, cross section area; eGFR, estimated glomerular filtration rate; EI, expansion index; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCx, left circumflex; LM, left main; STEMI, ST-segment elevation myocardial infarction.

Characteristics	n = 49
Lesion location	
Proximal	28
Mid	19
Distal	2
Reference vessel diameter, mm	3.67±0.34
Categorical variables are shown as number (%) and continuous variables are shown as mean ± standard deviation after confirming that the distribution is normal. CSA, cross section area; eGFR, estimated glomerular filtration rate; EI, expansion index; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCx, left circumflex; LM, left main; STEMI, ST-segment elevation myocardial infarction.	

Reverberation signal analysis in IVUS—A total of 300 effective observational points showed a single layer of reverberation, 83 with double layers and 42 with multiple layers (≥ 3 layers of reverberation signals) of reverberation by IVUS detection post-RA. Because the data were not normally distributed when analyzed by the Shapiro–Wilk test ($p < 0.001$), the median for interval_1 of reverberation was 0.633 mm (IQR: 0.478–0.795), that of interval_2 of reverberation was 0.630 mm (IQR: 0.480–0.790) and that of interval_3 of reverberation was 0.630 mm (IQR: 0.470–0.790). There was no significant difference in the distance between interval_1, interval_2 and interval_3 of reverberation using the paired Kruskal–Wallis rank sum test ($\chi2 = 40.76$, $P = 0.138$), and the three sets of data were equal in further analysis by the "rgl" package (Fig. 3). Interval_1 was positively correlated with D_i by the Spearman test ($r = 0.899$, $p < 0.001$) and was markedly linearly correlated with D_i, with a linearity of 0.92 (95% confidence intervals (CI): 0.90–0.93) by "ggstatsplot" package analysis (Fig. 4).

Reverberation signal analysis in both IVUS and OCT—For the first time, we studied the calcification characteristics of the reverberation signal in IVUS post-RA point-to-point at the same position post manual coregistration. By univariate Cox regression analysis, only the number of layers of reverberation by IVUS was positively correlated with the thickness of the corresponding point calcification by OCT ($r = 0.663$, $p < 0.001$), but not for interval_1 and D_i. After regrouping depending on the number of layers of reverberation signal, single, double, and multiple layers (≥ 3) of reverberation (named corrected grouping in this study) by IVUS corresponded to calcification thicknesses of 0.620 mm (IQR: 0.520–720), 0.950 mm (IQR: 0.840–1.040) and 1.185 mm (IQR: 1.068–1.373), respectively, by OCT detection. Moreover, a significant difference was found between groups, which showed that the thickness in the single-layer group was thinner than that in the double-layer group ($p < 0.001$), and the thickness in the double-layer group was thinner than that in the multiple-layer group ($p < 0.001$) by the Kruskal–Wallis test with post hoc analysis by the Dunn-Bonferroni test. These findings are summarized in Fig. 5, which was drawn using the "ggplot2" package along with "ggpubr".

Discussion

The main findings in our retrospective study were as follows: ( ) the number of layers of reverberation signal in IVUS indicated the relative thickness of calcification in OCT post RA; ( ) every interval between adjacent reverberation signals was equal for multiple reverberations in the same plane and in the same direction, and ( ) the intervals between reverberation signals were positive relative to the distance between the IVUS catheter center and the inner calcification surface.

Reverberation artifact formation mechanisms arise when acoustic waves encounter highly reflective smooth interfaces of different densities in parallel. Instead of the beam reflecting off a single interface and producing a strong echo that returns to the transducer, the acoustic wave is reflected between the interfaces back and forth multiple times.(14, 15) Initially, we considered that the ultrasound signal could not penetrate calcified lesions,(5, 7, 9) so reverberation only represented smooth interfaces of calcification, which was commonly seen post RA treatment for patients with severe coronary calcified lesion.(5, 7–9) However, we found that reverberation phenomena manifested differently in different patients or in different positions of the same patients, appearing as single-, double- or multilayer (≥ 3 layers) reflectivity. This manifestation could not be explained by the smooth interface alone. We designed this retrospective study to explore the correlation between the reverberation signal and the calcification thickness by combining IVUS and OCT post manual coregistration. A novel finding in our study was that the number of layers of reverberation was positively correlated with the thickness of calcification in the corresponding sites, and the larger the number of layers, the thicker the calcification in the same direction. Further statistics show that the reverberation signals of single-, double- and multilayers represent calcification thicknesses of 0.620 mm (0.520–0.720), 0.950 mm (0.840–1.040) and 1.185 mm (1.068–1.373), respectively. Although a previous study suggested that IVUS smooth surfaces with reverberation were more common in lesions with OCT calcification thicknesses < 0.5 mm than in those with IVUS irregular surfaces without reverberation,(5) and these signals were often considered to represent RA-related calcification modification with a concave-shaped lumen,(16) another view is that reverberation is an indication for RA treatment if IVUS detects a de novo lesion without treatment.(17) With so many different views, it is not clear what this type of reverberation truly indicates. Both IVUS and OCT have similar sensitivity and specificity for calcification detection,(5) and the main difference between the two lies in the measurement of calcification thickness. Our initial hypothesis was that this special calcification manifestation of reverberation might be related to the corresponding calcification thickness, which can only be measured by OCT. Therefore, we designed this retrospective study by point-to-point analysis after multiaspect manual coregistration of IVUS and OCT first found that only the number of layers of reverberation was positively correlated with the corresponding site calcification thickness but not for intervals between adjacent reverberation signals and the distance between the IVUS center and inner calcification surface. The potential clinical implications are not only the reverberation phenomena itself post-RA, which show calcification modification, but also the number of layers of reverberation, which indirectly reflects the thickness of the calcification by optimized lesion preparation.

It has been reported that the mechanism of reverberation formation is that the ultrasonic signal oscillates back and forth between the transducer and the calcified smooth surface. On imaging, this is seen as multiple equidistantly spaced linear reflections and is referred to as a reverberation artifact.(14, 15) A similar finding was obtained in our study, which showed that every interval between adjacent reverberation signals was equal for multiple reverberations in the same observational plane and direction in IVUS images. However, the intervals between the adjacent reverberation signals (including the corrected interval) in different planes (direction) and in different patients were different. We speculate that this may be related to the different calcification densities (different attenuation coefficients) in different sites and different patients, which affect the attenuation degree of the ultrasonic signal.

Another interesting finding in our study was that the intervals between adjacent reverberation signals were positive relative to the distance of the IVUS center to the inner calcification surface at the same level. This is consistent with the results of previous studies, which showed that ultrasound returned to the transducer after a single reflection and that the depth of an object is related to the time for this round trip.(14, 15)

LIMITATIONS

This was a retrospective observational study with a relatively small sample size. Every study point was carefully selected post manual coregistration of IVUS and OCT at the same segment and following calibration by two independent technicians. However, slight differences in measurement points are unavoidable unless an IVUS/OCT all-in-one machine is used. The number of reverberation signals in IVUS is only an indirect sign of calcification thickness, but a smooth calcification surface is the premise, which means that calcification thickness with an irregular surface without a reverberation signal cannot be measured by IVUS, and measurement by OCT can be more accurate. Therefore, multimodal intravascular imaging will be a promising tool for future coronary intervention.

Conclusions

The number of layers of reverberation by IVUS is positively associated with the thickness of calcification by OCT post-RA. Single-, double- and multilayers of reverberation represent calcification thicknesses of 0.620 mm (0.520–0.720), 0.950 mm (0.840–1.040) and 1.185 mm (1.068–1.373), respectively.

Abbreviation

CI	confidence interval
ICC	intraclass correlation coefficient
IQR	interquartile range
IVI	intravascular imaging
IVUS	intravascular ultrasound
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
RA	rotational atherectomy

Declarations

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Disclosures

None of the authors have anything to disclose.

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Figures

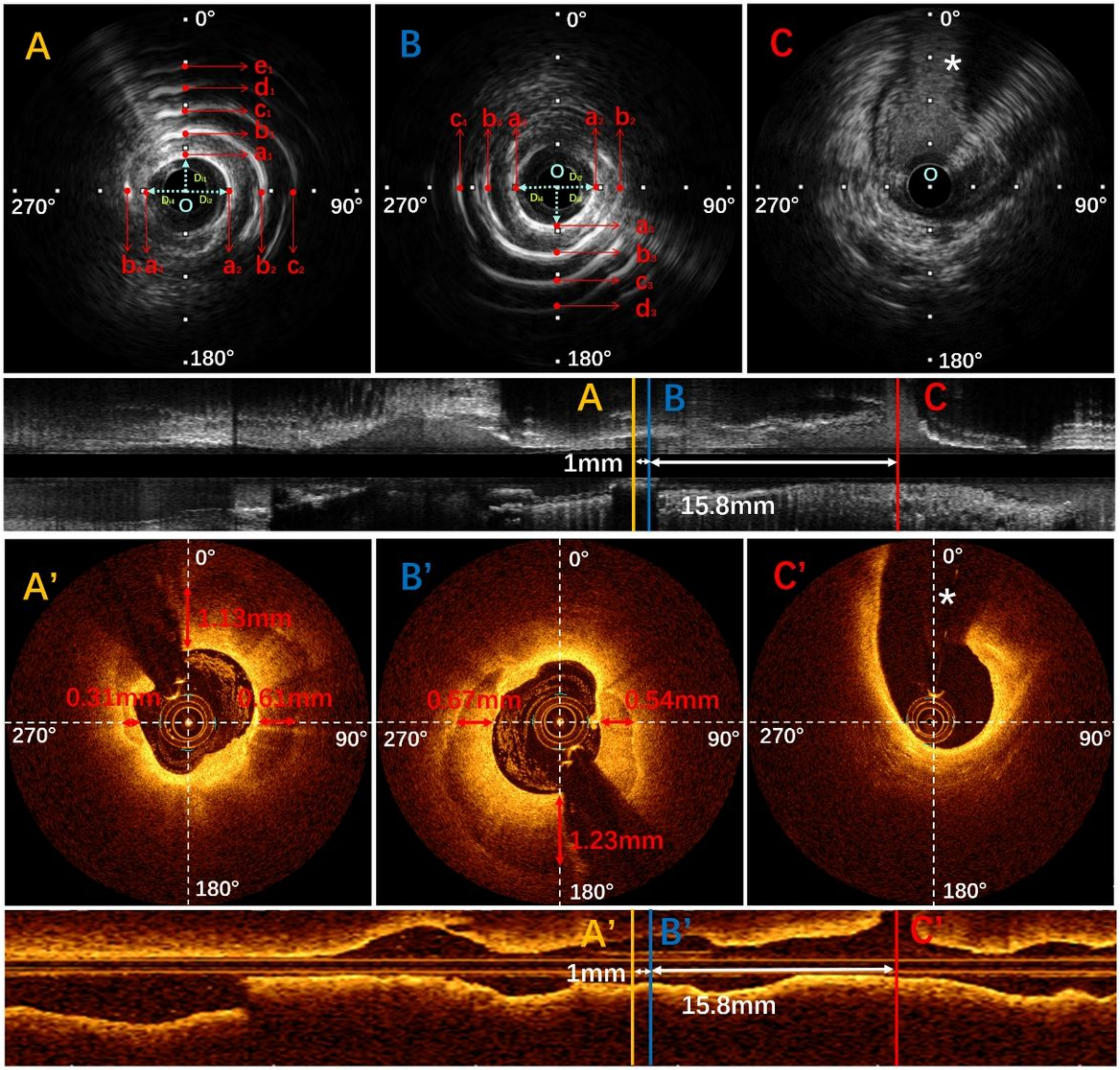

Figure 1

Number counting of layers of reverberation in IVUS and thickness of calcification measurement by OCT post manual coregistration Reverberation was found (A and B) with 1mm interval by IVUS detection and different thickness of calcification showed by OCT (A' and B') in corresponding segment after rotational atherectomy post coregistration by fiduciary side branch (C and C', white asterisk as the marker of calibration of radial and longitudinal positioning). Reverberation was measured at 0º, 90º, 180º and 270º respectively for the number of layers of reverberation (the number of layers of reverberation was 4 at 0º(a1-e1), 2 at 90º(a2-c2), and 1 at 270º(a4-b4) in IVUS, which corresponded to the calcification thickness of 1.13mm, 0.61mm and 0.31mm respectively in OCT), Di: distance between IVUS catheter center (point "O" in the figure) and inner surface of corresponding calcification and interval between jacent reverberation signals (interval1: distance between a and b, interval2: distance between b and c, interval3: distance between c and d, the rest can be done in interval4, interval5, interval6…).

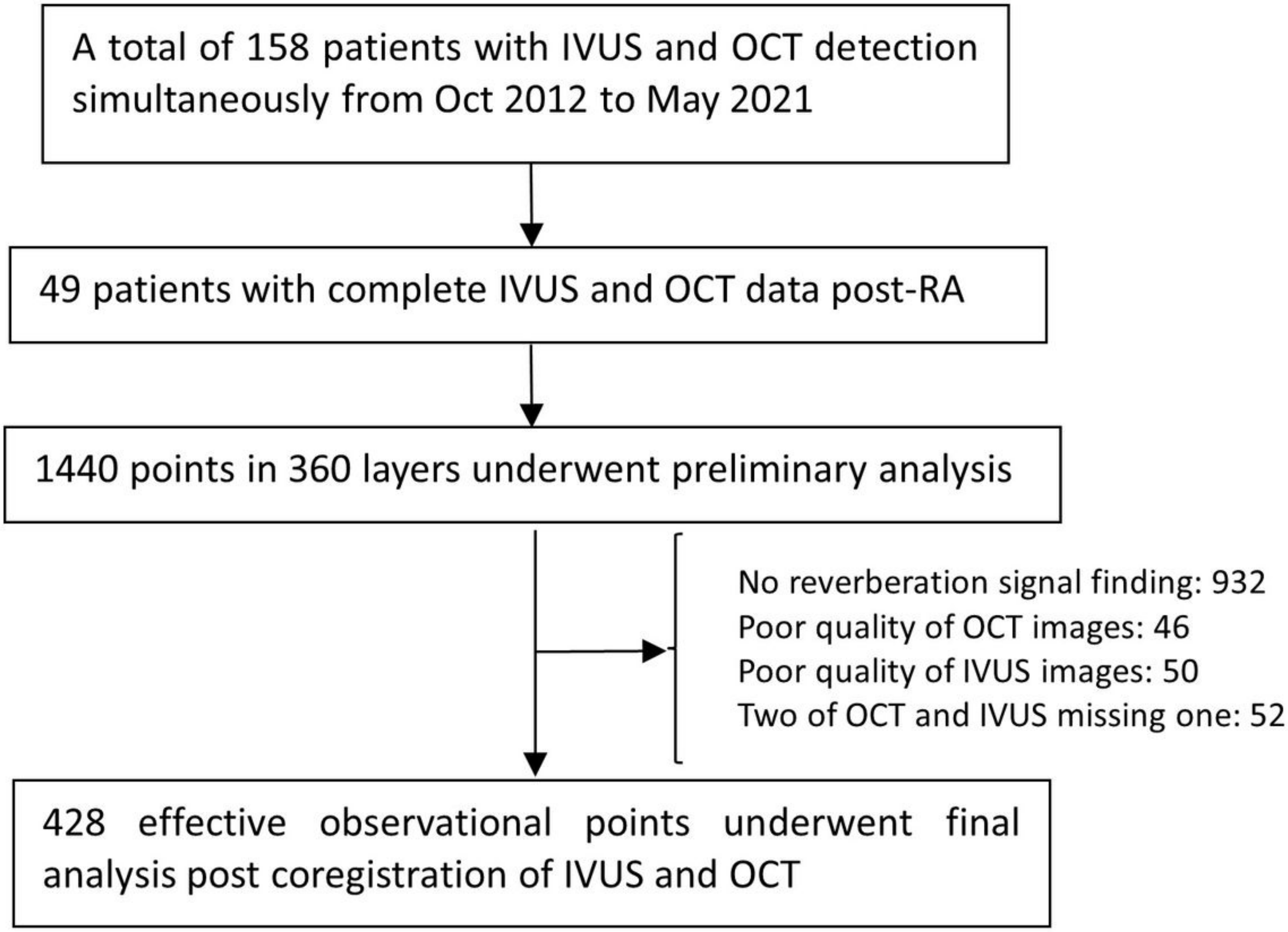

Figure 2

Study flow chart IVUS: intravascular ultrasound; OCT: optical coherence tomography

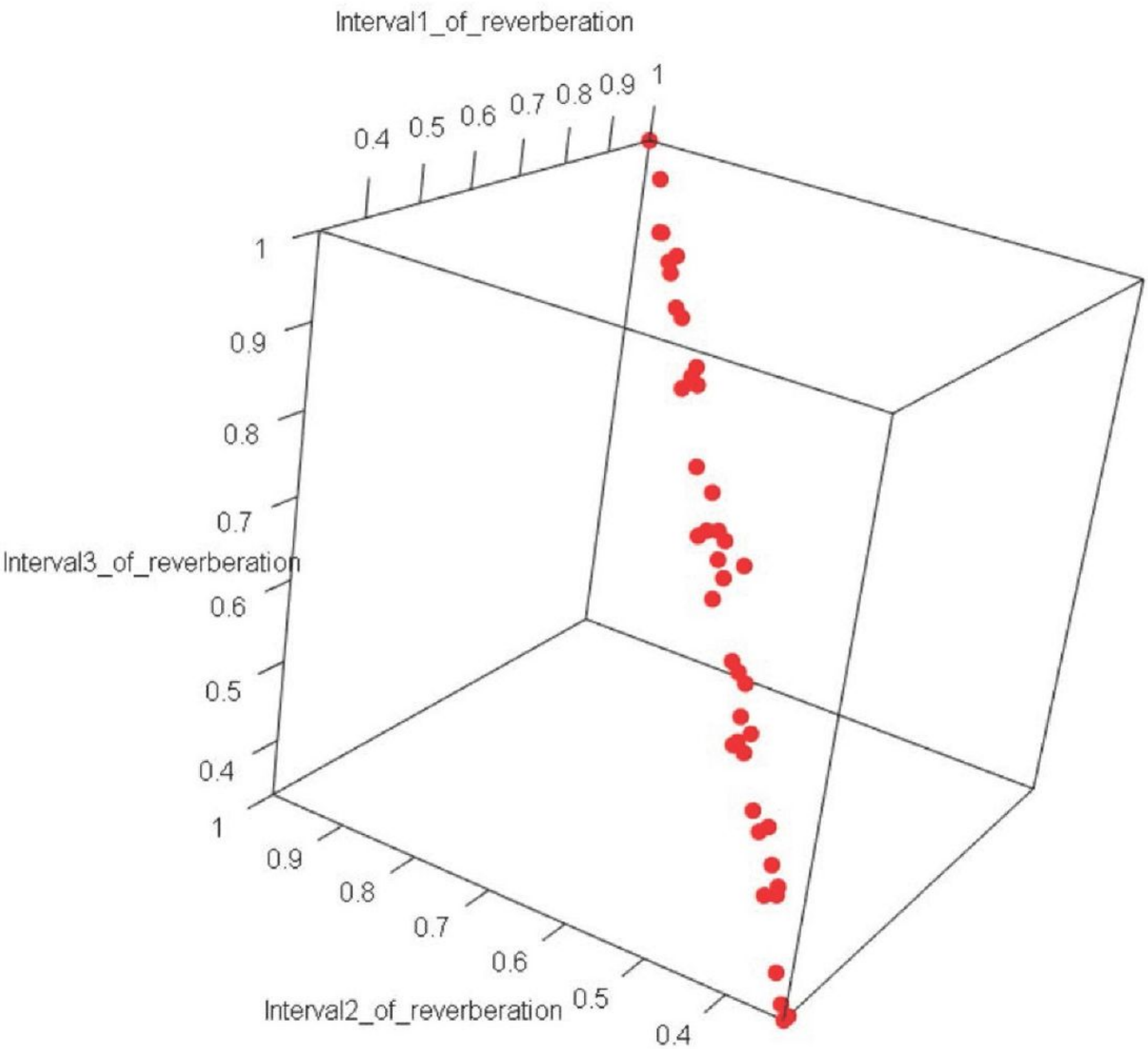

Figure 3

Comparation between distance of different interval between two adjacent reverberation signals at radial direction. A graph of three-dimensional scatters (drawn by “rgl” package) was plotted the describe the correlation between interval1, interval2 and interval3 of reverberation. The points inside are evenly distributed along the diagonal of the cube, the points are equidistant from all three axes, which means that the distance among interval1, interval2 and interval3 are almost equal in pairwise.

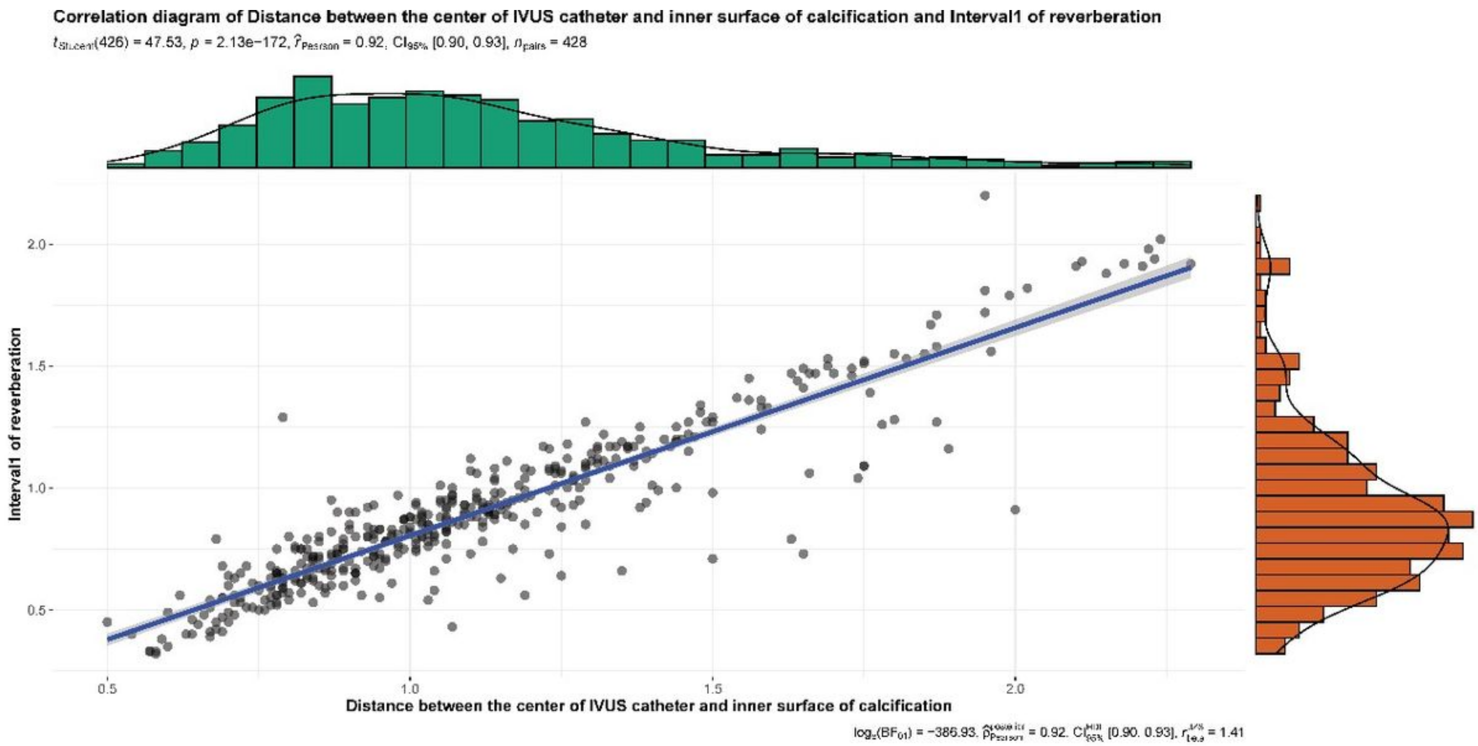

Figure 4

Correlation between interval of reverberation and distance of IVUS catheter center to inner calcification surface. By “ggstatsplot” package analysis, the interval1 of reverberation was remarkably correlated linearly with distance between the center of IVUS catheter and inner surface of calcification at same direction.

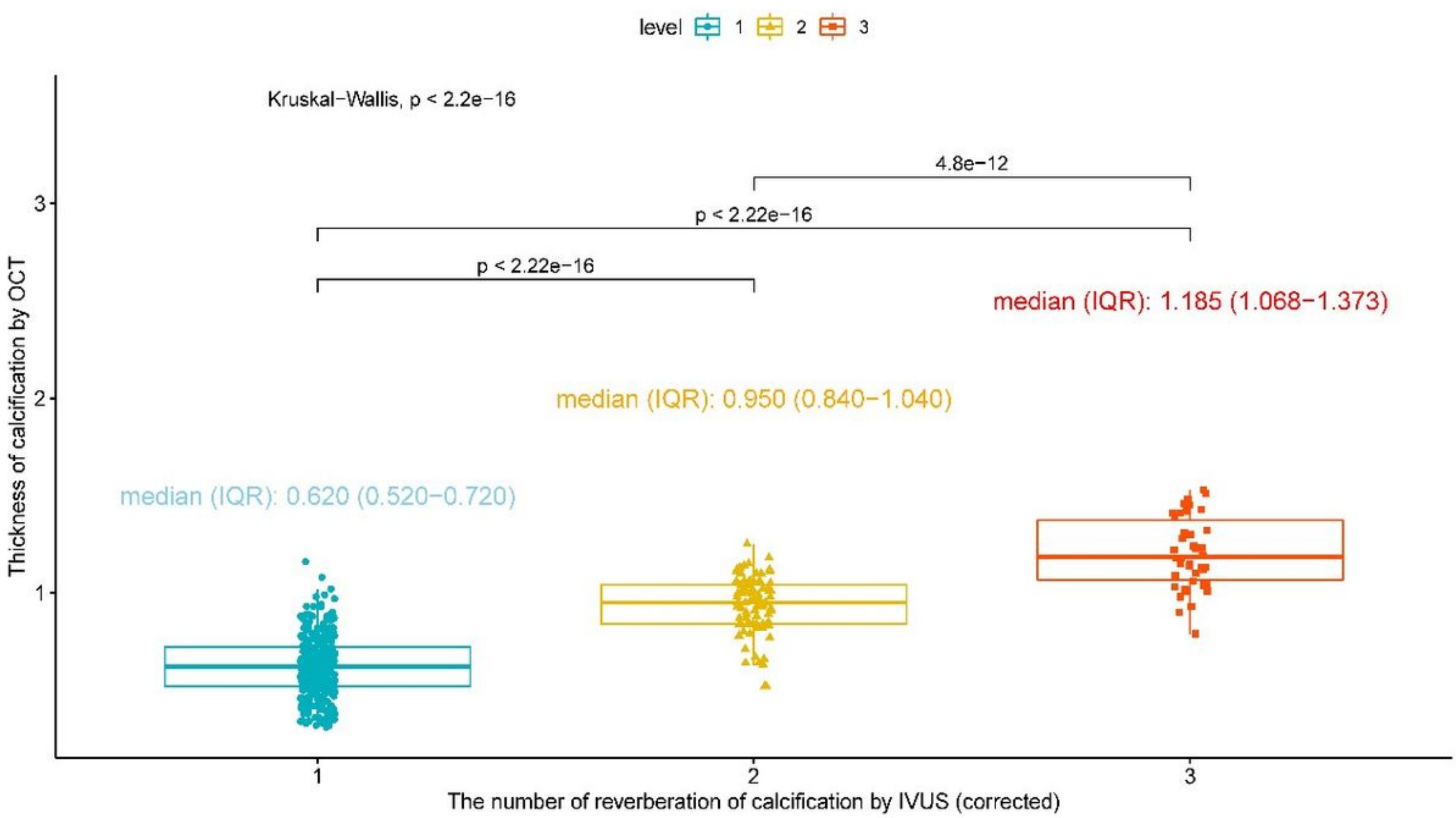

Figure 5

Correlation between the number of layers of reverberation of calcification by IVUS and thickness of calcification by OCT. The difference between groups divided by the corrected number of layers of reverberation of calcification by IVUS was analyzed by Krushal-Wallis analysis with post hoc analysis by Dunn-Bonferroni test (group 1: single layer of reverberation; group 2: double layers of reverberation; group 3: ≥3 layers of reverberation) and was drawn by “ggplot2” package along with “ggpubr”.