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ORIGINAL ARTICLE

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Spectral domain optical coherence tomography based imaging biomarkers for diabetic retinopathy

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Abstract

To evaluate the role of central subfield thickness (CST), cube average thickness (CAT), and cube volume (CV) as imaging biomarkers for severity of diabetic retinopathy within the ETDRS-based grades of retinopathy using spectral domain optical coherence tomography (SD-OCT). This study aims to evaluate the role of macular CST, CAT, and CV on SD-OCT as imaging biomarkers for severity of DR. One hundred ninety-four consecutive cases of type 2 diabetes mellitus were divided according to ETDRS classification: diabetes mellitus without retinopathy (No DR; $n = 65$), nonproliferative diabetic retinopathy (NPDR; $n = 66$), and proliferative diabetic retinopathy (PDR; $n = 63$). Sixty-three healthy controls were included. CST, CAT, and CV were analyzed using SD-OCT. Data were analyzed statistically. Analysis of variance revealed a significant increase in levels of CST, CAT, CV, and LogMAR visual acuity with the increase in severity of DR. Independent *t*-test revealed significant difference in CST, CAT, and CV between cases with DME and cases without DME. On multivariate linear regression analysis, increase in CST, CAT, and CV were found to indicate the increase in severity of DR. SD-OCT-based imaging biomarkers CST, CAT, and CV are effective tools for documenting the severity of diabetic retinopathy. These imaging biomarkers serve as significant indicators of severity of disease.

Keywords Diabetic retinopathy · Diabetic macular edema · Central subfield thickness · Cube average thickness · Cube volume · Spectral-domain optical coherence tomography

Introduction

The incidence of diabetes mellitus continues to grow worldwide with the number of people with diabetes expected to rise to 300 million by 2025 [1]. Diabetic retinopathy (DR), a major cause of blindness, is characterized by a number of interconnecting biochemical pathways [2]. Increased expression of biomolecules, such as vascular endothelial growth factor (VEGF), intercellular adhesion molecule-1 (ICAM-1) induced by VEGF, accelerated formation of advanced glycation end products like N epsilon-carboxymethyl lysine (Nε-CML) and increase in oxidative stress markers are the predominantly documented mediators

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of blood–retinal barrier breakdown that lead to diabetic macular edema (DME) [3–5].

Identification of disease in its early stages and timely intervention is crucial to improve visual outcome. Recognizing markers that can accurately predict the risk of disease severity and prognosticate the visual outcome would enable customizing clinical follow-up and tailoring therapeutic intervention.

National Institutes of Health Biomarkers Definition Working Group defined Biomarker as "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [6]. Imaging-based biomarkers provide a similar benefit by utilizing images of anatomical and physiological changes in the body, without the need for invasive procedures. Imaging biomarkers are potential clinical tools for Translational research, utilizing the knowledge from basic research to improve clinical practice.

Spectral domain optical coherence tomography (SD-OCT) has become an indispensable ancillary tool for qualitative and quantitative evaluation of pathological retinal changes. SD-OCT-based macular thickness parameters are reliable and reproducible tools for the evaluation of DME [7–10]. A significant increase in central subfield thickness (CST) and cube average thickness (CAT) and CV with an increase in the severity of retinopathy has been documented [11–14]. However, these parameters do not take into account the volumetric component, the cube volume (CV), which can be a useful predictor of severity of retinopathy. However, Ahuja et al. have highlighted the role of CST and CAT as imaging biomarkers. Cube volume has not been studied as a potential imaging biomarker.

Association of CST, CAT, and CV as imaging biomarkers for severity of DR has not been studied. Hence, the present study was undertaken to evaluate CST, CAT, and CV on SD-OCT as imaging biomarkers for severity of DR. The present study assesses the role of CST, CAT, and CV as markers of disease severity and as prognosticators of visual outcome. It also compares CV with CST and CAT to determine the relative indicate strengths for disease severity.

Methods

Our study had institutional review board clearance and was performed in accordance with the tenets of the Helsinki declaration. The sample size was calculated using 95% confidence limits with the two-sided α level of 0.05. The power of the study was 80% with respective z-value of 0.84. Informed consent was obtained from each subject before enrollment into the study. In this tertiary care center based cross-sectional study, 100 and 94 consecutive cases of type 2 diabetes mellitus were divided into three groups: diabetes without retinopathy (No DR; $n = 65$), nonproliferative DR (NPDR; $n = 66$), and proliferative DR (PDR; $n = 63$), according to early treatment diabetic retinopathy study (ETDRS) classification [12]. Sixty-three healthy age and gender matched controls were included. The right eye of controls and No DR group and the worse of the two eyes in NPDR and PDR groups were included for statistical analysis. Cases with ocular or systemic disease affecting retinal vascular pathology, previous ophthalmic surgical or laser interventions; intravitreal injections were excluded. Cases with signal strength 5 or below, on SD-OCT, were also excluded. The best corrected visual acuity was documented on the logMAR scale. Slit-lamp biomicroscopic examination was performed. Five milliliters of blood sample was drawn and analyzed for glycated hemoglobin (HbA1c) using the standard protocol.

All the study subjects underwent macular thickness analysis using the macular cube (512 × 128 scans) feature of SD-OCT [Cirrus High Definition OCT (Carl Zeiss Meditec Inc., CA, U.S.A)]. DME was also assessed [13]. CST (μm), CAT (μm), and CV (mm^3) were documented (Figs. 1 and 2). CST is defined as the thickness of the central circle of diameter 1 mm in the circular ETDRS Grid map [15]. Cube average thickness is defined as an overall average thickness of the internal limiting membrane-retinal pigment epithelium tissue (ILM-RPE) tissue layers over the entire 6 × 6 mm square scanned area, the mean of thicknesses in nine sections [16]. Cube volume is defined as an overall average volume for the ILM-RPE tissue layers over the entire 6 × 6 mm square scanned area [17]. Data are summarized and presented as mean ± SE. Chi-square (χ^2) test analyzed the difference in gender distribution between the groups. Pearson correlation was used to assess the correlation among CST, CAT, and CV. One way analysis of variance (ANOVA) followed by post hoc analysis (Fisher's least significant difference) was done to compare the values of CST, CAT, CV, LogMAR visual acuity, and HbA1c among the study groups. Independent t-test was used to compare CST, CAT, and CV between cases with and without DME.. Univariate followed by multivariate linear regression analysis was done taking visual acuity as a dependent variable with CST, CV, and CAT as independent variables, and adjusted for duration of diabetes and HbA1c.

The sensitivity and specificity of CST, CAT, and CV to predict severity of DR were evaluated using receiver operating characteristics (ROC) curves. An area under the ROC curve (AUC) of 1.0 represents perfect discrimination, whereas an AUC of 0.5 represents chance discrimination. $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS software (window version 21.0).

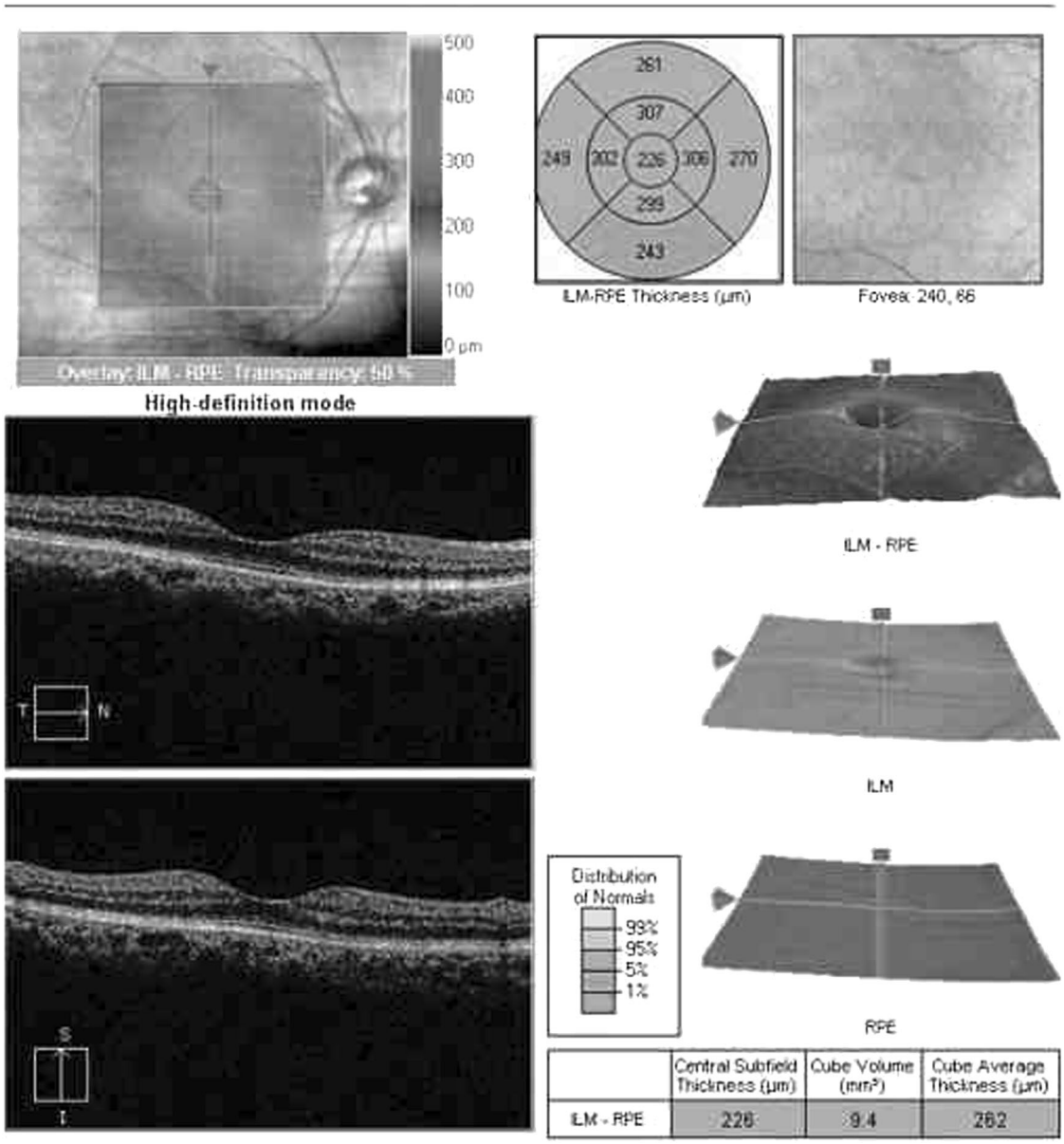

Fig. 1 SD-OCT cross-sectional image, ILM-RPE overlay, 3D macular thickness, segmented ILM and RPE maps and macular thickness parameters show normal retinal thickness in healthy controls

Results

The mean age in years was 51.25 ± 6.2 in controls, 52.53 ± 6.37 in No DR, 55.65 ± 7.32 in NPDR and 62.55 ± 6.32 in PDR. The gender distribution in the control group was found to be 33 males and 30 females. In No DR group, there were 28 males and 37 females, 30 males and 36 females in NPDR group, and 33 males and 30 females in PDR group. Chi-square revealed similar gender distribution among the groups ($\chi^2 = 1.61$; $p = 0.66$). Mean LogMAR visual acuity, HbA1c, duration of diabetes, CAT, CST, and CV among the study groups have been summarized in Table 1. None of the No DR cases had DME, whereas 72.73% cases with NPDR (48/66) had DME and all 63 cases of PDR had DME.

Pearson correlation analysis revealed statistically significant positive correlation between CST and CAT ($r = 0.55$; $p < 0.001$), CST and CV ($r = 0.52$; $p < 0.001$), and CV and CAT ($r = 0.83$; $p < 0.001$). ANOVA revealed significant increase in levels of CAT ($F = 13.88$; $p < 0.001$) (Fig. 3) and CST ($F = 16.28$; $P < 0.001$) (Fig. 4), CV ($F = 9.18$; $P < 0.001$) (Fig. 5), LogMAR visual acuity ($F = 84.05$; $p < 0.001$), and HbA1c ($F = 12.2$; $p = 0.03$) with increase in severity of DR. Independent *t*-test revealed a

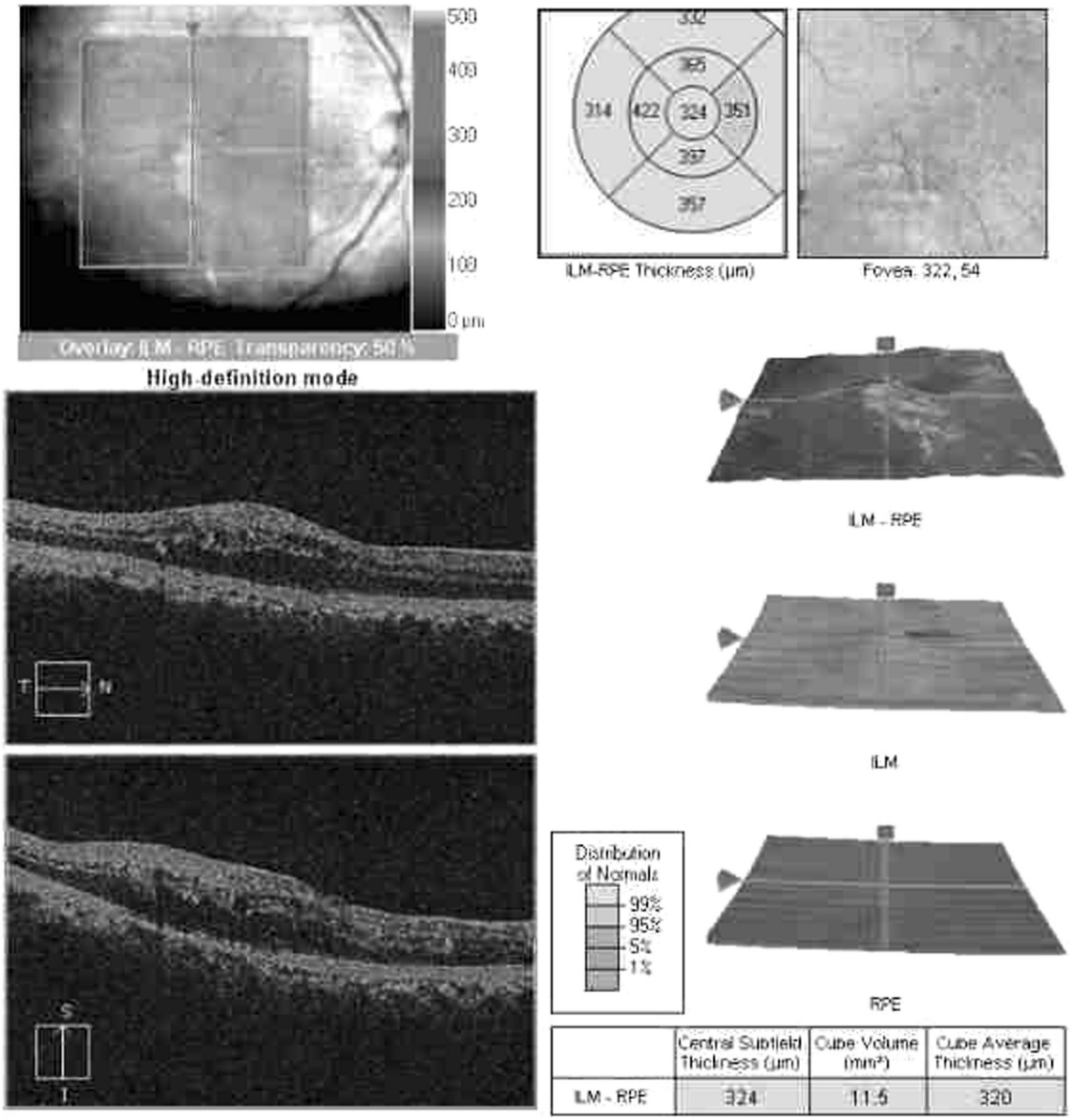

Fig. 2 SD-OCT cross-sectional image, ILM-RPE overlay, 3D macular thickness, segmented ILM and RPE maps and macular thickness parameters show increased retinal thickness in a case with diabetic macular edema

Table 1 Summary of mean ± SD of logMAR visual acuity, duration of diabetes, glycated hemoglobin, central subfield thickness, cube average thickness, and cube volume among the study groups

Variable	Groups			
	Control ($n = 63$) Mean ± SD	No DR ($n = 65$) Mean ± SD	NPDR ($n = 66$) Mean ± SD	PDR ($n = 63$) Mean ± SD
LogMAR visual acuity	0.10 ± 0.15	0.28 ± 0.24	0.63 ± 0.43	1.14 ± 0.56
Duration of diabetes (in years)	0.00 ± 0.00	6.41 ± 5.42	10.83 ± 6.11	11.02 ± 4.89
Glycated hemoglobin (% Hemoglobin)	5.73 ± 0.77	6.68 ± 0.83	7.96 ± 2.09	8.03 ± 1.65
Central subfield thickness (in µm)	247.14 ± 23.31	241.24 ± 35.71	264.86 ± 78.63	348.51 ± 166.71
Cube average thickness (in µm)	245.73 ± 12.52	256.73 ± 30.22	279.59 ± 57.88	302.88 ± 80.80
Cube volume (in mm^3)	9.19 ± 0.52	9.42 ± 1.06	10.20 ± 2.01	10.89 ± 3.14

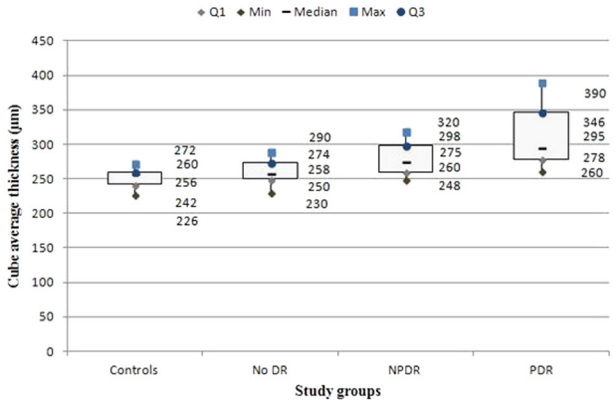

Fig. 3 Box and whisker plot illustrating cube average thickness among study groups. No DR No diabetic retinopathy, NPDR nonproliferative diabetic retinopathy, PDR proliferative diabetic retinopathy

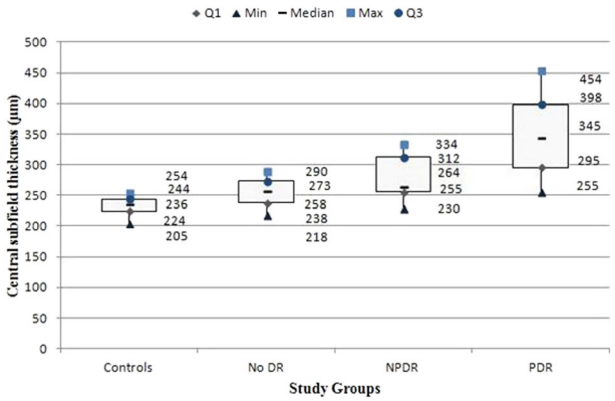

Fig. 4 Box and whisker plot illustrating central subfield thickness among study groups. No DR No diabetic retinopathy, NPDR nonproliferative diabetic retinopathy, PDR proliferative diabetic retinopathy

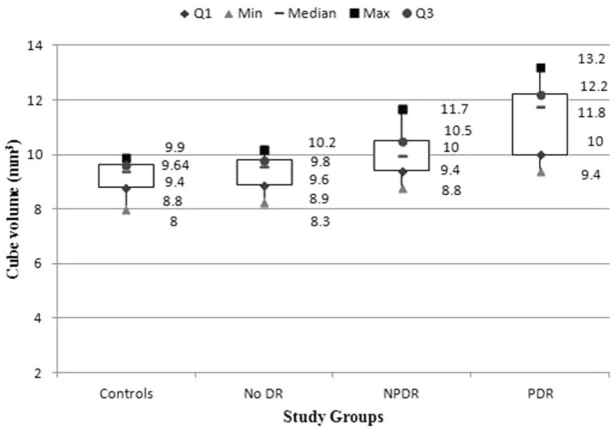

Fig. 5 Box and whisker plot illustrating cube volume among study groups. No DR No diabetic retinopathy, NPDR nonproliferative diabetic retinopathy, PDR proliferative diabetic retinopathy

statistically significant difference in CST ($t = 40.16$; $p < 0.001$), CAT ($t = 10.73$; $p = 0.001$), CV ($t = 8.05$; $p = 0.005$) and logMAR visual acuity ($t = 50.5$; $p < 0.001$) between cases with DME and cases without DME.

On univariate analysis with the severity of DR as the dependent variable and CST, CAT, CV as independent variables, a significant increase in severity was observed with increase in CST ($B = 0.004$; $p < 0.001$), CAT ($B = 0.008$; $p < 0.001$) and CV ($B = 0.17$; $p < 0.001$). On further multivariate linear regression analysis, adjusting for other factors like duration of diabetes and HbA1c, it was observed that increase in CST, CAT, and CV independently indicate an increase in the severity of retinopathy ($r^2 = 0.164$; $p < 0.009$; $p < 0.003$; $p < 0.008$, respectively).

On univariate analysis with visual acuity as the dependent variable and CST, CAT, CV as independent variables, a significant increase in logMAR visual acuity was observed with increase in CST ($B = 0.002$; $p < 0.001$), CAT ($B = 0.003$; $p < 0.001$) and CV ($B = 0.059$; $p < 0.001$). Subsequent multivariate linear regression analysis after adjusting for other factors like duration of diabetes and HbA1c revealed that increase in CST, CAT, and CV independently indicate an increase in logMAR visual acuity ($r^2 = 0.164$; $p < 0.008$; $p < 0.032$; $p < 0.001$, respectively).

The area under the ROC curves calculated as following: 0.78 for CST (95% confidence interval (CI), 0.72–0.84; $p < 0.001$) (Fig. 6), 0.77 for CAT (95% CI, 0.70–0.84; $p < 0.001$) (Fig. 7) and 0.78 for CV (95% CI, 0.72–0.84; $p < 0.001$) (Fig. 8). The curves showed a cutoff value of

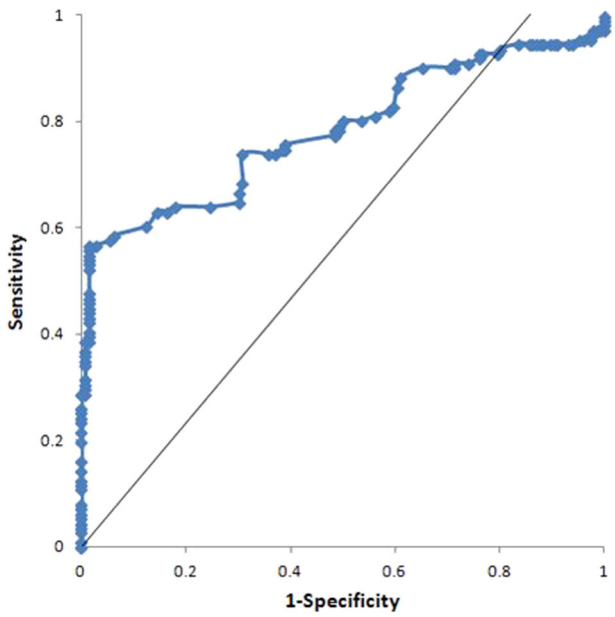

Fig. 6 Receiver operating characteristics curve for central subfield thickness with area under the curve calculated as 0.78 (95% confidence interval, 0.72–0.84)

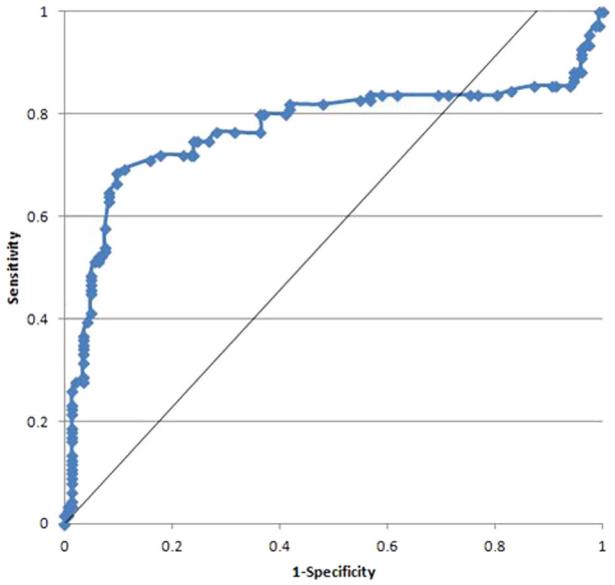

Fig. 7 Receiver operating characteristics curve for cube average thickness with area under the curve calculated as 0.77 (95% confidence interval, 0.70–0.84)

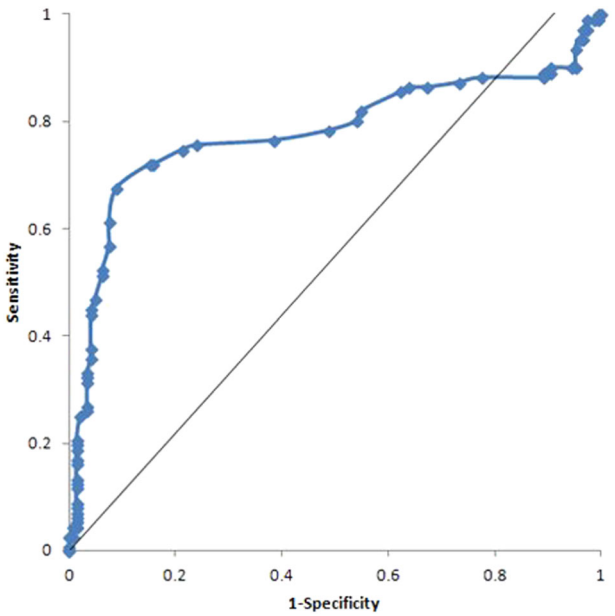

Fig. 8 Receiver operating characteristics curve for cube volume with area under the curve calculated as 0.78 (95% confidence interval, 0.72–0.84)

254.5 µm for CST, with the sensitivity of 73.9% and specificity of 69.2%. Similarly, the cutoff value for CAT was 264.5 µm, with the sensitivity of 74.8% and specificity of 76%. The cutoff value for CV was 9.65 mm^3, with the sensitivity of 75.7% and specificity of 76%. ROC data suggested CST, CAT, and CV as significant markers in discriminating disease severity.

Discussion

In the present study, CST, CAT, and CV were found to be independent markers of severity of retinopathy and prognosticators of visual acuity.

SD-OCT has been used for evaluation of retinal microstructural changes in DR. Disruption of external limiting membrane (ELM) and ellipsoid zone (EZ) has been documented to be an important marker of the severity of retinopathy [18]. Disruption of photoreceptor in patients with DR is known to be associated with a decrease in visual acuity [19, 20].

Studies have documented a significant increase in levels of various biomolecules, such as VEGF, ICAM, and N^{ε}-CML with an increase in the severity of retinopathy [3, 4]. Our recent study documented the role of serum levels of urea and creatinine as surrogate markers for disruption of retinal photoreceptor ELM and EZ on SD-OCT in DR [21–23]. Macular thickness parameters CAT and CST have also been found to be indicators, as well as imaging biomarkers of disease severity [13]. The increase in CST has also been found to be associated with disruption of photoreceptor EZ in DME [24–26].

Studies have highlighted that besides individual baseline measurement, SD-OCT is valuable in detecting subclinical retinal thickening in advanced retinopathy without DME. Such cases of subclinical macular edema have been recommended to be followed closely as they are at increased risk of DME [27]. In our study, we observed a significant difference in CST, CAT, and CV in No DR, NPDR, and PDR study groups. An increase in CST, CAT, and CV on SD-OCT was found with the increase in the severity of retinopathy. These imaging biomarkers serve as significant indicators of severity of disease process within the ETDRS-based grades of retinopathy, which may not be clinically evident. The widespread availability of the patient-friendly imaging tool complements the benefit of using SD-OCT-based imaging biomarkers as reliable objective standard estimates of severity of the disease. Documenting a precise baseline value will be useful for detection of subtle variations in retinal thickening for severity of retinopathy on follow-up. The advent of anti-VEGF pharmacotherapy has increased the utilization of SD-OCT in clinical practice for monitoring the treatment in DR. Several studies have correlated OCT-based retinal thickness with visual acuity in DME [28, 29]. SD-OCT imaging biomarkers would prove to be an efficient tool for rationalizing the decrease in visual acuity on follow-up when there is no change in ETDRS-based grading of DR that is evident clinically [30].

Use of retinal imaging biomarkers is an innovative approach to efficient large-scale management by identifying patients at high risk of severity to proliferative DR.

This would enable frequent follow-up of such patients and tailored therapeutic management to decrease the burden of retinopathy and improve the visual outcome. The present study, for the first time, documents the role of imaging biomarkers, CST, CAT, and CV, as effective tools for assessment of severity of DR within the ETDRS-based grades of retinopathy and valuable markers of visual acuity.

Conclusion

CST, CAT, and CV serve as SD-OCT-based imaging biomarkers and are effective tools for documenting the severity of DR. These imaging biomarkers also serve as significant indicators of the disease severity.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval 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.

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