Retinal vascular abnormalities in schizophrenia and bipolar disorder

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Retinal vascular abnormalities in schizophrenia and bipolar disorder: A window to the brain

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Abstract

Objectives: The examination of retinal microvascular abnormalities through fundus photography is currently the best available non-invasive technique for assessment of cerebral vascular status. Several studies in the last decade have reported higher incidences of adverse cerebrovascular events in Schizophrenia (SCZ) and bipolar disorder (BD). However, retinal microvasculature abnormalities in SCZ and BD have remained under-explored, and no study has compared this aspect of SCZ and BD till date.

Methods: Retinal Images of 100 SCZ patients, BD patients, and healthy volunteers each were acquired by trained individuals using a non-mydriatic camera with a 40-degree field of view. The retinal images were quantified using a valid semi-automated method. The average of left and right eye diameters of the venules and arterioles passing through the extended zone between 0.5 and 2 disc diameters from the optic disc were calculated.

Results: The groups differed significantly with respect to average diameters of both retinal venules ($P < 0.001$) and retinal arterioles ($P < 0.001$), after controlling for age and sex. Both SCZ and BD patients had significantly narrower arterioles and wider venules compared to HV. There were also significant differences between SCZ and BD patients; patients with BD had narrower arterioles and wider venules.

Conclusion: Considering the affordability and easy accessibility of the investigative procedure, retinal microvascular examination could serve as a potential screening tool to identify individuals at risk for adverse cerebrovascular events. The findings of the current study also provide a strong rationale for further systematic examination of retinal vascular abnormalities in SCZ and BD.

KEYWORDS
cerebrovascular event, fundus, neurodevelopment, peripheral marker, psychoses, retinal vessel

Abhishek Appaji and Bhargavi Nagendra contributed equally to the manuscript.

1 | INTRODUCTION

The retina and brain have common developmental origins and share anatomical, physiological, and autoregulational properties.[1-3] Examination of retinal microvascular abnormalities using fundus photography is currently the best available non-invasive technique to assess the status of systemic vascular health; narrower arterioles are associated with hypertension and obesity, while wider venules are linked to diabetes and altered lipid profiles.[4] Several studies in the last decade have reported that retinal vascular abnormalities reflect cerebral vascular abnormalities, with wider venules being predictive of stroke and other cerebrovascular diseases.[5] Narrower arterioles and wider venules have additionally been linked to poorer cognitive function and increased risk of dementia.[1]

Interestingly, vascular abnormalities have also been implicated in psychiatric disorders. Abnormal capillary bed in nail folds,[6] abnormal vascular response to niacin,[7] and abnormalities in genes regulating cerebral blood flow [8] have been reported in schizophrenia (SCZ). Patients with bipolar disorder (BD) have a higher incidence of vascular disorders and related premature mortality,[9] and an increased prevalence of deep white matter hyperintensities on magnetic resonance imaging (MRI), indicating cerebral microvascular disease.[10] Neuroimaging studies have reported reduced cerebral blood flow in the anterior brain regions in both SCZ[11] and BD.[12] However, despite the analogies between cerebral and retinal vasculatures, and easy access to the latter, retinal microvascular abnormalities have not been adequately examined in SCZ and BD. A single study that examined retinal vascular abnormalities in participants with SCZ, reported wider retinal venules compared to controls.[2] A related study examined twins discordant for psychotic symptoms with controls, and reported that abnormalities in retinal vessels reflect familial vulnerability to psychotic symptoms.[13] The only study in BD that has examined the retinal microvasculature had adolescent participants, and showed no abnormality.[14] The status of retinal vasculature in adults with BD remains unexplored.

While these studies have provided the first line of evidence for abnormal retinal vessels in SCZ and BD, the findings have not been further replicated. In addition, there have been no comparisons of such abnormalities across these two major psychoses. Considering the shared vascular co-morbidity in SCZ and BD[15,16] it is important to ascertain whether the retinal vascular abnormality is seen in all psychoses or specific to SCZ. The retinal vascular changes if found, are potential markers of future cardiovascular risk and could help in identifying at risk individuals. Hence, in the current study, we measured retinal microvascular parameters in patients with SCZ and BD, and healthy volunteers.

While previous studies in schizophrenia have reported wider retinal venules, studies in other neurological disorders have reported narrower retinal arterioles to be linked to stroke, cerebral small vessel disease, and dementia.[1,17] Based on these studies we hypothesized that, both SCZ and BD patients would have retinal vascular abnormalities, with wider venules and narrower arterioles, when compared to healthy volunteers; and that there would be no difference between SCZ and BD patients, considering the shared etiopathogenesis and shared vascular comorbidity.

2 | METHODOLOGY

2.1 | Subjects

One hundred patients with SCZ and 100 patients with BD were recruited from the outpatient and inpatient services of the National Institute of Mental Health and Neurosciences, Bangalore, India. Patients were clinically interviewed by a certified psychiatrist, and all patients meeting the diagnostic criteria for SCZ or BD according to the International Classification of Disorders (ICD-10)[18] were recruited. Patients with a diagnosis of substance use disorder (except nicotine), comorbid psychiatric disorders, medical, or neurological illness namely hypertension, diabetes, cerebrovascular accident, or history of ocular trauma were excluded. One hundred healthy volunteers (HV) were also recruited from same geographical location via flyers and word of mouth. Relatives of patients were not included as these measures could be endophenotypes. All HV were interviewed by a trained psychiatrist to rule out syndromal axis I psychiatric diagnosis. All HV underwent a clinical evaluation by a trained psychiatrist and were administered self-reported versions of the DSM-5 Cross cutting Symptom measures developed by the DSM-5 Task Force and Work Groups.[19] None of the HV had diagnoses of psychiatric disorder, substance use disorder, diagnosis of hypertension, diabetes, cerebrovascular accident, major neurological illness or history of eye trauma. All participants were between 18 and 50 years of age. The study was approved by the Institute Ethics Committee and all participants were recruited after valid documented informed consent.

2.2 | Assessments

The severity of clinical symptoms in SCZ was assessed using the Brief Psychiatric Rating Scale (BPRS),[20] which is designed to measure the severity of positive and negative symptoms, and general psychopathology. Young's Mania Rating Scale (YMRS),[21] a valid instrument to measure severity of mania, and Hamilton Depression Rating Scale (HDRS),[22] a sensitive tool to measure the severity of depression were used in BD. Functioning was assessed using Global assessment of functioning (GAF)[23] and Clinical Global Impression (CGI)[24] in both SCZ and BD.

2.3 | Retinal image acquisition

The process of retinal image acquisition was explained to the participants before the procedure. Images were acquired by trained individuals using a non-mydriatic camera with a 40-degree field of view, the "3nethra classic," which is manufactured by Forus Health Pvt ltd, India. Participants were seated in dark room for 5 minutes before the procedure to facilitate dark adaptation and pupillary dilatation. Optic disc centered posterior retinal images were captured

using a valid method described by previous authors.[25] Images were acquired from both the eyes separately and the average of vessel calibers from the right and left eyes was taken as the primary outcome measure as described in a former study.[2]

2.4 | Measurement of retinal vasculature

The retinal images were quantified using the semi-automated software VAMPIRE (Vessel Assessment and Measurement Platform for Images of the REtina).[26] The images were coded, and the person who performed the grading was blind to the diagnosis. VAMPIRE is a well validated tool for measurement of retinal vasculature and has been used in many studies. The tool provides automatic detection of retinal landmarks (optic disc) and quantifies frequently investigated key parameters such as vessel diameter and vessel branching coefficients. Details of the tool and computation process have been described elsewhere.[27] In brief, we computed the vessel diameter as the cross-sectional span of the vessel mask perpendicular to the vessel's estimated axis. Using Guos thinning algorithm, the vessel regions were initially converted to 1 pixel width. The arteriolar and venular diameters passing through the extended zone between 0.5 and 2 disc diameters from the optic disc were measured (Figure 1); as extended zone (0.5-2 disc diameters) measurements have been shown to have higher reliability compared to restricted zone (0.5-1-disc diameters) measurements.[2,28] Based on revised Knudtson-Parr-Hubbard formula, the six largest arterioles and venules present in this extended zone were chosen for calculations,[29] as this has been demonstrated to have better accuracy compared to 3 vessel measurements.[14] The Central Retinal Artery Equivalent (CRAE) for arterioles and Central Retinal Vein Equivalent (CRVE) for venules were calculated using an iterative process, by progressively replacing the largest and smallest vessel diameters at W_1 and W_2 in the formula mentioned in the Equations (1) and (2) until a single number was reached.

$$\text{Arterioles: } \hat{W} = 0.88 \times \sqrt{(w_1^2 + w_2^2)} \quad (1)$$

$$\text{Venules: } \hat{W} = 0.95 \times \sqrt{(w_1^2 + w_2^2)} \quad (2)$$

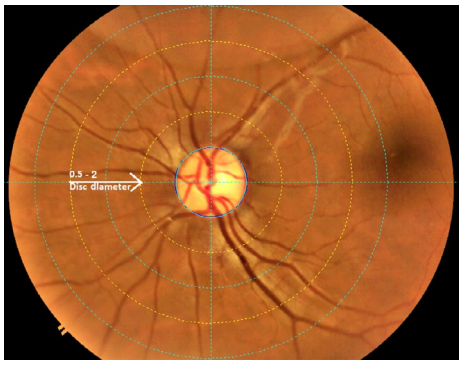

FIGURE 1 Representative figure showing zone-wise measurement of retinal vascular calibers

To convert the values obtained in pixels to micrometers (μm) we used a calibration factor. This calibration factor adjusted for the magnification differences due to optics of fundus camera, image resolution, and refractive errors of the patient as reported by previous study (reference). First, we measured the distance between the center of the optic disc and center of the macula for each individual subject's fundus image in pixels. Next, the calibration factor was calculated by using the formula.

$$\text{Calibration factor} = \frac{4500\mu\text{m}}{\text{Distance between centre of optic disc to centre of macula (in pixels)}} \quad (3)$$

The value, 4500 μm represents the average disc diameter in micron and was calculated based on previous studies; the average disc diameter measured by fundus camera was assumed to be 1800 μm and distance from the center of the optic disc to the center of the macula to be two and half times the disc diameter, that is, 4500 μm.[30] Next this calibration factor was multiplied by individual CRAE and CRVE of individual images obtained using Equations 1 and 2 to convert the vessel caliber from pixel to μm.

$$\text{CRAE in } \mu\text{m} = \text{Calibration factor for individual} \times \text{CRAE in pixels}$$

$$\text{CRVEin } \mu\text{m} = \text{Calibration factor for individual} \times \text{CRVE in pixels}$$

A sub-sample of 30 participants images were graded and analyzed by two persons to check the inter-rater reliability and a good inter-rater reliability of 0.8 was obtained for both CRVE and CRAE (Intra Class Correlation–Average vein–0.86, Average artery–0.84).

2.5 | Statistical analysis

All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 25. After establishing normative distribution of data using Shapiro-Wilk test, parametric statistical tests were used. Sex distribution across groups was examined using chi-square test and age difference was analyzed using one-way analysis of variance (ANOVA). As we measured two primary outcome measures, a Bonferroni corrected $\alpha = 0.025$ was considered significant. Age and sex-ratio being different across groups, our main outcome measures, that is, group differences in average CRVE and average CRAE were compared using multiple linear regression after adding age and sex as additional regressors to the model. To examine the relation between retinal vascular measures and clinical-demographic variables, separate stepwise linear regression analyses were conducted, with average CRVE and average CRAE as dependent variables, and scores on BPRS, YMRS, HDRS, number of episodes, and duration of illness as predictor variables.

TABLE 1 Comparison of demographic and clinical details between the groups

	HV (n = 92)	SCZ (n = 98)	BD (n = 87)	F/t/χ^2	*P*
Age	30.2 ± 7.8	32.7 ± 6.0	32.9 ± 6.0	4.536	0.012
Gender ratio (M/F)	41/51	64/34	54/33	9.479	0.009
Age at onset (y)	—	25.2 ± 5.3	23.7 ± 5.9	2.584	0.11
Duration of illness (y)	—	7.6 ± 5.1	9.0± 5.6	2.3	0.13
BPRS	—	28.7 ± 6.9	—	—	—
HDRS	—	—	3.9 ± 5.3	—	—
YMRS	—	—	1.9 ± 3.1	—	—

Abbreviations: χ^2, Chi square test; BD, patients with bipolar disorder; BPRS, Brief Psychiatric rating scale; HDRS, Hamilton depression rating scale; YMRS, Young's mania rating scale; *F*, Analysis of Variance; HV, healthy volunteer; SCZ, patients with schizophrenia; *t*, Independent *t* test.

TABLE 2 Retinal vascular diameters in the three groups

Parameter	HV (n = 92)	SCZ (n = 98)	BD (n = 90)	*F*	*P*
CRVE	196.5 ± 21.7	213.4 ± 27.4	227.6 ± 26.3	33.8	<0.001
CRAE	110.7 ± 21.7	102.5 ± 15.8	95.8 ± 16.9	14.9	<0.001

Abbreviations: BD, patients with bipolar disorder; CRAE, Average Central Retinal Artery Equivalent.; CRVE, Average Central Retinal Vein Equivalent; HV, healthy volunteer; SCZ, patients with schizophrenia.

3 | RESULTS

3.1 | Comparison of demographic variables

A total of 300 participants were recruited consisting of 100 healthy controls, 100 patients with SCZ and 100 patients with BD. Twenty-three of them were excluded following quality check of retinal images. The remaining 277 (98 patients with SCZ, 87 patients with BD and 92 healthy volunteers) were taken up for analyses. Demographic details and clinical variables are given in Table 1. We found significant differences in age and gender distribution across the 3 groups. Duration of illness and age at onset of illness were not significantly different between patients with SCZ and BD.

3.2 | Differences in retinal vascular measures between groups

There were significant differences across the 3 groups in both CRVE and CRAE ($P < 0.001$) (Table 2 and Figure 2). Further post-hoc analysis revealed that, both patients with BD ($P < 0.001$), and patients with SCZ ($P < 0.001$) had significantly wider CRVE in comparison to healthy volunteers. In addition, BD patients had significantly wider CRVE than SCZ patients ($P < 0.001$) (Figure 2). The CRAE on the other hand was significantly narrower in both patients with BD ($P < 0.001$) and patients with SCZ ($P = 0.002$) compared to healthy volunteers; and significantly narrower in BD patients compared to SCZ patients ($P = 0.014$) (Figure 2 and supplement Table S1). Since the groups were heterogeneous with respect to age and sex-ratio, we used them as additional regressors to control for possible confounding effects. Table 3 shows the regression analysis results between groups for both CRAE and CRVE, with and without adjustment for age and sex. The regression coefficient was comparable even after controlling for these confounding variables (further details in supplement Table S2). In addition, to rule out the confounding effects of the age and sex, we selected a sub-sample matched on these measures. Sixty-six HV (M:F = 32:34; age = 30.6 ± 5.4 years), 92 SCZ (M:F = 60:32; age = 32.3 ± 5.5 years), and 78 BD (M:F = 50:28; age = 32.24 ± 5.0 years) were selected. These 3 groups were matched on age ($F = 2.33$; $P = 0.1$) and sex ($\chi2 = 5.24$; $P = 0.07$). On regression analysis, there was still a significant difference between the 3 groups on CRVE (HV:197.5 ± 22.4, SCZ: 212.8 ± 28.0, BD: 228.8 ± 26.4; $F = 52.0$, $\beta = 0.4$, $P < 0.001$) and CRAE (HV: 106.5 ± 21.0; SCZ: 102.6 ± 16.1, BD: 95.2 ± 17.1; $F = 14.7$, $\beta = -0.24$, $P < 0.001$). Furthermore, the 2 patient groups were examined using this sub-sample. The 2 groups were matched on age ($t = 0.035$; $P = 0.158$) and sex ($\chi2 = 0.023$; $P = 0.88$). On regression analysis, these 2 patient groups had significant difference in CRVE ($F = 14.47$; $\beta = 0.3$, $P < 0.001$) and CRAE ($F = 8.63$; $\beta = -0.2$, $P = 0.004$). On stepwise linear regression between average CRAE, CRVE and clinical variables, none of the clinical variables showed significant contribution to the model suggesting absence of relationship between clinical variables and retinal vascular diameters ($P > 0.05$).

4 | DISCUSSION

To the best of our knowledge, this is the first study to have assessed retinal microvasculature abnormalities in both SCZ and BD in comparison with healthy individuals. Results from the study show that patients with both SCZ and BD have microvascular abnormalities, that is, wider venular and narrower arteriolar diameters when

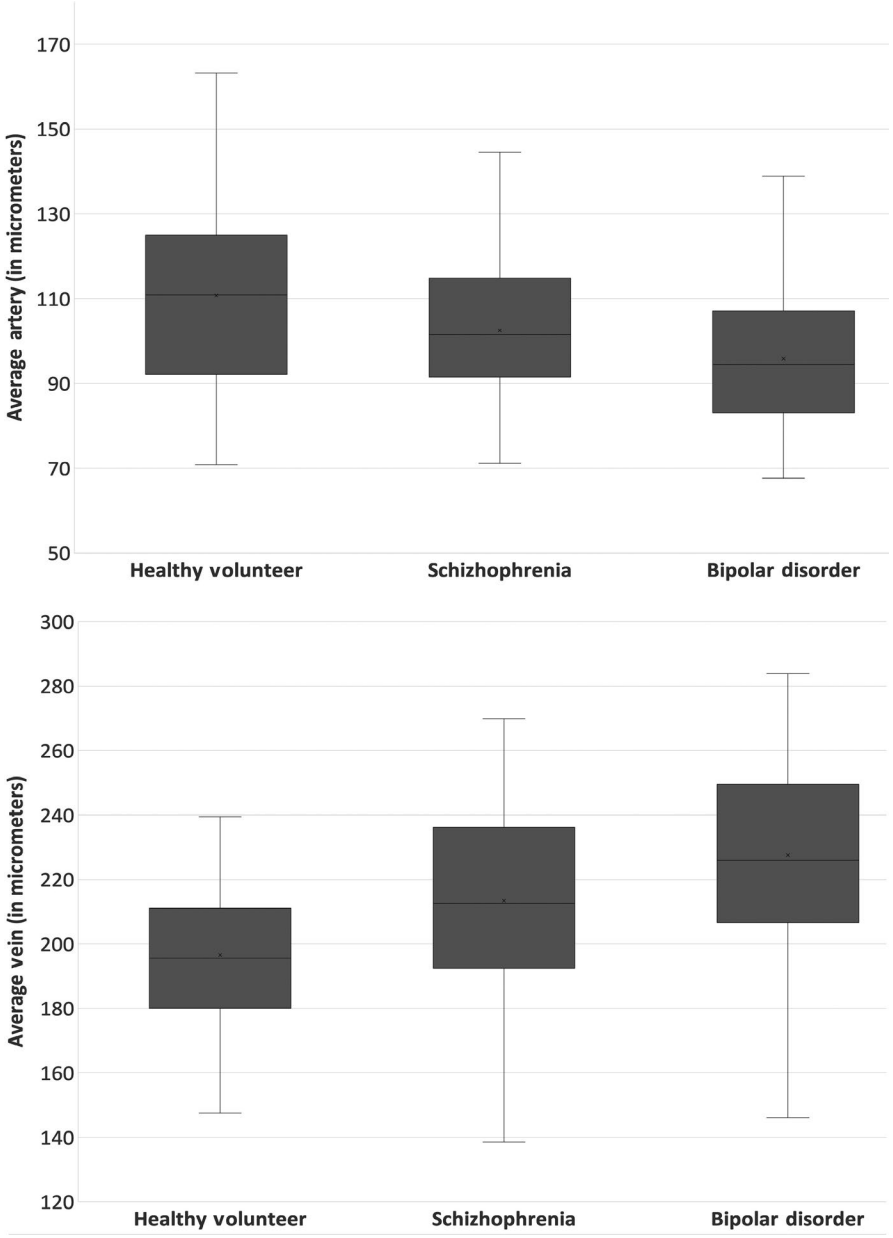

FIGURE 2 Representative boxplot diagrams showing mean comparison of CRVE and CRAE between groups

compared to healthy volunteers. Interestingly, patients with BD had significantly wider venules and narrower arterioles than patients with SCZ.

Our findings are in accord with, and support the only previous study on SCZ which also reported wider venules and narrower arterioles.[2] However, in contrast to a previous negative study in

TABLE 3 Mean difference of vascular diameter between groups adjusted for age and sex

	Group		Not adjusted for age and sex		Adjusted for age and sex	
			β (95% CI)	*P*	β (95% CI)	*P*
CRVE	HV	SCZ	0.3 (9.7 to 23.9)	<0.001	0.3 (9.4 to 24.2)	<0.001
	HV	BD	0.5 (23.9 to 38.2)	<0.001	0.5 (22.8 to 37.6)	<0.001
	SCZ	BD	0.3 (6.4 to 22.04))	<0.001	0.3 (6.4 to 22.1)	0.001
CRAE	HV	SCZ	−0.2 (−13.6 to −2.8)	0.003	−0.2 (−12.8 to −1.6)	0.012
	HV	BD	−0.4 (−20.7 to −9.1)	<0.001	−0.3 (−19.3 to −7.5)	<0.001
	SCZ	BD	−0.2 (−11.4 to −1.9)	0.006	−0.2 (−11.5 to −2.1)	0.004

β, regression coefficient; 95% CI, 95% confidence interval; BD, patients with bipolar disorder; CRAE, Average Central Retinal Artery Equivalent; CRVE, Average Central Retinal Vein Equivalent; HV, healthy volunteer; SCZ, patients with schizophrenia.

adolescent BD,[14] we have found that BD patients have wider venules and narrower arterioles in the retina. This could be due to a larger sample size (n = 100 vs n = 30) and the inclusion of adult patients in the current study. Our sample also had a higher proportion of patients with type I BD (65/100 vs 9/30). It is possible that retinal vascular abnormalities in BD have a progressive nature which could explain the findings in our adult sample with long duration of illness (9.3 ± 5.6 years) as opposed to adolescents with BD.

The mechanisms underlying retinal venular and arteriolar abnormalities are not completely known. Several theories have been proposed and epidemiological studies have shown that changes in retinal arteriolar and venular diameters are reflective of a wide range of environmental, genetic, and systemic influences[31] such as aging, inflammation, nitric oxide–dependent endothelial dysfunction and hypoxia/ischemia. Impaired fasting glucose, diabetes, dyslipidemia, obesity, elevated systemic markers of inflammation, endothelial dysfunction, and cigarette smoking are also associated with narrower arteriolar and wider venular diameters.[8] In the background of these findings, the results of the current study suggest that patients with BD and SCZ are at a higher risk of cerebrovascular accidents. A significantly increased risk of stroke in patients with BD and SCZ has also been reported in previous studies.[32,33] Examination of retinal microvasculature could prove to be an easy and affordable method to identify such patients at risk of adverse vascular events; the reliability of this investigative procedure needs to be explored in future studies.

The significant difference between SCZ and BD patients with respect to the retinal vessel diameters was an unexpected finding. Several studies in the recent past suggest shared risk factors and considerable overlap in pathophysiological processes between SCZ and BD.[15] Considering the common developmental origin between these disorders, we expected similarities, but the study results suggest significant difference between the disorders. The presence of a considerable number of BD-II and non-psychotic BD-I patients in our sample may explain the group differences demonstrated between SCZ and BD; while previous studies have reported considerable overlap between psychotic BD-I and SCZ,[34] it is yet unclear whether similar overlap is present between BD-II/non-psychotic BD-I and SCZ. It is also important to note that similar cross diagnostic differences between SCZ and BD have been reported by several previous studies that have examined neurocognition,[35,36] functional magnetic resonance imaging (fMRI)[37] and prevalence of metabolic syndrome.[38] Studies have reported that patients with SCZ have greater impairment in cognitive functions compared to BD.[36,39] A recent study has reported decreased volume of the CC (corpus callosum) associated with a lower degree of left hemispherical asymmetry for language in BD which was not replicated in SCZ. The authors have suggested that such distinct anomalies in both SCZ and BD may be considered specific biomarkers.[40] Hence, although some susceptibility genes are shared between SCZ and BD, one cannot rule out the possibility that other genetic and environmental factors may have differential effects.[41]

Findings of our study could have potential implications. The interesting observation of difference between SCZ and BD needs to be further examined and if replicated, has potential utility as a differential marker. It is important to note that patients who have psychotic symptoms during their first illness episode in BD are commonly misdiagnosed as SCZ or other psychotic disorders.[42,43] This could result in delay in initiation of specific treatment for BD resulting in more number of hospitalizations and poorer functional outcomes.[42] Hence, a biomarker which can differentiate BD from SCZ could aid early initiation of prompt treatment and better outcomes. A few studies have suggested that brain morphometric measures are potential biomarkers to differentiate BD from HV[44] and unipolar depression.[45] Further studies are required to ascertain whether retinal imaging measures have similar potential as neuroimaging measures to be used as biomarkers. However, in the background of several confounding factors it is important to note that our findings at this stage need to be considered preliminary and do not definitively suggest that retinal vascular changes are markers for psychosis but markers which may indicate risk for vascular events.

The following limitations of our study need to be considered while interpreting the results. All patients were on treatment with medications and hence the confounding effect of medication on CRVE or CRAE cannot be ruled out. However, there was no correlation between the antipsychotic dose used and retinal vascular measures ($P > 0.05$; details in supplement) suggesting absence of significant confounding effect of medication. Although study subjects were young adults and those subjects with known hypertension or diabetes mellitus were excluded to avoid their confounding effects, blood glucose levels and blood pressure were not documented for all participants on the day of retinal image acquisition. Hence one cannot rule out the possible confounding effect of pre-diabetic or pre-hypertensive status.[46] We excluded the diagnosis of medical disorders based on the history, which may risk the possibility of undiagnosed condition. However, in the sub-group of patients for whom the BMI and systolic blood pressure was available, there was no significant difference between the groups, and the results remained significant even after controlling for these variables (details in supplement). Future studies need to consider measuring the blood pressure, fasting glucose and renal functions using blood tests on the day of examination to control for their confounding effects. We did not collect the information regarding the lifestyle of subjects. As patients might have had sedentary lifestyle compared to HV, this could be a potential confounding factor increasing the risk for vascular events. Future studies need to include assessment of life style factors like diet, exercise, etc. As it was not the primary aim of the study, we did not have equal representation of BD-I and BD-II patients; this may have affected the results in the BD group as previously discussed. The groups were not age and sex matched. However, even after inclusion of age and sex as covariates the results have remained significant. Also, as seen in Table 3, the regression coefficient was comparable with and without age and sex as additional regressors in the model. Seventeen patients had documented nicotine use which may have affected their retinal vascular measures. However, even after excluding these 17 patients the results remained significant (details in supplement). Finally, while our study suggests abnormalities in retinal vasculature in BD and SCZ, the study population had varying lengths

of illnesses. With the cross-sectional nature of the study design it is not possible to determine whether the retinal micro-vascular changes were static or progressive. In our study, there was no significant relation between retinal vascular diameters and clinical variables including duration of illness, number of episodes, or severity of symptoms. However, a few longitudinal studies have reported changes in brain morphometric measures in individuals with BD[47] as well as those with high familial risk for BD.[48] Similarly, a few studies have also suggested an association between epigenetic factors and specific symptoms in BD.[49] Considering that the concept of staging in BD[43,50] is a relatively recent development, future longitudinal studies need to probe for changes in retinal vascular measures with progression of the illness.

5 | CONCLUSION

To summarize, our study indicates significant differences in retinal microvascular diameters in patients with SCZ and BD when compared to HV; patients with BD and SCZ have narrower arterioles and wider venules in comparison to HV, and patients with BD have narrower arterioles and wider venules in comparison to SCZ patients. This line of investigation has important implications as these findings suggest an increased risk of adverse vascular events in patients with SCZ and BD. Considering the affordability and easily accessible nature of the investigative procedure, retinal microvascular examination could serve as a potential screening tool to identify individuals at risk for adverse vascular events. However, with the cross-sectional design of the study we were not able to determine the threshold value for identifying at risk individuals. Future longitudinal studies will be able to provide the threshold value which may differentiate those at risk of cerebro/cardiovascular risk and the sensitivity, specificity metrics. The findings of current study provide a strong rationale for further systematic examination of retinal vascular abnormalities in patients with SCZ and BD.

CONFLICT OF INTEREST

Shyam Vasudeva Rao is the Co-founder and Director at Forus Health Pvt Ltd, India.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.[51] The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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