Retinal vascular occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy (DR) and is an important cause of vision loss in people with diabetes mellitus (DM). However, the pathogenesis of RVO is vaguely understood. This condition may be due to the combination of three systemic changes (Virchow’s triad), which include hemodynamic changes (venous stasis), degenerative changes in the vessel wall, and blood hypercoagulability. Systemic diseases such as hypertension (HTN) and dyslipidemia are the major risk factors for arteriolar thickening. Other systemic risk factors include diabetes and smoking. Ophthalmic risk factors include glaucoma, hypermetropia, and ocular inflammatory disease. Many studies have shown an inconsistent association of RVO with the above-mentioned risk factors.

This study has estimated the proportion of people with type 2 diabetes mellitus (T2DM) recruited into the Spectrum of Eye Disease in Diabetes (SPEED) study across India, also who had RVO, and explored the systemic associations.

### Methods

The SPEED study was a multicenter study that involved 14 eye care facilities in India. The details are described in report #
1. In brief, the SPEED was a descriptive observational study of consecutive ophthalmic patients with T2DM presenting to the vitreoretinal service of participating eye care facilities which were widespread across India between the period of August 2016 and January 2017. Approval was obtained from the institutional ethics committee of each study center and the study was conducted as per the tenets of the Declaration of Helsinki on human research, after taking a written consent. The approvals from the individual ethics committee were submitted to the Indian Institute of Public Health (IIPH), Hyderabad. No patient or family was given any financial assistance in cash or kind.

The pretested questionnaire was administered to people who were included in the study. The data collection software and app base using Java were supplied to all participating centers on-line. Stata14SE for Windows (Stata Corp., TX, USA) was used for statistical analysis.

The study proforma included age, gender, type of DM and duration, history of other systemic risk factors [HTN, cardiovascular diseases (CVDs), and history of stroke], treatment for diabetes, and status of diabetes-related biochemical parameters including HbA1c levels on presentation to the retina service. Ocular evaluation consisted of comprehensive eye examination (measurement of distance and near-visual acuity using the Snellen’s chart placed at 6 m, ocular motility, adnexal examination, slit-lamp examination of the anterior segment, and measurement of intraocular pressure with applanation tonometer, detailed slit-lamp biomicroscopy using 90D lens, and indirect ophthalmoscopy), and investigations such as fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) when needed were also done.

Retinal vein occlusion, when present, was classified into either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Based on the location and FFA characteristics, the BRVO was further classified into BRVO major and BRVO macula. The CRVOs were classified into ischemic or nonischemic CRVO. The diagnosis was separately made for the right and left eyes.

The status of the diabetes was determined based on the Indian Council of Medical Research (ICMR) guidelines.[15] We defined a good control of DM when the recent plasma glucose level was as follows: fasting: <110 mg/dL, 2-h post-load glucose <140 mg/dL, and HbA1c < 5.7%. We defined a person as diabetic when the recent plasma glucose level was >126 mg/dL, 2-h post-load glucose >200 mg/dL, random >200 mg/dL, and HbA1c >6.5%. HTN was defined (as per the Indian standards) as normal when the blood pressure was less than 130/85 mmHg and hypertensive when the blood pressure was more than 140/90 mmHg.[16] Stroke was defined as per the World Health Organization (WHO) standards by three criteria[17]; (1) in which an area of brain is transiently or permanently affected by ischemia or bleeding or (2) in which one or more brain blood vessels are primarily involved in a pathological process, or (3) a combination of these conditions.

Statistical analysis was performed using Stata14SE software for the Windows (Stata Corp, TX, USA) and the analysis was performed using Chi-square test. Univariate and multivariate logistic regression analyses were undertaken to identify the risk. To evaluate the effects of the systemic association, discrete logistic regression analysis was performed using the association of HTN and CVD, with stroke as an independent variable along with the RVO as the dependent variable. A $P$ value of $<0.05$ was considered statistically significant.

### Results

The study was conducted among all patients with T2DM who attended vitreoretina department with various eye complains in 14 different eye care facilities spread across different geographical locations of India. The study period was from August 2016 to January 2017. A total of 11,182 consecutive patients (22,364 eyes) suffering from T2DM were recruited for the study. All the cases fulfilled the inclusion criteria of the study.

In this cohort, a total of 380 (3.4%) subjects had RVO (both BRVO and CRVO together) and the remaining subjects had other vitreoretinal diseases. About 59.0% ($n = 6597$) of participants were male. The mean age of the patients was 58.2 ± 10.6 years. The duration of diabetes varied from ≥5 to ≥16 years.

BRVO was found in 294 eyes of 257 patients (67.6% of all RVO) and 37 patients (14.4%) of them had bilateral involvement. CRVO was found in 140 eyes of 123 patients (32.4% of all RVO) and 17 patients (13.8%) had bilateral involvement. The ratio between BRVO and CRVO in the diabetic population was found to be 2:1. Altogether, unilateral RVO is more common ($\chi^2 = 126.95, P < 0.001$) [Table 1]. Among the unilateral group, right eye involvement was marginally more than the left eye.

About 58.5% ($n = 172$) of eyes of BRVO had macula involvement, where superior temporal retinal vein or tributary branch vein was affected. Around 41.5% of eyes ($n = 122$) had BRVO in one of the four major venules without macular involvement. Macula-involving BRVO was found to be more common than nonmacula-involving BRVO. Ischemic CRVO ($n = 103$) was found 2.8 times more than the nonischemic CRVO ($n = 37$) [Table 2].

The maximum frequency of BRVO was within 5 years of detection of DM ($n = 151, 34.4$%), and thereafter the frequency is more or less the same in each 5 years interval up to more than 16 years of diabetic age, whereas CRVO was less in the group of patients who were within 6–10 years of diabetic age. In other age groups, the frequency distribution was similar [Table 3].

RVO is more common in patients with uncontrolled and poorly controlled diabetes ($n = 208, 72.5$%) [Table 4]. On the multivariate analysis, a history of HTN (57.2% of subjects) [odds ratio (OR): 1.7; 95% confidence interval (CI): 1.3–2.1; $P = 0.001$] and stroke (OR: 5.1; 95% CI: 2.1–12.4; $P < 0.001$) was significantly associated with RVO [Table 5].

### Discussion

The association of DM with RVO has been studied worldwide. This is the first study in India where data were collected from 14 different cities covering the entire country and a standard diagnostic criterion was adopted. DR is the important and blinding complication of DM in the adult population. RVO and DR share certain common clinical ophthalmoscopic findings in the ocular fundus. In retinal vein occlusion, the venules of the
Table 1: Clinical profile of RVO in diabetic population

| Category | No. of subjects | No. of eyes | No. of subjects Both eyes (n, %) | No. of subjects One eye involvement (n, %) | Right eye (n, %) | Left eye (n, %) |
|----------|----------------|-------------|---------------------------------|-----------------------------------------|-----------------|----------------|
| BRVO     | 257 (67.6%)    | 294         | 37 (14.40%)                     | 220 (85.60%)                            | 125 (48.64%)    | 95 (36.96%)   |
| CRVO     | 123 (32.4%)    | 140         | 17 (13.82%)                     | 106 (86.18%)                            | 53 (43.09%)     | 53 (43.09%)   |
| Total    | 380            | 434         | 54                              | 326                                      | 178             | 148           |

RVO: Retinal vascular occlusion; BRVO: branch retinal vein occlusion; CRVO: Central retinal vein occlusion. Total number of patients with T2DM with VR complaints screened = 11,182 (22,364 eyes); total number of RVO detected, n = 380 (434 eyes); male: n = 6697 (59%); female: n = 4562 (41%); average age = 58.2 ± 10.6 years; BRVO: CRVO ≈ 2:1.

Table 2: Vision-threatening RVO in diabetic population

| BRVO, no. of eyes (n, %) | CRVO, no. of eyes (n, %) |
|--------------------------|--------------------------|
| Macula involved          | Macula not involved      |
| Total                    | Ischemic                 |
| 172 (58.5%)              | 122 (41.5%)              |
| 294                      | 103 (73.6%)              |
| 37 (26.4%)               | 140                      |

RVO: Retinal vascular occlusion; BRVO: branch retinal vein occlusion; CRVO: Central retinal vein occlusion. About 58.5% of BRVO and 73.6% of CRVO presented with severe vision loss; as all the centers were tertiary eye care center, the RVO cases were not fresh cases.

Table 3: Duration of diabetes in people with retinal vascular occlusions

| Diabetes duration | Right eye | Left eye | Both eyes |
|-------------------|-----------|----------|-----------|
|                   | Patients | %        | Patients | %        | Patients | %        |
| ≤5 years          | 69       | 38.3     | 54       | 35.8     | 14       | 25.9     |
| 6-10 years        | 45       | 25       | 38       | 25.2     | 8        | 14.8     |
| >11-15 years      | 32       | 17.8     | 31       | 20.5     | 17       | 31.5     |
| >16 years         | 34       | 18.9     | 28       | 18.5     | 15       | 27.8     |
| Total             | 180      | 100      | 151      | 100.0    | 54       | 100      |

Table 4: Status of diabetes control at presentation in people with retinal vascular occlusions

| Control of diabetes | Right eye | Left eye | Both eyes |
|---------------------|-----------|----------|-----------|
|                     | Patients | %        | Patients | %        | Patients | %        |
| Well-controlled     | 40       | 22.2     | 39       | 25.8     | 8        | 14.8     |
| Some control        | 67       | 37.2     | 57       | 37.8     | 28       | 51.8     |
| Not controlled      | 46       | 25.6     | 36       | 23.8     | 15       | 27.8     |
| No data             | 27       | 15       | 19       | 12.6     | 3        | 5.6      |
| Total               | 180      | 100      | 151      | 100      | 54       | 100      |

health data (Brno, Czech Republic), Kolar[25] found that DM and some other systemic factors such as HTN, high-density lipoprotein, and PAD are strong risk factors for RVO. The authors also concluded that pathogenesis of CRVO and BRVO is multifactorial and ill-understood till date.

Hayreh[13] and others[14,26-29] documented that uncontrolled DM in the male gender and older age increases the risk of RVO. Beaver Dam Study[6] similarly documented strong association between BRVO and DM (OR: 2.43; 95% CI: 1.04–5.70) and HTN (OR: 542; 95% CI: 2.18–3.47). Stem et al.[26] in a longitudinal study conducted among 1,300 clinic-based patients in the United States found an association between CRVO and end-organ damage from DM [hazard ratio (HR) = 1.53; 95% CI: 1.28–1.84] along with other systemic risk factors. Several studies have also shown that uncontrolled DM in male gender and older age increases the risk of RVO in them.[13,14,26,27]

Klen et al.[26] and others[29-31] could not find any constant relationship between DM and RVO. The Eye Disease Case-control Study Group[7] documented that DM in a diverse group of patients in the United States did not increase the risk of CRVO, but HTN alone increases the risk of CRVO in 66% of subjects. However, DM, HTN, and HLD together increase the risk of developing CRVO in 58% of subjects in comparison to those who do not have the above three systemic conditions together.

Jeganathan et al.[32] compiled different studies and found a constant but varied association of DM and RVO. The Eye Disease Case-control Study Group[7] implicated HTN as a risk factor for BRVO in 50% of cases. Lam et al.[33] also could not find any association between DM and BRVO. Zhou et al.[14] and Rehak and Rehak[34] described only HTN as risk factor for RVO. In the Beijing eye study[6] (population-based longitudinal study), no risk association was found between DM and BRVO.

Singapore Malay Eye Study[35] recorded HTN as a risk factor for RVO rather than DM. The study also documented a lower prevalence of RVO in the Asian population than Caucasians as found in the Blue Mountains Eye Study.[9] However, Dodson et al.[12] described Asians are at higher risk for RVO than Caucasians in the diabetic population. Stem et al.[26] found a higher risk of CRVO in the African American general population but did not comment about the association between DM and RVO. So it is apparent that epidemiological and other studies could not establish a definite relationship between DM and RVO.

About 3.4% of the patients with diabetes with vitreoretinal problems of the present cohort had RVO. This is higher than in the population-based prevalence studies such as Blue Mountain Eye Study, the Framingham Eye Study,[25] and...
Beaver Dam Eye Study, where the prevalence of RVO was 1.6%, 0.15%, and 0.8%, respectively. Unlike other studies, this study was a facility-based study and almost 50% of RVO cases had a visual impairment. Opportunistic screenings explain the proportionally higher prevalence of RVO in the diabetic population in the study. All the recruited patients self-reported in the eye care facilities for treatment of their eye complaints. It probably reflects the eye-care-seeking behavior of the population. In this study, unilateral RVO was more frequent than bilateral disease (326/54 eyes) and it was statistically significant \( \chi^2 = 126.95, P < 0.001 \). BRVO was more frequent than CRVO which does not differ from other reports. More than half of the BRVO patients had a risk of developing vision loss due to macular edema. In diabetic population, ischemic CRVO was 2–8 times more in comparison to nonischemic group suggesting risk of vision loss.

We observed that uncontrolled or poorly controlled DM was related to RVO and not merely the duration of DM. We also report a strong association of HTN and CVD with RVO in the Indian population. On the multivariate analysis, a history of HTN (OR: 1.7; 95% CI: 1.3–2.1; \( P = 0.001 \)) and stroke (OR: 5.1; 95% CI: 2.1–12.4; \( P < 0.001 \)) was associated with RVO. Many investigators as described earlier also implicated HTN and stroke as risk factors for RVO.

The limitation of this study was that it was an opportunistic hospital-based screening among the patients who attended in VR department, and hence it did not estimate the prevalence of RVO in the population. We did not collect renal function or hematocrit data. This study did not measure anthropometry, particularly body mass index which is also associated with RVO.\(^{[12]}\) Despite the odds, the strength of the study was that it was the first pan India study and used a uniform protocol.

### Conclusion

This facility-based opportunistic study provides summary data on the occurrence and risk factors of RVO disease among people with T2DM in India. Though the patient pool was from different parts of the country, yet it did not represent the entire population in general. The study documented that vascular retinopathy was the second most common vascular lesion in people with diabetes and which occurred more often in uncontrolled diabetes. About 3.4% of the vitreoretinal problems in patients with diabetes are due to RVO. Stroke, HTN, and CVDs are important systemic association and HTN and stroke were significant risk factors. For prevention and holistic management of retinal vascular disease in people with diabetes, attention to the systemic condition is important.

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Conflicts of interest
There are no conflicts of interest.

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