Identification of risk factors for targeted diabetic retinopathy screening to urgently decrease the rate of blindness in people with diabetes in India

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Purpose: There is an exponential rise in the prevalence of diabetes mellitus (DM) in India. Ideally all people with DM should be periodically screening for diabetic retinopathy (DR) but is not practical with current infrastructure. An alternate strategy is to identify high-risk individuals with vision-threatening diabetic retinopathy (VTDR) for priority screening and treatment. Methods: We reanalyzed four population-based studies, conducted in South India between 2001 and 2010, and reclassified individuals above 40 years into known and newly diagnosed diabetes. Multiple regression analysis was done to identify risk factors in people with known and new DM. Results: The prevalence of DR in 44,599 subjects aged ≥40 years was 14.8% (18.4 and 4.7% in known and new DM, respectively), and the prevalence of VTDR was 5.1%. Higher risk factors of VTDR were older age >50 years, diabetes duration >5 years, and systolic blood pressure >140 mm Hg. Targeted screening of people with diabetes using high-risk criteria obtained from this study was able to detect 93.5% of all individuals with VTDR. Conclusion: In a limited resource country like India, a high-risk group-based targeted screening of individuals with DM could be prioritized while continuing the current opportunistic screening till India adopts universal screening of all people with DM.

Key words: Diabetic retinopathy, high-risk, risk factors, targeted screening, vision-threatening DR

Diabetes mellitus (DM) is one of the common noncommunicable diseases (NCDs) in the world. The global prevalence has increased nearly 8 times in the last five decades, from 1.2% in 1971 to 9.3% in 2019.[1] The increase in prevalence is disproportionately high in low- and middle-income countries. In India, the prevalence of DM in people aged 20–79 years has increased from 61.3 million in 2011 to 77 million in 2019, and another 77 million are considered prediabetic, raising a significant public health burden.[2,3] By the year 2030, approximately 101 million people in India are estimated to have diabetes.[3,5] Recent studies in India have shown a lower prevalence of DM in rural India (5.2% rural and 11.2% urban) and higher prevalence in certain Indian states (South – Kerala, Tamil Nadu, and Karnataka; North – Punjab, and Delhi; West – Goa).[2,5] We suspect, with rapid urbanization, this disparity may blur over time, and hence this must be factored into future planning for resources.[2,4]

Diabetic retinopathy (DR) is the most common complication of diabetes and is usually asymptomatic until late. Therefore, DR screening, either by fundus examination or fundus photography, is needed. This requires trained health personnel and retina specialists. The current infrastructure and human resources for health (HRH) in India are underprepared, and people with diabetes have suboptimal knowledge-attitude-practice.[7] These factors are mainly responsible for a high proportion of patients presenting with irreversible and advanced diabetic eye disease to India’s eye care facilities.[8] The two most common causes of vision-threatening DR (VTDR) are diabetic macular edema (DME) and proliferative diabetic retinopathy.[9] According to the National Diabetes and Diabetic Retinopathy Survey report 2015–2019, the prevalence of DR is 16.9% in the population ≥50 years, and the prevalence of VTDR is 3.6% in India.[9] Ideally, every individual with diabetes needs regular screening for VTDR. However, in India, the DR screening is predominantly opportunistic. Indian data indicates that we would need to identify 2,772,000 people with VTDR from 77 million people with diabetes through opportunistic screening and treat them to reduce the rate of blindness urgently. Left untreated, 26% of people with VTDR are likely to be severely vision impaired in 2 years, and this risk could decrease by 11%

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by timely retinal laser photocoagulation.\textsuperscript{[11]} Ideally, an effective screening program should result in a 20% risk reduction of the clinical sequelae.\textsuperscript{[13]} An opportunistic screening per se is unlikely to meet this target, and many people in urgent need of treatment could be left out. Hence, there is an urgent need to identify a more vulnerable population segment where a targeted screening could be more rewarding in reducing cost of care and impact in reducing DR-related blindness.

There is no primary care data of DM and DR, which could identify the high-risk group for targeted DR screening in India. Hence, we examined the population-based studies conducted from 2001 to 2010 in India that had required information to assess temporal trends in the prevalence of DM, DR, and VTDR.\textsuperscript{[13-16]} Similar studies in large numbers have not been conducted in India thereafter.

**Methods**

**Summary of selected studies**

Six large population-based studies have been conducted in India between 2001 and 2014 on the prevalence of DR and its risk factors.\textsuperscript{[13-18]} Four of these studies, conducted between 2001 and 2010, had patient-level data.\textsuperscript{[13-16]} [Table 1]. These studies had included both known and newly diagnosed individuals with diabetes. There were two levels of differences in recruitment into these studies: age (≥ 20 years,\textsuperscript{[13]} ≥30 years,\textsuperscript{[15]} and ≥40 years);\textsuperscript{[14,15]} and level of fasting blood sugar, FBS (≥100 mg/dL,\textsuperscript{[16]} ≥110 mg/dL,\textsuperscript{[14]} and >126 mg/dL)\textsuperscript{[Table 1].\textsuperscript{[13,15]}} Oral glucose tolerance test and glycated hemoglobin (HBA1c) were not performed in all studies. New diabetes in the individuals was confirmed after the second level of confirmatory test in two study groups (CURES and SN-DREAMS)\textsuperscript{[Table 1]. A history of antidiabetic medications was obtained to confirm people with known diabetes.

To obtain uniform data for analysis in this study, we included data on people aged 40 years and older to compare the studies. In the current study, the diagnosis of new diabetes was defined as FBS >7 mmol/L or >126 mg/dL at the time of initial screening.\textsuperscript{[13,16]} Overweight was defined as a body mass index (BMI) between 25 and 29.9 and obese as BMI ≥30.\textsuperscript{[21]} Sociodemographic and clinical parameters common to all studies were collated; these included age at presentation, duration of diabetes (for known individuals with diabetes), gender, history of hypertension, obesity, cardiovascular disease (CVD), and history of smoking.

**Statistical analysis**

Data from all four studies were entered in a Microsoft Excel spreadsheet and analyzed using Stata Statistical Software (Release 16, StataCorp, 2019, College Station, TX). Results were summarized as mean (± SD) for continuous variables or median (IQR) and percentages for categorical variables. A comparison of variables was performed using an independent t-test for continuous variables and Pearson Chi-square test for categorical variables. Univariate and multivariate logistic regression analyses were performed to evaluate risk factors, using DR, DME, and VTDR as dependent variables. A P value of < 0.05 was considered significant.

**Results**

Fig. 1a summarizes the reclassified total screened population’s overall results in each study based on the redefined age criteria of 40 years or older. A total of 44,599 of 71,048 individuals (62.8% of the original cumulated cohort) satisfied the reanalysis criteria. In this study, the prevalence of DM was 12.9% (9.6% having known diabetes and 3.3% having new diabetes). Study-specific prevalence of diabetes was 14.0% (2001–2004, CURES), 23.1% (2003–2006, SN-DREAMS I), 12.0% (2005–2006, ATDRES), and 8.6% (2005–2010, SN-DREAMS III). The residential classification originally considered in the studies was used to label each subject as belonging to a rural or urban household [Fig. 1b]. A total of 31.7% (1858/5784) subjects were from rural households, and the rest, 68.2%, were urban.

**Demography and diabetes**

Table 2 summarizes the demographic details of the study populations. In the studied cohort, 5,784 people had DM. The average age of patients was 54.98 ± 9.9 years (range, 53.9–56.4 years). The highest proportion of patients (34.5%; n = 1997) were in the 50–59 years age group; one-third patients were in the 40–49 years age group, and one-fourth patients were in the 60–69 years age group. Three of four studies had a higher proportion of females. Around 10% of each study population was obese, and 30–40% was overweight (even in a rural population cohort, SN-DREAMS-III). There was no change in individuals who were smokers throughout the studies. A significant proportion of each cohort gave no history of previously diagnosed CVD. Hypertension was present in 40% of the participants and was higher in the

**Table 1: Summary of DR prevalence studies from South India**

| Study            | Duration of study | Setting          | Sampling technique                | Age         | Screening of DM | Confirmation of DM |
|------------------|-------------------|------------------|----------------------------------|-------------|-----------------|--------------------|
| CURES\textsuperscript{[13]} | 2001-2004         | Urban + Rural    | Systematic random sampling       | >20 years   | FBS ≥126 mg/dL  | OGTT               |
| SNDREAMS-I\textsuperscript{[14]} | 2003-2006         | Urban            | Multistage systematic random sampling | >40 years   | FBS ≥110 mg/dL  | 2nd FBS >110 mg/dL |
| ATDRES\textsuperscript{[15]} | 2005-2006         | Urban + Rural    | Randomly selected clusters        | >30 years   | FBS ≥126 mg/dL  | -                  |
| SNDREAMS-III\textsuperscript{[16]} | 2005-2010         | Rural            | Multistage cluster sampling      | >40 years   | FBS ≥100 mg/dL  | OGTT               |

CURES: Chennai Urban Rural Epidemiology Study; SNDREAMS-I: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study for Urban Population; ATDRES: Aravind Theni Diabetic Retinopathy Epidemiology Study; SN-DREAMS-III: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study for Rural Population; FBS: Fasting blood sugar; OGTT: Oral glucose tolerance test
purely urban SN-DREAMS-I cohort [Table 2]. Considering data from SNDREAMS-I as an outlier, the overall prevalence of hypertension was 30% (26.8% in rural, 43.9% in urban).

The mean duration of diabetes in the subjects with known DM was around 5 years or more in three of the four studies (except the rural SN-DREAMS-III study with a mean of about 1 year) [Table 2]. In all the studies, about 60% of subjects with known DM had received their diagnosis within the last 5 years (except 95.6% in the rural cohort of SN-DREAMS-III). Overall, around 60% of the rural population received their diagnosis within the previous 5 years, with a mean duration of diagnosis being 2.38 years. However, the urban population seemed to have an earlier diagnosis of DM, with around 50% diagnosed within 5 years and about 20% diagnosed 6–10 years ago, with a mean duration of DM 6.24 years. In this cohort, 74.2% people were known DM.

Prevalence of DR

Fig. 1 summarizes the prevalence of DR and DME in people with diabetes recruited in each study based on the status of diabetes (known or new). The overall range of DR prevalence in the studies was 11.6–20.3% [Table 2]. After combining the data of all studies, the prevalence of DR was 14.8% (known diabetes: 18.4% and new diabetes: 4.7%); the prevalence of DME was 3.7% (known diabetes: 4.8%; new diabetes, 0.6%); and the prevalence of VTDR was 5.1% (known diabetes: 6.5%; new diabetes: 0.8%) [Table 3]. The prevalence of DR was higher in the urban than rural population as follows: any DR – urban: 16.4%, rural: 11.5%; DME – urban: 4.2%, rural: 2.6%; and VTDR – urban: 5.3%, rural: 4.6%.

Table 4 shows that DR, DME, and VTDR prevalence was the highest in 50–59 years. In this age group, any DR was 17.0% (all ages: 14.8%), DME was 4.8% (all ages: 3.7%), and VTDR was 6.2% (all ages: 5.1%). The prevalence increased with
Table 2: Descriptive statistics of subjects with diabetes in individual studies

| Parameters | CURES (n=1316) | SNDREAMS-I (n=1336) | ATDRES (n=2078) | SNDREAMS-III (n=1054) | Rural (n=1838) | Urban (n=3946) | Overall (n=5784) |
|------------|----------------|---------------------|----------------|------------------------|---------------|---------------|-----------------|
| Age in years |                |                     |                |                        |               |               |                 |
| Median (IQR) | 53 (47-60)      | 55 (49-64)          | 54 (47-62)     | 55 (46-61)             | 55 (47-62)   | 54 (47-62)   | 54 (47-62)      |
| Age groups (years) (%)* | 40-49 | 439 (33.4)         | 367 (27.5)     | 687 (33.1)             | 333 (31.6)   | 567 (30.9)   | 1259 (31.9)     |
| | 50-59 | 511 (38.8)         | 476 (35.6)     | 666 (32.0)    | 344 (32.6)            | 602 (32.7)  | 1395 (35.3)  | 1997 (34.5)    |
| | 60-69 | 288 (21.9)         | 338 (25.3)     | 509 (24.5)    | 291 (27.6)            | 491 (26.7)  | 935 (23.7)   | 1426 (24.7)    |
| | >70 | 78 (5.9)           | 155 (11.6)      | 216 (10.4)    | 86 (8.2)             | 178 (9.7)   | 357 (9.1)    | 535 (9.2)      |
| Gender (%)* | 1. Male | 589 (44.8)         | 714 (53.4)     | 911 (43.8)           | 489 (46.4)  | 862 (46.9)   | 1841 (46.6)    |
| | 2. Female | 727 (55.2)         | 622 (46.6)     | 1167 (56.2)   | 565 (53.6)           | 976 (53.1)  | 2105 (53.4)  | 3081 (53.3)    |
| BMI categories* (%)* | 1. Normal | 663 (50.4)         | 465 (34.8)     | 1057 (50.9)         | 566 (53.7)  | 995 (54.1)   | 1756 (44.5)    |
| | 2. Overweight | 432 (32.8)         | 415 (31.0)     | 638 (30.7)     | 285 (27.0)            | 490 (26.7)  | 1280 (32.4)  | 1770 (30.6)    |
| | 3. Obese | 160 (12.2)         | 123 (9.2)       | 213 (10.3)     | 97 (9.2)             | 152 (8.3)   | 439 (11.1)   | 593 (10.3)     |
| BMI values | Median (IQR) | 24.6 (22.1-27.4)   | 23.6 (18.6-26.7) | 24.0 (21.5-27.1) | 23.4 (20.6-26.5) | 23.4 (20.7-26.3) | 24.7 (22.3-27.5) | 23.9 (21.2-26.9) |
| Smoking status (%)* | 1. Nonsmokers | 1077 (81.8)      | 1075 (80.5)  | 1648 (79.3) | 904 (85.8) | 1505 (81.9) | 3199 (81.1) | 4704 (81.3) |
| | 2. Smokers | 239 (18.2)         | 261 (19.5)     | 426 (20.5)    | 150 (14.2)            | 331 (18.0)  | 745 (18.9)   | 1076 (18.6)    |
| Cardiac comorbidity (%)* | 1. No | 358 (27.2)         | 1175 (87.9)    | 1956 (94.1)       | 1033 (98.0) | 1765 (96.0) | 2757 (69.9)   |
| | 2. Yes | 59 (4.5)           | 161 (12.1)     | 122 (5.9)     | 21 (2.0)             | 73 (4.0)    | 290 (7.3)    | 363 (6.3)      |
| Hypertension* | 1. No | 796 (60.5)         | 488 (36.5)     | 1440 (69.3)       | 791 (75.1)  | 1346 (73.2) | 2169 (55.0)   |
| | 2. Yes | 476 (36.2)         | 848 (63.5)     | 638 (30.7)    | 263 (24.9)            | 492 (26.8)  | 1733 (43.9)  | 2225 (38.5)    |
| Duration of diabetes in subjects with known diabetes (years) | Mean (SD) | 6.23 (5.47)       | 6.69 (6.29)    | 5.29 (5.39)        | 1.17 (2.09) | 2.38 (3.81) | 6.24 (5.83)   |
| Duration of diabetes in subjects with known diabetes (years) | Median (IQR) | 5 (2-9)          | 5 (2-10)       | 4 (2-7)            | 0.4 (0.2-1) | 0.83 (0.17-3.0) | 4.5 (2-10) |
| Diabetic status (%)* | 1. subjects with known diabetes | 1195 (90.8)   | 1166 (87.3) | 1065 (51.3) | 865 (82.1) | 1267 (68.9) | 3024 (76.6) |
| | 2. subjects with new diabetes | 121 (9.2)       | 170 (12.7)     | 1013 (48.7)   | 189 (17.9)          | 571 (31.1)  | 922 (23.4)   | 1493 (25.8)    |
| Duration of known diabetes categories (%)* | ≤ 5 years | 708 (59.3)         | 686 (58.8)     | 721 (67.7)        | 827 (95.6)  | 1109 (60.3) | 1833 (46.5)   |
| | 6-≤ 10 years | 311 (26.0)         | 260 (22.3)     | 232 (21.8)    | 33 (3.8)            | 116 (6.3)   | 720 (18.2)   | 836 (19.5)     |
| | >10 years | 172 (14.4)         | 220 (18.9)     | 112 (10.5)    | 5 (0.6)             | 42 (2.3)    | 467 (11.8)   | 509 (11.9)     |
| SBP | Median (IQR) | 130 (115-141)   | 138 (124-150) | 130 (120-140) | 120 (120-130) | 120 (120-138) | 130 (120-148) |

Contd...
the duration of diabetes and was maximum in people with the duration of diabetes 10 years or longer. Subjects with systolic blood pressure (SBP) ≥140 mm Hg had a higher prevalence of DR, DME, and VTDR. The prevalence of DR and VTDR increased with increasing SBP of risk factor analysis [Table 4].

Logistic regression was performed to evaluate the risk of DR, DME, and VTDR [Table 4]. In multivariable logistic regression analysis for any DR, a significant positive association with risk of DR was observed with age group 50–59 years, male gender, urban residence, duration of diabetes ≥6 years, and SBP ≥140 mm Hg. A positive association of DME risk was found with age group 50–59 years, CVD, duration of diabetes ≥6 years, and SBP ≥140 mm Hg. A positive association of risk of VTDR was found with age range 50–59 years, duration of diabetes ≥6 years, and SBP ≥140 mm Hg. In this study cohort, overweight/obesity and newly diagnosed DM did not carry significant risk for any DR, DME, and VTDR.

Table 5 calculates the number of people included or excluded by a targeted screening of people with VTDR. In universal screening, i.e., if all people with diabetes would be screened, then one is expected to examine 292 people with VTDR. By priority screening of people with known DM in the vulnerable 50–69 years age group (61.5% of people with known DM), it would decrease to 198, which is 67.8% of all VTDR cases (from 292 to 198). Our analysis also indicated that people with SBP ≥140 mm Hg and duration of DM above 5 years are equally vulnerable. By adding these groups of people, the targeted screening detection would increase to 273 people (from 198), i.e. 93.5% of all people with VTDR.
Table 4: Univariate and multivariate logistic regression for diabetic retinopathy, diabetic macular edema and vision-threatening diabetic retinopathy (Severe NPDR, PDR, DME)

| Parameter          | Total population (n=857) | Prevalence (%) | Univariate model | Multivariable model | Total population (n=214) | Prevalence (%) | Univariate model | Multivariable model | Total population (n=292) | Prevalence (%) | Univariate model | Multivariable model |
|--------------------|--------------------------|----------------|------------------|---------------------|--------------------------|------------------|------------------|------------------|--------------------------|------------------|------------------|------------------|
|                    | Risk Ratio (95% CI)      | P              | Risk Ratio (95% CI) | P                | Risk Ratio (95% CI)      | P              | Risk Ratio (95% CI) | P                | Risk Ratio (95% CI)      | P                | Risk Ratio (95% CI) | P                | Risk Ratio (95% CI) | P                |
| Age in years       |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 1. Age 40-49*      | 1826                     | 217 (11.9%)    | 1                | 1                  |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 2. Age 50-59       | 1997                     | 340 (17.0%)    | 1.3 (1.1-1.5)    | <0.001             | 1.2 (1.0-1.4)           | 0.034           |                  |                    |                          |                |                  |                    |                          |                |                  |
| 3. Age 60-69       | 1426                     | 229 (16.1%)    | 1.3 (1.1-1.5)    | 0.005             | 1.0 (0.8-1.2)           | 0.91            |                  |                    |                          |                |                  |                    |                          |                |                  |
| 4. Age 70 +        | 535                      | 71 (13.3%)     | 1.1 (0.9-1.4)    | 0.339             | 0.8 (0.6-1.1)           | 0.199           |                  |                    |                          |                |                  |                    |                          |                |                  |
| Gender             |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 1. Male*           | 2703                     | 473 (17.5%)    | 1                | 1                  |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 2. Female          | 3081                     | 384 (12.5%)    | 0.8 (0.7-0.9)    | <0.001             | 0.8 (0.7-0.9)           | 0.002           |                  |                    |                          |                |                  |                    |                          |                |                  |
| BMI                |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 1. Normal*         | 2751                     | 482 (17.5%)    | 1                | 1                  |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 2. Overweight      | 1770                     | 230 (12.9%)    | 0.7 (0.6-0.8)    | <0.001             | 0.7 (0.6-0.8)           | <0.001          |                  |                    |                          |                |                  |                    |                          |                |                  |
| 3. Obese           | 593                      | 55 (9.3%)      | 0.5 (0.4-0.7)    | <0.001             | 0.5 (0.4-0.7)           | <0.001          |                  |                    |                          |                |                  |                    |                          |                |                  |
| Area of residence  |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| Rural*             | 1838                     | 211 (11.5%)    | 1                | 1                  |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| Urban              | 3946                     | 646 (16.4%)    | 1.2 (1.1-1.4)    | 0.004             | 1.2 (1.0-1.4)           | 0.025           |                  |                    |                          |                |                  |                    |                          |                |                  |
| Smoking status     |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 1. Nonsmokers*     | 4704                     | 664 (14.1%)    | 1                | 1                  |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 2. Smokers         | 1076                     | 193 (17.9%)    | 1.2 (1.0-1.4)    | 0.024             | 0.9 (0.8-1.2)           | 0.81            |                  |                    |                          |                |                  |                    |                          |                |                  |
| Cardiac status     |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 1. No*             | 4522                     | 618 (13.7%)    | 1                |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 2. Yes             | 363                      | 63 (17.4%)     | 1.1 (0.9-1.4)    | 0.309             |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| Hypertension*      |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 1. No*             | 3027                     | 415 (13.7%)    | 1                |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 2. Yes             | 1377                     | 243 (17.6%)    | 1.2 (1.1-1.4)    | 0.004             | 1.1 (0.9-1.2)           | 0.716           |                  |                    |                          |                |                  |                    |                          |                |                  |
| Duration of diabetes |                     |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 1. Up to 5 years*  | 2942                     | 379 (12.9%)    | 1                | 1                  |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 2. 6-10 years      | 836                      | 225 (26.9%)    | 2.0 (1.8-2.4)    | <0.001             | 1.9 (1.7-2.3)           | <0.001          |                  |                    |                          |                |                  |                    |                          |                |                  |
| 3. Above 10 years  | 509                      | 187 (36.7%)    | 2.5 (2.2-2.9)    | <0.001             | 1.3 (1.2-1.6)           | <0.001          |                  |                    |                          |                |                  |                    |                          |                |                  |
| SBP categories     |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| <120*              | 1189                     | 155 (13.0%)    | 1                |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 120-139            | 2504                     | 333 (13.3%)    | 0.9 (0.8-1.2)    | 0.71              | 1.1 (0.9-1.4)           | 0.28            |                  |                    |                          |                |                  |                    |                          |                |                  |
| 140-159            | 1400                     | 216 (15.4%)    | 1.3 (1.1-1.6)    | 0.005             | 1.5 (1.2-1.9)           | 0.001           |                  |                    |                          |                |                  |                    |                          |                |                  |
| 160-179            | 504                      | 114 (22.6%)    | 1.6 (1.3-1.9)    | <0.001             | 1.8 (1.4-2.3)           | <0.001          |                  |                    |                          |                |                  |                    |                          |                |                  |
| 180 and above      | 186                      | 39 (20.6%)     | 1.5 (1.1-2.0)    | 0.008             | 1.6 (1.1-2.3)           | 0.013           |                  |                    |                          |                |                  |                    |                          |                |                  |
| DBP categories     |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| <80*               | 1931                     | 317 (16.4%)    | 1                |                    |                          |                |                  |                    |                          |                |                  |                    |                          |                |                  |
| 80-89              | 2212                     | 277 (12.5%)    | 0.9 (0.7-0.9)    | 0.041             | 0.9 (0.7-1.0)           | 0.09            |                  |                    |                          |                |                  |                    |                          |                |                  |
| 90 and above       | 1640                     | 263 (16.0%)    | 1.2 (1.1-1.4)    | 0.003             | 1.1 (0.9-1.3)           | 0.4             |                  |                    |                          |                |                  |                    |                          |                |                  |

Contd...
Table 4: Contd...

| Parameter | Diabetic Macular Edema (DME) | Vision-threatening diabetic retinopathy (VTDR) |
|-----------|------------------------------|---------------------------------|
|           | (n=214) | Univariate model | Multivariable model | (n=292) | Univariate model | Multivariable model |
|           | Prevalence (%) | Risk ratio (95% CI) | P | Risk Ratio (95% CI) | P | Risk Ratio (95% CI) | P |
| Gender | | | | | | | |
| 1. Male* | 98 (3.6%) | 1 | - | - | 144 (5.3%) | 1 | - | - |
| 2. Female | 116 (3.8%) | 1.1 (0.8-1.4) | 0.703 | 148 (4.8%) | 0.9 (0.7-1.1) | 0.364 | |
| BMI | | | | | | | |
| 1. Normal* | 129 (4.7%) | 1 | 1 | 172 (6.3%) | 1 | - | - |
| 2. Overweight | 50 (2.8%) | 0.6 (0.4-0.8) | 0.002 | 68 (3.8%) | 0.6 (0.5-0.8) | 0.001 | 0.6 (0.5-0.8) | 0.002 |
| 3. Obese | 11 (1.9%) | 0.4 (0.2-0.8) | 0.004 | 15 (2.5%) | 0.4 (0.2-0.7) | 0.001 | 0.3 (0.2-0.6) | 0.001 |
| Area of residence | | | | | | | |
| Rural* | 47 (2.6%) | 2.4 (1.8-3.3) | <0.001 | 1.1 (0.7-1.5) | 0.847 | 85 (4.6%) | 1 | - | - |
| Urban | 167 (4.2%) | 1 | - | - | 207 (5.3%) | 1.1 (0.9-1.5) | 0.316 | |
| Smoking status | | | | | | | |
| 1. Nonsmokers* | 175 (3.7%) | 1 | 1 | 243 (5.2%) | 1 | - | - |
| 2. Smokers | 39 (3.6%) | 0.7 (0.5-1.0) | 0.077 | 49 (4.6%) | 0.9 (0.6-1.2) | 0.41 | |
| Cardiac status | | | | | | | |
| 1. No* | 140 (3.1%) | 1 | 1 | 198 (4.4%) | 1 | 1 | - |
| 2. Yes | 23 (6.3%) | 2.2 (1.4-3.4) | <0.001 | 1.8 (1.2-2.9) | 0.01 | 27 (7.4%) | 1.7 (1.2-2.5) | 0.007 | 1.4 (0.9-2.0) | 0.164 |
| Hypertension* | | | | | | | |
| 1. No* | 105 (3.5%) | 1 | 1 | 147 (4.9%) | 1 | 1 | - |
| 2. Yes | 72 (5.2%) | 1.7 (1.2-2.2) | 0.001 | 1.3 (0.9-1.9) | 0.144 | 102 (7.4%) | 1.5 (1.2-1.9) | 0.001 | 1/2 (0.9-1.6) | 0.276 |
| Duration of diabetes | | | | | | | |
| 1. Up to 5 years* | 84 (2.9%) | 1 | 1 | 98 (4.0%) | 1 | 1 | - |
| 2. 6-10 years | 58 (6.9%) | 2.6 (1.8-3.6) | <0.001 | 2.8 (1.9-4.2) | <0.001 | 72 (10.0%) | 2.5 (1.9-3.3) | <0.001 | 2.6 (1.8-3.8) | <0.001 |
| 3. Above 10 years | 63 (12.4%) | 1.3 (0.9-1.8) | 0.084 | 1.3 (0.9-1.9) | 0.12 | 116 (7.2%) | 1.8 (1.4-2.3) | <0.001 | 1.6 (1.2-2.3) | 0.004 |
| SBP categories | | | | | | | |
| <120* | 37 (3.1%) | 1 | 1 | 49 (4.1%) | 1 | 1 | - |
| 120-139 | 72 (2.9%) | 0.8 (0.5-1.2) | 0.27 | 1.5 (0.8-2.7) | 0.2 | 104 (4.2%) | 1.0 (0.7-1.4) | 0.963 | 1.5 (0.9-2.5) | 0.134 |
| 140-159 | 64 (4.6%) | 1.2 (0.8-1.8) | 0.287 | 2.9 (1.5-5.5) | 0.002 | 80 (5.7%) | 1.4 (0.9-1.9) | 0.065 | 2.5 (1.4-4.5) | 0.002 |
| 160-179 | 33 (6.6%) | 1.8 (1.2-2.9) | 0.01 | 4.9 (2.4-10.1) | <0.001 | 47 (9.3%) | 2.3 (1.5-3.3) | <0.001 | 4.3 (2.3-8.3) | <0.001 |
| 180 and above | 8 (4.3%) | 1.2 (0.6-2.6) | 0.608 | 2.3 (0.8-6.9) | 0.1 | 12 (6.5%) | 1.6 (0.8-2.9) | 0.151 | 2.5 (0.9-6.3) | 0.056 |
| DBP categories | | | | | | | |
| <80* | 79 (4.1%) | 1 | 1 | 107 (5.5%) | 1 | 1 | - |
| 80-89 | 64 (2.9%) | 0.6 (0.4-0.8) | <0.001 | 0.6 (0.4-0.9) | 0.15 | 90 (4.1%) | 0.7 (0.6-0.9) | 0.027 | 0.9 (0.6-1.2) | 0.41 |
| 90 and above | 71 (4.3%) | 0.8 (0.6-1.1) | 0.175 | 0.9 (0.5-1.4) | 0.5 | 95 (5.8%) | 1.0 (0.8-1.4) | 0.746 | 1.1 (0.8-1.7) | 0.524 |

*Reference category; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; *outlier data excluded

Table 5: Comparison of numbers screened in universal versus targeted screening (model prepared from risk factors identified in the current study)

| n | Numbers of VTDR detected | Numbers of VTDR missed |
|---|--------------------------|------------------------|
| All patients screened (Universal screening model) | 5784 (all DM) | 292 (5.1% of all DM) | 0% |
| Risk groups (targeted screening model) | | | |
| 1. Only age group 50-69 years with known DM | | | |
| 2640 (61.5% of known DM; 45.6% of all DM) | 198 (3.4% of all DM; 67.8% of all VTDR) | 94/292 (32.2%) |
| 2. Others outside of 50-69 years age group | | | |
| Systolic BP >140 mm Hg | 358 (6.2% of all DM) | 26 (8.9% of all VTDR) | 266/292 (91.1%) |
| 3. Others outside of 50-69 years age group with known DM duration >5 years | | | |
| 810 (18.9% of known DM; 14% of all DM) | 49 (16.8% of overall VTDR) | 243/292 (83.2%) |
| Total numbers screened by targeted screening | 3808 (65.8% of all DM) | 273 (93.5% of all VTDR) | 19/292 (6.5%) |
Discussion

The temporal trends of DR over a decade [2001–2010; Table 1] in South India show that the prevalence of DR and VTDR has not changed much. Our study showed that 74.2% of people had known diabetes [Table 3], with an overall prevalence of DR and VTDR of 14.8 and 5.1%, respectively [Table 3]. Targeted screening of people with high-risk factors [Table 4] would identify 93.5% of people with VTDR by screening nearly one-third lesser population than a universal screening strategy [Table 5].

Extrapolating these findings to the current population of 77 million people with diabetes in India, 57 million people would have known diabetes (74.2% of 77 million), and 3.9 million people would have VTDR (5.1% of 77 million). Considering that a potential targeted screening program is put in place in the country according to the high-risk groups identified in our analysis, as of today, 93.5% of the total VTDR population would be detected by the same; this amounts to 3.7 million people (93.5% of 3.9 million) with VTDR. Thus, a targeted screening may result in a reduction of 200,000 individuals. But equally important is that it could be pooled from 51 million people [65.8% of all people with DM – Table 5]; the reduction of 26 million fewer people screened to obtain 93.5% of people with VTDR who need urgent care is cost-effective. With the current infrastructure for both screening and treatment and available HRH in India, this may be a cost-effective strategy. With the current infrastructure for both screening and treatment and available HRH in India, this may be a cost-effective strategy; this reduces the proportion of people becoming screen positive before the allocated screening date by >50% and allowed targeting resources toward the patients more at risk.

While we acknowledge the necessity of universal screening for detection of DR and VTDR, our study provides evidence that in a resource-restraint situation like India, targeted screening of people in high-risk of developing VTDR such as older age (50–69 years), known diabetes of longer duration (more than 5 years), and high SBP (>140 mm Hg) should be a priority. While this strategy in no way undermines the importance of screening every individual with diabetes for DR, we understand that we might be able to detect higher numbers of VTDR by the targeted strategy; this may reduce the burden of future blindness as a priority. The recommendations are to obtain high-quality retinal images and measure both glycated hemoglobin and blood pressure. This is not always possible at every point of care, particularly the measurement of glycated hemoglobin. The Government of India has created a dedicated program, the NPCDCS (National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease, and Stroke) in 2010 with objectives of health promotion, opportunistic screening, setting up of NCD clinics, capacity building, health financing, and a robust surveillance system. By March 2016, the program had set up 298 district NCD cells and 293 district NCD clinics (India has 718 districts). These new facilities could be equipped with all recommendations for high-risk population screening. We suggest a basic eye examination and a fundus photography system in the NCD cells clinics, risk-based referral to a district hospital for reconfirmation of diabetes status (glycated hemoglobin test) and retinopathy (repeat fundus examination/photography), followed by treatment of all eligible patients immediately, till India develops enough resources to practice routine and systematic screening of all people with diabetes.

Post hoc analysis of decade or longer old data is a major weakness of the study. However, a recent population-based study in India done in 2019 showed no difference in the prevalence of DR (14.3%) or VTDR, despite a high prevalence of diabetes (21.9%), substantiating a near stable prevalence of DR in India. The strength of this study is our ability to derive the main risk factors of DR in India that could be used for priority screening, be it opportunistic or otherwise.

We recognize that there is limited data from other parts of India on the prevalence of DR and VTDR. There may be regional variations of DR and VTDR in India, given the diverse lifestyles in each state. We hope the multicenter SMART-India (Statistical Modelling And Risk assessment of Type 2 diabetes in India) study currently underway in 11 states and one union territory would bridge this knowledge gap.

Conclusion

In India, the number of people with diabetes is increasing, so would the people with DR and VTDR, despite the prevalence rate remaining relatively stable. Given the resource limitations, one could prioritize screening the high-risk group while not ignoring others. From the results of this study, we can infer that prioritizing the detection of VTDR, alongside opportunistic screening, which aims at detecting any DR, may be more
useful for India till we have an appropriate number of qualified vitreoretinal specialists or till all ophthalmologists become sufficiently trained in indirect ophthalmoscopy and conversant with medical management of DR. This study also does not deny the current practice of opportunistic screening for DR in India and recommends universal systemic screening in the coming years.

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Conflicts of interest

There are no conflicts of interest.

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