

The Inferior, Superior, Temporal Rim Width Pattern (IST Rule) Detects Glaucoma in a Japanese Population

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Précis: The inferior > superior > temporal rim width rate (IST pattern) rather than inferior ≥ superior ≥ nasal ≥ temporal (ISNT) pattern was suited for screening glaucoma in Japanese subjects. Failure of the IST pattern was associated with several important risk factors for glaucoma.

Purpose: The purpose of this study was to find a rim width rate pattern to yield the highest positive likelihood ratio (LR+) in detecting glaucoma eyes and to identify risk factors for glaucoma correlating with its failure in a population-based setting.

Methods: Disc stereophotographs of 2474 eyes of 2474 normal subjects and 237 eyes of 237 glaucoma subjects found in the Kumejima Study were analyzed using computer-assisted planimetry. Among all combinations of the inferior (I), superior (S), nasal (N) and/or temporal (T) rim width rate, a pattern showing the highest LR+ was selected and risk factors for glaucoma correlating with its failure were determined using multiple logistic regression analysis.

Results: The average I, S, N, and T rim widths (SD) were 0.45 (0.10), 0.39 (0.09), 0.47 (0.11), and 0.27 (0.07) mm. Among all combinations, the I>S>T rim width rate pattern (IST pattern) disregarding the N rim width showed the highest LR+ of 2.002 (95% confidence interval, 1.778–2.253). Failure of the IST pattern in normal eyes correlated with a smaller disc area ($P < 0.001$) and disc ovality ($P = 0.005$) and larger β -peripapillary area ($P < 0.001$) and compliance with in glaucoma eyes with a smaller β -PPA area ($P = 0.027$), thicker central corneal thickness ($P = 0.017$), lower intraocular pressure ($P = 0.019$), and higher body mass index ($P = 0.037$).

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Conclusion: Among all combinations, the I>S>T rim width pattern, the IST pattern, yielded the highest LR+ in detecting glaucoma in Japanese glaucoma eyes and its failure of or compliance with the pattern significantly correlated with several known risk factors for glaucoma.

Key Words: ISNT rule, population-based study, glaucoma, optic nerve head

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Glaucoma is characterized by progressive morbidity of the retinal ganglion cells and axons at the optic nerve head (ONH) with characteristic abnormalities of the neuroretinal rim tissue. For screening glaucoma, the inferior ≥ superior ≥ nasal ≥ temporal (ISNT rule) rim width rate has been considered useful and important,^{1–4} and some previous studies, including a population-based glaucoma survey, adopted this rule as a diagnostic criterion.^{5–8} However, several later studies have reported conflicting results about the clinical usefulness of the ISNT rule in screening for glaucoma.^{9–21} Since the ISNT rule is used to screen glaucoma in routine clinical practice, its clinical usefulness should be evaluated based on the ophthalmoscopically, biomicroscopically, or photographically determined rim width along the cardinal meridian (9, 12, 3, and 6 o'clock positions)¹ or in narrow segmental areas centered on these meridians.¹⁹ Many of the previous studies that have evaluated the clinical usefulness of the ISNT rule have adopted the average rim thickness over 3-hour sectors,⁹ sectoral rim area,^{10–13} or circumpapillary retinal nerve fiber thickness^{14–17} measured by recently developed glaucoma imaging devices such as laser scanning tomography or optical coherence tomography, which may not be routine for evaluating the rim widths in daily clinical practice by general ophthalmologists. Further, evaluation of a screening method for glaucoma in a general population such as the ISNT rule in a population-based setting rather than in hospital-based setting should be more important. Only the Chennai Glaucoma Study²² and Beijing Eye Study³ have addressed the validity of the ISNT rule in a population-based setting, but the latter included only 92 subjects, and no subjects with glaucoma in these studies were evaluated. The optic disc morphology reportedly varies among ethnic groups; black populations generally have larger discs and a smaller rim area to disc area ratio, while white populations generally have smaller discs than other ethnic groups.^{9,23–25} The Kumejima Study is a population-based epidemiologic study that focused on ocular diseases in Kumejima in Southwest Japan.^{26,27} Sequential stereophotographs were obtained with a nonmydriatic digital fundus camera during the screening examination, and the results were analyzed using computer-assisted planimetry.^{28,29}

The purposes of the current study were 2-fold, that is, (1) to reevaluate the accuracy and clinical usefulness of the ISNT rule and its variations in the Kumejima Study that included numerous normal subjects and subjects with glaucoma using photographically determined rim widths in narrow segmental rim areas centered on the cardinal meridian, an expected routine clinical approach in evaluating the rim widths, and (2) to identify risk factors for glaucoma significantly correlating with failure of or compliance with the ISNT rule or its variation which yielded the highest positive likelihood ratio (LR+) for screening glaucoma in this population.

METHODS

Population Sampling

The Kumejima Study conformed to the tenets of the Declaration of Helsinki and regional regulations; the ethics board of the regional council approved the study protocol. All participants provided written informed consent before the examinations. The study was conducted between May 2005 and August 2006 in Kumejima, an island in the Southwestern section of Okinawa Prefecture, Japan. All residents aged 40 years or older were encouraged to participate. Kumejima had 5249 residents aged 40 years or older in 2005, according to the official household registration database. After excluding 617 residents who died, moved, or could not be located during the study period, 4632 residents were eligible for the study.

Examinations and Diagnosis

The details of the examinations and diagnoses have been reported previously.^{26,27} Briefly, the screening examination included a structured interview; measurements of body weight, height, and systemic blood pressure; and ocular examinations performed by experienced ophthalmologists and examiners. The ophthalmic examinations included measurement of the uncorrected and best-corrected visual acuities, refraction, intraocular pressure (IOP), central corneal thickness (CCT), anterior chamber depth (ACD), axial length (AL), slit-lamp examination, gonioscopy, ophthalmoscopy, fundus photography, and visual field (VF) testing. One experienced technician obtained a pair of sequential stereoscopic ONH photographs at a parallax of about 8 degrees and plain fundus photographs using a digital nonmydriatic fundus camera (TRC-NW7; Topcon, Tokyo, Japan) in both eyes of each subject. The refraction was measured using an autorefractometer (ARK-730; Topcon); the IOP was measured 3 times using a Goldmann applanation tonometer and the median value recorded; the CCT was measured by specular microscopy (SP-2000; Topcon); the central ACD and AL were measured using the IOL Master (Carl Zeiss Meditec, Dublin, CA). The peripheral ACD was scored according to the van Herick method³⁰ and the gonioscopic findings according to Shaffer's grading system using a Goldmann 2-mirror lens. The VFs were studied using frequency doubling technology perimetry with the C-20-1 screening program (Carl Zeiss Meditec). Participants were referred for a definitive examination if they were suspected of having ocular abnormalities including glaucoma and met 1 or more of the following criteria during the screening examination: corrected visual acuity <20/30, IOP exceeding 19 mm Hg, vertical cup/disc (v-C/D) ratio of 0.6 or more, superior (11 to 1 o'clock hours) or inferior (5 to 7 o'clock hours) rim width/disc diameter of

0.2 or less, bilateral asymmetry of the v-C/D of 0.2 or more, a nerve fiber layer defect or splinter disc hemorrhage, abnormal findings on slit-lamp examination or fundus photographs, a van Herick grade of 2 or less, and at least 1 abnormal test point ($P < 0.05$) in the C-20-1 test results of the frequency doubling technology VF test. The definitive examination included detailed slit-lamp, gonioscopic, and fundus examinations after pupillary dilation and VF testing with the Humphrey Field Analyzer Central 24-2 Swedish interactive threshold algorithm standard (SITA) program (Carl Zeiss Meditec).

The details of the glaucoma diagnosis have been reported,^{26,27} with diagnosis based on the clinical records obtained during all examinations; evaluations of slit-lamp, gonioscopic findings, stereo disc photographs, disc, retinal nerve fiber layer, retina, and VFs; and the ISGEO criteria.³¹

Planimetry on Stereoscopic Fundus Photographs

The details of the current planimetric method have been reported previously.^{28,32} An experienced ophthalmologist (T.T.) reexamined all stereophotographs. The stereoscopic pair of photographs was subsequently flickered on a high-resolution liquid crystal display computer monitor at a speed of 100 Hz and viewed 3-dimensionally using an electronic shutter glass (CrystalEyes3; Stereophotographics, San Rafael, CA) that was synchronized with the liquid crystal display monitor flickering. While stereoscopically viewing the optic disc, the disc contour, defined as the inner boundary of the peripapillary scleral ring, was determined by a series of 7 points with spline interpolation, and the cup contour, defined as the point of change of the slope from the cup wall to the neural rim, was determined as a closed curve by an unlimited number of points placed on the computer monitor using a computer mouse. The β -peripapillary atrophy (PPA) area was characterized by visible sclera and large choroidal vessels owing to the absence of the retinal pigment epithelium and also determined as a closed curve by an unlimited number of points placed on the outer boundary of the β -zone and that of the peripapillary scleral ring on the computer monitor. The fovea also was determined. The disc center was calculated automatically as the center of gravity of the disc area. After correcting for magnification by the corneal curvature, AL, and refractive error according to the formula provided by the manufacturer, the planimetric parameters, disc, rim, cup and β -PPA areas in millimeters squared, rim width defined as that on an axis through the center of the disc at a given angle in millimeters, vertical and horizontal cup/disc ratios, disc ovality (long diameter/short diameter of an ellipse fitted to the clinical disc margin), disc-fovea distance and disc torsion angle (angle between the long axis of an ellipse fitted to the clinical disc margin and an axis perpendicular to the disc center-fovea axis and passing through the disc center) were calculated automatically. In the current study, all orientations were not relative to the horizontal meridian of the acquired image frame, but an axis connecting the disc center and fovea (disc center-fovea axis), and all eyes were converted to the right-eye format for the following reasons: the superior and inferior poles of the disc defined relative to the disc center-fovea axis are anatomically and geometrically more correct than those defined relative to the horizontal meridian of the acquired image frame; and an eye with an oval optic disc that was temporally or nasally rotated makes application of the ISNT rule difficult if the inferior (I), superior (S), nasal (N), or temporal (T) rim was defined relative to the horizontal

meridian. Those rim widths were determined along an axis perpendicular to the disc center-fovea axis (90 to 270 degrees) and the disc center-fovea axis (0 to 180 degrees), respectively. The I, S, N, and T rim widths were calculated as the mean rim widths at the following degrees: 270 (inferior pole of disc), 265, and 275; 90 (superior pole of disc), 85, and 95; 0 (3 o'clock position), 355 and 5; and 180 (9 o'clock position), 175 and 185, respectively. The current planimetric software yielded the rim width in millimeters out to 4 decimal places, and the order of the rim widths was determined based on the raw calculated values without rounding.

The reproducibility of the current planimetric measurements has been reported.^{28,32} In a preliminary study, 2 examiners including T.T. checked the reproducibility of the I, S, N, and T rim width measurements by measuring 20 normal and 20 glaucomatous eyes extracted randomly from the clinical records of the Tajimi Iwase Eye Clinic, Tajimi, Gifu, at a 1-week interval. Further, κ coefficient values for classifying eyes into some patterns of the rim width rate also were determined.

RESULTS

In the Kumejima Study, 3762 (participation rate, 81.2%) of the 4632 eligible residents aged 40 years or older underwent screening examinations. The participants were younger than the 870 nonparticipants (59.1 ± 14.9 vs. 61.8 ± 14.0 y, respectively; $P < 0.001$, unpaired t test) and more women than men participated (female: male ratio, 1929/1833 vs. 315/555, respectively; $P < 0.001$, χ^2 test).

Since it is likely that the disc area and the disc shape and PPA area affect the rim widths, the study eyes were those in which the contour lines of the disc, rim, β -PPA, and fovea were determined reliably on the stereo fundus photographs. Of the 7524 eyes of the 3762 participants, acceptable stereo fundus photographs were unobtainable in 376 right and 421 left eyes because of cataracts, corneal opacities, large pterygia, or small pupils.

Pseudophakic (440 right, 433 left) or aphakic (13 right, 10 left) eyes were excluded, because accurate magnification corrections of the fundus image were unavailable in these eyes. Eyes also were excluded when optic disc diseases or anomalies (36 right, 25 left eyes) or retinal or brain diseases (148 right, 156 left eyes) were present that could affect the optic disc morphology or when the spherical equivalent refraction was < -8.0 or $> +5.0$ D (14 right, 11 left eyes). Among the normal eyes, eyes were excluded that had glaucoma and primary angle closure or were considered glaucoma suspects (279 right, 272 left eyes) as were the nonglaucomatous fellow eyes of subjects with glaucoma and those considered glaucoma suspect (90 right, 118 left eyes); 6 right and 8 left eyes also were excluded because the foveal location was not determined with confidence. The eyes were excluded in that order and no excluded eye was duplicated. When both eyes of a subject met the inclusion criteria, 1 eye was chosen randomly. As a result, 2474 normal eyes of 2474 subjects (1 randomly chosen eye of 2194 subjects and 1 eye of 280 subjects) comprised the normal group. Two hundred seventy subjects were diagnosed with definite glaucoma according to the ISGEO criteria (Foster and colleagues) in at least 1 eye; in 33 of these, stereo fundus photographs meeting the above criteria were unobtainable. One hundred forty-seven subjects had definite glaucoma in 1 eye and 90 subjects bilateral definite glaucoma. When 1 eye was chosen randomly

TABLE 1. Demographic Data From 2474 Normal Eyes of 2474 Subjects Without Glaucoma

| | |
|--|--------------|
| Women/men | 1232/1242 |
| Right/left | 1210/1264 |
| Age (y) | 57.3 (12.1) |
| Height (cm) | 156.1 (9.1) |
| Body mass index | 5.1 (3.6) |
| Mean blood pressure (mm Hg) | 99.4 (15.3) |
| Mean ocular perfusion pressure (mm Hg) | 51.5 (10.0) |
| Intraocular pressure (mm Hg) | 14.8 (3.0) |
| Spherical equivalent error (D) | 0.09 (1.69) |
| Axial length (mm) | 23.4 (0.9) |
| Central corneal thickness (μ m) | 515 (33) |
| Disc area (mm^2) | 2.53 (0.50) |
| Rim area (mm^2) | 1.67 (0.30) |
| β -PPA area (mm^2) | 0.45 (0.66) |
| Disc ovality | 1.11 (0.06) |
| Disc-fovea distance (mm) | 4.7 (0.3) |
| Disc torsion (deg.) | -17.6 (35.0) |
| Inferior neuroretinal rim width (mm) | 0.45 (0.10) |
| Superior neuroretinal rim width (mm) | 0.39 (0.09) |
| Nasal neuroretinal rim width (mm) | 0.47 (0.11) |
| Temporal neuroretinal rim width | 0.27 (0.07) |

The data are expressed as the mean (SD). The values of the systemic parameters and ocular parameters were obtained from 2474 eyes of 2474 subjects (1 randomly chosen eye of 2194 patients, 166 right eyes of 166 patients, and 114 left eyes of 114 subjects).

A positive value indicates inferotemporal torsion and a negative value indicates superotemporal torsion.

β -PPA indicates β -peripapillary atrophy; disc ovality = long axis of the ellipse fitted to the disc contour/short axis; mean ocular perfusion pressure = $2/3 \times$ mean blood pressure - intraocular pressure; disc-fovea distance = distance between the gravity center of the clinical disc and fovea and disc torsion angle of the long axis of the disc relative to an axis perpendicular to a line connecting the disc center and fovea.

from these 90 subjects, 237 eyes with definite glaucoma from 237 subjects (142, 71, and 24 primary open-angle glaucoma, primary angle-closure glaucoma, and secondary glaucoma eyes, respectively) comprised the glaucoma group.

The demographics of the normal and glaucoma groups and mean I, S, N, and T rim widths of both groups are shown in Tables 1 and 2, respectively. The pattern distributions of the rim width rates in descending order in 2474 normal eyes and 237 definite glaucoma eyes are shown in Tables 3 and 4.

Twenty eyes of 20 normal subjects (average age, 50.3 ± 4.7 y) and 20 eyes of 20 patients with open-angle glaucoma (average age, 66.0 ± 14.8 y and -6.5 ± 5.1 dB) were included in a preliminary study to assess the measurement reproducibility of the rim widths and other main morphologic disc parameters.

The interclass correlation coefficient for the intra-examiner reproducibility [95% confidence interval (CI)] were 0.998 (0.977–0.993), 0.953 (0.912–0.975), 0.947 (0.902–0.971), 0.898 (0.815–0.945), 0.852 (0.737–0.919), 0.881 (0.786–0.935) and 0.880 (0.785–0.935), for disc area, rim area, v-C/D ratio, and N, S, T, and I rim width, respectively. The interexaminer κ coefficient values for classifying eyes into the $N > I > S > T$ rim width rate (NIST pattern) and the $I > S > T$ rim width rate (IST pattern), which were the most frequently seen in normal eyes among the patterns of the 4 rim widths and the 3 rim width rates, respectively, were 0.77 (95% CI, 0.47–1.00) and 0.54 (0.28–0.80), respectively. The order of the mean rim widths in normal eyes was $N > I > S > T$ rim width ($P < 0.001$). The N rim width was the broadest in 52.9% and the I rim width in 41.4% of the normal eyes,

TABLE 2. Demographic Data From 237 Eyes With Definite Glaucoma of 237 Patients in the Kumejima Study

| | |
|--|--------------|
| Women/men | 121/116 |
| Right/left | 117/120 |
| Age (y) | 71.8 (12.3) |
| Height (cm) | 152.0 (9.8) |
| Body mass index | 24.6 (3.7) |
| Mean blood pressure (mm Hg) | 100.7 (15.7) |
| Mean ocular perfusion pressure (mm Hg) | 51.0 (10.7) |
| Intraocular pressure (mm Hg) | 16.1 (4.5) |
| Spherical equivalent error (D) | -0.20 (2.03) |
| Mean deviation (dB) | -7.1 (7.0) |
| Axial length (mm) | 23.5 (1.5) |
| Central corneal thickness (µm) | 508 (39) |
| Disc area (mm ²) | 2.54 (0.60) |
| Rim area (mm ²) | 1.13 (0.54) |
| β-PPA area (mm ²) | 1.09 (1.22) |
| Disc ovality | 1.11 (0.06) |
| Disc-fovea distance (mm) | 4.7 (0.4) |
| Disc torsion (deg.) | -15.6 (38.0) |
| Inferior neuroretinal rim width (mm) | 0.28 (0.13) |
| Superior neuroretinal rim width (mm) | 0.26 (0.11) |
| Nasal neuroretinal rim width (mm) | 0.35 (0.12) |
| Temporal neuroretinal rim width | 0.19 (0.07) |

The data are expressed as the mean (SD). The values of the systemic parameters and ocular parameters were obtained from 237 eyes of 237 subjects (1 randomly chosen eye of 117 right eyes of 117 subjects, and 120 left eyes of 120 subjects).

A positive value indicates inferotemporal torsion and a negative value indicates superotemporal torsion.

β-PPA indicates β-peripapillary atrophy; disc ovality = long axis of the ellipse fitted to the disc contour/short axis; mean ocular perfusion pressure = 2/3 × mean blood pressure - intraocular pressure; disc-fovea distance = distance between the gravity center of the clinical disc and fovea and disc torsion angle of the long axis of the disc relative to an axis perpendicular to a line connecting the disc center and fovea.

while the T rim width was thinnest in 90.7% and the S rim width in 6.0%. The I rim width was broader than the S rim width in 76.4%, while the N rim was broader than the T rim width in 97.0%. Among the combinations of the 4 rim widths, the NIST pattern was the most prevalent followed by the INST pattern, while the ISNT rule was complied with in 6.7% of the normal eyes. If we do not consider the N rim width, which has reportedly less value in diagnosing glaucoma,³³ the IST pattern was complied with in 70% and the IS pattern in 76%, if the N and T rim widths were not considered (Table 3). In the glaucoma group, the ISNT, IST, and IS patterns failed in 95%, 61%, and 41%, respectively (Table 4). Table 5 shows the sensitivity/specificity and positive and negative likelihood ratio (LR+ and LR-) of each pattern of rim width rate in detecting glaucoma eyes. Among all combinations of the I, S, N, and/or T rim width rate, the IST pattern showed the highest LR+ of 2.002 (95% CI, 1.778-2.253) followed by the IS pattern of 1.716 (1.448-2.034). The IS pattern had the highest specificity, 0.764 (0.747-0.781) followed by the IST pattern, 0.696 (0.678-0.715). In contrast, the LR+ of the ISNT pattern in the Kumejima Study participants was 1.022 (0.992-1.053) with a specificity of 0.067 (0.058-0.078) (Table 5).

The systemic and ocular factors related to failure of the IST pattern, which showed the highest LR+, in the normal eyes and compliance with this pattern in glaucoma eyes were examined using logistic regression analysis (JMP Pro13.0; SAS Institute Inc.), with the explanatory variables of age, sex, blood pressure, height, body mass index (BMI), CCT, IOP, disc area, rim area, disc ovality, disc-fovea distance, disc torsion angle and β-PPA area. In glaucoma eyes, the mean deviation value (dB) obtained with the Humphrey Field Analyzer SITA program and the glaucoma type (primary open-angle glaucoma, primary angle-closure

TABLE 3. Pattern Distributions of the Neuroretinal Rim Widths in Descending Order in 2474 Normal Eyes of 2474 Subjects Without Glaucoma

| Pattern | Compliance With the Pattern [No. Eyes (%)] |
|---------|---|
| NIST | 832 (33.6) |
| INST | 694 (28.1) |
| NSIT | 429 (17.3) |
| ISNT | 166 (6.7) |
| INTS | 98 (4.0) |
| SNIT | 80 (3.2) |
| SINT | 42 (1.7) |
| NITS | 35 (1.4) |
| ISTN | 31 (1.3) |
| ITSN | 17 (0.7) |
| Others | 1-12 (0.0-0.5) |
| IST | 1723 (69.6) |
| SIT | 557 (22.5) |
| ITS | 162 (6.5) |
| STI | 24 (1.0) |
| TIS | 5 (0.2) |
| TSI | 3 (0.1) |
| IS | 1690 (76.4) |
| SI | 584 (23.6) |

I indicates inferior rim width; N, nasal rim width; S, superior rim width; T, temporal rim width, which was determined using the disc center-fovea axis as a reference line.

TABLE 4. Pattern Distributions of the Neuroretinal Rim Widths in Descending Order in 237 Definite Glaucoma Eyes of 237 Patients in the Kumejima Study

| Pattern | Failure in the Pattern [No. Eyes (%)] |
|---------|--|
| NIST | 175 (73.8) |
| INST | 217 (91.6) |
| NSIT | 200 (84.4) |
| ISNT | 226 (95.4) |
| INTS | 214 (90.3) |
| SNIT | 226 (95.4) |
| SINT | 234 (98.7) |
| NITS | 222 (93.7) |
| ISTN | 237 (100.0) |
| ITSN | 235 (99.2) |
| Others | 218-237 (92.0-100.0) |
| IST | 144 (60.8) |
| SIT | 185 (78.1) |
| ITS | 196 (82.7) |
| STI | 206 (86.9) |
| TIS | 230 (97.0) |
| TSI | 224 (94.5) |
| IS | 96 (40.5) |
| SI | 141 (59.5) |

I indicates inferior rim width; N, nasal rim width; S, superior rim width; T, temporal rim width, which was determined using the disc center-fovea axis as a reference line.

TABLE 5. Diagnostic Performance of the ISNT-Based Criteria

| Pattern | Sensitivity | Specificity | Positive Likelihood Ratio | Negative Likelihood Ratio |
|---------|---------------------|---------------------|---------------------------|---------------------------|
| NIST | 0.738 (0.678–0.793) | 0.336 (0.318–0.355) | 1.113 (1.026–1.206) | 0.778 (0.624–0.970) |
| INST | 0.916 (0.873–0.948) | 0.281 (0.263–0.299) | 1.273 (1.216–1.332) | 0.301 (0.197–0.460) |
| NSIT | 0.844 (0.791–0.888) | 0.173 (0.159–0.189) | 1.021 (0.964–1.082) | 0.900 (0.661–1.225) |
| ISNT | 0.954 (0.918–0.977) | 0.067 (0.058–0.078) | 1.022 (0.992–1.053) | 0.692 (0.381–1.255) |
| INTS | 0.903 (0.858–0.937) | 0.040 (0.032–0.048) | 0.940 (0.901–0.981) | 2.450 (1.587–3.782) |
| SNIT | 0.954 (0.918–0.977) | 0.032 (0.026–0.040) | 0.985 (0.957–1.014) | 1.435 (0.775–2.658) |
| SINT | 0.987 (0.963–0.997) | 0.017 (0.012–0.023) | 1.004 (0.989–1.020) | 0.746 (0.233–2.387) |
| NITS | 0.937 (0.898–0.964) | 0.014 (0.010–0.020) | 0.950 (0.919–0.982) | 4.474 (2.480–8.071) |
| ISTN | 1.000 (0.977–1.000) | 0.013 (0.009–0.018) | 1.013 (1.008–1.017) | 0.000 (0.000) |
| ITSN | 0.992 (0.970–0.999) | 0.007 (0.004–0.011) | 0.998 (0.986–1.011) | 1.228 (0.285–5.283) |
| IST | 0.608 (0.542–0.670) | 0.696 (0.678–0.715) | 2.002 (1.778–2.253) | 0.563 (0.480–0.662) |
| SIT | 0.781 (0.722–0.832) | 0.225 (0.209–0.242) | 1.007 (0.939–1.081) | 0.975 (0.758–1.253) |
| ITS | 0.827 (0.773–0.873) | 0.065 (0.056–0.076) | 0.885 (0.834–0.939) | 2.642 (1.927–3.623) |
| STI | 0.869 (0.820–0.909) | 0.010 (0.006–0.014) | 0.878 (0.835–0.922) | 13.49 (8.049–22.59) |
| TIS | 0.970 (0.940–0.988) | 0.002 (0.001–0.005) | 0.972 (0.951–0.994) | 14.61 (4.675–45.69) |
| TSI | 0.945 (0.908–0.970) | 0.001 (0.000–0.004) | 0.946 (0.918–0.976) | 45.24 (12.98–157.62) |
| IS | 0.405 (0.342–0.471) | 0.764 (0.747–0.781) | 1.716 (1.448–2.034) | 0.779 (0.700–0.867) |
| SI | 0.595 (0.529–0.658) | 0.236 (0.219–0.253) | 0.779 (0.700–0.867) | 1.716 (1.448–2.034) |

The numbers in the parentheses indicate the 95% confidence interval.

Positive likelihood ratio = sensitivity/(1–specificity); negative likelihood ratio = (1–sensitivity)/specificity.

Inferior (I) rim width, superior (S) rim width, nasal (N) rim width, and temporal (T) rim width, which was determined using the disc center-fovea axis as a reference line.

glaucoma, and secondary glaucoma) were also included as explanatory variables.

Failure of the IST pattern in normal eyes was associated with a smaller disc area ($P < 0.001$) and disc ovality ($P = 0.005$) and larger β -PPA area ($P < 0.001$), while compliance with the pattern in glaucomatous eyes was associated with a higher BMI ($P = 0.037$), thicker CCT ($P = 0.017$), lower IOP ($P = 0.019$), and smaller β -PPA area ($P = 0.027$) (Table 6). When the N, S, I, or T rim width was defined relative to the horizontal meridian of the acquired image frame as proposed originally,¹ similar results as above were obtained. Among the combinations of the 4 rim widths, the NIST pattern was the most prevalent and the ISNT pattern was complied with in 4.4% of the normal eyes, the IST pattern in 63%, and the IS pattern in 72%. In the glaucoma group, the ISNT, IST, and IS patterns failed in 96%, 62%, and 41%, respectively. Among all combinations,

the IST pattern had the highest LR+, 1.670 (1.491–1.870) followed by the IS pattern, 1.452 (1.226–1.719).

DISCUSSION

Jonas et al¹ first reported the ISNT rule based on findings from 457 normal white eyes. Since this rule is to be applied by general ophthalmologists in routine clinical practice to easily screen for glaucoma, simple parameters should be clinically more relevant and useful while examining patients, such as the rim width as proposed originally rather than the rim area or circumpapillary retinal nerve fiber layer thickness yielded by modern imaging devices. A computer-assisted planimetric method of stereoscopic fundus photographs was currently used to measure the rim width to efficiently analyze a large number of disc stereophotographs. The current computer-assisted method is, however, essentially the same to the estimation of stereophotographs in routine clinical practice with human eyes, since the rim width was determined using a ruler installed in the program based on the disc and rim margin determined with human eyes. Considering the situations in which this rule is applied, it would be more desirable to evaluate the clinical performance of this rule in a population-based setting rather than a hospital-based setting. The advantage of the current study was that the ISNT rule and its variations were studied in a population-based setting with a much larger sample size than previous studies.^{2,3,9–22} Two population-based studies have included 92 and 623 normal subjects, respectively, and included the rim width as a comparative parameter; Wang et al³ randomly selected 92 eyes of 92 subjects from 4439 participating in the Beijing Eye Study and reported that the order of the mean of the rim width was I > S > N > T and the ISNT rule was complied with in 52% of the adult Chinese subjects. Arvind et al²² carried out planimetry of the optic disc stereophotographs in 623 right eyes of 623 healthy phakic participants in the Chennai Glaucoma Study and reported that the order of the mean of the rim width was I > N > S > T and that the ISNT rule was violated in a significant minority. In the current 2474 normal Japanese subjects, the mean N rim width was broadest followed

TABLE 6. Parameters Associated Significantly With Failure of the IST Pattern in Normal Eyes and Those Compliance With of This Pattern in Glaucomatous Eyes

| | OR (95% CI) | P |
|---|----------------------|---------|
| Parameters associated with failure of the IST pattern in normal eyes | | |
| Disc area (mm ²) | 0.650 (0.587–0.720) | < 0.001 |
| Disc ovality | 0.805 (0.745–0.871)* | 0.005 |
| β -peripapillary area (mm ²) | 1.344 (1.251–1.444) | < 0.001 |
| Parameters associated compliance with of the IST pattern in glaucomatous eyes | | |
| Body mass index | 1.096 (1.048–1.146) | 0.037 |
| Central corneal thickness (μ m) | 1.011 (1.006–1.016) | 0.017 |
| Intraocular pressure (mm Hg) | 0.898 (0.856–0.941) | 0.019 |
| β -peripapillary area (mm ²) | 0.665 (0.546–0.811) | 0.027 |

*Per 0.1 U change in disc ovality.

CI indicates confidence interval; I, inferior rim width; OR, odds ratio; S, superior rim width; T, temporal rim width.

by the I rim width, and the NIST pattern (N > I > S > T rim width rate) was the most frequently seen and complied with in 34% of normal Japanese subjects, while the ISNT pattern was the fourth prevalent pattern in this population-based study. The LR+ by the formula, sensitivity/(1-specificity), is a quantitative index of how many times the probability of establishing diagnosis was multiplied when a clinical test yielded a positive result. For example, if the sensitivity and specificity of a test are 100% and 95%, respectively, the LR+ of the test is 20. The LR+ of the ISNT rule in this population was 1.022, suggesting its limited clinical usefulness in Japanese subjects probably due to racial difference in the optic disc and rim morphology.^{23-25,34} Compared with several previous hospital-based studies of the performance of the ISNT rule when adopting the rim width or its equivalent,^{2,18-20,35} the currently obtained sensitivity/specificity or LRs+ were comparable to those reported by Morgan et al,¹⁹ (sensitivity/specificity, 0.92 to 0.96/0.00 to 0.10, LR+, 1.06 to 1.11) but considerably lower than those reported by Haizman et al² (0.72/0.79, 3.43) and Law et al¹⁸ (0.85/0.46, 1.59) or by Pogrebnik et al²⁰ and Lopes et al³⁵ (specificity, 0.73 and 0.91, respectively, in normal subjects with nonlarge cupped disc). In the current subjects, the N rim width was broadest, which likely is attributable to reported racial difference in optic disc and rim morphology,^{23-25,34} and suggested the importance of providing reference data for each ethnic group. If we exclude the N rim width, which has reportedly less clinical relevance in glaucoma,³³ the IST pattern showed a sensitivity/specificity of 0.61/0.70 and the highest LR+ of 2.002 among all combinations of the I, S, N, and/or T rim widths. These values were comparable to those of the IS pattern reported by Law et al¹⁸ (sensitivity/specificity, 0.41/0.85, LR+, 2.66) or the specificity of the IST pattern of 0.71 obtained using the Heidelberg Retina Tomograph that yielded a 90-degree segmental rim area.¹⁰ Arvind et al²² reported that a broader S than I rim width was associated significantly with male sex and disc torsion and the narrowest T rim width with the ratio of the vertical disc diameter to the horizontal disc diameter, type of cupping, and astigmatism. Since male sex may be a risk factor for glaucoma,^{6,27,36,37} and recent studies have suggested a correlation between the disc ovality (maximal disc diameter/minimal disc diameter) or torsion and progression of glaucomatous damage,³⁸⁻⁴⁰ it may be of interest to study whether the systemic and ocular factors, including the previously mentioned factors, are associated with failure of the IST pattern in normal subjects and compliance with this pattern in subjects with glaucoma. We found that the IST pattern was significantly more likely to fail in otherwise normal eyes with smaller disc size and disc ovality (that is, discs that are more rounded) and a larger β -PPA, which may be of help in differentiating normal eyes using this rule. In contrast, the IST pattern was significantly more likely to be complied with in glaucomatous eyes with thicker CCT, lower IOP, and smaller β -PPA, and in persons with a higher BMI. Thinner CCT, higher IOP, and larger β -PPA have been reported as factors associated with progression and/or development of glaucoma.^{26,41-47} One population-based study reported that people with a lower BMI were associated with smaller rim area and larger cup/disc ratio,⁴⁸ suggesting association with a higher BMI and greater rim area and smaller cup/disc ratio. The current results of logistic regression analysis suggested that otherwise normal eyes where the IST pattern failed might be relatively more vulnerable to glaucomatous insults (a larger β -PPA), while glaucomatous eyes violating this pattern might be associated with relatively worse prognostic factors (thinner CCT, higher IOP, greater β -PPA area), after adjustment for other confounding factors. In addition to the

highest LR+ in detecting glaucoma eyes, the results may have clinical implications in measuring the I, S, and T rim widths in Japanese subjects.

The current study had limitations. The results were obtained in participants of the Kumejima Study who had good-quality stereo fundus photographs and not in all the Kumejima Study participants. In clinical practice, however, it also would be difficult to determine accurately the I, S, N or T rim widths to apply the ISNT rule or its variations in patients in whom it was difficult to observe the ONH details and consequently to obtain good stereo fundus photographs. The reproducibility of the measurements of the I, S, N, and T rim widths was not so good, while the reproducibility of the measurements of the disc area, rim area, or v-C/D ratio were considered acceptable. The current planimetric method included subjective determination of the disc and rim margin on stereo fundus photographs. So, it likely is difficult for 2 independent examiners to draw the disc and rim margin at the same coordinates on the same meridian of the disc at a 1-week interval, while with the disc or rim area or v-C/D ratio, such errors could be rounded. Automatic determination may yield better measurement reproducibility of the rim width at any given disc meridians in the future. A long-term follow-up data of the study population, if available, would have been very useful in validating the result obtained using the logistic regression analysis. Unfortunately, the untimely passing of the principal investigator of the study (S.S.) resulted in discontinuation of the Grant, and 10-year follow-up data of the study population could not be obtained.

In summary, the current study in a Japanese population-based setting included sufficient large numbers of normal subjects and those with glaucoma and indicated that the nasal rim width was the broadest in this population, and among all combinations of the I, S, N, and/or T rim width rates along the cardinal meridian, the IST pattern showed the highest positive LR+ of 2.002 in detecting glaucoma eyes. Failure of the IST pattern in normal eyes was associated significantly with smaller and rounder discs and larger β -PPA. In contrast, complying with this pattern in glaucoma eyes was associated with thicker CCTs, lower IOPs, smaller β -PPAs, and higher BMIs, suggesting that the IST pattern failed in glaucoma eyes with worse prognostic factors. These findings have clinical implications in applying the IST pattern for screening for glaucoma in Japanese subjects.

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