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Keywords:	dry eye disease, ocular surface disease index, OSDI, reliability, validity

Original article–Clinical Science

Reliability and Validity of the Japanese Version of the Ocular Surface Disease Index for Dry Eye Disease

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ABSTRACT

Objectives: The ocular surface disease index (OSDI) questionnaire is widely used to evaluate subjective symptoms of dry eye disease (DED) as a primary diagnostic criterion. This study aimed to develop a Japanese version of the OSDI (J-OSDI) and assess its reliability and validity.

Design and Setting: Hospital-based cross-sectional observational study.

Participants: A total of 209 patients recruited from the Department of Ophthalmology at Juntendo University Hospital.

Methods: We translated and culturally adapted the OSDI into Japanese. The J-OSDI was then assessed for internal consistency, reliability, and validity. We also evaluated the optimal cut-off value to suspect DED using an area under the receiver operating characteristic curve (AUC) analysis.

Primary Outcome Measures: Internal consistency, test-retest reliability, and discriminant validity of the J-OSDI as well as the optimal cut-off value to suspect DED.

Results: Of the participants, 152 had DED and 57 did not. The J-OSDI total score showed good internal consistency (Cronbach alpha = 0.884), test-retest reliability (interclass correlation coefficient = 0.910), and discriminant validity by known-group comparisons (non-DED, 19.4 ± 16.0; DED, 37.7 ± 22.2; $p < 0.001$). Factor validity was used to confirm 3 subscales within the J-OSDI according to the original version of the questionnaire. Concurrent validity was assessed by Pearson correlation analysis, and the J-OSDI total score was positively associated with the Dry Eye-Related Quality-of-Life Score ($\gamma = 0.829$). The optimal cut-off value of the J-OSDI total score was 36.3 (AUC = 0.744).

Conclusions: The J-OSDI was validated in terms of reliability and validity as an effective tool for DED assessment and monitoring in the Japanese population.

Keywords: dry eye disease, J-OSDI, ocular surface disease index, OSDI, reliability, validity

Strengths and limitations of this study:

- This study provides the first validation data on the Japanese version of the ocular surface disease index (J-OSDI) questionnaire as the primary evaluation for dry eye disease (DED) diagnosis.
- The validated J-OSDI allows across-country epidemiological comparisons of patient-reported subjective symptoms of DED.
- The main limitation is that this study was conducted at a single university hospital, which may limit the generalizability of the findings.

INTRODUCTION

The prevalence of dry eye disease (DED) continues to grow due to several psychosocioeconomic factors, including an increase in digital screen usage time, an aging population, and stressful social environments.[1, 2] DED can cause ocular surface damage, eye discomfort and impaired vision, and can also lead to substantial economic problems due to decreased quality of life and work productivity.[3, 4]

Diagnosis of DED can be made using various methods, including tear film breakup time (TFBUT), ocular surface staining, and osmolarity as a homeostasis marker. Additionally, the use of a questionnaire to determine if symptoms of DED are present is recommended as a primary examination method in the DED diagnosis protocol by the TFOS DEWS II Diagnostic Methodology report and in the 2016 Asia Dry Eye Society (ADES) consensus report.[5, 6] Although previous research has established a divergence between the subjective symptoms of DED and clinical severity of the disease,[7-9] questionnaires that can quantitatively measure the subjective symptoms of DED are indispensable for DED diagnosis and management.

The 2016 dry eye diagnostic criteria published by the ADES[6] recommend that DED be diagnosed according to both subjective symptoms and TFBUT, indicating that subjective symptoms are now widely recognized as playing an important role in DED. We previously showed that this change in diagnostic criteria could lead to a 28.0% increase in DED patients in Japan[2]; thus, the need for effective DED treatments may increase in the future. Both the OSDI and the Dry Eye-Related Quality-of-Life Score (DEQS)[10] are widely used to assess subjective symptoms of DED in Japan, but the reliability and validity of the OSDI have not been confirmed in Japan.[11] Determining the reliability and validity of the Japanese version of the OSDI (J-OSDI) is essential for making epidemiological and symptomatic comparisons with other countries.[11-14]

In this study, we developed and evaluated the reliability and validity of J-OSDI and determined the cut-off value of the J-OSDI total score using the 2016 diagnostic criteria put forth by the ADES.[6]

MATERIALS AND METHODS

Translation of the Japanese version of the Ocular Surface Disease Index

The OSDI questionnaire contains 12 questions divided into three subscales: ocular symptoms, vision related function, and environmental triggers.[11] The questionnaire asks patients to rate each symptom on a 5-point scale according to their frequency, from "all of the time" (score 4) to "none of the time" (score 0). The OSDI total score and each subscale score are separately translated to scores of 0–100. According to the OSDI total score, patients are classified as normal (0–12 points), mild (13–22 points), moderate (23–32 points), or severe DED (33–100 points). To obtain a scientifically accurate translation and to perform a transcultural validation of the original version of the questionnaire, a forward-backward procedure was applied to translate the OSDI from English to Japanese. The translation and transcultural adaptation process included translation of the original English version (Allegan Inc., Irvine, CA) of the OSDI into Japanese by five bilingual ophthalmologists, two bilingual epidemiologists, and one native-English researcher, each working individually. A cultural adaptation was conducted to ensure that the translated questionnaire is easily understandable for Japanese patients. The J-OSDI was then translated into English by five native-English researchers and was assessed for comprehensibility.

Study design and participants

This cross-sectional observational study included 209 patients recruited between September 2017 to May 2018 from the Department of Ophthalmology at Juntendo University Hospital in Tokyo, Japan. Written informed consent was obtained from all participants. The study was approved by the Independent Ethics Committee at Juntendo University Hospital (Approval number, 17-088 and 18-082) and adhered to the tenets of the Declaration of Helsinki as revised in Brazil in 2013.

Exclusion criteria

We excluded patients with BCVA values < 20/20 and those with a history of eyelid disorder, ptosis, Parkinson disease, ocular surface surgery, eyelid surgery, hereditary corneal disease, or any other disease that could affect blinking.

Environmental conditions

The temperature and humidity of the examination room were controlled at 26°C in the summer and 24°C in the winter with 50% relative humidity, according to the Guideline for Design and Operation of Hospital HVAC Systems established by the Healthcare Engineering Association of Japan.[15]

Dry eye disease diagnosis and classification

All patients underwent a complete ophthalmic evaluation for both eyes, including measuring BCVA, IOP, and subjective symptoms. Additionally, TFBUT, CFS for kerato-conjunctival vital staining, MBI, and Schirmer test I for reflex tear production were assessed for both eyes. TFBUT, CFS, and Schirmer test I values from the worst eye were examined. The mean value of MBI was used in accordance with a previous study.[16] For each patient, we evaluated TFBUT, CFS, and MBI before performing the Schirmer test I. We diagnosed DED and non-DED using the ADES 2016 diagnostic criteria,[6] which is based on two positive items: the presence of subjective symptoms and decreased TFBUT (≤ 5 seconds).

Subjective symptoms and DEQS

Subjective symptoms were evaluated by interviewing subjects with DED. The DEQS questionnaire was administered to subjects in order to assess the severity of dry eye-associated symptoms and the multifaceted effects of DED on daily life.[10] The score derived from this questionnaire is a subjective measurement of DED symptoms, where 0 indicates the best score (no symptoms) and 100 indicates the worst score (maximum symptoms).

TFBUT

TFBUT was measured using a fluorescein dye according to the standard methodology.[6] Only a small quantity of dye was administered using the wetted fluorescein strip in order to minimize the effect of the dye on tear volume and TFBUT. Each subject was instructed to blink three times after the dye was applied to ensure adequate mixing of the dye and tears. The time interval between the last blink and the appearance of the first dark spot on the cornea was measured with a stopwatch. The mean value of three measurements was used. A cut-off value of TFBUT $\leq$ 5 seconds was used to diagnose DED.[6]

Kerato-conjunctival vital staining (CFS)

CFS was graded according to the van Bijsterveld grading system,[17] which divides the ocular surface into three zones: the nasal bulbar conjunctiva, the temporal bulbar conjunctiva, and the cornea. Each zone was evaluated on a scale of 0–3, with 0 indicating no staining and 3 indicating confluent staining. The maximum possible score was thus 9.

MBI

MBI was considered as the length of time that subjects could keep their eyes open before blinking.[16] We calculated MBI twice by stopwatch under a light microscope without using the light. MBI was recorded as 30 seconds if the blink interval exceeded 30 seconds.

Schirmer test I

The Schirmer test I was performed without topical anesthesia after all other examinations had been completed. Schirmer's test strips (Ayumi Pharmaceutical Co., Tokyo, Japan) were placed on the outer third of the temporal lower conjunctival fornix for 5 minutes. The strips were then removed, and the length of dampened filter paper (in mm) was recorded.

Reliability

The internal consistency of the J-OSDI was assessed using Cronbach's alpha coefficient, with an alpha > 0.70 considered to be acceptable.[18] Test-retest reliability was evaluated by calculating the ICC values from the first and second entries. An ICC value of ≥ 0.70 was considered acceptable for test-retest reliability.[19]

Validity

Discriminant validity was evaluated by comparing the non-DED and DED groups. For factor validity, confirmatory factor analysis was conducted by an equamax rotation to determine whether the subscales in the J-OSDI cluster together in the same way as in the original OSDI. Factors with an eigenvalue > 0.90 were retained. Concurrent validity was assessed by calculating the correlations (Pearson coefficients) between J-OSDI total score or subscale scores and DEQS or other clinical results, including TFBUT, CFS, MBI, and Schirmer test I values.

Statistical analyses

To compare general characteristics between DED and non-DED participants, 2-tailed *t* tests were used for continuous variables and χ^2 tests were used for categorical variables. Pearson rank correlation coefficients were calculated to determine the correlations between J-OSDI, DEQS, TFBUT, MBI, and Schirmer test I results. ROC analysis was used to determine the optimal cut-off value of the J-OSDI total score for suspecting DED. AUC was computed using the trapezoidal rule. Data are presented as mean ± standard deviation (SD) or proportion (%). Statistical analyses were performed using STATA version 15 (Stata Corp, TX) and SPSS Statistics v.1.0.0 (IBM Corp, Chicago, IL). $p < 0.05$ was considered significant.

Patient and public involvement

No patients were involved in the research design and conception of this research study.

RESULTS

Participant characteristics

Table 1 shows the general characteristics of the study participants. All subjects responded to the questionnaires, completed the examination, and were eligible for the study. Overall, 209 participants were included. The average age was 58.9 ± 15.3 years, and 83.7% of the participants were women. Using the diagnostic criteria put forth by the ADES,[6] 152 and 57 patients were classified as DED (72.7%) and non-DED (27.3%), respectively. The mean best corrected visual acuity (BCVA) value for both eyes was -0.07 ± 0.02 logMAR. The mean intraocular pressure (IOP) for both eyes was 14.1 ± 2.9 mmHg. Both the J-OSDI total score and DEQS were significantly higher in the DED group than in the non-DED group, indicating that DED patients showed a greater rate of subjective symptoms. Furthermore, both TFBUT and maximum blink interval (MBI) were significantly lower in the DED group than the non-DED group. Neither BCVA, IOP, corneal fluorescence staining (CFS), nor Schirmer test I results differed significantly between DED and non-DED participants.

Table 1. Characteristics of study participants.

	non-DED **n = 57**	**DED** **n = 152**	**p value**	**Total** **n = 209**
Age, year ± SD	61.4 ± 15.5	57.9 ± 15.2	0.149	58.9 ± 15.3
Gender, female (%)	48 (84.2)	127 (83.6)	1.000	175 (83.7)
BCVA, logMAR ± SD	-0.1 ± 0.0	-0.1 ± 0.0	0.513	-0.1 ± 0.0
IOP, mmHg ± SD	14.6 ± 2.9	13.8 ± 2.7	0.062	14.0 ± 2.8
Subjective symptoms, yes (%)	5 (8.8)	152 (100)	***< 0.001	157 (75.1)
J-OSDI, 0–100 ± SD	19.4 ± 16.0	37.7 ± 22.2	***< 0.001	32.7 ± 29.7

DEQS, 0–100 ± SD	16.0 ± 14.7	32.7 ± 21.6	***< 0.001	28.1± 21.3
TFBUT, seconds ± SD	2.5 ± 2.4	1.5 ± 0.8	***< 0.001	1.7 ± 1.5
CFS, 0–9 ± SD	2.8 ± 2.5	3.3 ± 2.6	0.192	3.2 ± 2.6
Schirmer I, mm ± SD	7.2 ± 8.2	5.7 ± 6.2	0.162	6.1 ± 6.8
MBI, seconds ± SD	15.1 ± 8.1	10.5 ± 6.3	***< 0.001	11.7 ± 7.1

DED, dry eye disease; BCVA, best-corrected visual acuity; IOP, intraocular pressure; J-OSDI, Japanese version of ocular surface disease index; DEQS, Dry Eye-Related Quality-of-Life Score; TFBUT, tear film breakup time; CFS, corneal fluorescein staining; MBI, maximum blink interval. p values were determined using the Student's t-test (two-tailed) for continuous variables and the chi-square test for categorical variables. ***p < 0.001.

Reliability

We tested the J-OSDI total score and subscale scores for internal consistency and test-retest reliability, and the results are shown in Table 2. For internal consistency, the Cronbach's alpha coefficient was 0.884 for the J-OSDI total score and 0.788, 0.669, and 0.902 for the ocular symptoms, vision-related function, and environmental triggers subscales, respectively. Test-retest reliability was evaluated in 173 participants, with a median (IQR) period of 119 (81–182) days between the test and retest. The intraclass correlation coefficient (ICC) values were 0.910, 0.649, 0.817, and 0.859 for the J-OSDI total score, ocular symptoms subscale, vision-related function subscale, and environmental triggers subscale, respectively.

Table 2. Reliability for each subscale

	Number of items	**Cronbach α (n = 209)**	**ICC (n = 173)**
J-OSDI total score	12	0.884	0.910
Ocular symptoms	5	0.788	0.649
Vision-related function	4	0.669	0.817

Environmental triggers	3	0.902	0.859

J-OSDI, Japanese version of the ocular surface disease index; ICC; intra-class correlation coefficient.

Discriminant validity

Table 3 shows the mean values for the J-OSDI total score, each of the subscale scores, and each of the component scores. The mean J-OSDI total score was significantly higher in the DED group than in the non-DED group (DED, 37.7 ± 22.2; non-DED, 19.4 ± 16.0; $p < 0.001$). Additionally, all three subscales were significantly higher in the DED group than in the non-DED group (ocular symptoms: DED, 34.6 ± 21.6; non-DED, 20.9 ± 17.4; $p < 0.001$; vision-related function: DED, 36.5 ± 27.7; non-DED, 20.8 ± 22.0; $p < 0.001$; environmental triggers: DED, 45.2 ± 29.7; non-DED, 15.5 ± 19.8; $p < 0.001$). Eleven of the 12 (92%) component scores were significantly higher in the DED group than in the non-DED group, with only question 2 showing a non-significant difference.

Table 3. J-OSDI score for each question.

Classification, score ± SD, score	**non-DED**	**DED**		**Total**
	n = 57	**n = 152**	**p value**	**n = 209**
J-OSDI total score, 0–100	19.4 ± 16.0	37.7 ± 22.2	***< 0.001	32.7 ± 22.2
Ocular symptoms, 0–100	20.9 ± 17.4	34.6 ± 21.6	***< 0.001	30.9 ± 21.4
1. Eyes that are sensitive to light?	0.8 ± 0.9	1.5 ± 1.3	***< 0.001	1.3 ± 1.3
2. Eyes that feel gritty?	0.8 ± 1.2	1.0 ± 1.0	0.338	1.0 ± 1.1
3. Painful or sore eyes?	0.4 ± 0.7	1.0 ± 1.0	***< 0.001	0.8 ± 1.0
4. Blurred vision?	1.1 ± 1.0	1.6 ± 1.2	**0.002	1.5 ± 1.2
5. Poor vision?	1.1 ± 1.1	1.8 ± 1.3	***< 0.001	1.6 ± 1.3
Vision-related function	20.8 ± 22.0	36.5 ± 27.7	***< 0.001	32.2 ± 27.2

6. Reading?	0.8 ± 1.1	1.6 ± 1.3	***< 0.001	1.4 ± 1.3
7. Driving at night?	0.4 ± 0.6	1.1 ± 1.4	*0.022	0.9 ± 1.3
8. Working with a computer or bank machine (ATM)?	1.1 ± 1.3	1.6 ± 1.4	*0.030	1.5 ± 1.4
9. Watching TV?	0.7 ± 1.0	1.3 ± 1.2	**0.002	1.1 ± 1.1
Environmental triggers	15.5 ± 19.8	45.2 ± 29.7	***< 0.001	37.1 ± 30.4
10. Windy conditions?	0.7 ± 0.9	1.9 ± 1.4	***< 0.001	1.5 ± 1.3
11. Places or areas with low humidity (very dry)?	0.5 ± 0.8	1.6 ± 1.3	***< 0.001	1.3 ± 1.3
12. Areas that are air conditioned?	0.6 ± 0.9	2.0 ± 1.3	***< 0.001	1.6 ± 1.3

DED, Dry eye disease; J-OSDI, Japanese version of ocular surface disease index. p values were determined using the Student's t-test. *p < 0.05, **p < 0.01, and ***p < 0.001.

Factor validity

Factor validity was assessed by confirmatory factor analysis to determine the subscales. As shown in Figure 1, correspondent with the three homogeneous content domains that were identified and constructed; three factors were rotated to an equamax solution. These three factors accounted for 71.9% of the total variance, and each factor was comprised of sets of items that were interpretable and relevant in content. Factor 1, accounting for 53.0% of the total variance and 23.6% of the common variance, was comprised of items assessing the frequency of ocular symptoms (5 items). Factor 2, accounting for 11.1% of the total variance and 22.8% of the common variance, was comprised of items assessing the frequency of vision-related function (4 items). Factor 3, accounting for 7.7% of the total variance and 17.7% of the common variance, was comprised of items assessing the frequency of environmental triggers (3 items). All factors were in accordance with the subscales in the original version. The factor

matrix of each J-OSDI component can be viewed in Supplemental Table 1. All subscales and the total instrument underwent formal reliability and validity testing.

Concurrent validity

Table 4 shows the correlations between J-OSDI total score, subscale scores, and other clinical items related to DED diagnosis, including DEQS, TFBUT, CFS, Schirmer test I results, and MBI. J-OSDI total score was significantly and positively correlated with DEQS (γ = 0.829). Among the clinical items related to DED diagnosis, there was a modest but significant negative correlation between J-OSDI total score and MBI (γ = -0.258). The subscales were each significantly and positively correlated with DEQS score (γ = 0.786, 0.702 and 0.650, respectively), while ocular symptoms and environmental triggers were significantly and negatively correlated with MBI (γ = -0.195 and -0.370, respectively).

Table 4. Correlation between J-OSDI total score and other clinical assessments.

	OSDI total score		Ocular symptoms		Vision-related function		Environmental triggers	
Clinical Items	**γ**	**p value**	**γ**	**p value**	**γ**	**p value**	**γ**	**p value**
DEQS	0.829	***< 0.001	0.786	***< 0.001	0.702	***< 0.001	-0.650	***< 0.001
TFBUT	-0.066	0.349	-0.044	0.532	-0.057	0.416	-0.131	0.063
CFS	0.018	0.791	-0.013	0.852	-0.137	*0.049	0.161	*0.022
Schirmer I	-0.090	0.195	-0.013	0.844	-0.071	0.311	-0.129	0.067
MBI	-0.283	***< 0.001	-0.215	**0.002	-0.135	0.053	-0.407	***< 0.001

J-OSDI, Japanese version of the ocular surface disease index; DEQS, Dry Eye-Related Quality-of-Life Score; TFBUT, tear film breakup time; CFS, corneal fluorescein staining; MBI, maximum blink interval. Pearson rank correlation coefficient was used to determine

the correlations between the J-OSDI total score and subscale scores and various clinical assessments. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

J-OSDI severity results and cut-off value for detecting DED

Figure 2A shows the proportion of DED participants in each severity category as determined by J-OSDI total score. The clinically diagnosed DED patients were divided according to their J-OSDI scores as follows: 22.0% were categorized as normal, 17.2% were categorized as mild DED, 12.9% were categorized as moderate DED, and 47.8% were categorized as severe DED. Figure 2B shows the proportion of patients who were clinically diagnosed with DED in each severity category determined by J-OSDI total scores. Overall, 47.8% of the patients who were classified as normal by their J-OSDI total score were clinically diagnosed with DED, while 66.7%, 74.0%, and 86.0% of patients classified as mild, moderate, and severe, respectively, were clinically diagnosed with DED. Figure 2C shows the receiver operating characteristic (ROC) curve of the J-OSDI total score from the non-DED and DED groups, which was used to determine the diagnostic efficacy of the J-OSDI total score. The optimum cut-off value for detecting DED was 36.3 points, with an area under the curve (AUC), sensitivity, and specificity of 0.744, 51.3%, and 87.7%, respectively. Supplemental Table 1 shows the details of the J-OSDI total score sensitivity and specificity analysis.

DISCUSSION

DED is a major ocular disease that affects at least 344 million people worldwide and causes a variety of symptoms.[1, 5, 6]. Particularly in Japan, many people have DED due to genetic risk factors and increasing usage of digital devices.[2, 20] Therefore, quantifying the symptoms and severity of DED is important for the diagnosis, monitoring, and treatment of this condition. Indeed, evaluation of subjective symptoms for DED diagnosis is regarded as the primary examination tool in both the DEWS II report[5] and the 2016 ADES diagnostic

criteria.[6] In particular, the diagnostic criteria from the ADES use the presence of subjective symptoms and a decreased TFBUT, indicating the importance of accurately quantifying subjective symptoms in DED. The OSDI is a questionnaire widely used to quantify subjective symptoms in DED but the reliability and validity of this test has not been examined in Japan. In this study, we assessed the reliability and validity of the J-OSDI, which is the Japanese version of OSDI, and determined a cut-off value using the ADES diagnostic criteria of 2016. Our results validate the use of the J-OSDI in Japan and make it possible to compare epidemiological results between Japan and other countries.

We used factor analysis to confirm three subscales within the J-OSDI: ocular symptoms, vision-related function, and environmental triggers. All of these were in accordance with the subscales in the original English version (Figure 1). The J-OSDI total score showed both high internal consistency and test-retest reliability (Table 2). For the subscales, factor analysis confirmed three subscales which were in accordance with the subscales in the original English version (Figure 1). Two of the subscales, ocular symptoms and environmental triggers, showed good internal consistency, while the third subscale, vision-related function, only showed modest internal consistency. Because the questions in the vision-related function subscale are concerned with daily activities, including reading, driving at night, working with a computer or bank machine (ATM), and watching TV, the individual variation for these behaviors naturally affects the internal consistency of this subscale. The test-retest reliability of the subscales demonstrates that vision-related function and environmental triggers have good reliability. However, the reliability of the ocular symptoms subscale was only modest, indicating that the answers to this subscale may have varied because of the known fluctuations in the subjective symptoms of DED.[21, 22]

The J-OSDI total score and subscale scores were significantly higher in the DED group compared to the non-DED group, verifying the discriminant validity of the J-OSDI (Table 3). Further, the percentage of participants who were clinically diagnosed with DED increased proportionally in each severity category, indicating that the J-OSDI total score can discriminate

DED (Figure 2B). Our study also determined that the optimal J-OSDI total score cut-off value for detecting DED according to ADES criteria was 36.3. One previous study reported an OSDI total score cut-off value of 15.[11] However, the difference between this cut-off value and that of the current study is probably the result of differences in the methods used to clinically diagnose severity of DED, as the previous study used lissamine green staining, Schirmer test I, and patient perception of ocular symptoms. In contrast, the current study used TFBUT as an essential part of our diagnostic criteria.[5, 6] Supplemental Table 2 shows the sensitivity and specificity of our reported cut-off value and the cut-off values for the different severity categories: normal (0–12), mild (13–22), moderate (23–32) and severe (33–100).[11] Our results suggest that it is necessary to re-evaluate the OSDI total score cut-off values for diagnosis and severity categories to reflect the changes made to the diagnostic criteria for DED.[5, 6, 23-28]

Table 4 shows the correlations between J-OSDI total score and other clinical tests, including DEQS, TFBUT, CFS, MBI, and Schirmer test I. J-OSDI total score showed a strong positive correlation with DEQS score. Because the DEQS has been validated in Japan,[10] this result supports the use of the J-OSDI as a valid method of quantifying subjective symptoms. In contrast, the respective correlations between J-OSDI total score and TFBUT, CFS, and Schirmer I were relatively low. This is consistent with previous studies that reported low correlations and high divergence between subjective symptoms assessed by questionnaires and clinical tools,[2, 19, 25] underscoring the importance of combining knowledge about subjective symptoms and clinical tools in order to effectively evaluate and monitor DED. Our group[16] has proposed MBI as a simple self-check screening test for DED because it is highly correlated with subjective symptoms compared with other dry eye items (Table 4). Because of the divergence between the subjective and clinical symptoms of DED,[2] it is necessary to perform multilateral evaluations using not only OSDI total scores but also the subscales and each component. In the present study, we assessed the respective relationship between each subscale and various clinical tools for DED examination and found that the ocular symptoms and

environmental trigger subscales were negatively correlated with MBI. We recently reported that MBI is also significantly associated with TFBUT and CFS.[16] Our previous results and those of this study suggest that MBI reflects both TFBUT and CFS results, possibly explaining its negative correlation with the ocular symptoms and environmental triggers subscale scores of J-OSDI.

This study has several limitations. First, it was conducted at a single university hospital in Japan, possibly introducing selection bias into our sample. Second, under the simplified ADES diagnostic criteria, those with low TFBUTs can still be classified as non-DED due to a lack of subjective symptoms; thus, our non-DED group showed a low TFBUT. Third, the test-retest method that we used to confirm reliability introduced recall bias from the necessary length of the test-retest period. Next, we did not account for differences in variables such as socioeconomic status or education level, possibly affecting the responses. Finally, this study was designed to investigate the J-OSDI as a primary evaluation and monitoring method for DED. Thus, rose bengal stain scores, tear osmolality, meibomian gland dysfunction assessments, and corneal sensations were not applied in this study. Despite these limitations, we verified the reliability and validity of the J-OSDI for DED assessment and monitoring in Japan.

In summary, we validated the J-OSDI by assessing its reliability and validity. We report that a J-OSDI score of 36.3 is the optimal cut-off value for suspecting DED under the 2016 ADES criteria. We believe that J-OSDI will be useful for primary assessment and monitoring of DED in routine clinical practice and in remote diagnosis.

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Author Contributions:

A.MI.: Performance of the research, data collection, data analysis, and writing of the paper; T.I.: Performance of the research, research design, data analysis, and writing of the paper; S.N.: Research design, data analysis; M.N.: Data analysis; M.I.: Research design, data analysis; K.F.: Data collection, data analysis; Y.O.: Data collection, data analysis; N.I.: Data collection, data analysis; A. E.: Data collection, data analysis; H.H.: Data collection, data analysis; H.K.: Performance of the research; A.M.: Research design, writing of the paper; H.K.: Research design, writing of the paper.

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Figure 1. Three subscales of J-OSDI as determined by factor analysis. The existence of 3 clusters that were used as subscales are shown. These were in accordance with the subscales that are used in the original version of OSDI: vision-related function (components 1–5), ocular symptoms (components 6–9), and environmental triggers (components 10–12).

Figure 2. Clinical utility of J-OSDI for evaluating dry eye disease (DED). (a) The proportion of patients in each DED severity category as determined by the J-OSDI total score. **(b)** The proportion of patients who were clinically diagnosed with DED by category of severity according to the J-OSDI total score. **(c)** The Receiver Operator Characteristic (ROC) curve for the diagnosis of DED determined by the Asia Dry Eye Society 2016 criteria using J-OSDI. The area under the ROC curve (AUC) is 0.744.

Supplementary Information

Supplemental Table 1: Factor matrix of each J-OSDI question. Results of factor analysis of each J-OSDI question. All of three subscales were in accordance with the subscales in the original version.

Supplemental Table 2: J-OSDI total score sensitivity and specificity analysis results. Full results of the sensitivity and specificity analysis. Our reported cut-off value for suspecting dry eye disease was 36.3.

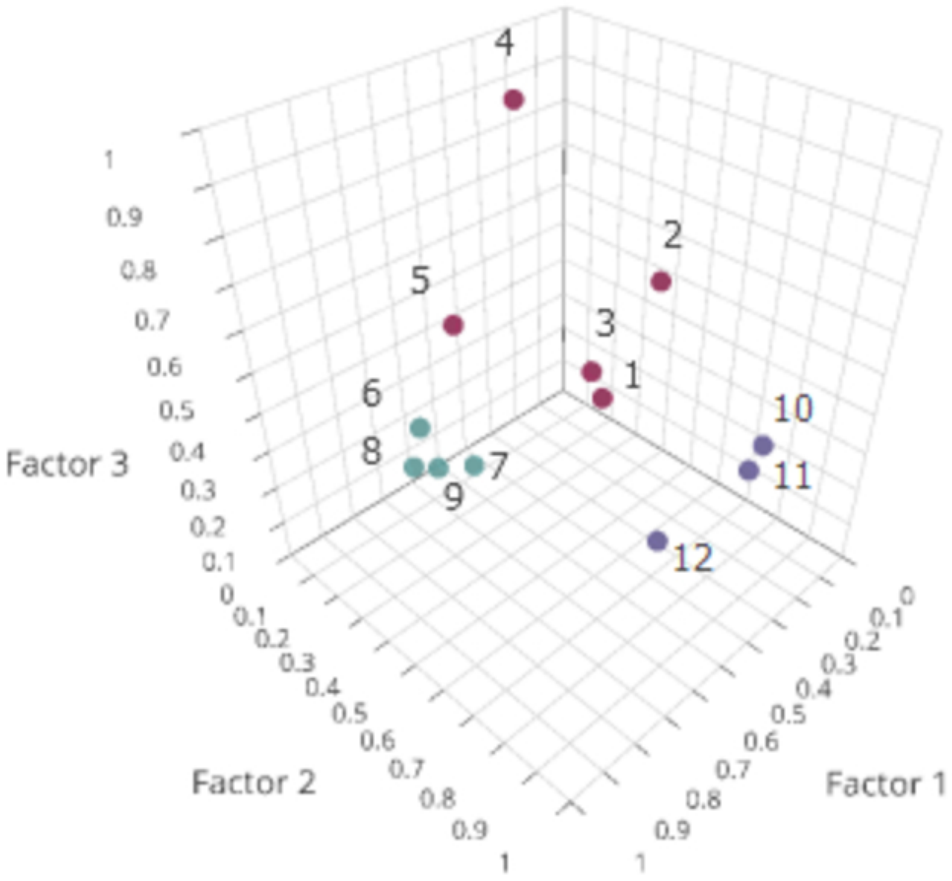

Figure 1

185x173mm (90 x 90 DPI)

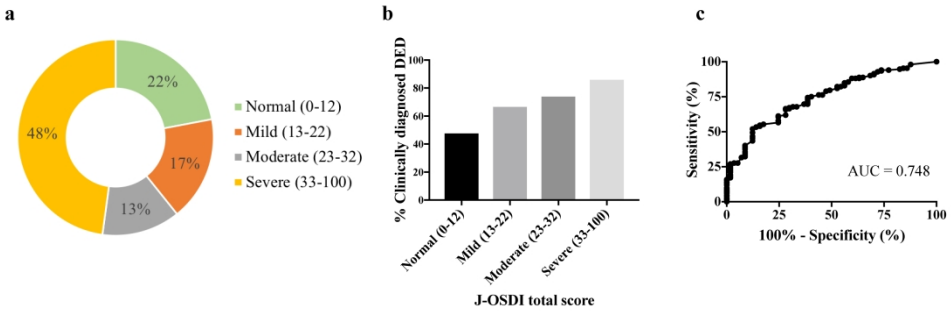
a
22%
17%
13%
48%
Normal (0-12)
Mild (13-22)
Moderate (23-32)
Severe (33-100)
b
% Clinically diagnosed DED
100
80
60
40
20
0
Normal (0-12)
Mild (13-22)
Moderate (23-32)
Severe (33-100)
J-OSDI total score
c
Sensitivity (%)
100
75
50
25
0
AUC = 0.748
0
25
50
75
100
100% - Specificity (%)

Figure 2

Supplementary Information

From: Reliability and Validity of the Japanese Version of the Ocular Surface Disease Index for Dry Eye Disease

Akie Midorikawa-Inomata RN, MPH, Takenori Inomata MD, PhD, MBA, Soko Nojiri, MPH, Masahiro Nakamura MD, PhD, Masao Iwagami MD, MPH, MSc, PhD, Keiichi Fujimoto MD, Yuichi Okumura MD, Nanami Iwata, Atsuko Eguchi, Hitomi Hasegawa MD, Hikaru Kinouchi, Akira Murakami MD, PhD, and Hiroyuki Kobayashi MD, PhD.

Supplemental Table 1: Factor matrix of each J-OSDI question

	Factor		
Components	1	2	3
1	0.352	0.474	0.361
2	0.055	0.393	0.504
3	0.256	0.349	0.331
4	0.335	0.167	0.927
5	0.632	0.269	0.573
6	0.706	0.208	0.323
7	0.576	0.246	0.171
8	0.710	0.172	0.198
9	0.719	0.283	0.260
10	0.156	0.815	0.307
11	0.239	0.837	0.295
12	0.441	0.742	0.159

J-OSDI, Japanese version of the Ocular Surface Disease Index.
Extraction Method: Maximum likelihood method; Rotation Method: Equamax with Kaiser normalization

Supplemental Table 2: J-OSDI total score sensitivity and specificity analysis results

J-OSDI total score	Sensitivity (%)	Specificity (%)
> 1.05	98.03	12.28
> 2.2	95.39	14.04
> 2.4	95.39	15.79
> 3.35	94.74	17.54
> 4.9	94.08	22.81
> 5.95	94.08	26.32
> 6.55	92.76	28.07
> 6.95	91.45	29.82
> 7.3	90.79	29.82
> 7.9	90.13	31.58
> 9.15	88.82	35.09
> 10.2	88.82	36.84
> 10.9	88.16	38.6
> 11.95	88.16	40.35
> 13.05	84.87	42.11
> 14.1	84.21	43.86
> 14.8	82.24	43.86
> 15.3	81.58	45.61
> 15.75	81.58	47.37
> 16.3	80.26	47.37
> 17.45	78.95	50.88
> 18.5	78.29	52.63
> 19.1	75.66	54.39
> 19.7	75.66	56.14

> 20.25	74.34	59.65
> 20.65	73.68	61.4
> 21.35	72.37	61.4
> 22.05	71.05	61.4
> 22.35	70.39	61.4
> 22.6	69.08	61.4
> 23.85	69.08	63.16
> 26.15	67.11	66.67
> 27.4	67.11	68.42
> 27.8	66.45	70.18
> 28.65	65.79	70.18
> 29.35	65.13	71.93
> 29.75	61.18	71.93
> 30.3	60.53	75.44
> 30.95	59.87	75.44
> 31.55	57.24	75.44
> 32.55	55.92	75.44
> 33.7	54.61	82.46
> 34.55	53.95	84.21
> 35.2	53.29	84.21
> 35.75	52.63	85.96
> 36.25	51.32	87.72
> 36.95	48.68	87.72
> 38.55	46.05	87.72
> 39.8	44.74	87.72
> 40.85	42.76	87.72
> 42.1	39.47	91.23

> 42.85	38.82	91.23
> 43.5	38.16	91.23
> 44.4	36.84	91.23
> 45.4	34.87	91.23
> 46.5	33.55	91.23
> 47.35	32.89	91.23
> 47.6	32.24	91.23
> 47.8	31.58	91.23
> 48.95	30.92	92.98
> 51.05	27.63	94.74
> 52.2	26.97	98.25
> 52.4	25.66	98.25
> 53.35	25	98.25
> 54.35	23.03	98.25
> 55.4	21.71	98.25
> 56.55	21.05	98.25
> 57.15	20.39	98.25
> 57.9	18.42	98.25
> 58.7	17.11	98.25
> 59.75	16.45	98.25
> 61.45	15.79	100
> 63.05	15.13	100
> 63.75	13.82	100
> 64.25	13.16	100
> 66.05	11.84	100
> 67.7	9.868	100
> 68.35	9.211	100

> 69.65	8.553	100
> 70.65	7.895	100
> 71.85	7.237	100
> 75	6.579	100
> 77.2	5.921	100
> 78.25	4.605	100
> 82.1	3.947	100
> 85.7	2.632	100
> 87.5	1.974	100
> 89.3	1.316	100

J-OSDI, Japanese version of the Ocular Surface Disease Index

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	17
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A

		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Reliability and Validity of the Japanese Version of the Ocular Surface Disease Index for Dry Eye Disease

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Secondary Subject Heading:	Epidemiology
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Original article–Clinical Science

Reliability and Validity of the Japanese Version of the Ocular Surface Disease Index for Dry Eye Disease

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request. The J-OSDI is provided for others to use as Supplemental Figure 1.

ABSTRACT

Objectives: The ocular surface disease index (OSDI) questionnaire is widely used to evaluate subjective symptoms of dry eye disease (DED) as a primary diagnostic criterion. This study aimed to develop a Japanese version of the OSDI (J-OSDI) and assess its reliability and validity.

Design and Setting: Hospital-based cross-sectional observational study.

Participants: A total of 209 patients recruited from the Department of Ophthalmology at Juntendo University Hospital.

Methods: We translated and culturally adapted the OSDI into Japanese. The J-OSDI was then assessed for internal consistency, reliability, and validity. We also evaluated the optimal cut-off value to suspect DED using an area under the receiver operating characteristic curve (AUC) analysis.

Primary Outcome Measures: Internal consistency, test-retest reliability, and discriminant validity of the J-OSDI as well as the optimal cut-off value to suspect DED.

Results: Of the participants, 152 had DED and 57 did not. The J-OSDI total score showed good internal consistency (Cronbach alpha = 0.884), test-retest reliability (interclass correlation coefficient = 0.910), and discriminant validity by known-group comparisons (non-DED, 19.4 ± 16.0; DED, 37.7 ± 22.2; $p < 0.001$). Factor validity was used to confirm 3 subscales within the J-OSDI according to the original version of the questionnaire. Concurrent validity was assessed by Pearson correlation analysis, and the J-OSDI total score showed a strong positive correlation with the Dry Eye-Related Quality-of-Life Score ($\gamma = 0.829$). The optimal cut-off value of the J-OSDI total score was 36.3 (AUC = 0.744).

Conclusions: The J-OSDI was developed and validated in terms of reliability and validity as an effective tool for DED assessment and monitoring in the Japanese population.

Keywords: dry eye disease, J-OSDI, ocular surface disease index, OSDI, reliability, validity

Strengths and limitations of this study:

- This study provides the first validation data on the Japanese version of the ocular surface disease index (J-OSDI) questionnaire as the primary evaluation for dry eye disease (DED) diagnosis.
- We conducted a cross-cultural adaptability thoroughly compared by a committee of experts for conceptual equivalence.
- This study confirmed the reliability and validity of the J-OSDI in the 209 patients.
- The main limitation is that this study was conducted at a single university hospital, which may limit the generalizability of the findings.
- The validated J-OSDI allows across-country epidemiological comparisons of patient-reported subjective symptoms of DED.

INTRODUCTION

The prevalence of dry eye disease (DED) continues to grow due to several psychosocioeconomic factors, including an increase in digital screen usage time, an aging population, and stressful social environments.[1, 2] DED can cause ocular surface damage, eye discomfort, and impaired vision and can also lead to substantial economic problems due to decreased quality of life and work productivity.[3, 4] Therefore, quantifying the symptoms and severity of DED is important for the diagnosis, monitoring, and treatment of the condition.[5, 6]

Diagnosis of DED can be made using various methods, including tear film breakup time (TFBUT), ocular surface staining, and osmolarity as a homeostasis marker. Additionally, the use of a questionnaire to determine if symptoms of DED are present is recommended as a primary examination method in the DED diagnosis protocol by the TFOS DEWS II Diagnostic Methodology report and in the 2016 Asia Dry Eye Society (ADES) consensus report.[7, 8] Although previous research has established a divergence between the subjective symptoms of DED and clinical severity of the disease,[9-11] questionnaires that can quantitatively measure the subjective symptoms of DED are indispensable for DED diagnosis and management.

The 2016 dry eye diagnostic criteria published by the ADES[8] recommend that DED be diagnosed according to both subjective symptoms and TFBUT, indicating that subjective symptoms are now widely recognized as playing an important role in DED. We previously showed that this change in diagnostic criteria could lead to a 28.0% increase in DED patients in Japan[2]; thus, the need for effective DED treatments may increase in the future. Both the Ocular Surface Disease Index (OSDI) and the Dry Eye-Related Quality-of-Life Score (DEQS)[12] are widely used to assess subjective symptoms of DED in Japan, but the reliability and validity of the OSDI have not been confirmed in Japan.[13] Determining the reliability and validity of the Japanese version of the OSDI (J-OSDI) is essential for making epidemiological and symptomatic comparisons with other countries.[13-16]

In this study, we developed and evaluated the reliability and validity of the J-OSDI and determined the cut-off value of the J-OSDI total score using the 2016 diagnostic criteria put forth by the ADES.[8]

MATERIALS AND METHODS

OSDI questionnaire

The OSDI questionnaire contains 12 questions divided into three subscales: ocular symptoms, vision related function, and environmental triggers.[13] The questionnaire asks patients to rate each symptom on a 5-point scale according to their frequency, from "all of the time" (score 4) to "none of the time" (score 0). The OSDI total score and each subscale score are separately translated to scores of 0–100. According to the OSDI total score, patients are classified as normal (0–12 points), or as having mild (13–22 points), moderate (23–32 points), or severe DED (33–100 points).

Translation of the Japanese version of the Ocular Surface Disease Index

To obtain a scientifically accurate translation and to perform a transcultural validation of the original version of the questionnaire, a forward-backward procedure was applied to translate the OSDI (Allegan Inc., Irvine, CA) from English to Japanese following previously established guidelines.[17-19] First, a forward translation was carried out independently by five bilingual ophthalmologists to produce a consensus version. A cultural adaptation was conducted to ensure that the translated questionnaire is easily understandable by Japanese patients. Second, the consensus version was back-translated into English by two native-English researchers and was assessed for comprehensibility. Finally, the original translated and back-translated versions were thoroughly compared by a committee of experts for conceptual equivalence. The J-OSDI is provided for others to use in Supplemental Figure 1.

Study design and participants

This was a cross-sectional observational study. Adult patients (aged 20 years) who visited the Department of Ophthalmology at Juntendo University Hospital in Tokyo, Japan, between September 2017 to May 2018 were included. Of them, we excluded patients with best-corrected visual acuity (BCVA) values < 20/20 and those with a history of eyelid disorder, ptosis, Parkinson disease, ocular surface surgery, eyelid surgery, hereditary corneal disease, or any other disease that could affect blinking. Written informed consent was obtained from all participants. The study was approved by the Independent Ethics Committee at Juntendo University Hospital (Approval number, 17-088 and 18-141) and adhered to the tenets of the Declaration of Helsinki as revised in Brazil in 2013.

All patients underwent a complete ophthalmic evaluation for both eyes, including measuring BCVA, intraocular pressure (IOP), and subjective symptoms. Additionally, TFBUT, corneal fluorescein staining (CFS) for kerato-conjunctival vital staining, maximum blink interval (MBI), and Schirmer test I for reflex tear production were assessed for both eyes. TFBUT, CFS, and Schirmer test I values from the worst eye were examined. The mean value of the MBI was used in accordance with a previous study.[20] For each patient, we evaluated the TFBUT, CFS, and MBI before performing Schirmer test I. We diagnosed DED and non-DED using the ADES 2016 diagnostic criteria,[8] which are based on two positive items: the presence of subjective symptoms and decreased TFBUT (≤ 5 seconds).

Environmental conditions

The temperature and humidity of the examination room were controlled at 26°C in the summer and 24°C in the winter with 50% relative humidity, according to the Guideline for Design and Operation of Hospital HVAC Systems established by the Healthcare Engineering Association of Japan.[21]

Other instruments for DED diagnosis and management

Subjective symptoms were evaluated by interviewing subjects with DED. The DEQS questionnaire was administered to subjects in order to assess the severity of dry eye-associated symptoms and the multifaceted effects of DED on daily life.[12] The score derived from this questionnaire is a subjective measurement of DED symptoms, where 0 indicates the best score (no symptoms) and 100 indicates the worst score (maximum symptoms).

TFBUT was measured using a fluorescein dye according to the standard methodology.[8] Only a small quantity of dye was administered using the wetted fluorescein strip in order to minimize the effect of the dye on tear volume and TFBUT. Each subject was instructed to blink three times after the dye was applied to ensure adequate mixing of the dye and tears. The time interval between the last blink and the appearance of the first dark spot on the cornea was measured with a stopwatch. The mean value of three measurements was used. A cut-off value of TFBUT ≤ 5 seconds was used to diagnose DED.[8]

CFS was graded according to the van Bijsterveld grading system,[22] which divides the ocular surface into three zones: the nasal bulbar conjunctiva, the temporal bulbar conjunctiva, and the cornea. Each zone was evaluated on a scale of 0–3, with 0 indicating no staining and 3 indicating confluent staining. The maximum possible score was thus 9.

The MBI was considered as the length of time that subjects could keep their eyes open before blinking.[20] We calculated the MBI twice by stopwatch under a light microscope without using the light. The MBI was recorded as 30 seconds if the blink interval exceeded 30 seconds.

Schirmer test I was performed without topical anesthesia after all other examinations had been completed. Schirmer's test strips (Ayumi Pharmaceutical Co., Tokyo, Japan) were placed on the outer third of the temporal lower conjunctival fornix for 5 minutes. The strips were then removed, and the length of dampened filter paper (in mm) was recorded.

Statistical analyses

To compare general characteristics between DED and non-DED participants, 2-tailed *t* tests were used for continuous variables and χ^2 tests were used for categorical variables. Pearson rank correlation coefficients were calculated to determine the correlations between J-OSDI, DEQS, TFBUT, MBI, and Schirmer test I results. Receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off value of the J-OSDI total score for suspecting DED. The area under the curve (AUC) was computed using the trapezoidal rule. Data are presented as mean ± standard deviation (SD) or proportion (%). Statistical analyses were performed using STATA version 15 (Stata Corp, College Station, TX) and SPSS Statistics v.1.0.0 (IBM Corp, Chicago, IL). $p < 0.05$ was considered significant.

Reliability

The internal consistency of the J-OSDI was assessed using Cronbach's alpha coefficient, with an alpha > 0.70 considered to be acceptable.[23] Test-retest reliability was evaluated by calculating the intraclass correlation coefficient (ICC) values from the first and second entries. An ICC value of ≥ 0.70 was considered acceptable for test-retest reliability.[24]

Validity

Discriminant validity was evaluated by comparing the non-DED and DED groups. For factor validity, confirmatory factor analysis was conducted by an equamax rotation to determine whether the subscales in the J-OSDI clustered together in the same manner as in the original OSDI. Factors with an eigenvalue > 0.90 were retained. Concurrent validity was assessed by calculating the correlations (Pearson coefficients) between the J-OSDI total score or subscale scores and the DEQS or other clinical results, including TFBUT, CFS, MBI, and Schirmer test I values.

Patient and public involvement

No patients were involved in the research design and conception of this research study.

RESULTS

Participant characteristics

Table 1 shows the general characteristics of the study participants. All subjects responded to the questionnaires, completed the examination, and were eligible for the study. Overall, 209 participants were included. The average age was 58.9 ± 15.3 years, and 83.7% of the participants were women. Using the diagnostic criteria put forth by the ADES,[8] 152 and 57 patients were classified as DED (72.7%) and non-DED (27.3%), respectively. The mean BCVA value for both eyes was -0.07 ± 0.02 logMAR. The mean IOP for both eyes was 14.1 ± 2.9 mmHg. Both the J-OSDI total score and the DEQS were significantly higher in the DED group than in the non-DED group, indicating that DED patients showed a greater rate of subjective symptoms. Furthermore, both TFBUT and the MBI were significantly lower in the DED group than in the non-DED group. Neither BCVA, IOP, CFS, nor the Schirmer test I results differed significantly between DED and non-DED participants.

Table 1. Characteristics of study participants.

	non-DED n = 57	**DED** n = 152	**p value**	**Total** n = 209
Age, year ± SD	61.4 ± 15.5	57.9 ± 15.2	0.149	58.9 ± 15.3
Gender, female (%)	48 (84.2)	127 (83.6)	1.000	175 (83.7)
BCVA, logMAR ± SD	-0.1 ± 0.0	-0.1 ± 0.0	0.513	-0.1 ± 0.0
IOP, mmHg ± SD	14.6 ± 2.9	13.8 ± 2.7	0.062	14.0 ± 2.8
Subjective symptoms, yes (%)	5 (8.8)	152 (100)	***< 0.001	157 (75.1)
J-OSDI, 0–100 ± SD	19.4 ± 16.0	37.7 ± 22.2	***< 0.001	32.7 ± 29.7

DEQS, 0–100 ± SD	16.0 ± 14.7	32.7 ± 21.6	***< 0.001	28.1± 21.3
TFBUT, seconds ± SD	2.5 ± 2.4	1.5 ± 0.8	***< 0.001	1.7 ± 1.5
CFS, 0–9 ± SD	2.8 ± 2.5	3.3 ± 2.6	0.192	3.2 ± 2.6
Schirmer I, mm ± SD	7.2 ± 8.2	5.7 ± 6.2	0.162	6.1 ± 6.8
MBI, seconds ± SD	15.1 ± 8.1	10.5 ± 6.3	***< 0.001	11.7 ± 7.1

DED, dry eye disease; BCVA, best-corrected visual acuity; IOP, intraocular pressure; J-OSDI, Japanese version of ocular surface disease index; DEQS, Dry Eye-Related Quality-of-Life Score; TFBUT, tear film breakup time; CFS, corneal fluorescein staining; MBI, maximum blink interval. p values were determined using the Student's t-test (two-tailed) for continuous variables and the chi-square test for categorical variables. ***p < 0.001.

Reliability

We tested the J-OSDI total score and subscale scores for internal consistency and test-retest reliability, and the results are shown in Table 2. For internal consistency, the Cronbach's alpha coefficient was 0.884 for the J-OSDI total score and 0.788, 0.669, and 0.902 for the ocular symptoms, vision-related function, and environmental triggers subscales, respectively. Test-retest reliability was evaluated in 173 participants, with a median (interquartile range, IQR) period of 119 (81–182) days between the test and retest. The ICC values were 0.910, 0.649, 0.817, and 0.859 for the J-OSDI total score, ocular symptoms subscale, vision-related function subscale, and environmental triggers subscale, respectively.

Table 2. Reliability for each subscale

	Number of items	**Cronbach α (n = 209)**	**ICC (n = 173)**
J-OSDI total score	12	0.884	0.910
Ocular symptoms	5	0.788	0.649
Vision-related function	4	0.669	0.817

Environmental triggers	3	0.902	0.859

J-OSDI, Japanese version of the ocular surface disease index; ICC; intraclass correlation coefficient.

Discriminant validity

Table 3 shows the mean values for the J-OSDI total score, each of the subscale scores, and each of the component scores. The mean J-OSDI total score was significantly higher in the DED group than in the non-DED group (DED, 37.7 ± 22.2; non-DED, 19.4 ± 16.0; $p < 0.001$). Additionally, all three subscales were significantly higher in the DED group than in the non-DED group (ocular symptoms: DED, 34.6 ± 21.6; non-DED, 20.9 ± 17.4; $p < 0.001$; vision-related function: DED, 36.5 ± 27.7; non-DED, 20.8 ± 22.0; $p < 0.001$; environmental triggers: DED, 45.2 ± 29.7; non-DED, 15.5 ± 19.8; $p < 0.001$). Eleven of the 12 (92%) component scores were significantly higher in the DED group than in the non-DED group, with only question 2 showing a non-significant difference.

Table 3. J-OSDI score for each question.

Classification, score ± SD, score	**non-DED**	**DED**		**Total**
	n = 57	**n = 152**	**p value**	**n = 209**
J-OSDI total score, 0–100	19.4 ± 16.0	37.7 ± 22.2	***< 0.001	32.7 ± 22.2
Ocular symptoms, 0–100	20.9 ± 17.4	34.6 ± 21.6	***< 0.001	30.9 ± 21.4
1. Eyes that are sensitive to light?	0.8 ± 0.9	1.5 ± 1.3	***< 0.001	1.3 ± 1.3
2. Eyes that feel gritty?	0.8 ± 1.2	1.0 ± 1.0	0.338	1.0 ± 1.1
3. Painful or sore eyes?	0.4 ± 0.7	1.0 ± 1.0	***< 0.001	0.8 ± 1.0
4. Blurred vision?	1.1 ± 1.0	1.6 ± 1.2	**0.002	1.5 ± 1.2
5. Poor vision?	1.1 ± 1.1	1.8 ± 1.3	***< 0.001	1.6 ± 1.3
Vision-related function	20.8 ± 22.0	36.5 ± 27.7	***< 0.001	32.2 ± 27.2

6. Reading?	0.8 ± 1.1	1.6 ± 1.3	***< 0.001	1.4 ± 1.3
7. Driving at night?	0.4 ± 0.6	1.1 ± 1.4	*0.022	0.9 ± 1.3
8. Working with a computer or bank machine (ATM)?	1.1 ± 1.3	1.6 ± 1.4	*0.030	1.5 ± 1.4
9. Watching TV?	0.7 ± 1.0	1.3 ± 1.2	**0.002	1.1 ± 1.1
Environmental triggers	15.5 ± 19.8	45.2 ± 29.7	***< 0.001	37.1 ± 30.4
10. Windy conditions?	0.7 ± 0.9	1.9 ± 1.4	***< 0.001	1.5 ± 1.3
11. Places or areas with low humidity (very dry)?	0.5 ± 0.8	1.6 ± 1.3	***< 0.001	1.3 ± 1.3
12. Areas that are air conditioned?	0.6 ± 0.9	2.0 ± 1.3	***< 0.001	1.6 ± 1.3

DED, Dry eye disease; J-OSDI, Japanese version of ocular surface disease index. p values were determined using the Student's t-test. *p < 0.05, **p < 0.01, and ***p < 0.001.

Factor validity

Factor validity was assessed by confirmatory factor analysis to determine the subscales. As shown in Figure 1, correspondent with the three homogeneous content domains that were identified and constructed, three factors were rotated to an equamax solution. These three factors accounted for 71.9% of the total variance, and each factor comprised sets of items that were interpretable and relevant in content. Factor 1, accounting for 53.0% of the total variance and 23.6% of the common variance, comprised items assessing the frequency of ocular symptoms (5 items). Factor 2, accounting for 11.1% of the total variance and 22.8% of the common variance, comprised items assessing the frequency of vision-related function (4 items). Factor 3, accounting for 7.7% of the total variance and 17.7% of the common variance, comprised items assessing the frequency of environmental triggers (3 items). All factors were in accordance with the subscales in the original version. The factor matrix of each J-OSDI

component can be viewed in Supplemental Table 1. All subscales and the total instrument underwent formal reliability and validity testing.

Concurrent validity

Table 4 shows the correlations between the J-OSDI total score, subscale scores, and other clinical items related to DED diagnosis, including DEQS, TFBUT, CFS, Schirmer test I results, and the MBI. The J-OSDI total score showed a significant strong positive correlation with the DEQS ($\gamma = 0.829$). Among the clinical items related to DED diagnosis, there was a modest but significant negative correlation between the J-OSDI total score and MBI ($\gamma = -0.258$). The subscales were each significantly and positively correlated with the DEQS ($\gamma = 0.786$, 0.702 and 0.650, respectively), while ocular symptoms and environmental triggers were significantly and negatively correlated with the MBI ($\gamma = -0.195$ and -0.370, respectively).

Table 4. Correlation between the J-OSDI total score and other clinical assessments.

	OSDI total score		Ocular symptoms		Vision-related function		Environmental triggers	
Clinical Items	**γ**	**p value**	**γ**	**p value**	**γ**	**p value**	**γ**	**p value**
DEQS	0.829	***< 0.001	0.786	***< 0.001	0.702	***< 0.001	-0.650	***< 0.001
TFBUT	-0.066	0.349	-0.044	0.532	-0.057	0.416	-0.131	0.063
CFS	0.018	0.791	-0.013	0.852	-0.137	*0.049	0.161	*0.022
Schirmer I	-0.090	0.195	-0.013	0.844	-0.071	0.311	-0.129	0.067
MBI	-0.283	***< 0.001	-0.215	**0.002	-0.135	0.053	-0.407	***< 0.001

J-OSDI, Japanese version of the ocular surface disease index; DEQS, Dry Eye-Related Quality-of-Life Score; TFBUT, tear film breakup time; CFS, corneal fluorescein staining; MBI, maximum blink interval. Pearson rank correlation coefficient was used to determine

the correlations between the J-OSDI total score and subscale scores and various clinical assessments. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

J-OSDI severity results and cut-off value for detecting DED

Figure 2A shows the proportion of DED participants in each severity category as determined by the J-OSDI total score. The clinically diagnosed DED patients were divided according to their J-OSDI scores as follows: 22.0% were categorized as normal, 17.2% were categorized as mild DED, 12.9% were categorized as moderate DED, and 47.8% were categorized as severe DED. Figure 2B shows the proportion of patients who were clinically diagnosed with DED in each severity category determined by the J-OSDI total scores. Overall, 47.8% of the patients who were classified as normal by their J-OSDI total score were clinically diagnosed with DED, while 66.7%, 74.0%, and 86.0% of patients classified as mild, moderate, and severe, respectively, were clinically diagnosed with DED. Figure 2C shows the ROC curve of the J-OSDI total score from the non-DED and DED groups, which was used to determine the diagnostic efficacy of the J-OSDI total score. The optimum cut-off value for detecting DED was 36.3 points, with an AUC, sensitivity, and specificity of 0.744, 51.3%, and 87.7%, respectively. Supplemental Table 1 shows the details of the J-OSDI total score sensitivity and specificity analysis.

DISCUSSION

This study developed, and assessed the reliability and validity, of the J-OSDI, which is the Japanese version of OSDI, and determined a cut-off value for detecting DED using the ADES diagnostic criteria of 2016. Our results validate the use of the J-OSDI in Japan and make it possible to compare epidemiological results between Japan and other countries.

In this study, the J-OSDI total score showed both high internal consistency and test-retest reliability (Table 2). The factor analysis confirmed three subscales within the J-OSDI, ocular

symptoms, vision-related function, and environmental triggers, in accordance with the subscales in the original English version (Figure 1).[13] The environmental triggers subscale showed good internal consistency and reliability, whereas the other two subscales, ocular symptoms and vision-related function, showed lower internal consistency and reliability compared to environmental triggers. Vision-related function only showed modest internal consistency. Internal consistency denotes whether all items of an instrument measure the same characteristic.[25] In the sensitivity analysis, deleting question item 7 (i.e., night driving) provided the highest ICC value of 0.74 (Supplemental Table 2). This study was conducted in central Tokyo, where the traffic network was developed, and numerous elderly people were included. Therefore, question item 7 on night driving may have affected the internal consistency. This result indicates that the question items included in OSDI need to be adjusted to the changing demands. The ocular symptoms of DED patients have typically varied because of the known fluctuations in the subjective symptoms of DED,[26, 27] thus violating this assumption of reliability.

The discriminant validity of the J-OSDI was verified from the finding that the J-OSDI total score and subscale scores were significantly higher in the DED group than in the non-DED group (Table 3). Further, the percentage of participants who were clinically diagnosed with DED increased proportionally in each severity category, indicating that the J-OSDI total score can discriminate DED (Figure 2B). Our study also determined that the optimal J-OSDI total score cut-off value for detecting DED according to the ADES criteria was 36.3. One previous study reported an OSDI total score cut-off value of 15.[13] However, the difference between this cut-off value and that of the current study is probably the result of differences in the methods used to clinically diagnose the severity of DED, as the previous study used lissamine green staining, Schirmer test I, and patient perception of ocular symptoms. In contrast, the current study used TFBUT as an essential part of the diagnostic criteria.[7, 8] Supplemental Table 3 shows the sensitivity and specificity of our reported optimal cut-off value and the sensitivity and specificity for the different severity categories: normal (0–12), mild (13–22),

moderate (23–32), and severe (33–100).[13] Our results suggest that it is necessary to re-evaluate the OSDI total score cut-off values for diagnosis and the severity categories to reflect the changes made to the diagnostic criteria for DED.[7, 8, 28-33]

Table 4 shows the correlations between the J-OSDI total score and other clinical tests, including DEQS, TFBUT, CFS, MBI, and Schirmer test I. The J-OSDI total score showed a strong positive correlation with the DEQS. Because the DEQS has been validated in Japan,[12] this result supports the use of the J-OSDI as a valid method of quantifying subjective symptoms. In contrast, the respective correlations between the J-OSDI total score and TFBUT, CFS, and Schirmer I were relatively low. This is consistent with previous studies that reported low correlations and high divergence between subjective symptoms assessed by questionnaires and clinical tools,[2, 24, 30] underscoring the importance of combining knowledge about subjective symptoms and clinical tools in order to effectively evaluate and monitor DED. Our group[20] has proposed the MBI as a simple self-check screening test for DED because it is highly correlated with subjective symptoms compared with other dry eye items (Table 4). Because of the divergence between the subjective and clinical symptoms of DED,[2] it is necessary to perform multilateral evaluations using not only the OSDI total scores but also the subscales and each component. In the present study, we assessed the respective relationship between each subscale and various clinical tools for DED examination and found that the ocular symptoms and environmental trigger subscales were negatively correlated with MBI. We recently reported that the MBI is also significantly associated with TFBUT and CFS.[20] Our previous results and those of this study suggest that the MBI reflects both TFBUT and CFS results, possibly explaining its negative correlation with the ocular symptoms and environmental triggers subscale scores of the J-OSDI.

This study has several limitations. First, it was conducted at a single university hospital in Japan, possibly introducing selection bias into our sample. Second, under the simplified ADES diagnostic criteria, those with low TFBUTs can still be classified as non-DED due to lack of subjective symptoms; thus, our non-DED group showed a low TFBUT. Third, the test-retest

method that we used to confirm reliability introduced recall bias due to the required length of the test-retest period between 2 days to 2 weeks.[34]. Next, we did not account for differences in variables such as socioeconomic status or education level, possibly affecting the responses. Finally, this study was designed to investigate the J-OSDI as a primary evaluation and monitoring method for DED. Thus, rose bengal stain scores, tear osmolality, meibomian gland dysfunction assessments, and corneal sensations were not applied in this study. Despite these limitations, we verified the reliability and validity of the J-OSDI for DED assessment and monitoring in Japan.

In summary, we developed and validated the J-OSDI by assessing its reliability and validity. We report that a J-OSDI score of 36.3 is the optimal cut-off value for suspecting DED under the 2016 ADES criteria. We believe that the J-OSDI will be useful for primary assessment and monitoring of DED in routine clinical practice and in remote diagnosis.

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Author Contributions:

A.MI.: Performance of the research, data collection, data analysis, and writing of the paper; T.I.: Performance of the research, research design, data analysis, and writing of the paper; S.N.: Research design, data analysis; M.N.: Data analysis; M.I.: Research design, data analysis; K.F.: Data collection, data analysis; Y.O.: Data collection, data analysis; N.I.: Data collection, data analysis; A. E.: Data collection, data analysis; H.H.: Data collection, data analysis; H.K.: Performance of the research; A.M.: Research design, writing of the paper; H.K.: Research design, writing of the paper.

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Figure 1. Three subscales of the J-OSDI as determined by factor analysis. The existence of 3 clusters that were used as subscales are shown. These were in accordance with the subscales that are used in the original version of the OSDI: vision-related function (components 1–5), ocular symptoms (components 6–9), and environmental triggers (components 10–12).

Figure 2. Clinical utility of the J-OSDI for evaluating dry eye disease (DED). (a) The proportion of patients in each DED severity category as determined by the J-OSDI total score. **(b)** The proportion of patients who were clinically diagnosed with DED by category of severity according to the J-OSDI total score. **(c)** The receiver operator characteristic (ROC) curve for the diagnosis of DED determined by the Asia Dry Eye Society 2016 criteria using the J-OSDI. The area under the ROC curve (AUC) is 0.744.

Supplementary Information

Supplemental Figure 1: The Japanese version of Ocular Disease Index (J-OSDI). The J-OSDI questionnaire contains 12 questions divided into three subscales.

Supplemental Table 1: Factor matrix of each J-OSDI question. Results of factor analysis of each J-OSDI question. All three subscales were in accordance with the subscales in the original version.

Supplemental Table 2: Sensitivity analysis of the internal consistency of the vision-related function score. The total Cronbach's alpha was calculated by removing one item from a certain domain of the subscale of vision-related function.

Supplemental Table 3: J-OSDI total score sensitivity and specificity analysis results. Full results of the sensitivity and specificity analysis. Our reported cut-off value for suspecting dry eye disease was 36.3.

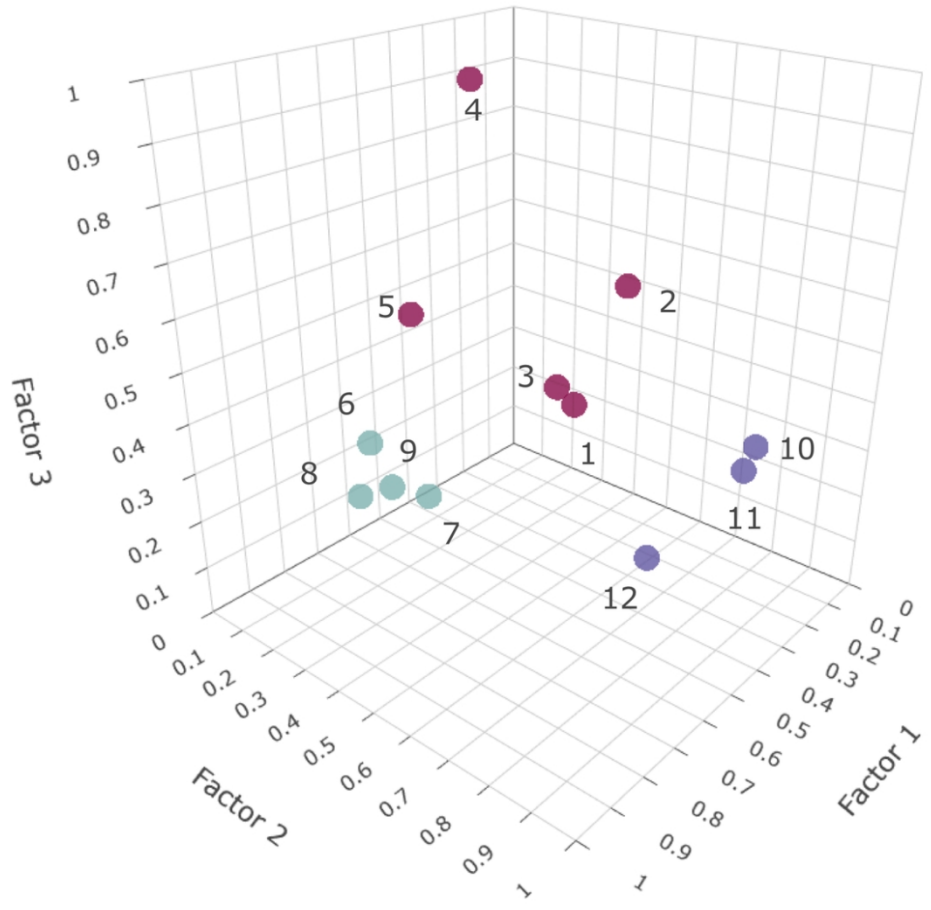

Figure 1

99x97mm (300 x 300 DPI)

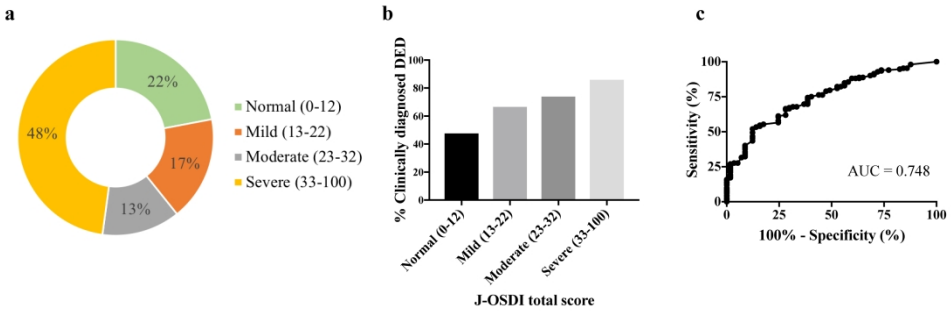
a
22%
17%
13%
48%
Normal (0-12)
Mild (13-22)
Moderate (23-32)
Severe (33-100)
b
% Clinically diagnosed DED
100
80
60
40
20
0
Normal (0-12)
Mild (13-22)
Moderate (23-32)
Severe (33-100)
J-OSDI total score
c
Sensitivity (%)
100
75
50
25
0
AUC = 0.748
0
25
50
75
100
100% - Specificity (%)

Figure 2

ドライアイ質問紙票（J-OSDI）

氏名 ： **ID：**

ご記入日　　年　　月　　日

下記の設問のあてはまる数字に〇をつけてください。

この一週間で下記の症状をどのくらい感じましたか？	いつも	ほとんど	半々	ときどき	全くない
1. まぶしさ	4	3	2	1	0
2. 目がゴロゴロする	4	3	2	1	0
3. 目の痛み	4	3	2	1	0
4. 目のかすみ	4	3	2	1	0
5. 見づらさ	4	3	2	1	0

この一週間で目の症状が原因で、下記の行動はどのくらい制限されましたか？	いつも	ほとんど	半々	ときどき	全くない	該当せず
6. 読書	4	3	2	1	0	—
7. 夜間の運転	4	3	2	1	0	—
8. パソコンや銀行ATMの使用	4	3	2	1	0	—
9. テレビ鑑賞	4	3	2	1	0	—

この一週間で次の環境において、目の不快感を感じましたか？	いつも	ほとんど	半々	ときどき	全くない	該当せず
10. 風が強いとき	4	3	2	1	0	—
11. 湿度が低い(乾燥している)場所	4	3	2	1	0	—
12. エアコンの効いている場所	4	3	2	1	0	—

Supplemental Information

From: Reliability and Validity of the Japanese version of the Ocular Surface Disease Index for Dry Eye Disease

Akie Midorikawa-Inomata RN, MPH, Takenori Inomata MD, PhD, MBA, Soko Nojiri, MPH, Masahiro Nakamura MD, PhD, Masao Iwagami MD, MPH, MSc, PhD, Keiichi Fujimoto MD, Yuichi Okumura MD, Nanami Iwata, Atsuko Eguchi, Hitomi Hasegawa MD, Hikaru Kinouchi, Akira Murakami MD, PhD, and Hiroyuki Kobayashi MD, PhD.

Table S1: Factor matrix of each J-OSDI question

	Factor		
Components	1	2	3
1	0.352	0.474	0.361
2	0.055	0.393	0.504
3	0.256	0.349	0.331
4	0.335	0.167	0.927
5	0.632	0.269	0.573
6	0.706	0.208	0.323
7	0.576	0.246	0.171
8	0.710	0.172	0.198
9	0.719	0.283	0.260
10	0.156	0.815	0.307
11	0.239	0.837	0.295
12	0.441	0.742	0.159

J-OSDI, Japanese version of the Ocular Surface Disease Index.
Extraction Method: Maximum likelihood method; Rotation Method: Equamax with Kaiser normalization

Table S2: Sensitivity analysis of the internal consistency of the vision related function score

	Cronbach α
Vision-related function	0.669
excluded 6. Reading?	0.529
excluded 7. Driving at night?	0.746
excluded 8. Working with a computer or bank machine (ATM)?	0.508
excluded 9. Watching TV?	0.497

Table S3: J-OSDI total score sensitivity and specificity analysis results

J-OSDI total score	Sensitivity (%)	Specificity (%)
> 1.05	98.03	12.28
> 2.2	95.39	14.04
> 2.4	95.39	15.79
> 3.35	94.74	17.54
> 4.9	94.08	22.81
> 5.95	94.08	26.32
> 6.55	92.76	28.07
> 6.95	91.45	29.82
> 7.3	90.79	29.82
> 7.9	90.13	31.58
> 9.15	88.82	35.09
> 10.2	88.82	36.84
> 10.9	88.16	38.6
> 11.95	88.16	40.35
> 13.05	84.87	42.11
> 14.1	84.21	43.86
> 14.8	82.24	43.86
> 15.3	81.58	45.61
> 15.75	81.58	47.37
> 16.3	80.26	47.37
> 17.45	78.95	50.88
> 18.5	78.29	52.63
> 19.1	75.66	54.39
> 19.7	75.66	56.14

> 20.25	74.34	59.65
> 20.65	73.68	61.4
> 21.35	72.37	61.4
> 22.05	71.05	61.4
> 22.35	70.39	61.4
> 22.6	69.08	61.4
> 23.85	69.08	63.16
> 26.15	67.11	66.67
> 27.4	67.11	68.42
> 27.8	66.45	70.18
> 28.65	65.79	70.18
> 29.35	65.13	71.93
> 29.75	61.18	71.93
> 30.3	60.53	75.44
> 30.95	59.87	75.44
> 31.55	57.24	75.44
> 32.55	55.92	75.44
> 33.7	54.61	82.46
> 34.55	53.95	84.21
> 35.2	53.29	84.21
> 35.75	52.63	85.96
> 36.25	51.32	87.72
> 36.95	48.68	87.72
> 38.55	46.05	87.72
> 39.8	44.74	87.72
> 40.85	42.76	87.72
> 42.1	39.47	91.23

> 42.85	38.82	91.23
> 43.5	38.16	91.23
> 44.4	36.84	91.23
> 45.4	34.87	91.23
> 46.5	33.55	91.23
> 47.35	32.89	91.23
> 47.6	32.24	91.23
> 47.8	31.58	91.23
> 48.95	30.92	92.98
> 51.05	27.63	94.74
> 52.2	26.97	98.25
> 52.4	25.66	98.25
> 53.35	25	98.25
> 54.35	23.03	98.25
> 55.4	21.71	98.25
> 56.55	21.05	98.25
> 57.15	20.39	98.25
> 57.9	18.42	98.25
> 58.7	17.11	98.25
> 59.75	16.45	98.25
> 61.45	15.79	100
> 63.05	15.13	100
> 63.75	13.82	100
> 64.25	13.16	100
> 66.05	11.84	100
> 67.7	9.868	100
> 68.35	9.211	100

> 69.65	8.553	100
> 70.65	7.895	100
> 71.85	7.237	100
> 75	6.579	100
> 77.2	5.921	100
> 78.25	4.605	100
> 82.1	3.947	100
> 85.7	2.632	100
> 87.5	1.974	100
> 89.3	1.316	100

J-OSDI, Japanese version of the Ocular Surface Disease Index

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	17
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	9-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A

		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.