Original Article

Ocular surface disease index questionnaire as a sensitive test for primary screening of chronic ocular graft-versus-host disease

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Background: After allogeneic hematopoietic stem cell transplantation (allo-HSCT), patients are followed up by transplant clinicians. Finding an effective primary screening method that transplant clinicians or patients can master is essential in the early referral of suspected chronic ocular graft-versus-host disease (coGVHD) to an ophthalmologist. This study investigated if the ocular surface disease index (OSDI) questionnaire could be used for coGVHD primary screening.

Methods: This case-controlled, cross-sectional study enrolled 161 allo-HSCT patients. All participants completed an OSDI questionnaire and underwent a silt-lamp examination. Bulbar conjunctival injection (BCI) was assessed using torchlight, while tear volume was measured via the Schirmer test (ST). The receiver operating characteristic curve was used to evaluate the sensitivity, specificity, and cutoff values of OSDI, ST, and BCI grading. Performance comparisons of the 3 tests applied in isolation, parallel, and series were made.

Results: There were 84 patients with and 77 patients without coGVHD. Compared to those without coGVHD, patients with coGVHD had significantly higher median values of OSDI, corneal fluorescein staining, conjunctival injection, conjunctival fibrosis, and meibum quality, but lower ST scores (All P values <0.001). The cutoff values for OSDI, ST, and BCI grade in the diagnosis of coGVHD were 19.4 points, 7 mm, and grade 0, respectively. The sensitivity and specificity of the tests based on the cutoff values were, respectively, 89.3% and 89.6% for OSDI, 91.7% and 59.7% for ST, and 78.6% and 70.1% for BCI. The area under the curve (AUC) value of OSDI was significantly higher than that of ST (0.931 *vs.* 0.826; P=0.010) and BCI grade (0.931 *vs.* 0.781; P<0.001). The AUC values of the combinations were lower than that of OSDI alone.

Conclusions: The OSDI questionnaire can be used as a simple screening test for coGVHD as demonstrated by its high sensitivity and specificity in the transplant clinic and patients' self-monitoring. An OSDI greater than 19.4 could be considered an ophthalmology referral criterion.

Keywords: Chronic ocular graft-versus-host disease (coGVHD); screening test; ocular surface disease index (OSDI)

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Introduction

Chronic graft-versus-host disease (cGVHD) is one of the most prevalent and severe complications after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Ocular involvement occurs in 40–60% of patients with cGVHD and compromises visual function and quality of life (1-3). The key features of chronic ocular GVHD (coGVHD) are refractory dry eye and manifold ocular surface damage, which manifest as symptoms such as ocular irritation, pain, redness, photophobia, and blurred vision (4,5). T cell-mediated inflammation and fibrosis are considered the pathogenesis of coGVHD (6,7), but the exact mechanisms are not completely understood.

Early diagnosis and treatment are important to avoiding severe complications and protecting vision. Ocular evaluations after allo-HSCT are critical for monitoring and the timely detection of coGVHD (8). Generally, ophthalmic examination by ophthalmologists is recommended to be performed before and after HSCT. Examination before HSCT is performed to determine existing dry eye disease and establish a baseline. After allo-HSCT, routine ophthalmological screening should start at 3 months and no later than 6 months, with annual rescreening (9,10). However, most patients cannot receive a comprehensive ophthalmic examination or regular ophthalmic follow-up (11). Since the onset of coGVHD is subtle, most patients overlook their ocular symptoms and only visit the ophthalmologist when symptoms become severe. Qiu *et al.* (12) observed that the time interval between the onset of initial ocular discomfort and the first visit to the ophthalmologist was over 6 months in nearly half of the patients examined. Compromised systemic health conditions, ignored subtle ocular symptoms, transportation inconveniences, and financial burdens may contribute to delayed ophthalmic consultation. Moreover, patients after allo-HSCT are prone to infection due to receiving long-term immunosuppressants. The global outbreak of COVID-19 has made this situation worse.

More severe coGVHD and ocular surface damage at baseline have been identified as risk factors for persistent corneal epithelial defects, which entails worse visual outcomes (13). Many transplant patients' access to ophthalmological evaluation, accurate diagnosis, and timely treatment have been restricted due to a limited number of eye doctors with experience in coGVHD and the absence of specialized outpatient clinics restrict. A survey in Germany found that only about half of the post-HSCT patients underwent ocular examinations. The author mentioned that their current healthcare structure was insufficient to treat all patients suffering from coGVHD (14). Simple and available self-testing may be critical in this demanding situation. The ocular surface disease index (OSDI) questionnaire is a simple, rapid, and accessible method that transplant physicians or patients can master. We thus sought to test the accuracy of OSDI in diagnosing coGVHD and to compare OSDI with the Schirmer test (ST) and bulbar conjunctival injection (BCI) assessment. We further aimed to determine the optimal cutoff values of these methods for coGVHD primary screening. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6946/rc).

Methods

Study design and participants

We conducted a prospective study to evaluate the validity and reliability of diagnostic tools for coGVHD. This study was approved by the Ethics Committee of the Zhongshan Ophthalmic Center (No. 2019KYPJ135) and was performed in compliance with the tenets of the Declaration of Helsinki (as revised in 2013). It was registered in the Chinese Clinical Trials Register (No. ChiCTR1900027485). Written informed consent was obtained from all participants.

We first collected medical history data. All patients aged over 14 years who underwent allo-HSCT that visited the cornea clinic of Zhongshan Ophthalmic Center and the hematology clinic of Nanfang Hospital from October 2019 to January 2021 were enrolled. Patients who were unable to cooperate with the examination, had an active ocular infection, had a history of ocular surgery or trauma within the past 3 months, or who were allergic to the fluorescein solutions were excluded.

For each patient, BCI and slit lamp examinations were performed by 2 experienced ophthalmologists. A third ophthalmologist was consulted when a disagreement occurred. CoGVHD was diagnosed using the International Chronic Ocular GVHD Consensus Group (ICCGVHD) diagnostic criteria, which includes 4 subjective and objective variables: OSDI, ST without anesthesia, corneal staining, and conjunctival injection. Consideration was also given to the presence or the absence of systemic GVHD (15). The National Institutes of Health (NIH) eye score was also used for the assessment of coGVHD (16).

Ocular examination

Assessment of ocular symptoms

Subjective ocular discomfort was evaluated using the OSDI questionnaire, which consisted of 12 questions associated with symptoms that presented over the previous week. The scale ranged from 0 to 100, with higher scores representing more severe symptoms and effect on vision function (17).

Evaluation of tear quantity

ST without anesthesia was performed to evaluate tear secretion. Standardized filter paper strips were placed in the lateral canthus away from the cornea and were left in place for 5 minutes with the eyes closed. Wetting length of the filter paper was recorded in millimeters (18).

Evaluation of conjunctival injection

BCI was examined using a torchlight and silt-lamp examination. The grading scale for conjunctival injection ranged from 0 to 2 points: grade 0, no injection; grade 1, mild or moderate injection; and grade 2, severe injection (15).

Corneal staining examination

Corneal fluorescein staining (CFS) was performed using a slit lamp under blue-light illumination. After administration of 2 μL of 1% sterile fluorescein in the conjunctival sac, patients were instructed to blink several times to mix the fluorescein dye into the tear film, which was followed by an examination of the cornea 3 minutes after fluorescein staining. The cornea was divided into 5 zones based on the National Eye Institute grading scheme: central, superior, temporal, nasal, and inferior. Punctate staining was recorded for each zone using a standardized grading system of 0 to 3. The stain was scored on a scale of 0–15 for each eye (19).

Other ocular surface assessments

With reference to eyelid margin assessment, lid margin irregularity and vascular engorgement were scored as either 0 (absence) or 1 (presence). Meibum quality from the upper eyelid was scored as follows: 0, clear fluid; 1, cloudy fluid; 2, cloudy particulate fluid; and 3, inspissated, like toothpaste. The worst quality was recorded (20). Conjunctival fibrosis in both eyes' upper and lower palpebral conjunctiva was evaluated as described in the literature (21). Values for the upper and lower lids were used for the analysis.

Statistical analysis

A sample of 80 from the positive group and 80 from the negative group was required to achieve 80% power to detect a difference of 0.10 between a diagnostic test with an acceptable area under the receiver operating characteristic (ROC) curve (AUC) of 0.80 and an expected diagnostic test with an AUC of 0.90 or above using a 2-sided z test at a significance level of 0.05. The correlation between the 2 diagnostic tests was assumed to be 0.50 for the positive and 0.50 for the negative groups. The sample size was calculated using PASS 16.0 software (NCSS LLC, Kaysville, UT, USA).

SPSS software 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc statistical software 19.1 (MedCalc Software, Ostend, Belgium) were used to perform statistical analyses. The eye with a higher score based on the ICCGVHD severity score was included in the analyses. The right eye was analyzed when both eyes were parallel. Normally distributed data were analyzed using a Student's t-test, while the Mann-Whitney U test was used to analyze nonnormally distributed data. Pearson chi-squared or continuity correction tests were used to analyze qualitative variables. Correlations were analyzed using Spearman rank correlation. ROC curves were used to evaluate the sensitivity and specificity of different screening tests and to establish the best cutoff values for OSDI, ST, and BCI for the diagnosis of coGVHD. Comparisons of AUCs were conducted using the DeLong test. Further, the screening tests were combined using different approaches to assess whether the AUC of multiple combinations was superior to a single test. A 2-sided significance level of 0.05 or less was the criterion for all comparisons.

Missing data

The proportion of missing data was low: 3 patients (1.9%) did not know their history of chemotherapy, and 3 patients (1.9%) did not know their history of radiotherapy. No data were missing for ocular surface parameters.

Results

Demographic characteristics

We approached 172 patients who had received allo-HSCT, Of these, 9 declined participation, 2 were excluded from the analysis, 1 due to early post–silicon oil tamponade period and 1 due to viral keratitis (*Figure 1*). A total of 161 patients (96 males and 65 females) with a mean age of 35.2±10.8 years (range, 16–64 years) were included in the study. Among these patients, 84 were diagnosed with coGVHD and 77 had no coGVHD. The mean time from

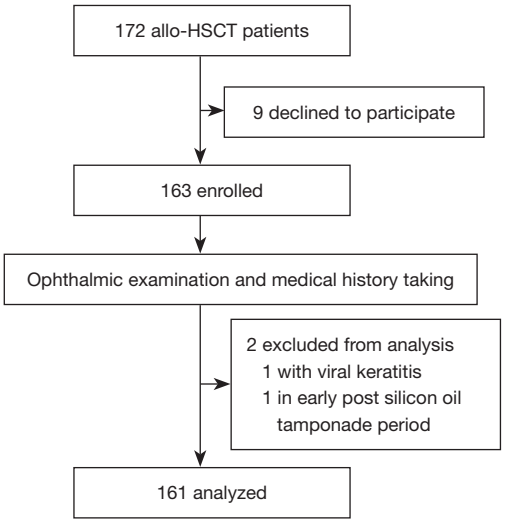

Figure 1 Flowchart of patient selection. allo-HSCT, allogeneic hematopoietic stem cell transplantation.

HSCT to enrollment was 23.8±28.8 months. The post-HSCT time in patients with and without coGVHD was 34.0±34.9 months and 12.6±13.2 months, respectively. Acute myeloid leukemia (AML; n=77, 47.8%) and acute lymphocytic leukemia (ALL; n=45, 28.0%) were the 2 most common primary hematologic diagnoses. Additionally, 150 patients (93.2%) had received combined chemotherapy and 37 patients (23.0%) had received radiotherapy. Peripheral blood was the most common graft source in coGVHD patients (n=44, 52.4%), while bone marrow was the main source of graft in patients without coGVHD (n=38, 49.4%). Most of the HSC donors were related (n=151, 93.8%). A majority of patients with coGVHD received human leukocyte antigen (HLA)-matched HSCTs (62/22, 73.8%). However, a considerable proportion of patients without coGVHD received HLA-unmatched HSCTs (41/36, 53.2%). In all patients after HSCT, the dominant systemic organ involvements of cGVHD were the skin (62.7%), eyes (52.2%), mouth (46.6%), liver (32.9%), gastrointestinal tract (24.2%), and lungs (14.3%; *Table 1*).

Ocular surface evaluation

The coGVHD group exhibited significantly higher OSDI (43.3±21.7 *vs.* 8.5±13.4), CFS (9.6±4.5 *vs.* 0.26±0.78), BCI (1.1±0.71 *vs.* 0.31±0.49), conjunctival fibrosis (2.0±1.6 *vs.* 0.78±1.1), and meibum quality scores (2.0±1.0 *vs.* 1.2±1.3) and lower ST scores (3.3±3.1 *vs.* 10.1±7.2) than did the non-coGVHD group (all P values <0.001). Lid margin hyperemia (88.1% *vs.* 53.2%; P<0.001) and irregular lid margin (39.3% *vs.* 20.8%; P=0.011) were more prevalent in the coGVHD group than in the non-coGVHD group. The NIH eye score was significantly higher in patients with coGVHD (1.9±0.72 *vs.* 0.17±0.38; P<0.001). There was no significant difference in lid margin keratosis between the 2 groups (38.1% *vs.* 24.7%; P=0.067; *Table 2*).

Correlation between OSDI, ST, BCI, and other ocular surface parameters

CFS score was moderately correlated with OSDI (P<0.001; Rs =0.71), ST (P<0.001; Rs =−0.58), and BCI (P<0.001; Rs =0.50). Moreover, a weak but statistically significant correlation was observed between OSDI and ST (P<0.001; Rs =−0.42), BCI (P<0.001; Rs =0.43), and conjunctival fibrosis (P<0.001; Rs =0.47). ST exhibited a weak negative correlation with BCI (P<0.001; Rs =−0.39), while BCI exhibited a weak positive correlation with conjunctival fibrosis (P<0.001; Rs =0.34) and lid margin hyperemia (P<0.001; Rs =0.30). No other significant correlations were observed (*Table 3*).

ROC curve analysis and the combination of screening tests for coGVHD

Performance comparisons of the 3 screening tests applied in isolation, parallel, and in series are listed in *Table 4*. When the cutoff value for OSDI was set at >19.4 points, the AUC, sensitivity, and specificity were 0.931, 89.3%, and 89.6%, respectively. When the cutoff value for ST was set at ≤7 mm, the AUC, sensitivity, and specificity were 0.826, 91.7%, and 59.7%, respectively. When the cutoff value for BCI in the diagnosis of coGVHD was set at >0 grade, the AUC, sensitivity, and specificity were 0.781, 78.6%, and 70.1%, respectively. A comparison of AUCs in ROC curve analyses based on the DeLong algorithm revealed that the AUC of OSDI was significantly higher than that of ST (0.931 *vs.* 0.826; P=0.010) and BCI (0.931 *vs.* 0.781; P<0.001). However, no statistically significant difference in AUCs was observed between ST and BCI (0.826 *vs.* 0.781; P=0.3; *Figure 2*).

The combination of OSDI with BCI, OSDI with ST, and ST with BCI in which the patient was referred after meeting either criterion yielded high sensitivities (98.8%, 97.6%, and 96.4%, respectively) but low specificities (64.9%, 49.4%, and 41.6%, respectively). Among the combinations in which the patient was referred after

Table 1 Demographic and transplant characteristics

	All (n=161)	coGVHD (n=84)	non-coGVHD (n=77)
Age, years (Mean ± SD)	35.2±10.8	34.4±9.4	36.0±12.0
Male/Female	96/65	52/32	44/33
Post HSCT, months			
Median (IQR)	14 (7.0–31.0)	24 (11.3–47.5)	9 (4.5–14.5)
Mean ± SD	23.8±28.8	34.0±34.9	12.6±13.2
Chemotherapy, n (%)			
Yes	150 (93.2)	78 (92.9)	72 (93.5)
No	8 (5.0)	5 (6.0)	3 (3.9)
Unknown	3 (1.9)	1 (1.2)	2 (2.6)
Radiotherapy, n (%)			
Yes	37 (23.0)	20 (23.8)	17 (22.1)
No	121 (75.2)	63 (75.0)	58 (75.3)
Unknown	3 (1.9)	1 (1.2)	2 (2.6)
Type of HSCT, n (%)			
BM	67 (41.6)	29 (34.5)	38 (49.4)
PBSC	64 (39.8)	44 (52.4)	20 (26.0)
BM + PBSC	30 (18.6)	11 (13.1)	19 (24.7)
Donor relationship, n (%)			
Related	151 (93.8)	79 (94.0)	72 (93.5)
Unrelated	10 (6.2)	5 (6.0)	5 (6.5)
HLA match, n (%)			
Matched	98 (60.9)	62 (73.8)	36 (46.8)
Unmatched	63 (39.1)	22 (26.2)	41 (53.2)
Underlying disease, n (%)			
AML	77 (47.8)	32 (38.1)	45 (58.4)
ALL	45 (28.0)	28 (33.3)	17 (22.1)
CML	8 (5.0)	7 (8.3)	1 (1.3)
MDS	19 (11.8)	9 (10.7)	10 (13.0)
Others	12 (7.5)	8 (9.5)	4 (5.2)
cGVHD organ involvement, n (%)			
Skin	101 (62.7)	64 (76.2)	37 (48.1)
Mouth	75 (46.6)	53 (63.1)	22 (28.6)
Liver	53 (32.9)	32 (38.1)	21 (27.3)
GI tract	39 (24.2)	19 (22.6)	20 (26.0)
Lung	23 (14.3)	20 (23.8)	3 (3.9)

coGVHD, chronic ocular graft-versus-host disease; SD, standard deviation; HSCT, hematopoietic stem cell transplantation; BM, bone marrow; PBSC, peripheral blood stem cell; HLA, human leukocyte antigen; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; GI, gastrointestinal; cGVHD, chronic graft-versus-host disease.

Table 2 Clinical parameters in patients with or without coGVHD

	coGVHD (n=84)	non-coGVHD (n=77)	P value
OSDI score			<0.001
Median (IQR)	41.7 (27.5–56.9)	3.6 (0.0–10.7)	
Mean ± SD	43.3±21.7	8.5±13.4	
Schirmer test, mm			<0.001
Median (IQR)	3.0 (1.0–4.0)	9.0 (4.0–13.0)	
Mean ± SD	3.3±3.1	10.1±7.2	
Bulbar conjunctival injection, grade			<0.001
Median (IQR)	1.0 (1.0–2.0)	0.0 (0.0–1.0)	
Mean ± SD	1.1±0.71	0.31±0.49	
Corneal fluorescein staining, points			<0.001
Median (IQR)	8.0 (5.0–11.8)	0.0 (0.0–0.0)	
Mean ± SD	9.6±4.5	0.26±0.78	
Conjunctival fibrosis, grade			<0.001
Median (IQR)	2.0 (1.0–3.0)	0.0 (0.0–1.0)	
Mean ± SD	2.0±1.6	0.78±1.1	
Irregular margin, n (%)	33 (39.3)	16 (20.8)	0.011[a]
Lid margin keratosis, n (%)	32 (38.1)	19 (24.7)	0.067[a]
Lid margin hyperemia, n (%)	74 (88.1)	41 (53.2)	<0.001[a]
Meibum quality, grade			<0.001
Median (IQR)	2.0 (1.0–3.0)	1.0 (0.0–3.0)	
Mean ± SD	2.0±1.0	1.2±1.3	
NIH eye score			<0.001
Median (IQR)	2.0 (1.0–2.0)	0.0 (0.0–0.0)	
Mean ± SD	1.9±0.72	0.17±0.38	

[a], Pearson chi-squared test. Mann-Whitney U test was used in the table except additional mentioned. coGVHD, chronic ocular graft-versus-host disease; OSDI, Ocular Surface Disease Index; NIH, National Institutes of Health.

meeting both criteria, OSDI and ST had a higher AUC value with high specificity (100%) and sensitivity (83.3%). However, there was no significant difference in AUC value between the combination of OSDI and ST and OSDI alone (0.917 *vs.* 0.931; P=0.565).

Discussion

After allo-HSCT, patients are advised to undergo a detailed eye examination by ophthalmologists during long-term follow-up. In practice, ocular assessments are insufficient. Initial screening by transplant physicians or patients themselves may be a complementary method in the early detection of coGVHD. However, there is limited information about the accuracy of OSDI for distinguishing coGVHD in patients following allo-HSCT.

The OSDI questionnaire is widely used for dry eye disease self-screening and can be implemented to follow symptoms in large populations with dry eye (22). Dry eye is also the most common clinical manifestation of coGVHD. Symptom assessment is essential for the diagnosis of coGVHD (15,23). Recently, a set of ICCGVHD diagnostic

Table 3 Correlations between OSDI, ST, BCI and other clinical parameters

	ST	CFS	BCI	CF	IM	LMK	LMH	MQ
OSDI								
Rs	−0.42	0.71	0.43	0.47	0.16	0.07	0.29	0.24
P	<0.001	<0.001	<0.001	<0.001	0.042	0.377	<0.001	0.002
ST								
Rs	–	−0.58	−0.39	−0.28	−0.14	−0.14	−0.24	−0.22
P	–	<0.001	<0.001	<0.001	0.086	0.086	0.002	0.006
BCI								
Rs	−0.39	0.50	–	0.34	0.05	0.09	0.30	0.09
P	<0.001	<0.001	–	<0.001	0.502	0.260	<0.001	0.268

Spearman's correlation test was used in the table. OSDI, ocular surface disease index; ST, Schirmer test; BCI, Bulbar conjunctival injection; CFS, corneal fluorescein staining; CF, conjunctival fibrosis; IM, irregular margin; LMK, lid margin keratosis; LMH, lid margin hyperemia; MQ, meibum quality.

Table 4 Sensitivity and specificity of the screening tests in isolation, parallel, or series

Referral criteria	Sensitivity (%)	Specificity (%)	AUC	95% CI
OSDI >19.4	89.3	89.6	0.931	0.880–0.965
ST ≤7	91.7	59.7	0.826[b]	0.758–0.881
BCI >0	78.6	70.1	0.781	0.709–0.842
OSDI >19.4 or ST ≤7[†]	97.6	49.4	0.735	0.660–0.801
OSDI >19.4 and ST ≤7[‡]	83.3	100.0	0.917[a]	0.863–0.954
OSDI >19.4 or BCI >0[†]	98.8	64.9	0.819	0.750–0.875
OSDI >19.4 and BCI >0[‡]	69.1	94.8	0.819	0.751–0.875
ST ≤7 or BCI >0[†]	96.4	41.6	0.690	0.612–0.760
ST ≤7 and BCI >0[‡]	73.8	88.3	0.811	0.741–0.868

[†], combination of two tests: the patient should be referred after meeting either criteria; [‡], combination of two tests: the patient should be referred after meeting both criteria; [a], the AUC of OSDI >19.4 and ST ≤7 *vs.* OSDI >19.4, P value was 0.565; [b], the AUC of ST ≤7 *vs.* OSDI >19.4 and ST ≤7, P value was 0.006. OSDI, ocular surface disease index; ST, Schirmer test; BCI, bulbar conjunctival injection; AUC, area under curve.

criteria for coGVHD was proposed as a more detailed disease assessment. This set of criteria, which includes OSDI, has shown good accuracy and reproducibility (24,25). In this study, we identified a novel rapid screening test for coGVHD based on the ICCGVHD diagnostic criteria by evaluating the diagnostic accuracy of OSDI. Our resulting correlation analyses revealed that OSDI was significantly associated with other ocular parameters, suggesting that it can effectively reflect ocular surface damage and has merit as a potential screening indicator for coGVHD.

Our results revealed that OSDI had the highest diagnostic sensitivity and specificity when a single test to detect coGVHD was used. Only one study has reported the diagnostic value of OSDI in coGVHD patients. However, the study compared coGVHD patients with healthy controls but not the posttransplant patients without coGVHD (26). In 2015, Curtis (27), a hematologist, revealed NIH eye score and ST to be independent predictors in a predictive model for the diagnosis of coGVHD according to NIH consensus criteria. The NIH eye score from 0–3 is based

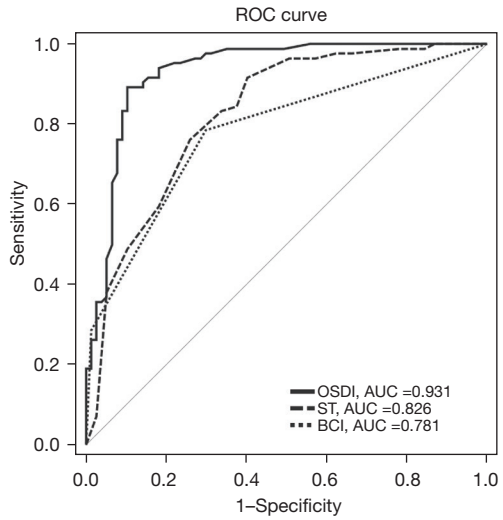

Figure 2 The receiver operating characteristic curves delineating the sensitivity and specificity of OSDI, ST, and BCI. Note the significant sensitivity and specificity of OSDI by receiver operating characteristic graph analysis. OSDI, ocular surface disease index; ST, Schirmer test; BCI, bulbar conjunctival injection.

on dry eye symptoms and the need for eye drops (16). Intriguingly, the need for eye drops usually indicates that the patient has already developed eye problems. A previous study recommended that the NIH eye score could be used as a sensitive measure of eye symptom changes in assessing the treatment of coGVHD (28). OSDI provides more detailed information than does the NIH eye score because OSDI assesses ocular symptoms, impact on the patient's life, and environmental sensitivity. In this study, the cutoff threshold of OSDI was >19.4 in screening coGVHD. A well-designed prospective cohort study is warranted to evaluate whether OSDI can be used as a predictor of coGVHD.

ST is a standard method for evaluating tear secretion (29). Nevertheless, it is not recommended for diagnosing coGVHD because of its poor reproducibility (8). Ogawa *et al.* also reported that ST had a false-positive rate of 19.4% and a false-negative rate of 36.4% in diagnosing coGVHD (30). In our study, ST exhibited superior sensitivity (91.7%) but relatively low specificity (59.7%). Therefore, despite being easy and rapid to perform, ST alone is not recommended for screening.

BCI is a sign of ocular inflammation and is generally associated with eye discomfort and ocular surface impairment. The BCI scoring is easy to implement by a nonophthalmologist using a torchlight. Anderson *et al.* (31) compared the diagnostic accuracy in assessing red eye between an ophthalmologist using a slit lamp biomicroscope and another ophthalmologist using a direct ophthalmoscope. The results showed that the lack of a slit-lamp biomicroscope did not prejudice the initial diagnosis of red eye. In our study, the sensitivity (78.6%) and specificity (70.1%) of BCI were moderate, suggesting the use of the BCI assessment alone is insufficient for screening.

To further improve screening potency, combinations of the above-mentioned parameters were further analyzed. The combination of OSDI and BCI in parallel, meeting the referral criteria in either test, exhibited the highest sensitivity of 98.8% and a lower specificity of 64.9%. However, the ROC curve analysis indicated that the combined use of these parameters did not yield better diagnostic performance than did the OSDI alone. Consequently, ocular symptom assessment using the OSDI questionnaire is recommended for coGVHD initial screening in patients after allo-HSCT. It is easy to perform and suitable for transplant physicians or self-testing. The use of OSDI may address the delayed eye evaluation by expanding the screened population to any transplant recipients. When the OSDI score is over 19.4, referral to an ophthalmologist for further evaluation is warranted.

Our results further suggested an association between HLA-matched donor and coGVHD. Similar results have been reported in previous studies (27,32). Post-HSCT cyclophosphamide is now the most widely used GVHD-prevention strategy in haploidentical transplantation. However, it is less commonly used in patients with matched donors (33).

The present study has some limitations. First, it was a single-center study with a relatively small sample size. Second, although the OSDI questionnaire showed a relatively high AUC value, there is a possibility of missed diagnosis or misdiagnosis. A series of ocular surface diseases, such as infection and allergy, can also increase the OSDI score. Additionally, symptoms and signs were not consistent in some patients. Patients without obvious symptoms might have been ignored. Future prospective multicenter studies are required to verify the efficiency and utility in real-world transplant clinical practice. Third, potential selection bias may exist. Since the patients were referred from transplant centers, the ocular data before HSCT were unavailable although most patients denied a prior history of

dry eye or symptoms. Nonetheless, an interesting study by Giannaccare *et al.* (34) showed that whether or not patients received a pretransplant ophthalmological examination had little impact on the diagnostic accuracy of ICCGVHD criteria. Moreover, we did not compare the coGVHD group to a control group with dry eye.

In conclusion, OSDI, with high sensitivity and specificity, could be an efficient tool in the primary screening of patients with coGVHD following allo-HSCT. It can be used for self-assessment to reduce the risk of infection in immunosuppressed patients during the COVID-19 pandemic. Rational and effective initial screening and referral may be beneficial for addressing the dearth of specialists and the uneven distribution of medical resources. Our study demonstrates that those with an OSDI score over 19.4 are at high risk of developing coGVHD; therefore, a further ophthalmological examination should be performed by an experienced specialist. Initial screening by OSDI might be a useful addition to the comprehensive ophthalmological screening evaluation and beneficial for the early detection of coGVHD.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6946/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6946/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Zhongshan Ophthalmic Center (No. 2019KYPJ135), and informed consent was acquired from all individual participants.

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