• Clinical Research •

Topographic tear film trend and new parameters for non-invasive break up time test

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Abstract

• **AIM:** To evaluate the quantitative and qualitative results of the noninvasive tear film break-up time (NI-BUT) test and investigate the predictive ability of the new NI-BUT parameter in discriminating between normal Ocular Surface Disease Index (OSDI; scores ≤12) and abnormal OSDI (scores ≥13).

• **METHODS:** A total of 341 eyes of 341 volunteers who applied for routine eye outpatient control were included in the prospective study. All participants' noninvasive first tear film break-up time (NIF-BUT), noninvasive average tear film break-up time (NIAvg-BUT) and average value of the first three break-up time (A3F-BUT) were analyzed. A3F-BUT, the new NI-BUT parameter, is calculated by adding the NIF-BUT value to the 2nd break-up time value that has a difference of at most 1 second from the NIF-BUT value and to the 3rd break-up time and then dividing the respective sum by 3. Receiver operating characteristic (ROC) curve and forward logistic regression analyses were performed to determine the parameter that had the best predictive ability between the OSDI groups.

• **RESULTS:** The NI-BUT values of 255 eyes of 255 volunteers included in the study were analyzed statistically. The mean NIF-BUT, NIAvg-BUT, and A3F-BUT values were calculated as 5.3±3.0, 8±3.1, and 5.8±3.0 seconds, respectively. All three parameters were found to be significantly lower in the abnormal OSDI group (P=0.014, 0.034, and 0.011, respectively). The area under the curve (AUC) of the A3F-BUT to predict abnormal OSDI was AUC=0.625 (0.529-0.720), P=0.011 and NIF-BUT was AUC=0.599 (0.502-0.696), P=0.043. The A3F-BUT parameter and NIF-BUT parameters were found to be significantly efficient in discriminating abnormal OSDI.

• **CONCLUSION:** The new parameter for the NI-BUT test has more predictive ability in the discrimination of OSDI groups.

• **KEYWORDS:** noninvasive break-up time; Ocular Surface Disease Index; tear film; topographic break-up time test

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INTRODUCTION

The tear film has a thickness of only approximately 3 microns[1] yet it assumes many critical functions. To give a few examples, in terms of optics, it serves as the first entry point of light into the eye, and the light is refracted here first[2]; in terms of mechanics, it lubricates the cornea, conjunctiva, and other ocular structures and enables them to perform sliding motion[3]; in terms of statics, it acts as a barrier between the external environment and the ocular surface epithelium when the eye is open[2,4]; and from an antimicrobial and immunomodulatory point of view, it is an extremely important structure for the eye and vision with proteins, antimicrobial peptides, and immunoglobulins in its content[3]. Therefore, the continuity and stability of the tear film is a crucial order for its abovementioned functions to be carried out[2]. Together with the synchronous functioning of other static and dynamic structures accompanying the complex movements of the eyelids, the tear film covers the ocular surface in its entirety and quite stably for a certain period of time[2]. This stable nature of the tear film and its duration of stability differ between living species. It may last up to several minutes in some species but usually less than 30s in an unblinking eye in humans[2]. It is an expected situation that all individuals will eventually experience a break in the tear film if not blinked long enough and thereby that the stability of the tear film is disrupted. Untimely or premature breaks and destabilizations in the tear film may cause deterioration in the aforementioned functions of the tear film and result in dry eye conditions in the clinical sense[2]. There is no controversy

regarding the importance of tear film stability[2,5-8], yet there is still controversy regarding the ideal test that can be used to diagnose a deteriorated or destabilized tear film[2,5-8]. Among the tests used to diagnose tear film stability, the tear break-up time (TBUT) test is the most frequently used test in clinical practice[2,9]. There are two common versions of the TBUT test.

Fluorescein Tear Break-up Time Test The first version of the TBUT test is the fluorescein tear break-up time (FBUT) test, which is commonly referred to as the traditional method of tear film testing in the literature and has been used in ophthalmology practice for almost half a century[2,9-10]. It can be performed anywhere where there is a slit lamp and fluorescein. This method measures the time interval in seconds between the scattering of fluorescein-impregnated strips or direct fluorescein drops on the ocular surface and the emergence of the first dark spot after the last blink under the cobalt blue light of the slit lamp. The emergence of the first dark spot in a time interval of less than 10s is considered impaired tear film stability[9]. The FBUT test is an easily performed and inexpensive procedure, yet it has some drawbacks. Among these drawbacks are that it has a nonstandard method of application (fluorescein strip or micropipette), and those different amounts of fluorescein can be used; it involves a wide range of normality. The results it generates can be inconsistent with subjective symptoms, it is non-reproducible[10] and coronavirus and adenoviral infections, which is a reality of today, can be transmitted through tears and ocular surfaces[11].

Non-Invasive Tear Break-up Time Test The second version of the TBUT test is the noninvasive tear break-up time (NI-BUT) test, which has been developed based on advancements in computer and software systems and is performed with devices integrated into corneal topographic instruments or specialized only for this test[2,10,12-16]. Numerous studies have been conducted on the NI-BUT test, and it has recently become very popular among ophthalmologists dealing with the ocular surface[7,10,13-16]. The noncontact and noninvasive, dye-free, objective, and documentable features of the devices used in the NI-BUT test are perceived as the advantages of the test from the point of view of both the physician and the patient. On the other hand, its high cost and lack of a standard cutoff value between devices used in the NI-BUT test because different measurement parameters are used and the devices are specific to different software are perceived as disadvantages[2,7,10,13-16]. Given its abovementioned advantages and disadvantages, improving the NI-BUT test remains a hot topic among ocular surface researchers.

In this context, this study focused on the results of the NI-BUT test in 255 eyes, the differences between the qualitative and quantitative values in those with and without dry eye based on the OSDI score, and the results associated with the new NI-BUT parameters developed by the authors of this study to render this test more sensitive. To the best of our knowledge, this study was conducted with the largest study group compared to the study groups of other NI-BUT studies available in the literature[6,12-14] and is the first study conducted on the new NI-BUT parameters investigated within the scope of this study.

SUBJECTS AND METHODS

Ethical Approval This study was conducted in accordance with the principles set forth in the Declaration of Helsinki. The study protocol was reviewed and approved by Bioethics Committee of the Medical University of Harran (No. HRU/21.21.24). Additionally, approval of the Provincial Health Directorate and written informed consent from all study participants were obtained.

Participants A total of 341 eyes of 341 volunteers who applied for routine eye outpatient control were included in the prospective study. To avoid disrupting the routine tear film pattern of the volunteers, NI-BUT tests were performed first. Only right eye of volunteers was examined. All study participants were given detailed information about the procedure to be used to examine the eye beforehand and the rules to be followed during the performance of the procedure. Accordingly, the volunteers were asked to blink twice when instructed to do so after placing their chin on the topography device and then keep their eyes open for as long as possible. Twenty-four volunteers were excluded from the study since they could not follow the test instructions as desired. Volunteers who underwent the NI-BUT test underwent detailed ophthalmic examinations, including slit lamp examination, by an ophthalmologist, and their medical histories were recorded. Volunteers who were determined to have lid, cornea, conjunctival or punctal deformities, concretions, keratitis, conjunctivitis, or blepharitis in the ophthalmic examination as well as volunteers who were determined to have been taking medication for these diseases were excluded from the study. Based on medical history taking, volunteers who were determined to have been diagnosed with a systemic disease such as Sjögren's syndrome, volunteers who were determined to have a history of cutaneous disease such as contact dermatitis, ocular or refractive surgery, volunteers who were determined to have been using contact lenses, and volunteers who were determined to have been diagnosed with glaucoma or have been using eye drops for glaucoma were also excluded from the study.

Volunteers who were determined to have been diagnosed with dry eye were not excluded from the study, with the exception of patients who were determined to have previously used medications for dry eye, such as long-acting cyclosporine or steroids. For the patients who were determined to have been

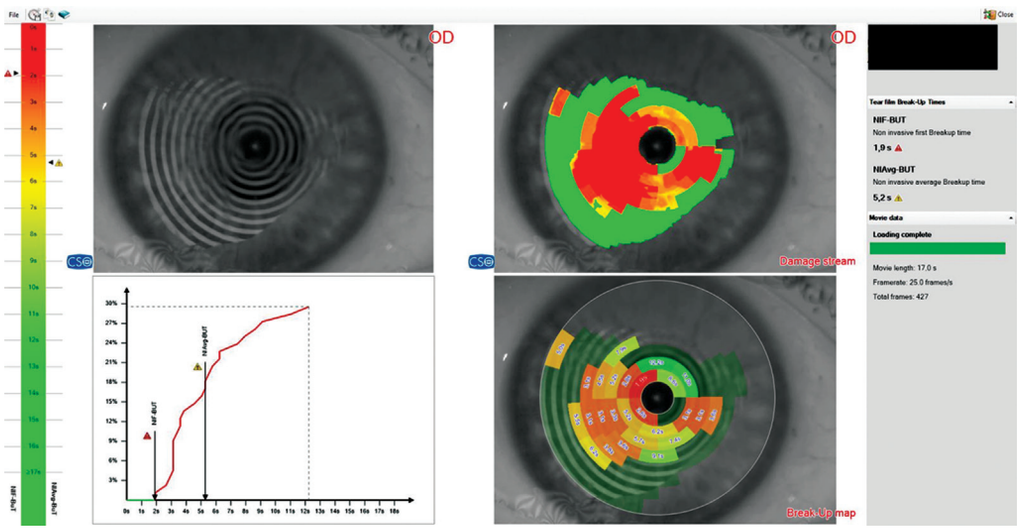

Figure 1 Non-invasive break-up time test (NI-BUT) report of the participant: non-invasive first break-up time value (NIF-BUT) was measured as 1.9s, average non-invasive tear film break-up time (NIAvg-BUT) value was measured as 5.2s and A3F-BUT value was measured as 2.4s. The first breakup was detected in the superotemporal and central localization.

using artificial tears for dry eye, only those who used artificial tears no later than 24h before the procedure were included in the study. Consequently, the NI-BUT values of 255 eyes of 255 volunteers included in the study were analyzed statistically.

Ocular Surface Disease Index Questionnaire All volunteers included in the study were administered the Ocular Surface Disease Index (OSDI) Questionnaire. Volunteers who were found to have an OSDI score of equal to or less than 12 were deemed to have a normal OSDI score, whereas the volunteers who were found to have an OSDI score of more than 12 were deemed to have an abnormal OSDI score, and the respective statistical analyses were performed thereafter.

Non-Invasive Break-up Time Test Device NI-BUT tests were performed using the Sirius^{TM} corneal topography device (Costruzione Strumenti Oftalmici; CSO, S.r.l, Italy). Assisted by the videokeratoscope and the software specific to the device, the corneal topography device detects tear film stabilization and breakup based on the images that it obtains from the ocular surface at a rate of 25 film frames per second and determines the noninvasive first tear film break-up time (NIF-BUT) and average noninvasive tear film break-up time (NIAvg-BUT) values in terms of seconds. Additionally, the visual results generated by the device enable researchers to analyze breakup both quantitatively and qualitatively[15-16].

Parameters NIF-BUT and NIAvg-BUT generated automatically by the device; Average of the first three tear film break-up times (A3F-BUT) is calculated by adding the NIF-BUT value to the 2nd break-up time value that has a difference of at most 1 second with the NIF-BUT value and to the 3rd break-up time and then dividing the respective sum by 3. For example, in Figure 1, the NIF-BUT value and 2nd and 3rd break-up times were 1.9s, 2.6s, and 2.8s, respectively. The A3F-BUT value was calculated to be 2.4s. The reasoning of the authors of this study in developing this parameter is that it is possible that a patient or device-induced artifact and/or the result of an incorrect analysis cause the first breakup. Given that, the finding of a 2nd break-up time value that is close to the NIF-BUT value would undermine that possibility, and the addition of a 3rd break-up time and taking the average of the three measurements would further strengthen the accuracy of the TBUT measurement. The A3F-BUT compatible parameter (A3F-BUTc) refers to the breakup times that meet the A3F-BUT test conditions.

Damaged is a qualitative parameter featuring at least one break-up during the measurement. Localization included: the first breakup emerged in the central half of all placido discs as a central breakup, whereas the first breakup emerged in the peripheral discs as a peripheral localized breakup. F5-BUT is NIF-BUT≤5s. F10-BUT is NIF-BUT≤10s. A5-BUT is NIAvg-BUT≤5s. A10-BUT is NIAvg-BUT≤10s.

Superonasal, inferonasal, inferotemporal, and superotemporal quadrants were defined by dividing the corneal surface into 4 quadrants of 90 degrees each. Hemifield parameter: The corneal surface was divided into superior and inferior regions based on a horizontal line that was passed right through the middle of the corneal surface (Figure 1).

Statistical Analysis SPSS 27.0 (IBM SPSS Statistics for Windows, version 27.0; IBM Corp., Armonk, NY, USA) software package was used for statistical analyses. Descriptive statistics were expressed using the mean, standard deviation, median, minimum, maximum, frequency and percentage values. The conformity of variables to a normal distribution was checked with the Kolmogorov-Smirnov test. Kruskal-Wallis *H* and Mann-Whitney *U* tests were used for the

Table 1 Age, gender, OSDI score distribution and non-invasive tear film trend of the participants

Parameters	Data
Age, mean±SD, y	27.5±7.5
Median (min-max)	26.0 (18.0-59.0)
Gender, *n* (%)	*n*=255
Male	99 (38.8)
Female	156 (61.2)
NIF-BUT, mean±SD, s	5.3±3.0
Median (min-max)	4.8 (1.2-14.4)
A3F-BUT, mean±SD, s	5.8±3.0
Median (min-max)	5.0 (1.4-15.1)
NIAvg-BUT, mean±SD, s	8.0±3.1
Median (min-max)	8.0 (1.7-15.2)
A3F-BUTc, *n* (%)	*n*=192
(+)	135 (70.3)
(-)	57 (29.7)
Damaged, *n* (%)	*n*=255
(+)	193 (75.7)
(-)	62 (24.3)
Localization, *n* (%)	*n*=193
Central	74 (38.5)
Peripheric	119 (62.0)
F5-BUT, *n* (%)	*n*=193
(+)	110 (57.0)
(-)	83 (43.0)
F10-BUT, *n* (%)	*n*=193
(+)	175 (90.7)
(-)	18 (9.3)
A5-BUT, *n* (%)	*n*=193
(+)	38 (19.7)
(-)	155 (80.3)
A10-BUT, *n* (%)	*n*=193
(+)	144 (74.6)
(-)	49 (25.4)
Quadrant, *n* (%)	*n*=193
SN	24 (12.4)
IN	52 (26.9)
IT	82 (42.5)
ST	35 (18.1)
Hemifild, *n* (%)	*n*=193
Superior	64 (33.2)
Inferior	129 (66.8)
Normal OSDI, *n* (%)	122 (47.8)
Abnormal OSDI, *n* (%)	133 (52.2)

NIF-BUT: Non-invasive first break-up time value; NIAvg-BUT: Non-invasive average break-up time value; A3F-BUT: Average of the first three tear film break-up time; A3F-BUTc: The break-up times that meet the A3F-BUT test conditions; F5-BUT: NIF-BUT≤5s; F10-BUT: NIF-BUT≤10s; A5-BUT: NIAvg-BUT≤5s; A10-BUT: NIAvg-BUT≤10s; SN: Superonasal quadrant; IN: Inferonasal quadrant; IT: Inferotemporal quadrant; ST: Supertemporal quadrant; OSDI: Ocular Surface Disease Index.

comparison of quantitative data, whereas Pearson's Chi-squared test was used for the comparison of qualitative data. Logistic regression and receiver operating characteristic (ROC) analyses were used to determine the effect levels. Probability values of $P<0.05$ was considered statistically significant.

RESULTS

Non-invasive Tear Film Break-up Time Test The mean age of the volunteers included in the study was 27.5±7.5 (range 18-59)y. Ninety-nine (38.8%) of the volunteers were male (Table 1). There was no statistically significant difference between the female and male genders in terms of NIF-BUT, A3F-BUT, A3F-BUTc values or OSDI scores (P=0.284, 0.115, 0.782, and 0.870, respectively).

Non-invasive Break-up Time Test Analysis based on the OSDI Scores NIF-BUT (P=0.014), A3F-BUT (P=0.011), and NIAvg-BUT (P=0.034) were significantly lower, whereas the cases that were met the A3F-BUTc (P=0.017), damaged tear film (P=0.000), F10-BUT (P=0.000), and A10-BUT (P=0.035) were significantly higher in the group of abnormal OSDI scores than volunteers with normal OSDI scores. The occurrence of the first breakup in the inferotemporal quadrant was more common in both the normal and abnormal OSDI groups, yet the rates of occurrence of the first breakup in four quadrants were not significantly different between the normal and abnormal OSDI groups (P=0.128). The localization of the first breakup in the peripheral area were higher in both the normal and abnormal OSDI groups, yet the difference was not statistically significant (P=0.620). There was no statistically significant difference between the groups in terms of hemifield, F5-BUT, and A5-BUT parameters (Table 2).

NIF-BUT (P=0.004), A3F-BUT (P=0.004), NIAvg-TBUT (P=0.016), and A3F-BUTc (P=0.018) parameters were found to have significant predictive ability in the univariate analysis to discriminate the abnormal OSDI group. A3F-BUT (P=0.004) was independent predictive factor in the multivariate regression analysis to discriminate the abnormal OSDI group (Table 3).

The NIF-BUT and A3F-BUT have significant predictive ability to discriminate the abnormal OSDI group (AUC=0.599, P=0.043; AUC=0.625, P=0.011; Table 4). The sensitivity, positive predictive value, specificity, and negative predictive value of the NIF-BUT cutoff value (7.85s) were 88.2%, 66.5%, 28.4%, and 60.0%, respectively and A3F-BUT cutoff value (7.85s) were 85.9%, 71.4%, 37.0%, and 58.8%, respectively (Table 5).

DISCUSSION

In our study, we found that A3F-BUT was superior to NIF-BUT and NIAvg-BUT to discriminating abnormal OSDI. According to the Tear Film and Ocular Surface Society and Dry Eye Workshop (TFOS DEWS) II, dry eye is defined as "a multifactorial disease of the tears and ocular surface that is accompanied by increased osmolarity of the tear film

Table 2 Analysis of NIF-BUT parameters according to OSDI scores

Parameters	Normal OSDI	Abnormal OSDI	*P*
Age, mean±SD, y	27.6±7.4	27.5±7.7	0.666[a]
Median	26.5	26.0	
Gender, *n* (%)			0.870[b]
Male	48 (39.3)	51 (38.3)	
Female	74 (60.7)	82 (61.7)	
NIF-BUT, mean±SD, s	6.2±3.5	4.8±2.6	0.014[a]
Median	5.2	4.5	
A3F-BUT, mean±SD, s	6.8±3.5	5.3±2.6	0.011[a]
Median	6.1	4.8	
NIAvg-BUT, mean±SD, s	8.7±3.3	7.6±2.9	0.034[a]
Median	8.4	7.5	
A3F-BUTc, *n* (%)			0.017[b]
(+)	44 (60.3)	91 (76.5)	
(-)	29 (39.7)	28 (23.5)	
Damaged, *n* (%)			0.000[b]
(+)	74 (60.7)	119 (89.5)	
(-)	48 (39.3)	14 (10.5)	
Localization, *n* (%)			0.620[b]
Central	30 (40.5)	44 (37.0)	
Peripheric	44 (59.5)	75 (63.0)	
F5-BUT, *n* (%)			0.065[b]
(+)	36 (48.6)	74 (62.2)	
(-)	38 (51.4)	45 (37.8)	
F10-BUT, *n* (%)			0.000[b]
(+)	62 (83.8)	113 (95.0)	
(-)	12 (16.2)	6 (5.0)	
A5-BUT, *n* (%)			0.089[b]
(+)	10 (13.5)	28 (23.5)	
(-)	64 (86.5)	91 (76.5)	
A10-BUT, *n* (%)			0.035[b]
(+)	49 (66.2)	95 (79.8)	
(-)	25 (33.8)	24 (20.2)	
Quadrant, *n* (%)			0.128[b]
SN	7 (9.5)	17 (14.3)	
IN	23 (31.1)	29 (24.4)	
IT	26 (35.1)	56 (47.1)	
ST	18 (24.3)	17 (14.3)	
Hemifild, *n* (%)			0.086[b]
Superior	30 (40.5)	34 (28.6)	
Inferior	44 (59.5)	85 (71.4)	

[a]Mann-Whitney *U* test; [b]Chi-square test. NIF-BUT: Non-invasive first break-up time; NIAvg-BUT: Non-invasive average break-up time; A3F-BUT: Average of the first three tear film break-up time; A3F-BUTc: Compatible meet the A3F-BUT test conditions; F5-BUT: NIF-BUT≤5s; F10-BUT: NIF-BUT≤10s; A5-BUT: NIAvg-BUT≤5s; A10-BUT: NIAvg-BUT≤10s; SN: Superonasal quadrant; IN: Inferonasal quadrant; IT: Inferotemporal quadrant; ST: Supertemporal quadrant; OSDI: Ocular Surface Disease Index.

Table 3 Univariate and multivariate model analyses by logistic regression

Parameters	Univariate model		Multivariate model	
	OR (95%CI)	*P*	OR (95%CI)	*P*
NIF-BUT	1.160 (1.050-1.281)	0.004		
A3F-BUT	1.180 (1.054-1.322)	0.004	1.180 (1.054-1.322)	0.004
NIAvg-BUT	1.126 (1.022-1.240)	0.016		
A3F-BUTc	2.142 (1.139-4.029)	0.018		

Logistic regression (Forward LR). NIF-BUT: Non-invasive first break-up time; NIAvg-BUT: Non-invasive average break-up time; A3F-BUT: Average of the first three tear film break-up time; A3F-BUTc: Compatible meet the A3F-BUT test conditions; OR: Odds ratio; CI: Confidence interval.

Table 4 Area under the receiver operator characteristic curve

Parameters	AUC (95%CI)	*P*
NIF-BUT	0.599 (0.502-0.696)	0.043
A3F-BUT	0.625 (0.529-0.720)	0.011
NIAvg-BUT	0.578 (0.481-0.675)	0.111

NIF-BUT: Non-invasive first break-up time; NIAvg-BUT: Non-invasive average break-up time; A3F-BUT: Average of the first three tear film break-up time; AUC: The area under the curve; CI: Confidence interval.

and inflammation of the ocular surface and which results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface"[8-9]. The fact that the word tear film was mentioned twice in the abovementioned definition indicates that tear film is of central importance for dry eye. Tear film is of central importance in terms of not only diagnosis but also follow-up treatment[17-19]. There is no gold standard diagnostic method in the diagnosis of dry eye, and therefore, it is recommended to perform all available tests and make a diagnosis as such[2,8,17]. Similarly, there is no gold standard diagnostic method in the diagnosis of tear film stability. In general, it is recommended that tear film stability tests are noninvasive, noncontact, documentable and objective and have high sensitivity, specificity, repeatability, and reproducibility[2,8,19] and that the results of these tests are obtained with the least number of examinations and shots as possible.

In the event that the patients presented to the outpatient clinic with a symptom, the test results of the patients in question were compared based on the symptoms. In fact, there are studies available in the literature that featured symptom-based comparisons[20-22]. In this study, the NI-BUT test results of 255 volunteers were analyzed both quantitatively and qualitatively. Additionally, results of these test, whether they differed according to age and gender were also investigated. And more importantly, the correlations of these results with OSDI scores were investigated. No correlation was found between the NIF-BUT value and age (r=-0.013; P=0.885). The respective results reported in the studies available in the literature are

Table 5 Cut-off value, sensitivity, specificity, and positive and negative predictive value of the break-up time values

Parameters	Cut-off value	Normal OSDI	Abnormal OSDI	Sensitivity	Positive predictive value	Specificity	Negative predictive value
NIF-BUT	≤7.85s	53	105	88.2%	66.5%	28.4%	60.0%
	>7.85s	21	14				
A3F-BUT	≤7.85s	34	85	85.9%	71.4%	37.0%	58.8%
	>7.85s	20	14				
NIAvg-BUT	≤12.5s	62	115	96.6%	65.0%	16.2%	75.0%
	>12.5s	12	4				

NIF-BUT: Non-invasive first break-up time; NIAvg-BUT: Non-invasive average break-up time; A3F-BUT: Average of the first three tear film break-up time; OSDI: Ocular Surface Disease Index.

contradictory. Some favor the finding of this study[23-24], while others do not[25-26]. This discrepancy between the results may be due to the difference in the device used, as well as the type of the noninvasively measured BUT parameter taken as the reference, that is, whether NIF-BUT or NIAvg-BUT values or the average of the two were used. Additionally, in this study, NIF-BUT value was not significant difference between males and females. This finding was compatible with the respective findings reported in various studies in the literature[23,26-28].

The NIAvg-BUT was determined to be 8.0±3.1 (range 1.7-15.2) seconds. This finding was comparable to the respective finding reported as 9.59±4.37 (range 1.4-17.1) seconds in the study conducted with 170 participants by Ozulken *et al*[29]. The minimal difference between this study and a previous study may be attributed to the relatively higher number of participants included in this study as well as to the higher difference between the minimum and maximum NIAvg-BUT values determined in a previous study. The mean A3F-BUT, which is the newly developed parameter of this study, was determined to be 5.8±3.0s. Roughly half of the cases (47.8%) were determined to be in the normal OSDI group, and the other half (52.2%) were in the abnormal OSDI group. The fact that the respective results of previous studies in which the NI-BUT values were compared using traditional methods[12,20,23-24,29-30] enabled the authors of this study to develop different parameters based on the invariant NI-BUT values of the participants included in this study. In this way, we think that the problem of mentioned in the TFOS DEWS II Diagnostic Methodology report "the difficulty in establishing true referent histograms when evaluating new diagnostic tests caused by the lack of a gold standard"[8] has been solved. Because, confusing parameters were eliminated and thus a newly developed parameter could easily be compared. It was observed that the A3F-BUT parameter developed within the scope of this study verified the NIF-BUT. Statistically, discrimination of the normal OSDI group from the abnormal OSDI group requires that discriminative analyses be conducted involving ROC analysis. The results of the discriminative tests revealed that NIF-BUT was a significant discriminator in the normal and abnormal OSDI groups. A3F-BUT had a higher AUC value and a lower *P* value with respect to discriminating the normal OSDI group from the abnormal OSDI group. As a result, it was proven that the A3F-BUT is statistically superior to the NIF-BUT and NIAvg-BUT. Additionally, the A3F-BUT parameter is sort of the repetition or the average of the three NIF-TBUT measurements. Nevertheless, it is important to take into account the results of artificial instability or non-natural tear film structure caused by tear film as a result of excessive blinking or reflex due to reflected rays while repeating the NIF-BUT measurements[6,8,15,30-32]. It is recommended that a time period of 3 to 15min elapse between two measurements[6,15,31-34], yet 3min can be too short and 15min can be too long, since tears can regenerate approximately 15% per minute[35]. Accordingly, keeping a period of 6 to 7min between the two measurements seems ideal. In other words, an NI-BUT test requires 9 to 45min, or ideally, an average of 20min, depending on the tear regeneration cycle. The ideal times and cycles mentioned above prompt the search for a more practical method. The A3F-BUT is superior not only because it has more predictive ability but also because it allows the NI-BUT test to be performed in approximately one-sixtieth of the time required for an ideal NI-BUT test, that is, in 20s compared to 20min.

NIAvg-BUT, which is a parameter automatically generated by the device, was not significantly effective in discriminating the normal OSDI group from the abnormal OSDI group. Compared to A3F-BUT in particular, the inferior predictive ability of the NIAvg-BUT, which is the average of all break-up times, may be questioned. However, this inference is not totally accurate since the NIAvg-BUT parameter is actually not a break-up time parameter but rather the average of the values in the time set of break-up times (the time interval when the eye is left open). For example, the 1st break-up time is 5s, the 2nd break-up time is 6s, and the 3rd break-up time is 7s, and so on, this string of numbers would continue as long as the eye remains open. In parallel, it is obvious that the NIAvg-BUT value will also increase, since it is a non-constant value that increases proportionally with the break-up times and the time that the eye is left open. Accordingly, the NIAvg-BUT is not a break-up time parameter but merely the mean break-up time in a given time interval. It is not a constant value

and will increase as the number of breakups at different time increases because of the increase in the test time, which is the reason why it was not found to be a successful parameter in discrimination. This was also the reason why the 2nd break-up time value that had a difference of at most 1s from the NIF-BUT value and the lowest 3rd break-up time following the 2nd break-up time was used in the development of the A3F-TBUT criteria. The sensitivities of the NIF-BUT and A3F-BUT at a cutoff value of 7.5s were found to be similar, contrary to the specificities thereof, which were found to be 37% and 28% for the A3F-BUT and NIF-BUT, respectively, and significantly different in favor of the A3F-BUT. Additionally, the sensitivity of the NIF-BUT at a cutoff value of 12.5s was found to be slightly higher, whereas its specificity remained at 16.2%. The sensitivity values of the parameters investigated were found to be comparable in general, yet the A3F-BUT developed within the scope of this study had by far the highest specificity in discrimination. Nevertheless, the specificity of the A3F-BUT was still not high enough, but it is possible to obtain an ideal specificity value by changing the cutoff values[8].

The limitations of this study are that ideal cutoff values of the A3F-BUT and NIF-BUT with sufficiently high sensitivity and specificity values to discriminate the normal OSDI group from the abnormal OSDI group were not studied.

In conclusion, A3F-BUT developed within the scope of this study provides more accurate and reliable information to the physician and significantly more time, as it reduces the time required to perform an NI-BUT test by sixty times. In addition, taking one recording instead of three recordings provides energy and mechanical savings, albeit slightly. A3F-BUT has made the NI-BUT test more specific and more practical.

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