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Ocular surface alterations in rheumatoid arthritis: multimodal imaging and clinical correlations

Hamza Benmoussa

hamza_benmoussa@hotmail.fr

Abdelmalek Essaâdi University ,University Hospital of Tangier,

Mohamed El Barkani

Abdelmalek Essaâdi University ,University Hospital of Tangier,

Chaimae Khodriss

Abdelmalek Essaâdi University ,University Hospital of Tangier,

Meriem El Bahloul

Abdelmalek Essaâdi University ,University Hospital of Tangier,

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Abstract

Background:

Dry eye disease is the most common ophthalmological manifestation in patients with rheumatoid arthritis (RA). Its diagnosis relies on clinical parameters and non-invasive imaging techniques. The aim of this study was to evaluate the correlations between clinical and paraclinical ocular surface parameters.

Methods:

This was a cross-sectional descriptive and analytical study conducted at the University Hospital of Tangier between April and July 2021. Patients with RA and an Ocular Surface Disease Index (OSDI) score > 20 were included. All patients underwent clinical evaluation (tear breakup time [TBUT], Schirmer test, slit-lamp examination) and paraclinical assessment using a multimodal ocular surface analysis platform (Lacrydiag®), including non-invasive breakup time (NIBUT), tear meniscus height, interferometry, and meibography. Correlations were analyzed using Pearson and Spearman tests, with a significance threshold set at $p < 0.05$.

Results:

Twenty-nine patients (58 eyes) were included, with a female predominance (89.7%) and a mean age of 47.8 ± 12.9 years. The mean OSDI score was 38.6 ± 23.1. The mean TBUT was 11.9 ± 7.4 seconds and the mean NIBUT was 10.4 ± 3.4 seconds. A moderate and statistically significant positive correlation was found between TBUT and NIBUT ($rs = 0.48$; $p < 0.001$). A significant correlation was also observed between meibography findings and the Arita score ($R^2 = 0.363$; $p < 0.001$). However, no significant correlation was found between NIBUT and the other studied parameters.

Conclusion:

Multimodal evaluation of the ocular surface is a valuable approach for the assessment of dry eye disease in patients with RA. NIBUT appears to correlate with TBUT but shows limited association with other parameters, highlighting the complexity of dry eye diagnosis and the need for a combined diagnostic approach.

INTRODUCTION

Dry eye disease is a common multifactorial condition characterized by a loss of tear film homeostasis and inflammation of the ocular surface (1). It represents a major cause of visual discomfort and reduced quality of life, particularly in patients with systemic diseases.

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that may be associated with ocular involvement, most commonly presenting as dry eye disease (2). This condition results from dysfunction of the lacrimal and meibomian glands, leading to tear film instability and ocular surface alterations.

The evaluation of dry eye disease traditionally relies on clinical tests such as tear breakup time (TBUT), Schirmer test, and symptom-based questionnaires including the Ocular Surface Disease Index (OSDI). However, these methods have limitations in terms of reproducibility and objectivity.

Recent advances in non-invasive imaging technologies have enabled a more comprehensive assessment of the ocular surface. Multimodal imaging platforms allow evaluation of multiple parameters, including non-invasive breakup time (NIBUT), tear meniscus height, lipid layer interferometry, and meibomian gland morphology, providing a more objective and reproducible approach to dry eye assessment.

MATERIALS AND METHODS

Study design and setting

This was a cross-sectional descriptive and analytical study conducted in the ophthalmology department of Al Kortobi Hospital, affiliated with the University Hospital of Tangier-Tetouan-Al Hoceima, in collaboration with the rheumatology department, between April and July 2021.

Study population

Patients with confirmed rheumatoid arthritis (RA) presenting signs of dry eye disease, defined by an OSDI score greater than 20, consistent with moderate to severe dry eye symptoms.

Patients without a confirmed diagnosis of RA, as well as those with ocular or systemic conditions that could interfere with ocular surface evaluation, were excluded.

Examination protocol

All patients underwent a comprehensive ocular surface evaluation performed by a single examiner according to a standardized protocol.

The examination included:

- functional assessment using the Ocular Surface Disease Index (OSDI) questionnaire, a validated and widely used instrument for assessing dry eye symptoms and their impact on vision-related quality of life (33). The validated Arabic version of the OSDI (ARB-OSDI) was used in this study (34);
- multimodal ocular surface analysis using a dedicated imaging platform (Lacrydiag®, Quantel Medical);

- slit-lamp examination with tear breakup time (TBUT) measurement and assessment for superficial punctate keratitis;
- Schirmer I test.

Clinical evaluation

TBUT was measured after fluorescein instillation under blue light at the slit lamp, and the mean of three consecutive measurements was recorded.

Tear production was assessed using the Schirmer I test after instillation of a topical anesthetic, with a duration of five minutes.

The presence of superficial punctate keratitis was assessed using fluorescein staining.

Meibomian gland dysfunction was evaluated using the clinical Arita score.

Paraclinical evaluation (Lacrydiag®)

Multimodal non-contact evaluation was performed using the Lacrydiag® device, allowing:

- measurement of non-invasive breakup time (NIBUT) through Placido ring analysis;
- assessment of tear meniscus height;
- evaluation of the lipid layer using interferometry;
- morphological analysis of meibomian glands using infrared meibography, with estimation of gland loss.

Statistical analysis

Data were recorded and analyzed using Microsoft Excel and SPSS software (version 20).

Quantitative variables were expressed as mean ± standard deviation, and qualitative variables as percentages.

Correlations between variables were analyzed using Pearson or Spearman tests after assessment of normality (Kolmogorov–Smirnov and Shapiro–Wilk tests).

Agreement between TBUT and NIBUT was assessed using Bland–Altman analysis.

A p-value < 0.05 was considered statistically significant.

Results

29 patients (58 eyes) were included., with a female predominance (89.7%) and a mean age of 47.8 ± 12.9 years (Fig. 1, Table 1). The mean disease duration of rheumatoid arthritis was 6.98 ± 6.95 years.

Table 1
Demographic and clinical characteristics of the study population

Parameter	Value
Number of patients	29
Number of eyes	58
Female (%)	89.7
Age (years)	47.8 ± 12.9
Disease duration (years)	6.98 ± 6.95

The mean OSDI score was 38.6 ± 23.1 (Fig. 2, Table 2). The mean Schirmer test value was 8.1 ± 7.4 mm (Fig. 3), and the mean TBUT was 11.9 ± 7.4 seconds (Fig. 4). The mean Arita score was 4.5 ± 1.9.

Table 2
Clinical and paraclinical parameters

Parameter	Mean ± SD
OSDI score	38.6 ± 23.1
Schirmer test (mm)	8.1 ± 7.4
TBUT (s)	11.9 ± 7.4
Arita score	4.5 ± 1.9
NIBUT (s)	10.4 ± 3.4

The mean NIBUT was 10.4 ± 3.4 seconds (Fig. 5), and the mean tear meniscus height was 0.25 ± 0.14 mm. The mean percentage of meibomian gland loss was 31.4 ± 11%.

Regarding interferometry, 31% of patients showed an average lipid layer thickness of 15 µm.

A significant correlation was found between meibography findings and the Arita score (Fig. 6, Table 3). A moderate positive correlation was observed between TBUT and NIBUT ($r_s = 0.48$; $p < 0.001$) (Fig. 7, Table 3).

Table 3
Correlations between main ocular surface parameters

Correlation	Coefficient (rs)	p-value
TBUT – NIBUT	0.48	< 0.001

No significant correlation was found between NIBUT and Schirmer test, OSDI score, tear meniscus height, or Arita score.

Bland–Altman analysis demonstrated a mean difference of -1.5 seconds between TBUT and NIBUT, indicating that TBUT values were systematically lower than NIBUT measurements (Fig. 8). A trend toward increasing differences with higher mean values was observed, suggesting a proportional bias.

Discussion

Dry eye disease is the most common ophthalmological manifestation in rheumatoid arthritis, resulting from a multifactorial impairment of the lacrimal functional unit (1, 2). In our study, multimodal ocular surface analysis revealed frequent alterations in both clinical and instrumental parameters, while confirming the heterogeneity of correlations between different diagnostic tests.

From an epidemiological perspective, our population was characterized by a marked female predominance and a relatively young mean age. These findings are consistent with both Moroccan and international data, which report a higher prevalence of rheumatoid arthritis in women, as well as a younger profile in certain North African cohorts (3–6). The disease duration observed in our series is also in line with these findings.

One of the major findings of our study was the demonstration of a moderate and highly significant positive correlation between TBUT and NIBUT ($rs = 0.48$; $p < 0.001$). This result is consistent with several previous studies using different imaging modalities, including Lacrydiag, Keratograph 5M, and Sirius topography, which have reported variable strengths of correlation between these parameters (7–9).

However, the direction and magnitude of this correlation remain controversial in the literature. Some studies have reported higher TBUT values compared to NIBUT, potentially related to the quantity of fluorescein instilled (10–12), while more recent studies have demonstrated the opposite trend, with higher NIBUT values (9, 14), as observed in our series.

This discrepancy may be explained by several factors, including reflex tearing induced by device illumination, differences between first and average NIBUT measurements depending on device versions, and the destabilizing effect of fluorescein on the tear film (14, 15).

Furthermore, Bland–Altman analysis in our study demonstrated a mean difference of − 1.5 seconds, indicating that TBUT values were systematically lower than NIBUT measurements, which is consistent

with recent reports using Lacrydiag showing similar trends (9).

A trend toward increasing differences with higher mean values was also observed, suggesting a proportional bias between the two measurements.

The absence of a significant correlation between NIBUT and OSDI observed in our study is consistent with several recent reports (16–18). This discrepancy between objective signs and subjective symptoms is now a central concept in the pathophysiology of dry eye disease. It may be explained by complex mechanisms involving chronic inflammation, neurosensory alterations, and individual variability in symptom perception (14, 19).

Similarly, no correlation was found between NIBUT and other parameters such as the Schirmer test and tear meniscus height. These findings are in agreement with studies demonstrating that these tests assess different aspects of the ocular surface (20–22). The Schirmer test, in particular, remains limited by significant variability and poor reproducibility due to reflex tearing and examination conditions (20–23).

Regarding clinical parameters, the absence of correlation between OSDI, TBUT, and Schirmer test has also been widely described (16, 24). This lack of concordance further highlights the multifactorial nature of dry eye disease and supports the multimodal diagnostic approach recommended by TFOS DEWS II (1, 32).

Analysis of the meibomian glands did not show a significant correlation between meibography and interferometry in our study. Although some studies have reported a correlation between gland loss and lipid layer thickness (25, 26), more recent data suggest a frequent dissociation between structure and function of the meibomian glands (27, 28). This dissociation may reflect the biphasic progression of meibomian gland dysfunction, characterized by an initial functional impairment with preserved glandular morphology, followed by a later atrophic stage in which both function and structure are progressively altered.

Moreover, semi-automated quantification of meibography using Lacrydiag may introduce operator-dependent bias, particularly in the selection of regions of interest. Previous studies have demonstrated significant inter-observer variability in meibographic image analysis, highlighting current limitations of these tools (29).

In contrast, a significant correlation was found between meibography and the clinical Arita score, confirming the relevance of this score in the evaluation of meibomian gland dysfunction. This result is consistent with the original findings described by Arita et al. and subsequent studies supporting its reproducibility and diagnostic value (30, 31).

Overall, our results support the value of multimodal ocular surface analysis platforms in the evaluation of dry eye disease. However, their main strength lies in the combined interpretation of multiple parameters rather than reliance on a single isolated test (9, 32). The integration of automated techniques

and artificial intelligence-based approaches may further enhance reproducibility and standardization in the future (32).

Our study has several limitations, including its single-center design and relatively small sample size. In addition, some parameters assessed using Lacrydiag remain operator-dependent and influenced by acquisition conditions. Finally, symptom evaluation may have been affected by linguistic and sociocultural factors.

Conclusion

Dry eye disease is a frequent and multifactorial condition in patients with rheumatoid arthritis, requiring a comprehensive evaluation of the ocular surface. In our study, a moderate correlation was observed between TBUT and NIBUT, whereas other parameters showed weak or no significant correlations, highlighting the complexity of dry eye disease.

Multimodal assessment of the ocular surface using non-invasive imaging platforms represents a valuable approach for dry eye evaluation. However, no single parameter appears sufficient to establish the diagnosis. A combined approach integrating both clinical and instrumental data therefore remains essential

Declarations

Ethics approval and consent to participate

According to local regulations and institutional practices at the University Hospital of Tangier, ethical approval was not required for this type of observational study. The study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Consent for publication

Not applicable.

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Author Contribution

Author ContributionsH.B. conceived and designed the study, collected the data, performed the analysis, and wrote the main manuscript text.M.E.B. contributed to data collection and analysis. C.K. contributed

to study supervision and critically revised the manuscript.M.E.Ba. contributed to data interpretation and manuscript revision.All authors reviewed and approved the final manuscript.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

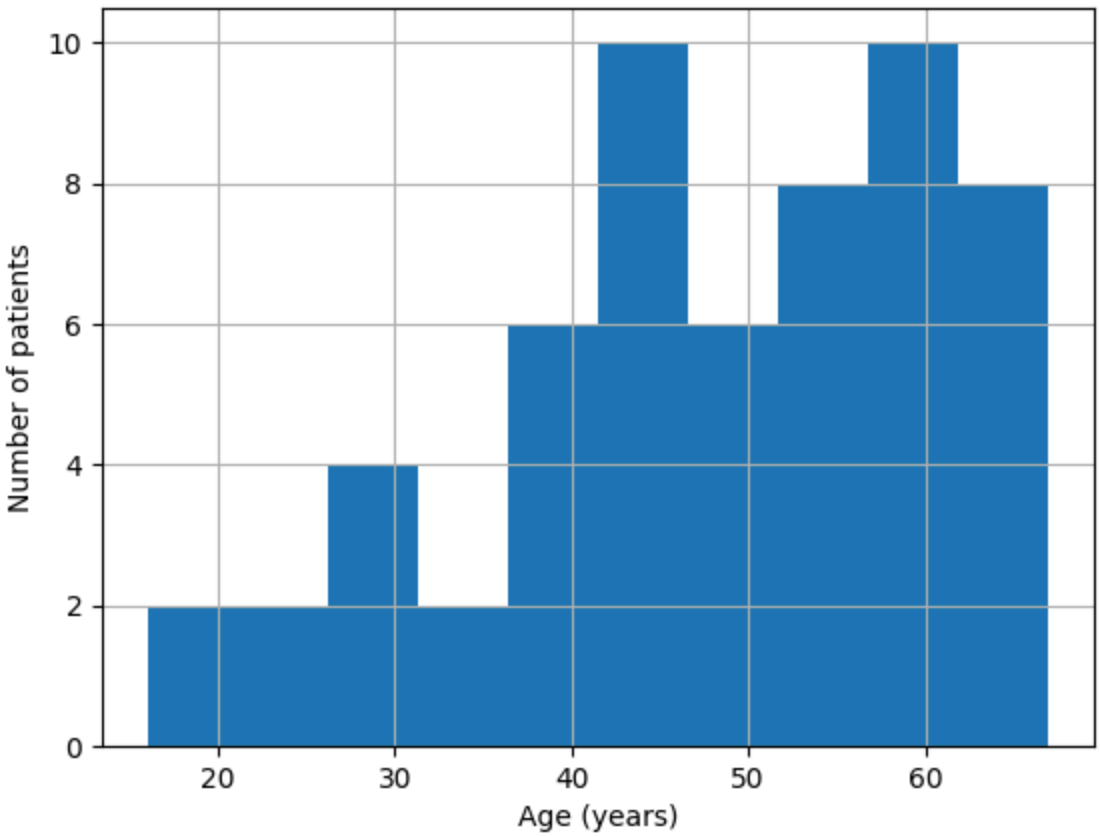


Figure 1

Distribution of patient age in the study population

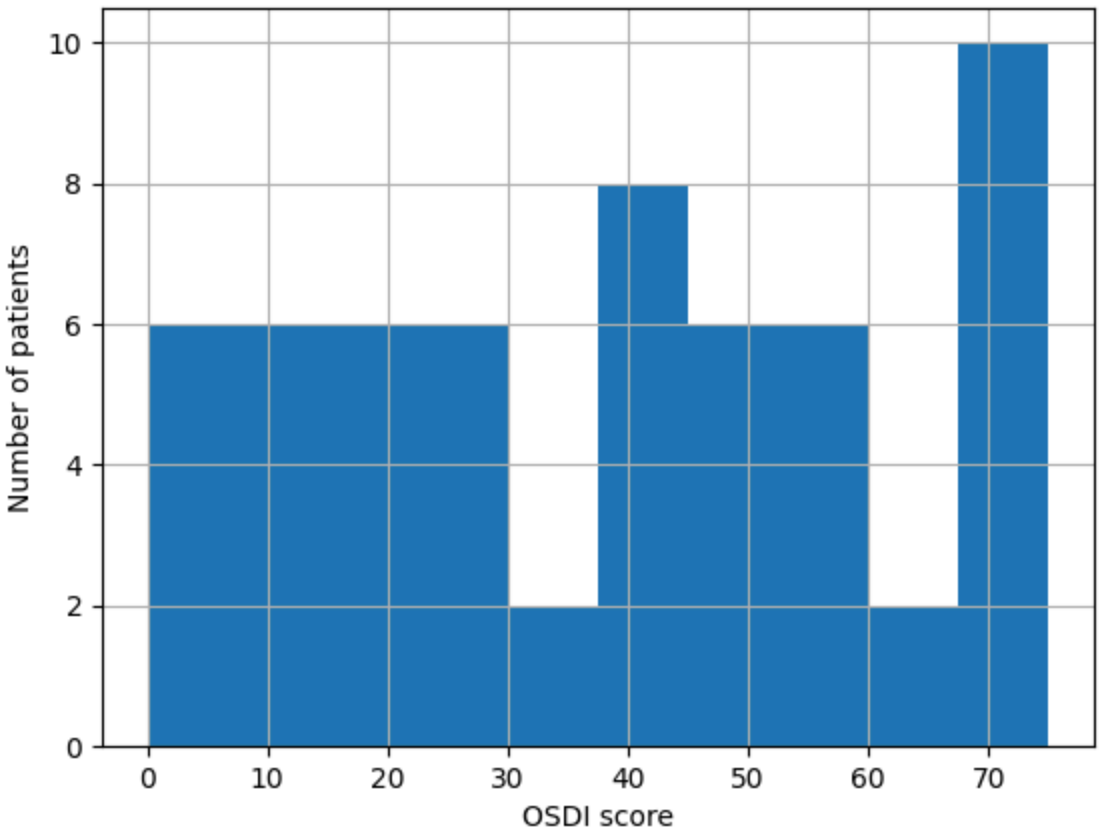


Figure 2

Distribution of OSDI scores according to dry eye severity

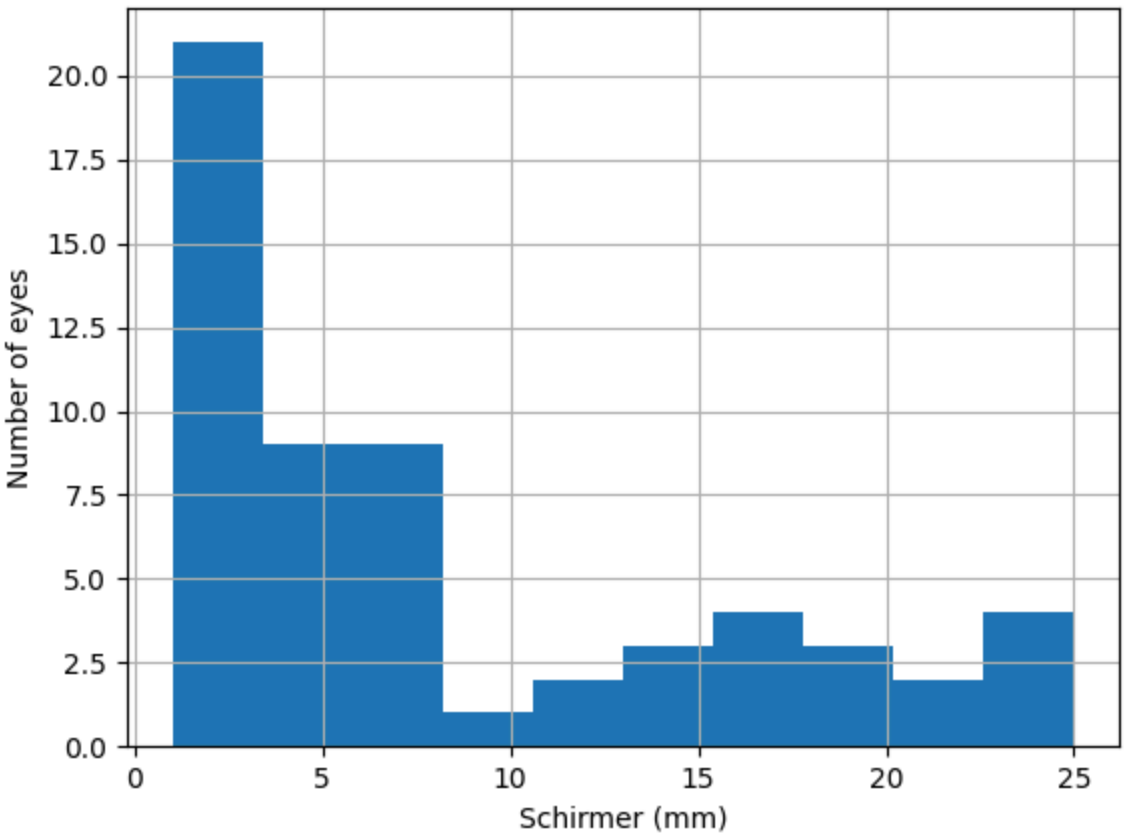


Figure 3

Distribution of Schirmer test values

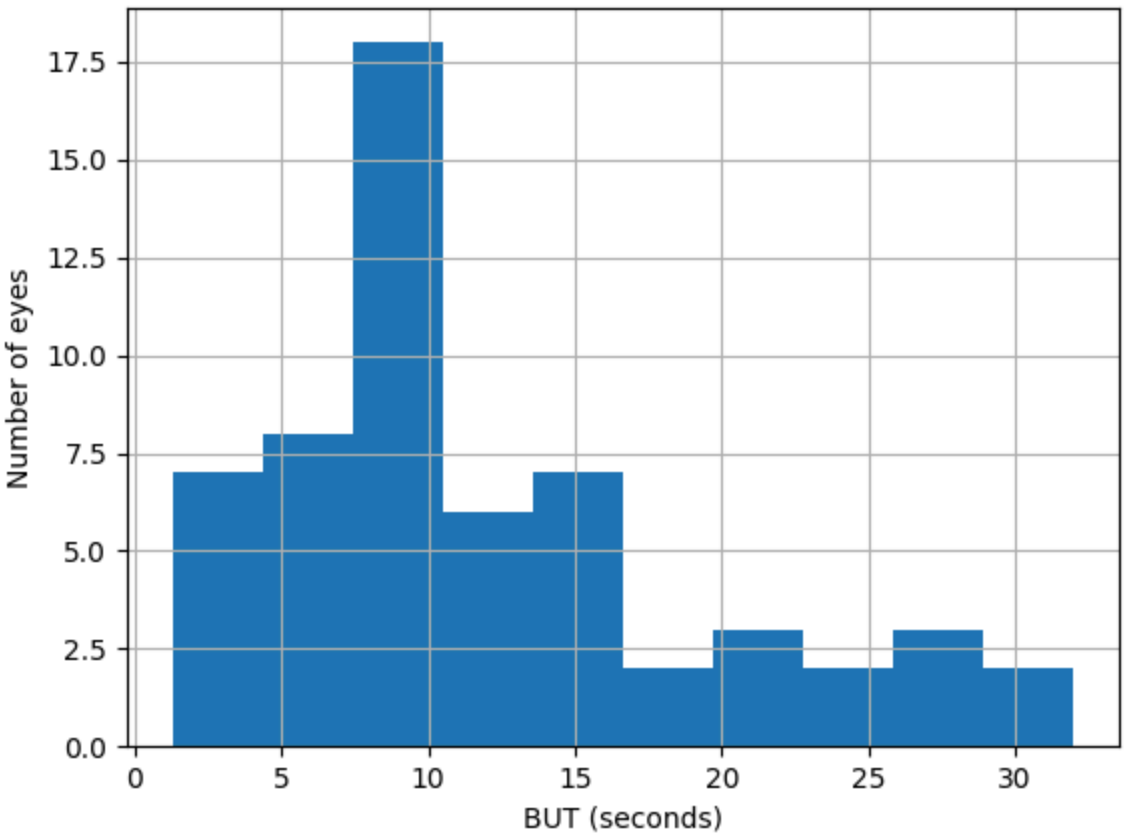


Figure 4

Distribution of tear breakup time (TBUT) values

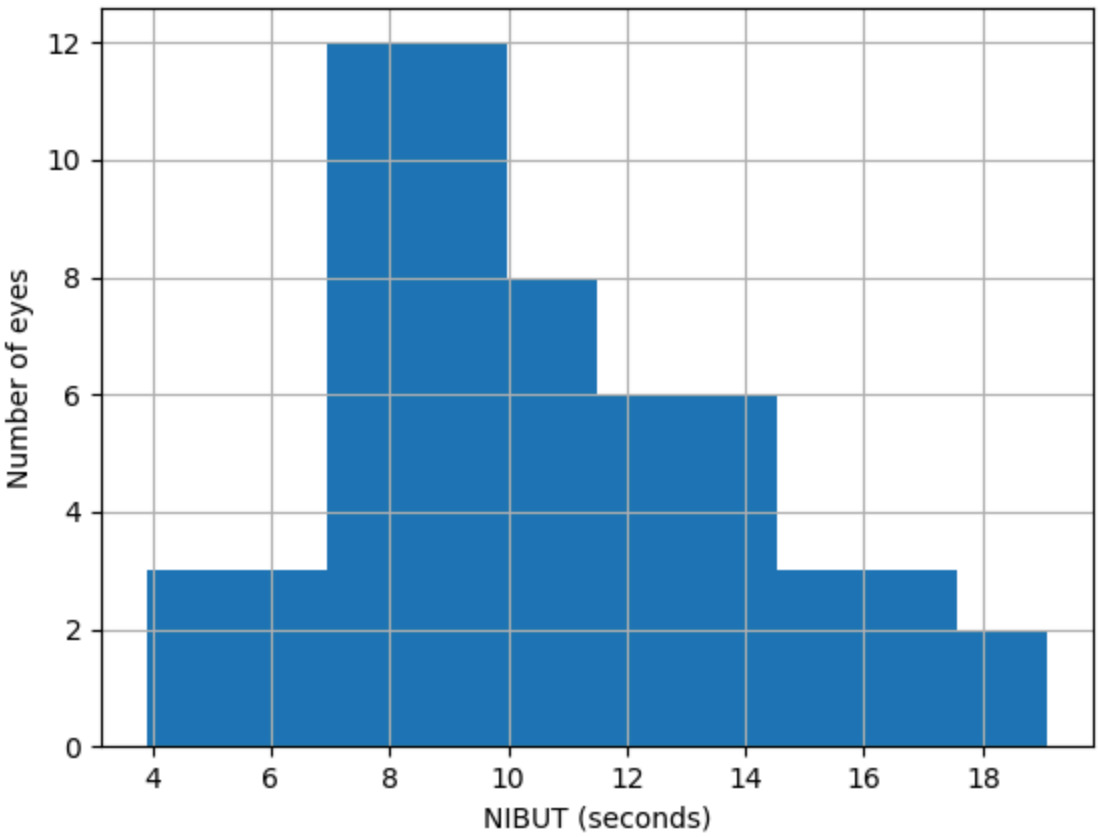


Figure 5

Distribution of non-invasive breakup time (NIBUT) values

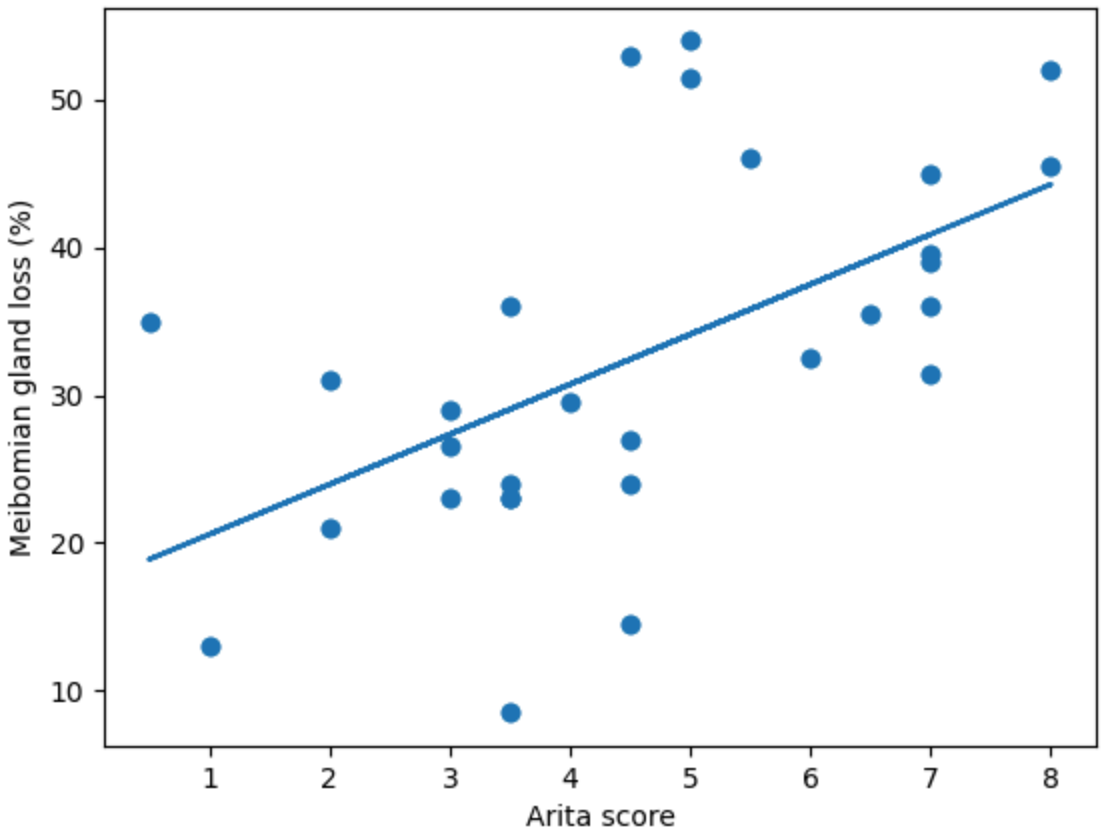


Figure 6

Correlation between Arita score and meibomian gland loss (R^2 = 0.363; p < 0.001)

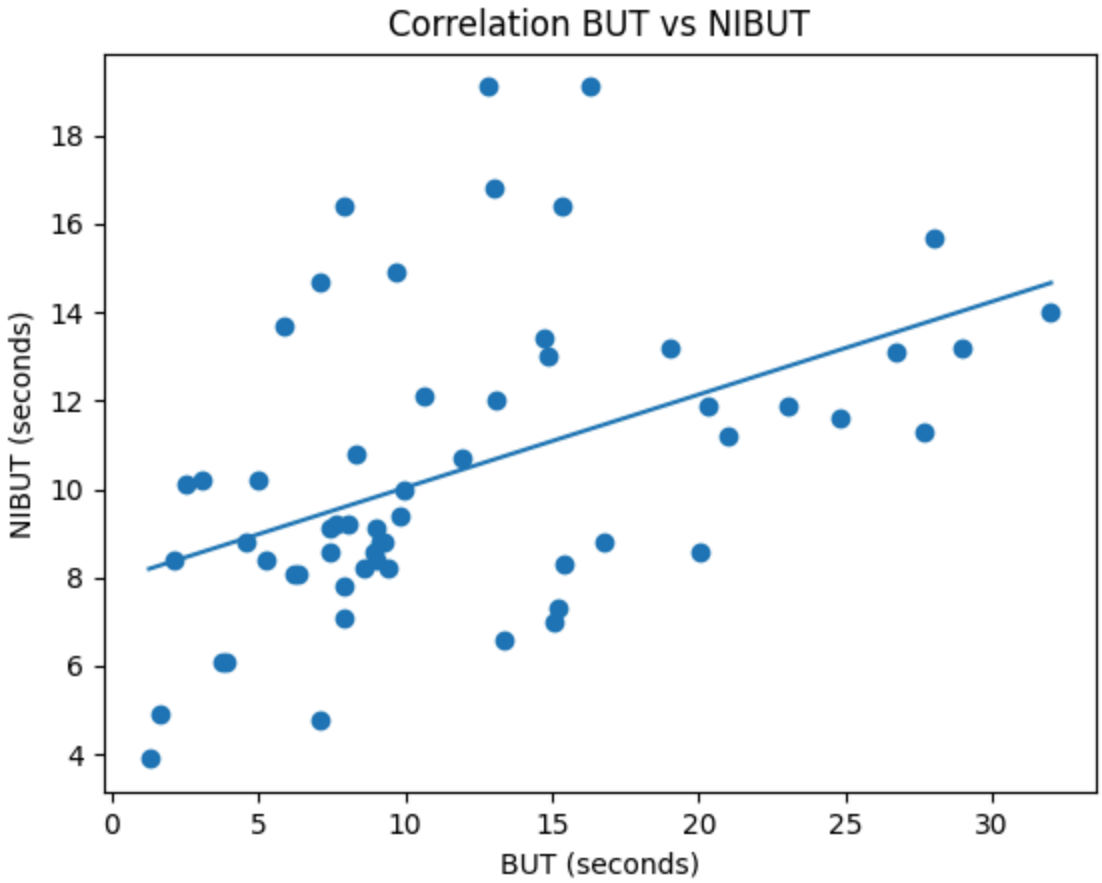


Figure 7

Correlation between TBUT and NIBUT (rs = 0.48; p < 0.001)

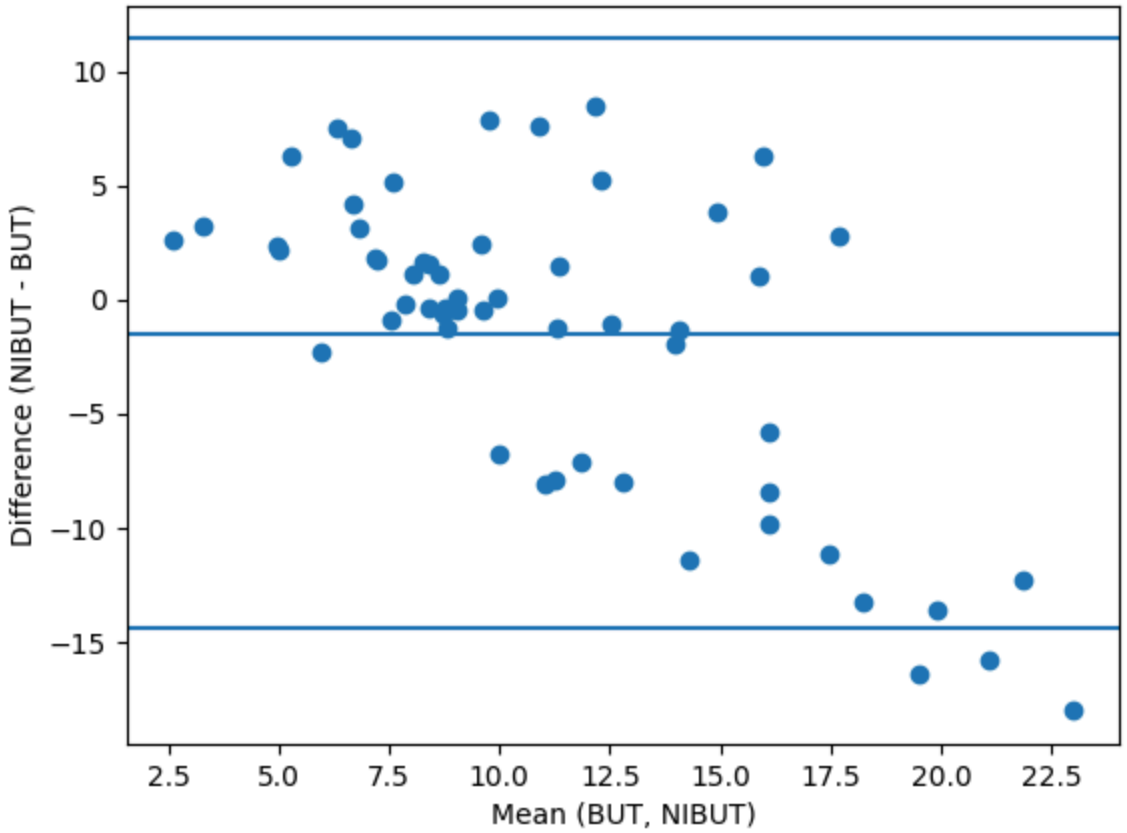


Figure 8

Bland–Altman analysis comparing TBUT and NIBUT