Ophthalmology

The Ocular Surface Frailty Index as a predictor of ocular surface symptoms onset after cataract surgery

--Manuscript Draft--

Manuscript Number:	OPHTHA_2019_193R4
Article Type:	Manuscript
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Abstract:	Purpose : The identification of healthy subjects more susceptible to develop post-surgical ocular surface symptoms is still an unmet need. We performed this study to build a new Ocular Surface Frailty Index (OSFI) and to assess its predictive value for dry eye (DED) symptoms onset after cataract surgery. Design : Single-centre, observational, longitudinal study. Participants : We screened 405 consecutive patients scheduled for phacoemulsification for age-related cataract. 284 eyes of 284 patients without pre-operative DED symptoms who underwent uneventful cataract surgery were included in the analysis. Methods : Borrowing a concept from geriatric surgery and following a previously validated procedure, we built an OSFI. Starting from a preliminary list of 19 potential items, the final OSFI, including 10 “deficits in ocular surface health and/or factors potentially able to affect it”, was developed by a stepwise approach. Pre-operative OSFI was calculated for each patient and diagnostic tests for DED were performed (following the TFOS DEWS II recommendations) at the screening visit and 1 week (V1), 1 month (V2), and 3 months (V3) after surgery. We evaluated OSFI predictivity for the presence of DED symptoms at V2 AND/OR V3. Main Outcome Measures : The rate of ocular surface symptoms at V2 AND/OR V3. Results : Our patients’ OSFI score ranged from 0 to 0.666, with a median value of 0.200 (0.133-0.266). The percentage of patients with post-surgical ocular surface symptoms was 17%. Using an OSFI cut-off of 0.300, we identified a small group (19% of the asymptomatic subjects) of patients with frail ocular surfaces, who had a significantly higher risk to develop post-surgical DED symptoms (50.0% vs 9.6%; $P<0.001$, $\chi 2$ test). Logistic regression analysis showed that OSFI≥0.3 (but not age, gender or any pre-operative sign) was a good predictor of ocular surface symptoms onset (odds ratio (OR) =9.45; 95%CI (4.74-18.82). Regression was still significant when performed on 200 bootstrapped samples. Conclusions : The OSFI can be easily and quickly calculated using non-invasive and low-tech procedures and it showed to be predictive of post-operative ocular surface symptoms onset. This novel tool might allow cataract surgeons to perform a useful pre-operative personalized risk assessment.
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Department of Clinical Sciences and Community Health

Milan, December 11th 2019

To Prof. Stephen D. McLeod,
Editor-in-Chief, Ophthalmology

Dear Prof McLeod,

Thank you for the opportunity to revise and improve our manuscript Ref: OPHTHA_2019_193R3, "The Ocular Surface Frailty Index as a predictor of ocular surface symptoms onset after cataract surgery".

We tried to address all the remaining concerns of the reviewer.

We hope that you will find our manuscript acceptable for publication in this revised form.

Kind regards
Sincerely,

Edoardo Villani

Point by point response to editors and reviewers (R4).

Changes in the document are highlighted in the “track changes” version of the manuscript.

Suggestions, questions, or comments from the Reviewer #2	**Author’s Response**	**Change in the manuscript**
Reviewer 2: The authors have re-revised their manuscript and made substantive changes. There are some minor concerns. My comments refer to the chronology of the marked up revised copy:		
1 - Lines 129-130 are written as a double negative	Changed as suggested	Patients with DED signs without symptoms were included.19
2 - Line 146; the word "on" should be changed to the regarding	Changed as suggested	Each patient completed a questionnaire regarding his/her medical history
3 - Lines 185 -186; please explain the phrase "doesn't saturate too early."	Explained as suggested	… paying attention to include variables which were associated with ocular surface health status, whose prevalence generally increase with age, and which don’t saturate too early (for instance, presbyopia is nearly universal by age 55, saturating too early to be included in this type of frailty index)[12]
4 - Lines 290-293 are of questionable value and could/should be removed	Thank you for your observation. In order to address your concern and, at the same time, to avoid to skip an essential concept, we rephrased this sentence.	Even if the advanced age can carry increased risk of post-surgical adverse events, the chronological age is not suitable to be used as a tool for pre-operative risk

		assessment and stratification.22, 23, 24
5 - Lines 322-324 are clumsy and should be re-written	Re-written as suggested.	We designed and developed the OSFI starting from the concept of frailty and its different applications for pre-operative risk assessment in general and geriatric surgery.

We developed a novel Ocular Surface Frailty Index and we internally validated that as the only significant predictor of post-operative ocular surface symptoms onset in asymptomatic patients undergoing cataract surgery.

TITLE PAGE

The Ocular Surface Frailty Index as a predictor of ocular surface symptoms onset after cataract surgery

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Financial Support: None

No conflicting relationship exists for any author

Short title: OSFI as a predictor of cataract surgery-related DED symptoms onset

ABSTRACT

Purpose: The identification of healthy subjects more susceptible to develop post-surgical ocular surface symptoms is still an unmet need. We performed this study to build a new Ocular Surface Frailty Index (OSFI) and to assess its predictive value for dry eye (DED) symptoms onset after cataract surgery.

Design: Single-centre, observational, longitudinal study.

Participants: We screened 405 consecutive patients scheduled for phacoemulsification for age-related cataract. 284 eyes of 284 patients without pre-operative DED symptoms who underwent uneventful cataract surgery were included in the analysis.

Methods: Borrowing a concept from geriatric surgery and following a previously validated procedure, we built a tool to assess ocular surface frailty. Starting from a preliminary list of 19 potential items, the final OSFI, including 10 “deficits in ocular surface health and/or factors potentially able to affect it”, was developed by a stepwise approach. Pre-operative OSFI was calculated for each enrolled patient and diagnostic tests for DED were performed (following the TFOS DEWS II recommendations) at the screening visit and 1 week (V1), 1 month (V2), and 3 months (V3) after surgery. We evaluated OSFI predictivity for the presence of DED symptoms at V2 AND/OR V3.

Main Outcome Measures: The rate of ocular surface symptoms at V2 AND/OR V3.

Results: Our patients’ OSFI score ranged from 0 to 0.666, with a median value of 0.200 (0.133-0.266). The percentage of patients with post-surgical ocular surface symptoms was 17%. Using an OSFI cut-off of 0.300, we identified a small group (19% of the asymptomatic subjects) of patients with frail ocular surfaces, who had a significantly higher risk to develop post-surgical DED symptoms (50.0% vs 9.6%; $P<0.001$, $\chi 2$ test). Logistic regression analysis showed that OSFI≥0.3 (but not age, gender or any pre-operative sign) was a good predictor of ocular surface symptoms onset (odds ratio (OR)

=9.45; 95%CI (4.74-18.82). Regression was still significant when performed on 200 bootstrapped samples.

Conclusions: The OSFI can be easily and quickly calculated using non-invasive and low-tech procedures and it showed to be predictive of post-operative ocular surface symptoms onset. This novel tool might allow cataract surgeons to perform a useful pre-operative personalized risk assessment.

Age related cataract surgery with phacoemulsification and intraocular lens (IOL) implantation is the most commonly performed ophthalmic surgery in adults of developed countries[1]. This constantly improving procedure leads to a marked improvement of patients' vision and quality of life, even when performed in eyes with concomitant diseases.[1]

Dry Eye Disease (DED), as well, represents a heavy social and economic burden, especially in developed countries,[2] and its prevalence is expected to increase, considering the global aging of population[3].

Cataract and DED are commonly associated in elderly.[4] Moreover, phacoemulsification can independently transiently induce or exacerbate DED symptoms, which are a major complaint in the early post-operative period,[4,5] with a peak in the first weeks after surgery, usually followed by gradual improvement.[6,7]

At present, there is a growing consensus on the multifactorial origin of the cataract surgery-related DED symptoms and on the importance of a careful peri-operative management of the ocular surface, especially in patients with pre-operative symptoms.[4, 8] However, the identification of healthy asymptomatic subjects more susceptible to develop post-operative ocular surface symptoms is still an unmet need.

Frailty, or frailty syndrome, may be conceptually defined as a clinically recognizable state of older adults with increased vulnerability to stressors, resulting from age-associated declines in physiologic reserve and function across multiple organ systems, such that the ability to cope with stressors is compromised, leading to adverse health outcome.[9] This condition is currently considered as an emerging public health problem[10] and its importance has been recently highlighted by the World Health Organization in the "World Report on Ageing and Health".[11]

There is large consensus on the use of Frailty Index (FI) as a frailty assessment tool. This score, which can be developed following a previously published standard procedure,[12] has

been validated as a predictor of surgical adverse outcomes in several fields,[13] including otolaryngology[14], ambulatory general surgery[15], and cardiac surgery.[16]

Interestingly, Esses GJ et al. recently examined the relationship between frailty and postsurgical pain in older adults, concluding that frailty was an independent predictor of intrusive pain at 3 months following surgery.[17] The authors speculated that the assessment of preoperative frailty might become a tool for the healthcare provider to focus attention on the individual patient's needs and to identify patients with high postsurgical risk to develop symptoms.

We hypothesized that the concept of frailty might be applied to the ocular surface morpho-functional unit of patients undergoing age-related cataract surgery. The purpose of this study was to build a new Ocular Surface Frailty Index (OSFI) and to assess its predictive value for the onset of cataract surgery-related ocular surface symptoms in the early post-operative period.

Methods

This single-centre, observational, longitudinal study included a large convenient sample of patients without DED symptoms who underwent uneventful cataract surgery at the San Giuseppe Eye Clinic-University Hospital of Milan during a period of four months, from March to June 2018.

We screened 405 consecutive patients scheduled for sutureless small-incision cataract surgery with phacoemulsification and posterior chamber monofocal IOL implantation. Inclusion criteria were diagnosis of age-related cataract and willingness to participate in the study and to subscribe the informed consent. Patients with pre-operative DED symptoms, defined as Ocular Surface Disease Index (OSDI) ≥13,[18] were excluded. Patients with DED signs without symptoms were included.~~DED signs without symptoms were not considered as exclusion criteria.~~[19]

We included 284 out of 405 patients. 114 patients were excluded before surgery (70 because of pre-operative DED symptoms, 14 of which without DED diagnostic signs, and 44 refused to participate) and 7 patients were excluded after surgery (2 because of intra-operative complications - posterior capsule rupture requiring anterior vitrectomy – and 5 were lost to follow-up).

The study protocol contemplated 4 visits: screening/baseline visit (V0, 7±3 days before surgery), aimed to verify the respect of inclusion and exclusion criteria and to calculate the OSFI score; 1° follow up (V1, 7±2 days after surgery), 2° follow up (V2, 30±7 days after surgery), and 3° follow up (V3, 90±7 days after surgery) visits, all aimed to verify the respect of inclusion and exclusion criteria, the onset of ocular surface symptoms and the presence of DED. Table 1, available at www.aaojournal.org, shows the procedures scheduled for each visit.

The study adhered to the tenets of the Declaration of Helsinki, it was approved by the local IRB, and written informed consent was obtained by each patient.

Procedures

Each patient completed a questionnaire regarding ~~on~~ his/her medical history, including information on ocular and systemic diseases, topical and systemic therapies, computer usage, and contact lens wear, and an Ocular Surface Disease Index (OSDI) questionnaire.[18]

The questionnaire specifically investigated if the patient had previous diagnosis of diabetes, rosacea, connective tissue diseases, thyroid malfunction, affective, somatoform disorders, anxiety and depression, the use of systemic and topical medications, computer usage >4 hours/day for at least 5 days/week, contact lens wear >4 hours/day for at least 5 days/week. Each patients completed the questionnaire autonomously and then discussed that with the investigator.

Clinical procedures for ocular surface examination included, when appropriate (Table 1, available at www.aaojournal.org), measurement and quantification of: tear film osmolarity (by TearLab, TearLab Corporation, Escondido, CA),[19] fluorescein tear film break-up time (T-BUT),[19] fluorescein ocular surface staining,[19] meibomian glands expressibility (grade 0-3),[19, 20] lid parallel conjunctival folds (LIPCOF; grade 0-3),[19, 21] and tear secrection (Schirmer test without anesthesia, performed at least 15 minutes after the end of the previous procedure).[19]

All the procedures were performed following the recommendations of the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Diagnostic Methodology report,[19] and the test sequence was arranged in order to best preserve their integrity.[19]

Ocular surface symptoms onset definition

Our main outcome was the onset of cataract surgery-related ocular surface symptoms, which was assessed using the OSDI questionnaire. We defined this condition as (OSDI Vn ≥13) AND (OSDI Vn – OSDI baseline ≥4)[18, 22] at V2 AND/OR V3.

DED diagnosis

Our secondary outcome was the presence of DED. According to the TFOS DEWS II Diagnostic Methodology report, DED was diagnosed in presence of a “screening” OSDI≥13 plus at least 1 of the following “homeostasis markers”: tear film osmolarity ≥308mOsm/L or interocular difference >8mOsm/L, T-BUT<10seconds, and positive corneal, conjunctival or lid margin staining.[19]

OSFI development

We borrowed the concept of frailty and we built the OSFI following and adapting the “standard procedure for creating a frailty index” previously described and validated by Searle SD et al.[12]

Briefly, OSFI is based on a count of “deficits in ocular surface health and/or factors potentially able to affect it”. Each investigator independently proposed a list of 30

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"candidate items". Agreement on the preliminary list of 19 items was then obtained through open discussion, paying attention to include variables which were associated with ocular surface health status, whose prevalence generally increase with age, and which don't saturate too early (for instance, presbyopia is nearly universal by age 55, saturating too early to be included in this type of frailty index)[12] ~~paying attention to include variables which were associated with ocular surface health status, whose prevalence generally increases with age, and which doesn't saturate too early.~~ Moreover, when considering the candidate deficits as a group, we selected the preliminary list trying to cover a range of systems and mechanisms having an impact on the ocular surface health. Finally we prioritized variables easily, quickly and cheaply assessable.

All binary variables were recorded using the convention that "0" indicates the absence of the deficit, and "1" the presence of it. Continuous and ordinal variables were graded into a score between "0" and "1", after testing different strategies for their categorization. The index is then expressed as: positive items/total number of assessed items.

The preliminary OSFI composition is reported in Table 2 (available at www.aaojournal.org).

In order to optimize the OSFI composition, we performed Spearman correlation and univariate logistic analysis to assess associations between each preliminary OSFI item and the development of post-surgical DED symptoms. We excluded the items showing a negative correlation coefficient and then we adopted a stepwise approach, progressively excluding the items with the weakest association for the outcome, defined as the highest P value in the regression model. At each step, OSFI score was re-calculated and its predictive value for the main outcome was re-tested on a bootstrap of 200 samples. This process was stopped when, moving from 10 to 9 items, the OSFI predictive value decreased, showing an higher P value of the regression analysis (Table 3).

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We tested different strategies for continuous and ordinal items categorization, selecting the ones providing the best OSFI predictive value.

The final OSFI composition, including 10 items, is reported in Table 4.

We assessed OSFI Inter-observer reproducibility on an external group of 20 patients undergoing cataract surgery. Two investigators (EV, FB) independently examined the patients and quantified the OSFI score in 2 consecutive days.

Statistical analysis

In descriptive statistics, normally distributed variables were presented as mean ± standard deviation (SD), non-normally distributed variables were presented as median (interquartile range), and categorical variables as number (percentage).

Comparisons between groups were made using Mann-Whitney U test for continuous variables, dependent on distribution, and χ^2 test for categorical variables.

Correlations between continuous variables were tested by Spearman's correlation coefficient.

Receiver Operating Characteristic (ROC) curve analysis was used to identify the optimal OSFI cut-off point for development of post-surgical DED symptoms.

Multivariable logistic regression analysis was performed in a standard stepwise approach, with inclusion of significant variables ($P < 0.05$) after univariable regression.

Bootstrapping was performed on 200 samples, with simple sampling strategy and 95%CI.

Inter-observer reproducibility was assessed by Interclass Correlation Coefficient (ICC).The minimum criterion for tests of significance was $P<0.05$.

Statistical analysis was conducted using a commercial software (SPSS for Windows, v. 20; SPSS Sciences, Chicago, IL).

Results

The mean age of the 284 included patients was 74.53±8.16 years; 105 (37%) were males.

At baseline, given the exclusion criteria, none of the included patients showed DED

symptoms (OSDI≥13). However, 206 patients (72.5%) had at least one DED sign without symptoms. Specifically, positive values of tear osmolarity, T-BUT and ocular surface fluorescein staining[19] were found in 64 (22.5%), 185 (65.1%), and 53 (18.7%) patients, respectively.

The overall cumulative percentage of patients showing ocular surface symptoms at V2 AND/OR V3 was 17% (48 of 284), Table 5. Of these patients, 36 (75%) fulfilled the DED diagnostic criteria in at least 1 follow-up visit.

Univariate logistic regression showed that age and gender had no association with DED symptoms onset after cataract surgery (OR=0.98 (0.95-1.02), P=0.38 and OR=1.26 (0.65-2.41), P=0.49, respectively)..

Moreover, no baseline DED sign showed to be a significant predictor for post-operative onset of symptoms (P=0.25, P=0.10, and P=0.44 for osmolarity, T-BUT, and staining, respectively).

Our patients' OSFI score ranged from 0 to 0.666, with a median value of 0.200 (0.133-0.266).

The prevalence of each OSFI item is shown in Figure 1 (available at www.aaojournal.org) and in Table 3; the 5 most common components were reduced T-BUT (185 [65%]), computer usage (83 [29%]), psychiatric conditions (80 [28%]), LIPCOF=3 (54 [19%]), and MGs expressibility=3 (41 [14%]).

The twenty patients assessed for inter-observer reproducibility showed almost perfect agreement (ICC=0.93) in OSFI score quantification between EV (0.216 [0.162-0.370]) and FB (0.225 [0.162-0.362]).

OSFI score of patients who showed DED symptoms at V2 AND/OR V3 (0.300 [0.233-0.399]) was significantly higher of the score (0.166 [0.116-0.249]) of patients without post-surgical symptoms (P<0.001, Mann-Whitney U test).

In order to support the OSFI construct validity, we compared the rate of post-operative

symptoms of patients with the lowest OSFI values (10th percentile) vs the rate of symptoms of patients with the highest OSFI values (90th percentile): 0 vs 18/28 (64%); P<0.001, χ^2 test. Moreover, we compared OSFI values of patients with the lowest max post-operative OSDI values (10th percentile) vs OSFI values of patients with the highest max post-operative OSDI values (90th percentile): 0.183 (0.108-0.249) vs 0.333 (0.233-0.433); P<0.001, Mann-Whitney U test.

In a logistic regression model, none of the OSFI components showed to be a significant predictor of DED symptoms' onset (Table 3).

On ROC curve analysis, the area under the curve was 0.821. OSFI value of 0.241, with sensitivity of 74% and specificity of 77%, showed the highest Youden index. However, setting the specificity to 90%, we found a cut-off of 0.3 (sensitivity =53%) (Figure 2).

In our population, we found 230 (81%) patients with OSFI<0.3 and 54 (19%) patients with frail ocular surface (OSFI≥0.3); figure 3.

The rate of post-operative DED symptoms was significantly higher in patients with frail ocular surface (27 of 54; 50%) than in patients with robust ocular surface (22 of 230; 9%); P<0.001, χ^2 test.

Logistic regression analysis showed that OSFI≥0.3 was a good predictor of ocular surface symptoms onset (odds ratio (OR)=9.45; 95%CI (4.74-18.82). P<0.001). No significant changes were found after adjusting the analysis for age and gender (OR=9.35 (4.68-18.68), P<0.001).

Bootstrapping 200 samples, CI of this logistic analysis remained above 1.0 (1.58-2.99); P<0.01.

OSFI≥0.3 was a significant predictor also for the development of post-surgical DED (defined as symptoms + at least 1 sign): OR=3.54; 95%CI (1.73-7.21); P<0.001.

Discussion

Even if the advanced age can carry increased risk of post-surgical adverse events,

the chronological age is not suitable to be used as a tool for pre-operative risk assessment and stratification.[22, 23, 24] ~~Geriatric surgery taught us that advanced age can carry increased risk of adverse events, including mortality and morbidity, after surgery.[23] However, the scientific literature clearly showed that the chronological age should not be used as a tool for pre-operative risk assessment and stratification.[23, 24]~~

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The concept of frailty arises from the need to identify those individual with decreased functional capacity, and therefore to identify patients with an increased risk of post-surgical negative events.[11, 23, 24] A large growing body of literature shows the importance of measuring frailty before performing several different types of surgeries and the Frailty Indexes, although not yet optimized and adequately standardized, are reported to be one of the most prominent tools for patients' risk stratification.[23, 24]

Age-related cataract surgery is a very common geriatric surgery with no (or maybe with beneficial) impact on mortality and systemic morbidity,[25] able to clearly improve visual function and quality of life,[26] but associated with a relevant risk of inducing or worsening ocular surface symptoms.[4] Several studies focused on the multifactorial pathophysiological mechanisms underlying cataract surgery-induced DED, including the use of topical anesthetics and exposure desiccation, possible light toxicity from the operating microscope, nerve transection, elevation of inflammatory factors, goblet cell loss, and meibomian gland dysfunction, and on the most effective therapeutic approaches for this condition.[4] However, at present, there are no validated tools to be used for stratifying the risk of a clinically relevant negative impact of cataract surgery on the ocular surface health. Previous studies, with heterogeneous designs, populations, and methodologies, explored the predictive value of several peri-operative parameters (e.g. age, diabetes, socio-economic status, site of incision, microscope light exposure time, …).[27-29] These reports showed conflicting results and failed to provide consistent evidence[3] supporting the use of any of these parameters for risk assessment. Our results confirmed this issue,

showing that no baseline personal or clinical data would be a significant predictor of the development of post-surgical symptoms.

The TFOS DEWS II Iatrogenic report generically stated that “even in the absence of DED, ocular surface disease should be managed before cataract surgery”.[4] This recommendation highlights the peculiar challenge represented by the relevant percentage (17% in our study population) of asymptomatic patients developing ocular surface symptoms after surgery.

We designed and developed the OSFI starting from the concept of frailty and its different applications for pre-operative risk assessment in general and geriatric surgery.~~Borrowing from researches on general and geriatric surgery the concept of frailty and the procedure to develop a tool for its quantification, and adapting them to the ocular surface, we built the OSFI~~. This novel tool, simultaneously evaluating several different potential mechanisms and markers of “deficits in ocular surface health”, might allow performing effective pre-operative risk stratification. The identification of non-DED patients more susceptible to develop surgery-related ocular surface symptoms and DED might be useful to improve patient-doctor communication, to adjust patients’ expectations, reducing the subsequent dissatisfaction and to plan a more personalized and successful management of the patients’ ocular surface.

We included in the preliminary OSFI 19 items, related to medical history and clinical findings, that we considered being potentially important “deficits in ocular surface health or factors potentially able to affect it”. Most of these items have been classified by the TFOS DEWS II Epidemiology Report as “consistent” or “probable” risk factors for DED.[3] Moreover, we paid attention to select items suitable to be easily, quickly and cheaply assessed in the context of a general ophthalmic clinical setting/ cataract service. For this reason, we avoided to include in the OSFI data requiring high-tech, time-consuming, expensive exams or procedures broadly used just in cornea/ocular surface reference

centers (e.g. OCT meniscometry, tear film osmolarity, infrared meibography, …).

In order to improve both the OSFI predictive value and clinical utility, we excluded from the preliminary index the items showing negative and weak positive correlations with the outcome. This process led to the definition of the final OSFI, including 10 items.

Nevertheless, OSFI quantification would require adding some extra minutes to the pre-operative examination of patients and this might limit its spread and use in daily clinical practice. However, given the relevance of the potential post-operative issue,[4, 8] this seems to be a reasonable effort to be done in order to perform an effective risk assessment.

Our selection of OSFI components is somewhat arbitrary and might be refined through future studies. However, this issue is inherent in all the processes aimed to build new tools for frailty assessment and, interestingly, previous studies showed that, if the selection criteria are properly applied, the results are insensitive to the precise composition of the index.[12, 30]

The OSFI cut-off of 0.3 allowed us to identify a small group (19% of the asymptomatic subjects) of patients with a frail ocular surface morpho-functional unit, at high risk to develop post-operative ocular surface symptoms. These patients might be managed with a personalized approach, both before and after surgery, including not only tailored therapies but also a peculiar communication effort.

In order to validate the OSFI score, we considered its inter-observer reproducibility, and content and construct validity.

Reproducibility was tested in the most challenging conditions, with 2 independent investigators quantifying the Index in 2 different days, and it showed an almost perfect inter-observer agreement.

Content validity of the preliminary OSFI was partly assured by its development procedure, based on agreement among experts (the investigators) working on updated evidences on the topic, recently selected by the TFOS DEWS II panel.[3] Content validity of the final OSFI

was assessed arranging in a matrix 4 key etiologic domains of DED[31] and the OSFI items (Table 6, available at www.aaojournal.org). The final OSFI items seem to be well-distributed and related to tear film instability, ocular surface inflammation, neuro-sensory abnormalities, and ocular surface epithelial damage. Interestingly, the stepwise process excluded ocular surface fluorescein staining and Schirmer test from the final OSFI. Patients with severe epitheliopathy and/or severely reduced tears secretion are generally symptomatic and they were excluded at the screening visit. About mild epitheliopathy and/or hypersecretion, these results might further confirm the well-known lack of correlation between DED signs and symptoms.[32] Moreover, a proportion of normal corneas, especially after the age of 50, show punctate fluorescein uptake.[33]

This is the first paper theorizing and proposing the concept of ocular surface frailty, and developing a tool for its assessment. In the absence of other reference tools for ocular surface frailty quantification and in order to support the OSFI construct validity, we demonstrated that the rate of post-operative symptoms of the patients with the lowest OSFI values (10th percentile) was 0 and the rate of symptoms of the patients with the highest OSFI values (90th percentile) was 64%. We also demonstrated that the patients with the highest max post-operative OSDI values (90th percentile) had significantly higher OSFI values than the patients with the lowest max post-operative OSDI values (10th percentile).

We did not assess OSFI internal consistency. The presence of strong correlations among the items is important in scales including items tapping a single domain or attribute. In indexes like OSFI, the items are not manifestations of an underlying construct (effect indicators) but the items themselves define the construct (causal indicators). In this type of tools, the items may or may not covariate, irrespective of their relationship with the construct.[34]

Finally, we supported the internal validation of OSFI performing the stepwise process for

the final index definition and the logistic regression analysis of the index cut-off predictivity on a bootstrap of 200 samples.

External validation, however, remains the gold standard to assess the true validity of OSFI when applied to other patient samples, and this will be our next step. External validation will have to be performed on a larger, multi-centric, more heterogeneous population, including patients undergoing cataract surgery with multifocal IOL implantation. This latter point is of particular importance since these patients have especially high pre-operative expectations and ocular surface symptoms may significantly affect patients' perception of the surgery's outcome.

This study has other limitations, including the short follow-up. However, this research was focused on cataract surgery-related DED symptoms onset, reported mainly in the first weeks after surgery,[6,7] and not on their course.

In conclusion, we built a novel tool in order to assess the frailty of the ocular surface of patients undergoing cataract surgery. The OSFI, which showed to be the only significant predictor of ocular surface symptoms onset in our patients, will have to be validated in different and larger populations. This tool might be refined and maybe adapted to the reality of the different Countries, but we think that this type of novel application of the concept of frailty could contribute to improve our capabilities to have an effective and personalized approach to the ocular surface of patients undergoing cataract surgery.

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Figure legends

Figure 1. Population prevalence of OSFI components.

The prevalence of OSFI components ranged from 65% for BUT<10seconds to 0.7% for connective tissue diseases. T-BUT: fluorescein tear film break-up time; LIPCOF: lid parallel conjunctival folds; MGs: Meibomian glands; OSDI: Ocular Surface Disease Index.

Figure 2. Receiver Operating Curve Analysis for post-operative DED symptoms onset.

The Area Under the Curve (AUC) was 0.821. OSFI score of 0.241 showed the highest, with sensitivity of 74% and specificity of 77%, showed the highest Youden index. OSFI cut-off of 0.3 had sensitivity of 53% and specificity of 90%.

Figure 3. Distribution of Ocular Surface Frailty Index scores.

Higher values indicate a higher degree of frailty. 54 patients (19%) had a frail ocular surface, with OSFI≥0.3.

TITLE PAGE

The Ocular Surface Frailty Index as a predictor of ocular surface symptoms onset after cataract surgery

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Financial Support: None

No conflicting relationship exists for any author

Short title: OSFI as a predictor of cataract surgery-related DED symptoms onset

ABSTRACT

Purpose: The identification of healthy subjects more susceptible to develop post-surgical ocular surface symptoms is still an unmet need. We performed this study to build a new Ocular Surface Frailty Index (OSFI) and to assess its predictive value for dry eye (DED) symptoms onset after cataract surgery.

Design: Single-centre, observational, longitudinal study.

Participants: We screened 405 consecutive patients scheduled for phacoemulsification for age-related cataract. 284 eyes of 284 patients without pre-operative DED symptoms who underwent uneventful cataract surgery were included in the analysis.

Methods: Borrowing a concept from geriatric surgery and following a previously validated procedure, we built a tool to assess ocular surface frailty. Starting from a preliminary list of 19 potential items, the final OSFI, including 10 “deficits in ocular surface health and/or factors potentially able to affect it”, was developed by a stepwise approach. Pre-operative OSFI was calculated for each enrolled patient and diagnostic tests for DED were performed (following the TFOS DEWS II recommendations) at the screening visit and 1 week (V1), 1 month (V2), and 3 months (V3) after surgery. We evaluated OSFI predictivity for the presence of DED symptoms at V2 AND/OR V3.

Main Outcome Measures: The rate of ocular surface symptoms at V2 AND/OR V3.

Results: Our patients’ OSFI score ranged from 0 to 0.666, with a median value of 0.200 (0.133-0.266). The percentage of patients with post-surgical ocular surface symptoms was 17%. Using an OSFI cut-off of 0.300, we identified a small group (19% of the asymptomatic subjects) of patients with frail ocular surfaces, who had a significantly higher risk to develop post-surgical DED symptoms (50.0% vs 9.6%; $P<0.001$, $\chi 2$ test). Logistic regression analysis showed that OSFI≥0.3 (but not age, gender or any pre-operative sign) was a good predictor of ocular surface symptoms onset (odds ratio (OR)

=9.45; 95%CI (4.74-18.82). Regression was still significant when performed on 200 bootstrapped samples.

Conclusions: The OSFI can be easily and quickly calculated using non-invasive and low-tech procedures and it showed to be predictive of post-operative ocular surface symptoms onset. This novel tool might allow cataract surgeons to perform a useful pre-operative personalized risk assessment.

Age related cataract surgery with phacoemulsification and intraocular lens (IOL) implantation is the most commonly performed ophthalmic surgery in adults of developed countries[1]. This constantly improving procedure leads to a marked improvement of patients' vision and quality of life, even when performed in eyes with concomitant diseases.[1]

Dry Eye Disease (DED), as well, represents a heavy social and economic burden, especially in developed countries,[2] and its prevalence is expected to increase, considering the global aging of population[3].

Cataract and DED are commonly associated in elderly.[4] Moreover, phacoemulsification can independently transiently induce or exacerbate DED symptoms, which are a major complaint in the early post-operative period,[4,5] with a peak in the first weeks after surgery, usually followed by gradual improvement.[6,7]

At present, there is a growing consensus on the multifactorial origin of the cataract surgery-related DED symptoms and on the importance of a careful peri-operative management of the ocular surface, especially in patients with pre-operative symptoms.[4, 8] However, the identification of healthy asymptomatic subjects more susceptible to develop post-operative ocular surface symptoms is still an unmet need.

Frailty, or frailty syndrome, may be conceptually defined as a clinically recognizable state of older adults with increased vulnerability to stressors, resulting from age-associated declines in physiologic reserve and function across multiple organ systems, such that the ability to cope with stressors is compromised, leading to adverse health outcome.[9] This condition is currently considered as an emerging public health problem[10] and its importance has been recently highlighted by the World Health Organization in the "World Report on Ageing and Health".[11]

There is large consensus on the use of Frailty Index (FI) as a frailty assessment tool. This score, which can be developed following a previously published standard procedure,[12] has

been validated as a predictor of surgical adverse outcomes in several fields,[13] including otolaryngology[14], ambulatory general surgery[15], and cardiac surgery.[16]

Interestingly, Esses GJ et al. recently examined the relationship between frailty and postsurgical pain in older adults, concluding that frailty was an independent predictor of intrusive pain at 3 months following surgery.[17] The authors speculated that the assessment of preoperative frailty might become a tool for the healthcare provider to focus attention on the individual patient's needs and to identify patients with high postsurgical risk to develop symptoms.

We hypothesized that the concept of frailty might be applied to the ocular surface morpho-functional unit of patients undergoing age-related cataract surgery. The purpose of this study was to build a new Ocular Surface Frailty Index (OSFI) and to assess its predictive value for the onset of cataract surgery-related ocular surface symptoms in the early post-operative period.

Methods

This single-centre, observational, longitudinal study included a large convenient sample of patients without DED symptoms who underwent uneventful cataract surgery at the San Giuseppe Eye Clinic-University Hospital of Milan during a period of four months, from March to June 2018.

We screened 405 consecutive patients scheduled for sutureless small-incision cataract surgery with phacoemulsification and posterior chamber monofocal IOL implantation. Inclusion criteria were diagnosis of age-related cataract and willingness to participate in the study and to subscribe the informed consent. Patients with pre-operative DED symptoms, defined as Ocular Surface Disease Index (OSDI) ≥13,[18] were excluded. Patients with DED signs without symptoms were included.[19]

We included 284 out of 405 patients. 114 patients were excluded before surgery (70 because of pre-operative DED symptoms, 14 of which without DED diagnostic signs, and

44 refused to participate) and 7 patients were excluded after surgery (2 because of intra-operative complications - posterior capsule rupture requiring anterior vitrectomy – and 5 were lost to follow-up).

The study protocol contemplated 4 visits: screening/baseline visit (V0, 7±3 days before surgery), aimed to verify the respect of inclusion and exclusion criteria and to calculate the OSFI score; 1° follow up (V1, 7±2 days after surgery), 2° follow up (V2, 30±7 days after surgery), and 3° follow up (V3, 90±7 days after surgery) visits, all aimed to verify the respect of inclusion and exclusion criteria, the onset of ocular surface symptoms and the presence of DED. Table 1, available at www.aaojournal.org, shows the procedures scheduled for each visit.

The study adhered to the tenets of the Declaration of Helsinki, it was approved by the local IRB, and written informed consent was obtained by each patient.

Procedures

Each patient completed a questionnaire regarding his/her medical history, including information on ocular and systemic diseases, topical and systemic therapies, computer usage, and contact lens wear, and an Ocular Surface Disease Index (OSDI) questionnaire.[18]

The questionnaire specifically investigated if the patient had previous diagnosis of diabetes, rosacea, connective tissue diseases, thyroid malfunction, affective, somatoform disorders, anxiety and depression, the use of systemic and topical medications, computer usage >4 hours/day for at least 5 days/week, contact lens wear >4 hours/day for at least 5 days/week. Each patients completed the questionnaire autonomously and then discussed that with the investigator.

Clinical procedures for ocular surface examination included, when appropriate (Table 1, available at www.aaojournal.org), measurement and quantification of: tear film osmolarity (by TearLab, TearLab Corporation, Escondido, CA),[19] fluorescein tear film break-up time

(T-BUT),[19] fluorescein ocular surface staining,[19] meibomian glands expressibility (grade 0-3),[19, 20] lid parallel conjunctival folds (LIPCOF; grade 0-3),[19, 21] and tear secrection (Schirmer test without anesthesia, performed at least 15 minutes after the end of the previous procedure).[19]

All the procedures were performed following the recommendations of the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Diagnostic Methodology report,[19] and the test sequence was arranged in order to best preserve their integrity.[19]

Ocular surface symptoms onset definition

Our main outcome was the onset of cataract surgery-related ocular surface symptoms, which was assessed using the OSDI questionnaire. We defined this condition as (OSDI Vn ≥13) AND (OSDI Vn – OSDI baseline ≥4)[18, 22] at V2 AND/OR V3.

DED diagnosis

Our secondary outcome was the presence of DED. According to the TFOS DEWS II Diagnostic Methodology report, DED was diagnosed in presence of a “screening” OSDI≥13 plus at least 1 of the following “homeostasis markers”: tear film osmolarity ≥308mOsm/L or interocular difference >8mOsm/L, T-BUT<10seconds, and positive corneal, conjunctival or lid margin staining.[19]

OSFI development

We borrowed the concept of frailty and we built the OSFI following and adapting the “standard procedure for creating a frailty index” previously described and validated by Searle SD et al.[12]

Briefly, OSFI is based on a count of “deficits in ocular surface health and/or factors potentially able to affect it”. Each investigator independently proposed a list of 30 “candidate items”. Agreement on the preliminary list of 19 items was then obtained through open discussion, paying attention to include variables which were associated with ocular surface health status, whose prevalence generally increase with age, and which

don't saturate too early (for instance, presbyopia is nearly universal by age 55, saturating too early to be included in this type of frailty index)[12] Moreover, when considering the candidate deficits as a group, we selected the preliminary list trying to cover a range of systems and mechanisms having an impact on the ocular surface health. Finally we prioritized variables easily, quickly and cheaply assessable.

All binary variables were recorded using the convention that "0" indicates the absence of the deficit, and "1" the presence of it. Continuous and ordinal variables were graded into a score between "0" and "1", after testing different strategies for their categorization. The index is then expressed as: positive items/total number of assessed items.

The preliminary OSFI composition is reported in Table 2 (available at www.aaojournal.org).

In order to optimize the OSFI composition, we performed Spearman correlation and univariate logistic analysis to assess associations between each preliminary OSFI item and the development of post-surgical DED symptoms. We excluded the items showing a negative correlation coefficient and then we adopted a stepwise approach, progressively excluding the items with the weakest association for the outcome, defined as the highest P value in the regression model. At each step, OSFI score was re-calculated and its predictive value for the main outcome was re-tested on a bootstrap of 200 samples. This process was stopped when, moving from 10 to 9 items, the OSFI predictive value decreased, showing an higher P value of the regression analysis (Table 3).

We tested different strategies for continuous and ordinal items categorization, selecting the ones providing the best OSFI predictive value.

The final OSFI composition, including 10 items, is reported in Table 4.

We assessed OSFI Inter-observer reproducibility on an external group of 20 patients undergoing cataract surgery. Two investigators (EV, FB) independently examined the patients and quantified the OSFI score in 2 consecutive days.

Statistical analysis

In descriptive statistics, normally distributed variables were presented as mean ± standard deviation (SD), non-normally distributed variables were presented as median (interquartile range), and categorical variables as number (percentage).

Comparisons between groups were made using Mann-Whitney U test for continuous variables, dependent on distribution, and χ^2 test for categorical variables.

Correlations between continuous variables were tested by Spearman's correlation coefficient.

Receiver Operating Characteristic (ROC) curve analysis was used to identify the optimal OSFI cut-off point for development of post-surgical DED symptoms.

Multivariable logistic regression analysis was performed in a standard stepwise approach, with inclusion of significant variables ($P < 0.05$) after univariable regression.

Bootstrapping was performed on 200 samples, with simple sampling strategy and 95%CI.

Inter-observer reproducibility was assessed by Interclass Correlation Coefficient (ICC).The minimum criterion for tests of significance was $P<0.05$.

Statistical analysis was conducted using a commercial software (SPSS for Windows, v. 20; SPSS Sciences, Chicago, IL).

Results

The mean age of the 284 included patients was 74.53±8.16 years; 105 (37%) were males.

At baseline, given the exclusion criteria, none of the included patients showed DED symptoms (OSDI≥13). However, 206 patients (72.5%) had at least one DED sign without symptoms. Specifically, positive values of tear osmolarity, T-BUT and ocular surface fluorescein staining[19] were found in 64 (22.5%), 185 (65.1%), and 53 (18.7%) patients, respectively.

The overall cumulative percentage of patients showing ocular surface symptoms at V2 AND/OR V3 was 17% (48 of 284), Table 5. Of these patients, 36 (75%) fulfilled the DED

diagnostic criteria in at least 1 follow-up visit.

Univariate logistic regression showed that age and gender had no association with DED symptoms onset after cataract surgery (OR=0.98 (0.95-1.02), P=0.38 and OR=1.26 (0.65-2.41), P=0.49, respectively)..

Moreover, no baseline DED sign showed to be a significant predictor for post-operative onset of symptoms (P=0.25, P=0.10, and P=0.44 for osmolarity, T-BUT, and staining, respectively).

Our patients' OSFI score ranged from 0 to 0.666, with a median value of 0.200 (0.133-0.266).

The prevalence of each OSFI item is shown in Figure 1 (available at www.aaojournal.org) and in Table 3; the 5 most common components were reduced T-BUT (185 [65%]), computer usage (83 [29%]), psychiatric conditions (80 [28%]), LIPCOF=3 (54 [19%]), and MGs expressibility=3 (41 [14%]).

The twenty patients assessed for inter-observer reproducibility showed almost perfect agreement (ICC=0.93) in OSFI score quantification between EV (0.216 [0.162-0.370]) and FB (0.225 [0.162-0.362]).

OSFI score of patients who showed DED symptoms at V2 AND/OR V3 (0.300 [0.233-0.399]) was significantly higher of the score (0.166 [0.116-0.249]) of patients without post-surgical symptoms (P<0.001, Mann-Whitney U test).

In order to support the OSFI construct validity, we compared the rate of post-operative symptoms of patients with the lowest OSFI values (10th percentile) vs the rate of symptoms of patients with the highest OSFI values (90th percentile): 0 vs 18/28 (64%); P<0.001, χ^2 test. Moreover, we compared OSFI values of patients with the lowest max post-operative OSDI values (10th percentile) vs OSFI values of patients with the highest max post-operative OSDI values (90th percentile): 0.183 (0.108-0.249) vs 0.333 (0.233-0.433); P<0.001, Mann-Whitney U test.

In a logistic regression model, none of the OSFI components showed to be a significant predictor of DED symptoms' onset (Table 3).

On ROC curve analysis, the area under the curve was 0.821. OSFI value of 0.241, with sensitivity of 74% and specificity of 77%, showed the highest Youden index. However, setting the specificity to 90%, we found a cut-off of 0.3 (sensitivity =53%) (Figure 2).

In our population, we found 230 (81%) patients with OSFI<0.3 and 54 (19%) patients with frail ocular surface (OSFI≥0.3); figure 3.

The rate of post-operative DED symptoms was significantly higher in patients with frail ocular surface (27 of 54; 50%) than in patients with robust ocular surface (22 of 230; 9%); P<0.001, χ^2 test.

Logistic regression analysis showed that OSFI≥0.3 was a good predictor of ocular surface symptoms onset (odds ratio (OR)=9.45; 95%CI (4.74-18.82). P<0.001). No significant changes were found after adjusting the analysis for age and gender (OR=9.35 (4.68-18.68), P<0.001).

Bootstrapping 200 samples, CI of this logistic analysis remained above 1.0 (1.58-2.99); P<0.01.

OSFI≥0.3 was a significant predictor also for the development of post-surgical DED (defined as symptoms + at least 1 sign): OR=3.54; 95%CI (1.73-7.21); P<0.001.

Discussion

Even if the advanced age can carry increased risk of post-surgical adverse events, the chronological age is not suitable to be used as a tool for pre-operative risk assessment and stratification.[22, 23, 24] The concept of frailty arises from the need to identify those individual with decreased functional capacity, and therefore to identify patients with an increased risk of post-surgical negative events.[11, 23, 24] A large growing body of literature shows the importance

of measuring frailty before performing several different types of surgeries and the Frailty

Indexes, although not yet optimized and adequately standardized, are reported to be one of the most prominent tools for patients' risk stratification.[23, 24]

Age-related cataract surgery is a very common geriatric surgery with no (or maybe with beneficial) impact on mortality and systemic morbidity,[25] able to clearly improve visual function and quality of life,[26] but associated with a relevant risk of inducing or worsening ocular surface symptoms.[4] Several studies focused on the multifactorial pathophysiological mechanisms underlying cataract surgery-induced DED, including the use of topical anesthetics and exposure desiccation, possible light toxicity from the operating microscope, nerve transection, elevation of inflammatory factors, goblet cell loss, and meibomian gland dysfunction, and on the most effective therapeutic approaches for this condition.[4] However, at present, there are no validated tools to be used for stratifying the risk of a clinically relevant negative impact of cataract surgery on the ocular surface health. Previous studies, with heterogeneous designs, populations, and methodologies, explored the predictive value of several peri-operative parameters (e.g. age, diabetes, socio-economic status, site of incision, microscope light exposure time, …).[27-29] These reports showed conflicting results and failed to provide consistent evidence[3] supporting the use of any of these parameters for risk assessment. Our results confirmed this issue, showing that no baseline personal or clinical data would be a significant predictor of the development of post-surgical symptoms.

The TFOS DEWS II Iatrogenic report generically stated that "even in the absence of DED, ocular surface disease should be managed before cataract surgery".[4] This recommendation highlights the peculiar challenge represented by the relevant percentage (17% in our study population) of asymptomatic patients developing ocular surface symptoms after surgery.

We designed and developed the OSFI starting from the concept of frailty and its different applications for pre-operative risk assessment in general and geriatric surgery.. This novel

tool, simultaneously evaluating several different potential mechanisms and markers of "deficits in ocular surface health", might allow performing effective pre-operative risk stratification. The identification of non-DED patients more susceptible to develop surgery-related ocular surface symptoms and DED might be useful to improve patient-doctor communication, to adjust patients' expectations, reducing the subsequent dissatisfaction and to plan a more personalized and successful management of the patients' ocular surface.

We included in the preliminary OSFI 19 items, related to medical history and clinical findings, that we considered being potentially important "deficits in ocular surface health or factors potentially able to affect it". Most of these items have been classified by the TFOS DEWS II Epidemiology Report as "consistent" or "probable" risk factors for DED.[3]

Moreover, we paid attention to select items suitable to be easily, quickly and cheaply assessed in the context of a general ophthalmic clinical setting/ cataract service. For this reason, we avoided to include in the OSFI data requiring high-tech, time-consuming, expensive exams or procedures broadly used just in cornea/ocular surface reference centers (e.g. OCT meniscometry, tear film osmolarity, infrared meibography, …).

In order to improve both the OSFI predictive value and clinical utility, we excluded from the preliminary index the items showing negative and weak positive correlations with the outcome. This process led to the definition of the final OSFI, including 10 items.

Nevertheless, OSFI quantification would require adding some extra minutes to the pre-operative examination of patients and this might limit its spread and use in daily clinical practice. However, given the relevance of the potential post-operative issue,[4, 8] this seems to be a reasonable effort to be done in order to perform an effective risk assessment.

Our selection of OSFI components is somewhat arbitrary and might be refined through future studies. However, this issue is inherent in all the processes aimed to build new tools for frailty assessment and, interestingly, previous studies showed that, if the selection

criteria are properly applied, the results are insensitive to the precise composition of the index.[12, 30]

The OSFI cut-off of 0.3 allowed us to identify a small group (19% of the asymptomatic subjects) of patients with a frail ocular surface morpho-functional unit, at high risk to develop post-operative ocular surface symptoms. These patients might be managed with a personalized approach, both before and after surgery, including not only tailored therapies but also a peculiar communication effort.

In order to validate the OSFI score, we considered its inter-observer reproducibility, and content and construct validity.

Reproducibility was tested in the most challenging conditions, with 2 independent investigators quantifying the Index in 2 different days, and it showed an almost perfect inter-observer agreement.

Content validity of the preliminary OSFI was partly assured by its development procedure, based on agreement among experts (the investigators) working on updated evidences on the topic, recently selected by the TFOS DEWS II panel.[3] Content validity of the final OSFI was assessed arranging in a matrix 4 key etiologic domains of DED[31] and the OSFI items (Table 6, available at www.aaojournal.org). The final OSFI items seem to be well-distributed and related to tear film instability, ocular surface inflammation, neuro-sensory abnormalities, and ocular surface epithelial damage. Interestingly, the stepwise process excluded ocular surface fluorescein staining and Schirmer test from the final OSFI. Patients with severe epitheliopathy and/or severely reduced tears secretion are generally symptomatic and they were excluded at the screening visit. About mild epitheliopathy and/or hypersecretion, these results might further confirm the well-known lack of correlation between DED signs and symptoms.[32] Moreover, a proportion of normal corneas, especially after the age of 50, show punctate fluorescein uptake.[33]

This is the first paper theorizing and proposing the concept of ocular surface frailty, and

developing a tool for its assessment. In the absence of other reference tools for ocular surface frailty quantification and in order to support the OSFI construct validity, we demonstrated that the rate of post-operative symptoms of the patients with the lowest OSFI values (10th percentile) was 0 and the rate of symptoms of the patients with the highest OSFI values (90th percentile) was 64%. We also demonstrated that the patients with the highest max post-operative OSDI values (90th percentile) had significantly higher OSFI values than the patients with the lowest max post-operative OSDI values (10th percentile).

We did not assess OSFI internal consistency. The presence of strong correlations among the items is important in scales including items tapping a single domain or attribute. In indexes like OSFI, the items are not manifestations of an underlying construct (effect indicators) but the items themselves define the construct (causal indicators). In this type of tools, the items may or may not covariate, irrespective of their relationship with the construct.[34]

Finally, we supported the internal validation of OSFI performing the stepwise process for the final index definition and the logistic regression analysis of the index cut-off predictivity on a bootstrap of 200 samples.

External validation, however, remains the gold standard to assess the true validity of OSFI when applied to other patient samples, and this will be our next step. External validation will have to be performed on a larger, multi-centric, more heterogeneous population, including patients undergoing cataract surgery with multifocal IOL implantation. This latter point is of particular importance since these patients have especially high pre-operative expectations and ocular surface symptoms may significantly affect patients' perception of the surgery's outcome.

This study has other limitations, including the short follow-up. However, this research was focused on cataract surgery-related DED symptoms onset, reported mainly in the first

weeks after surgery,[6,7] and not on their course.

In conclusion, we built a novel tool in order to assess the frailty of the ocular surface of patients undergoing cataract surgery. The OSFI, which showed to be the only significant predictor of ocular surface symptoms onset in our patients, will have to be validated in different and larger populations. This tool might be refined and maybe adapted to the reality of the different Countries, but we think that this type of novel application of the concept of frailty could contribute to improve our capabilities to have an effective and personalized approach to the ocular surface of patients undergoing cataract surgery.

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Figure legends

Figure 1. Population prevalence of OSFI components.

The prevalence of OSFI components ranged from 65% for BUT<10seconds to 0.7% for connective tissue diseases. T-BUT: fluorescein tear film break-up time; LIPCOF: lid parallel conjunctival folds; MGs: Meibomian glands; OSDI: Ocular Surface Disease Index.

Figure 2. Receiver Operating Curve Analysis for post-operative DED symptoms onset.

The Area Under the Curve (AUC) was 0.821. OSFI score of 0.241 showed the highest, with sensitivity of 74% and specificity of 77%, showed the highest Youden index. OSFI cut-off of 0.3 had sensitivity of 53% and specificity of 90%.

Figure 3. Distribution of Ocular Surface Frailty Index scores.

Higher values indicate a higher degree of frailty. 54 patients (19%) had a frail ocular surface, with OSFI≥0.3.

Figure 2

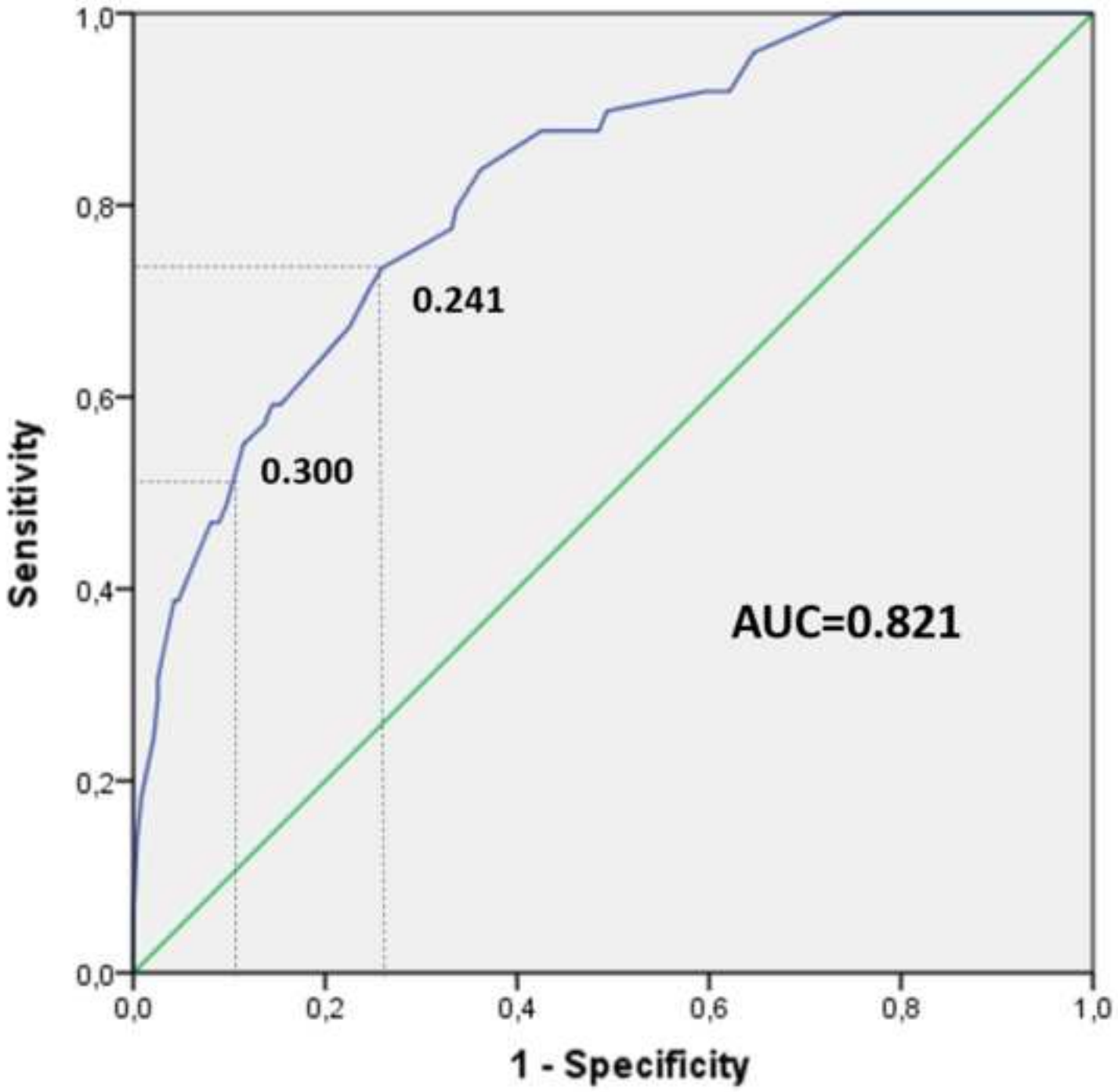

Figure 3

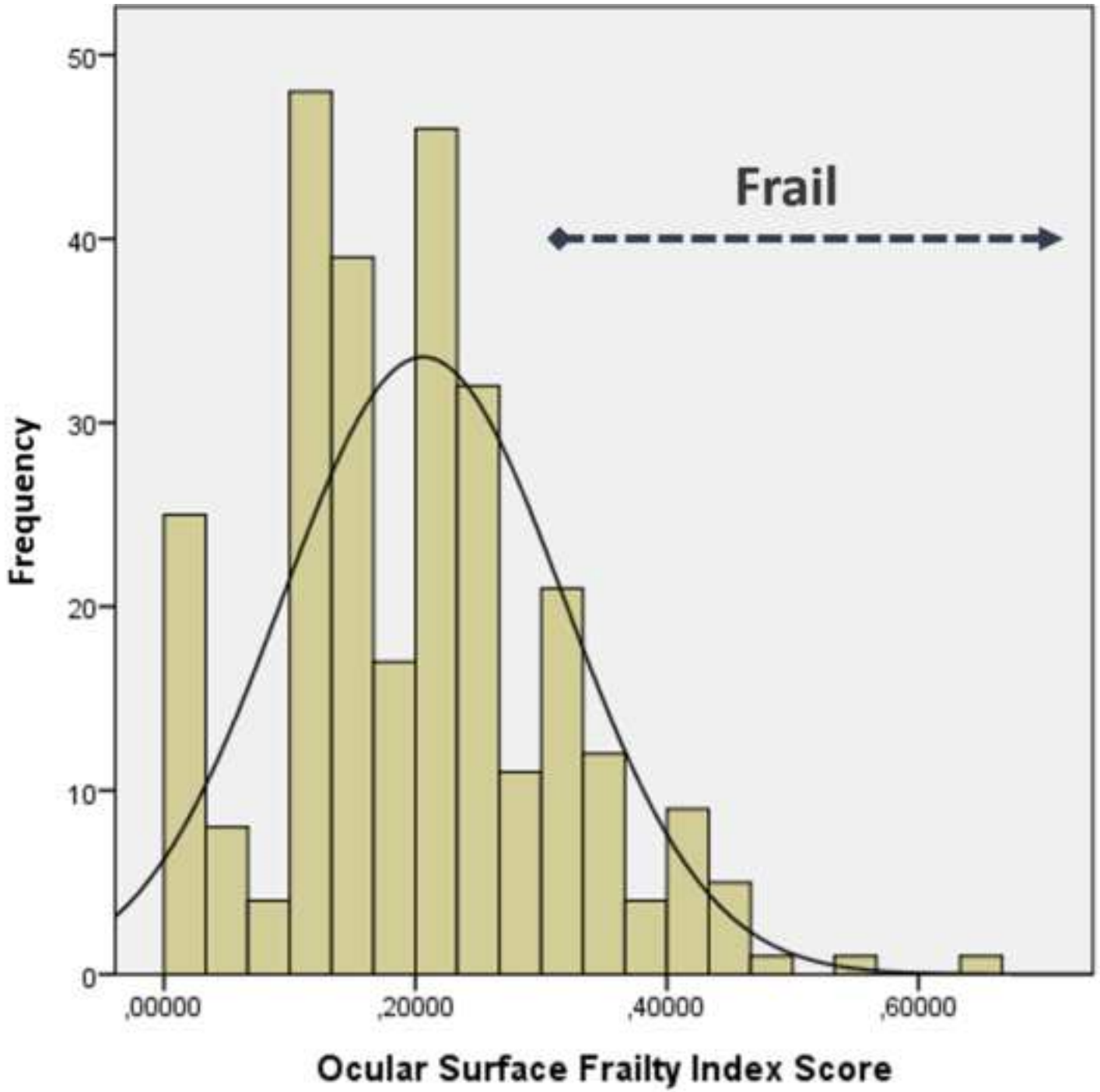

Table 5. Ocular surface symptoms at each follow-up visit: prevalence and first onset.

	V1 (1 week)	V2 (1 month)	V3 (3 months)	V2 AND/OR V3
Prevalence of ocular surface symptoms: n (%)	3 (1%)	28 (10%)	36 (13%)	48 (17%)
First onset of ocular surface symptoms: n (%)	3 (1%)	26 (10%)	20 (7%)	-

Table 3. Logistic regression model for each preliminary OSFI item and stepwise OSFI optimization

Item		Spearman	Single items logistic regression analysis			OSFI logistic regression analysis bootstrapping 200 samples		
	Prevalence N (%)	r	OR	95% CI	P	N items included in OSFI	95% CI	P
Pterygium	0	-	-	-	-	19	0.67-9.01	0.030
Rosacea	3 (1%)	-0.047	ND	ND	ND	18	0.05-7.96	0.035
Contact lenses wear	6 (2%)	-0.001	ND	ND	ND	17	0.40-7.41	0.025
Fluorescein staining	53 (19%)	0.008	1.63	0.09-11.50	0.53	16	0.87-7.64	0.025
Schirmer test	52 (18%)	0.008	1.21	0.44-3.29	0.71	15	1.13-7.00	0.020
Diabetes	40 (14%)	0.016	1.12	0.51-2.75	0.69	14	1.37-7.11	0.005
Topical drugs	29 (10%)	0.026	1.08	0.32-3.18	0.62	13	1.06-7.56	0.005
Conjunctivochalasis	238 (84%)	0.016	1.12	0.54-2.81	0.61	12	1.37-7.71	0.005
Hormone replacement therapy	7 (2%)	0.074	3.36	0.33-8.73	0.60	11	2.18-8.29	0.005
LIPCOF	54 (19%)	0.030	1.52	0.39-5.95	0.55	10	2.04-8.07	0.005
Thyroid malfunction	37 (13%)	0.077	1.65	0.64-4.27	0.30	9	1.30-6.99	0.015
TBUT	185 (65%)	0.096	1.95	0.64-5.78	0.26	8	1.08-7.52	0.015
Ocular allergy	19 (7%)	0.105	2.22	0.72-6.86	0.16	7	0.96-6.63	0.015
Psychiatric conditions	80 (28%)	0.098	2.25	0.76-6.61	0.14	6	0.98-6.25	0.020
Systemic medications	124 (44%)	0.179	1.70	0.83-3.48	0.15	5	-0.17-4.83	0.055
Meibomian glands expressibility	41 (14%)	0.110	1.88	0.78-5.82	0.15	4	ND	ND
Computer use	83 (29%)	0.123	1.90	0.82-4.34	0.13	3	ND	ND
Connective tissue diseases	2 (0.7%)	0.184	ND	ND	ND	2	ND	ND
History of refractive surgery	2 (0.7%)	0.184	ND	ND	ND	1	ND	ND

Table 4. Final Ocular Surface Frailty Index composition

1. Connective tissue diseases	No Yes	0 points 1 point
2. Thyroid malfunction	No Yes	0 points 1 point
3. Psychiatric conditions*	No Yes	0 points 1 point
4. Computer use**	No Yes	0 points 1 point
5. Ocular allergy	No Yes	0 points 1 point
6. History of refractive surgery	No Yes	0 points 1 point
7. Topical drugs***	No Yes	0 points 1 point
8. TBUT with fluorescein	≥10 s 5-9 s 0-4 s	0 points 0,50 points 1 point
9. Meibomian glands expressibility (digital expression)	Grade 0: clear meibum easily expressed Grade 1: cloudy meibum expressed with mild pressure Grade 2: cloudy meibum expressed with moderate pressure Grade 3: meibum not expressed with more than moderate pressure	0 points 0,33 points 0,66 points 1 point
10.LIPCOF	Grade 0 Grade 1 Grade 2 Grade 3	0 points 0,33 points 0,66 points 1 point

*: Including affective, somatoform disorders, anxiety and depression
**: Exposure >4 hours/day
***: Current use of at least one of the following topical drugs: antiglaucomatous, antiallergic, antiviral, decongestants, miotics, mydriatics, non-steroidal anti-inflammatory OR at least 3 drops/day BAK preserved

Supplemental Figure 1(online only)

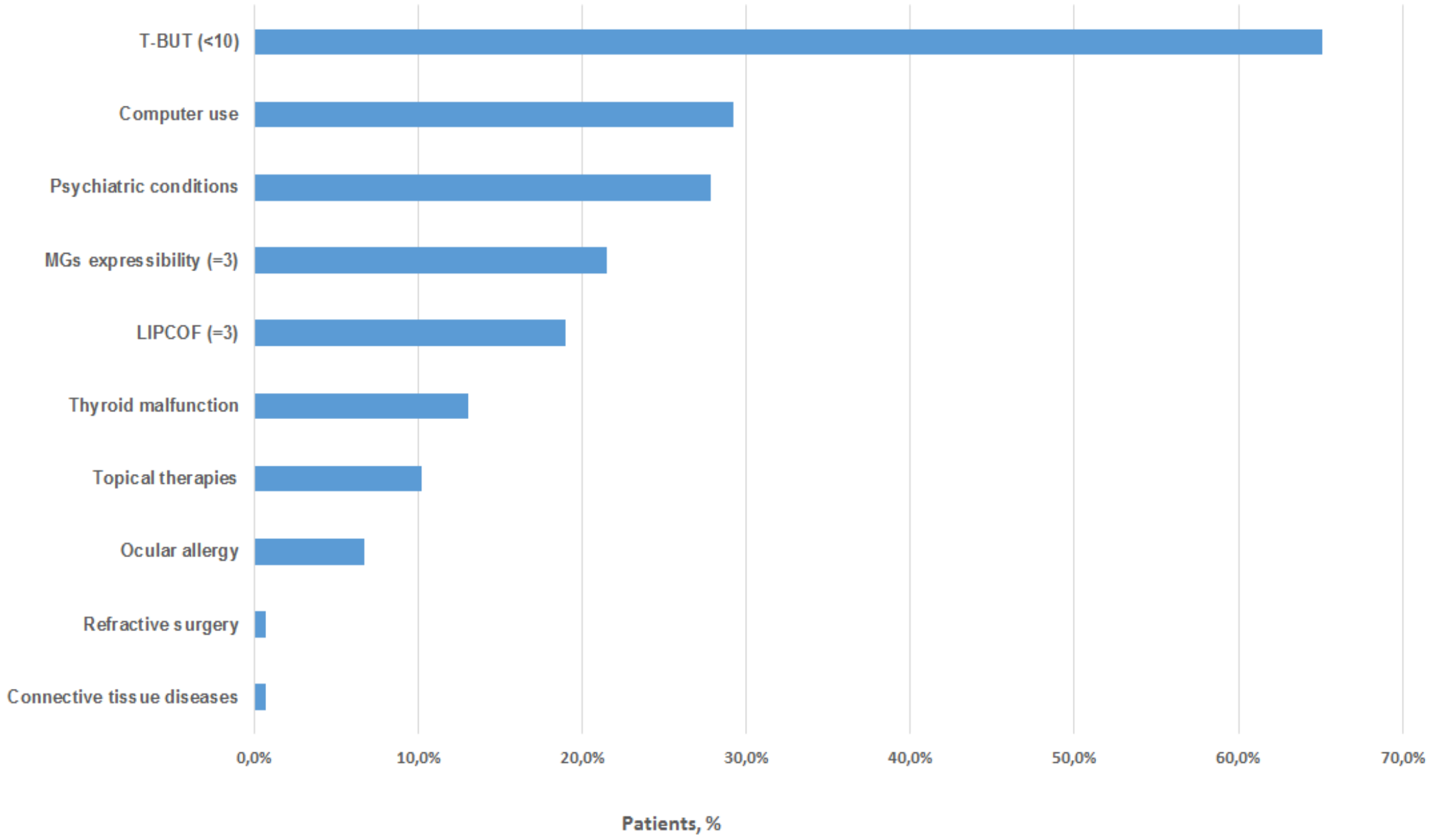

Table 1. Procedures scheduled at each visit

Procedures	V0	V1	V2	V3
Anamnestic questionnaire	X			
OSDI	X	X	X	X
Tear film osmolarity	X	X*	X*	X*
T-BUT	X	X*	X*	X*
Fluorescein staining	X	X*	X*	X*
Meibomian glands expression	X			
Slit lamp examination	X	X	X	X
Schirmer test**	X			

OSDI: Ocular Surface Disease Index; T-BUT: Fluorescein tear film break-up time.

* Performed only if OSDI>13; ** Performed at least 15 minutes after the end of the previous procedure

Table 2. Preliminary Ocular Surface Frailty Index composition

1. Connective tissue diseases	No Yes	0 points 1 point
2. Diabetes	No Yes	0 points 1 point
3. Rosacea	No Yes	0 points 1 point
4. Thyroid malfunction	No Yes	0 points 1 point
5. Psychiatric conditions*	No Yes	0 points 1 point
6. Systemic medications**	No Yes	0 points 1 point
7. Hormone replacement therapy	No Yes	0 points 1 point
8. Computer use***	No Yes	0 points 1 point
9. Ocular allergy	No Yes	0 points 1 point
10. History of refractive surgery	No Yes	0 points 1 point
11. Contact lenses wear	No Yes	0 points 1 point
12. Topical drugs****	No Yes	0 points 1 point
13. Presence of conjunctivochalasis	No Yes	0 points 1 point
14. Pterygium	No Yes	0 points 1 point
15. TBUT with fluorescein	≥10 s 8-9 s 6-7 s 4-5 s 2-3 s 0-1 s	0 points 0,20 points 0,40 points 0,60 points 0,80 points 1 point
16. Fluorescein staining (Oxford scale)	Grade 0 Grade 1 Grade 2 Grade 3 Grade 4 Grade 5	0 points 0,20 points 0,40 points 0,60 points 0,80 points 1 point
17. Meibomian glands expressibility (digital expression)	Grade 0: clear meibum easily expressed Grade 1: cloudy meibum expressed with mild pressure Grade 2: cloudy meibum expressed with moderate pressure Grade 3: meibum not expressed with more than moderate pressure	0 points 0,33 points 0,66 points 1 point

18. LIPCOF	Grade 0 Grade 1 Grade 2 Grade 3	0 points 0,33 points 0,66 points 1 point
19. Schirmer test without anesthesia	≥10 mm 8-9 mm 6-7 mm 4-5 mm 2-3 mm 0-1 mm	0 points 0,20 points 0,40 points 0,60 points 0,80 points 1 point

*: Including affective, somatoform disorders, anxiety and depression
**: Current use of at least one of the following drugs: anticholinergic, antihistamines, antidepressants, anxiolytics, betablockers, diuretics OR concomitant use of at least 5 systemic drugs
***: Exposure >4 hours/day
****: Current use of at least one of the following topical drugs: antiglaucomatous, antiallergic, antiviral, decongestants, miotics, mydriatics, non-steroidal anti-inflammatory OR at least 3 drops/day BAK preserved

Table 6. Matrix presentation of Ocular Surface Frailty Index Content Validity

DOMAINS ITEMS	Tear film instability	Ocular surface inflammation	Neuro-sensory abnormalities	Ocular surface damage
Connective tissue diseases		X		X
Thyroid malfunction		X		
Psychiatric conditions			X	
Computer use	X			
Ocular allergy	X	X		X
History of refractive surgery			X	X
Topical drugs		X	X	X
TBUT	X			
Meibomian glands expressibility	X			X
LIPCOF	X			
Diabetes			X	
Rosacea	X	X		X
Systemic medications		X	X	
Hormone replacement therapy		X		
Contact lens wear	X		X	X
Conjunctivochalasis	X			
Pterygium	X	X		
Fluorescein staining				X
Schirmer test	X			X

Bold: items included in the final OSFI;
Italics: items included in the preliminary OSFI but excluded from the final OSFI.

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