CONFLICT OF INTEREST DISCLOSURES: SEE THE ORIGINAL article for any disclosures of the authors.

Comment on: Corneal Epithelial Thickness Measured Using AS-OCT as a Diagnostic Parameter for Limbal Stem Cell Deficiency

EDITOR:

WE READ WITH INTEREST THE ARTICLE BY LIANG AND ASSOciates that evaluated the diagnostic performance of the corneal epithelium thickness (CET) measured using an anterior segment optical coherence tomography (AS-OCT) and in vivo confocal microscopy (IVCM) in patients with limbal stem cell deficiency (LCSD).[1] The measurements obtained were the average of 3 independent scans performed by 2 independent, masked observers. The authors reported the interobserver variation of these measurements by calculating the interobserver differences only. Furthermore, they analyzed the CET data using a 3-point measurement on the AS-OCT (OCT-CET3) only, but not the 1-point measurement (OCT-CET1) because of the greater correlation with IVCM-CET in the former than the latter CET. We have reservations regarding these statistical approaches.

Multiple measurements were manually obtained by 2 observers from the AS-OCT and IVCM. The reliability of these measurements should be assessed by both the interrater reliability and intrarater reliability using the intraclass correlation coefficient (ICC). The repeatability coefficient (RC), defined as $1.96 \times \sqrt{(2 \times \text{within-subject variance})}$, is the 95% confidence limit of the difference of measurements between examinations. RC is another reliability index that should be considered because it lends itself to easy clinical interpretation, since it is quantified in the same unit as the measurement device. Without the ICC and/or RC reliability evaluations, it is difficult to interpret the results presented by the authors in a clinically meaningful context.

Although the authors found a higher correlation between IVCM-CET with OCT-CET3 than OCT-CET1, a higher correlation does not imply there is a better agreement between these 2 methods. This concept has been discussed in detail by Bland and Altman in their article, one of the most highly cited papers in medical research, highlighting that the correct approach is to calculate the limits of agreement and not correlation.[2] Without considering the limits of agreement, systemic bias, and scaling bias between these 3 measurements, the OCT-CET1 data should not have been disregarded entirely in their analysis, as it might have been a useful diagnostic and staging biomarker.

Lastly, without calculating the area under the receiver operator characteristic curve (AUC) for OCT-CET1 or IVCM-CET and comparing these AUCs with OCT-CET3 using a statistical test (ie, DeLong's test[3]), it is premature to state that OCT-CET3 has the highest diagnostic value for LSCD in the present study. It would be of interest if the authors could provide the analyses described above so that the results can be better put into a clinical perspective to address the question the authors set out to answer.

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Reply to Comment on: Corneal Epithelial Thickness Measured Using AS-OCT as a Diagnostic Parameter for Limbal Stem Cell Deficiency

REPLY

WE SINCERELY THANK DR. WAN AND COLLEAGUE FOR THEIR interest in our recent article, entitled "Corneal Epithelial Thickness Measured Using AS-OCT as a Diagnostic Parameter for Limbal Stem Cell Deficiency",[1] and for giving us the opportunity to further elaborate on our study. We previously showed that central corneal epithelial thickness (CET) obtained using in vivo confocal microscopy (IVCM-CET) decreased substantially in eyes with limbal stem cell deficiency (LSCD).[2,3] In addition, the degree of epithelial thinning in the central cornea reflected the global function of limbal stem cells. The purpose of our recent study was to develop the methodology of CET measurement using anterior segment optical coherence tomography (OCT) as a diagnostic test for LSCD. Our decision to

evaluate the 3-point measurement (OCT-CET3) stemmed from our clinical observation that CET could vary within the central 2 mm zone in eyes with sectoral LSCD and the 1-point measurement (OCT-CET1) might not be as accurate.

We showed that the inter-observer measurements of CET were highly consistent (<5% variation) between the 2 masked observers. We calculated the repeatability coefficient of OCT-CET1 and OCT-CET3 measurements to be 11.15 μm and 3.58 μm, respectively. The intraclass correlation coefficient of OCT-CET1 and OCT-CET3 was 0.859 and 0.985, respectively. These results support a higher degree of reliability and smaller measurement error of OCT-CET3 than OCT-CET1.

Limit of Agreement (LOA) would be necessary if the purpose of the study was to establish OCT as a surrogate of a gold standard test. We did not consider IVCM as the gold standard for CET measurement but as a control. Nevertheless, we performed the analysis and found that LOA of OCT-CET1 was larger than that of OCT-CET3 (-11.96 ± 11.61 μm vs -9.78 ± 9.67 μm), which is consistent with the correlation analysis.

The area under the receiver operator characteristics curve (AUC) of OCT-CET3 was evaluated in our study, which was higher than that of the maximum limbal epithelial thickness in all four limbal regions. The AUC of OCT-CET1 (0.932) and IVCM-CET (0.911) were smaller than that of OCT-CET3 (0.973), which supports our conclusion that OCT-CET3 is a reliable value of CET as a diagnostic parameter to confirm LSCD.

We agree with Dr. Wan and colleague that appropriate statistical analyses is necessary to support the conclusion of all research. In depth knowledge of the subject of investigation and correct data acquisition are equally important in conducting a sound and meaningful study.

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A Lesson Not To Be Forgotten. Ophthalmologists in Northern Italy Become Internists During the SARS-CoV-2 Pandemic

EDITOR:

IMPORTANT LESSONS TAUGHT TO US BY DR. LI WENLIANG of Wuhan, China, the ophthalmologist who first sounded the alarm over new coronavirus infections, must not be forgotten.[1] Ophthalmologists from around the world have been inspired by his sacrifice, and many have followed his lead by caring for severely ill patients during the coronavirus 2019 (COVID-19) pandemic.

The Lombardy region in Northern Italy was hit particularly hard by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic during the first quarter of 2020.[2] On March 11, the San Raffaele hospital in Milan was bursting with COVID-19 patients when the Chairman of Ophthalmology, Professor Francesco Bandello, invited department members to join the primary care efforts. By that time, the workload within the ophthalmology department was significantly reduced, and many of us, unaccustomed to such light workloads, were feeling useless. In our hearts, we knew what had to be done.

The decision to join the front-line efforts was not easy, but 11 of the ophthalmology residents volunteered to care for COVID-19 patients. To acquire the necessary knowledge and skills for this task, we quickly reviewed old internal medicine and pulmonary textbooks, researched the newest information about the coronavirus, and learned the correct use of personal protective equipment. Confronted by the daunting task ahead of us, 2 things frightened us, first, becoming infected with the virus, and second and more importantly, not providing proper care to our patients. As ophthalmologists, most of the care we deliver is for non-life-threatening conditions, but patients in the COVID-19 units are critically ill with numerous serious comorbidities. We were unaccustomed to administering oxygen, managing noninvasive and invasive ventilation, and interpreting arterial blood gases of patients with severe interstitial pneumonia.

At the time of this writing, we appear to have moved beyond the peak of the mortality curve,[3,4] and we are beginning to see light at the end of the tunnel. Those of us who worked with COVID-19 patients hope to become eye doctors again soon, but we will be forever proud that we helped during this emergency. When we became doctors, we swore an oath to provide care during a medical emergency or in case of a calamity, but this was not the