

Correlation Between Corneal Topographic, Densitometry, and Biomechanical Parameters in Keratoconus Eyes

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Received: 5 September 2018

Accepted: 24 February 2019

Published: 6 May 2019

Keywords: biomechanics; corneal structure; CorVis ST; keratoconus; Pentacam HR

Citation: Shen Y, Han T, Jhanji V, Shang J, Zhao J, Li M, Zhou X. Correlation between corneal topographic, densitometry, and biomechanical parameters in keratoconus eyes. *Trans Vis Sci Tech.* 2019;8(3):12. <https://doi.org/10.1167/tvst.8.3.12>
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Purpose: To investigate the correlation between corneal densitometry, corneal topographic parameters, and corneal biomechanical properties in keratoconus.

Methods: A total of 76 eyes of 76 keratoconus patients were enrolled in this cross-sectional study. Corneal densitometry and topography were measured using Pentacam HR. Corneal biomechanical properties were measured using CorVis ST.

Results: The corneal densitometry values of the anterior 0 to 2 and 2 to 6 mm layers significantly correlated with the maximum keratometry values ($R = 0.373$, $P = 0.001$ and $R = 0.276$, $P = 0.016$, respectively), thinnest corneal thickness values ($R = -0.331$, $P = 0.003$ and $R = -0.234$, $P = 0.042$, respectively), anterior corneal elevation ($R = 0.392$, $P < 0.001$ and $R = 0.323$, $P = 0.004$, respectively), and posterior corneal elevation ($R = 0.450$, $P < 0.001$ and $R = 0.367$, $P = 0.001$, respectively). The stiffness parameter-applanation time 1 (SP-A1) significantly correlated with the corneal densitometry values for the anterior 0 to 2 mm ($R = -0.397$, $P < 0.001$), anterior 2 to 6 mm ($R = -0.331$, $P = 0.004$), central 0 to 2 mm ($R = -0.306$, $P = 0.007$), central 2 to 6 mm ($R = -0.228$, $P = 0.048$), posterior 2 to 6 mm ($R = -0.243$, $P = 0.035$), total 0 to 2 mm ($R = -0.291$, $P = 0.011$), and total 2 to 6 mm ($R = -0.295$, $P = 0.010$) layers.

Conclusions: The corneal densitometry values correlated with the severity of keratoconus and the SP-A1 values.

Translational Relevance: Corneal densitometry values may serve as markers to predict the severity of keratoconus.

Introduction

Diagnosis of keratoconus remains a challenge and a significant area of interest. Corneal tomography remains the diagnostic modality of choice. The sensitivity and specificity of screening for keratoconus has improved significantly with the advances in corneal imaging.¹⁻³ Pentacam HR (Oculus, Wetzlar, Germany), an anterior segment analyzer, is based on the Scheimpflug principle. The attached Scheimpflug camera rotates 2.5 circuits to yield 25 tomographic images. Subsequently, it reconstructs the anterior segment of the target eye, thereby yielding measure-

ments of the dimensions of the anterior segment. Pentacam HR also performs corneal densitometry by evaluating gray scale units, which reflect the corneal transparency (range, 0–100).⁴ Corneal Visualization Scheimpflug Technology (CorVis ST) also uses a high-speed Scheimpflug camera and provides a series of deformation parameters, such as applanation time, applanation length, applanation velocity, deformation and deflection amplitude, peak distance, stiffness parameter-applanation time 1 (SP-A1), Corvis Biomechanical index, and tomography and biomechanical index.^{5,6} These parameters serve as markers for the corneal biomechanical properties. Studies have indicated significant differences in the corneal biome-

chanical parameters between keratoconic and normal eyes.^{7–9} A Corvis biomechanical index of >0.50 is able to classify 98.8% of the cases of keratoconus correctly with a sensitivity of 98.4% and specificity of 100%.¹⁰ A tomography and biomechanical index of >0.79 has 100% sensitivity and specificity for detecting clinical ectasia.^{6,11} The extent of decrease in the biomechanical strength correlates with the severity of keratoconus.¹² Likewise, the corneal densitometry has been shown to be significantly increased in keratoconic eyes.⁴

We investigated the correlations between the corneal densitometry and biomechanics in patients with keratoconus.

Subjects and Methods

In this cross-sectional study, keratoconus was diagnosed using an anterior segment analyzer (Pentacam HR; Oculus) based on the Amsler-Krumeich grading system. Patients with keratoconus of stages 1 to 3 or forme fruste keratoconus (cornea with no abnormal findings on slit-lamp examinations and corneal topography, with keratoconus of the fellow eye) were enrolled from the Eye and ENT Hospital of Fudan University. In total, 76 eyes of 76 participants (50 men, 26 women; mean age, 23.93 ± 6.81 years) were included. This study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee of the hospital. Informed consent was obtained from all the participants.

Ophthalmologic Examination

Each patient underwent corneal tomography examination using the anterior segment analyzer Pentacam HR. The corneal biomechanical parameters were assessed using CorVis ST (Oculus). All measurements were obtained by a single examiner (YS). The corneal tomography images were acquired in the sitting position. Participants were required to keep their eyes wide open and to place their chins on the chin rest during the examination. The examiner maneuvered the joystick based on the image on the monitor. When the camera was aimed at the corneal apex, the images were captured automatically.

Statistical Analyses

Statistical analyses were performed using SPSS Version 20 (IBM, Armonk, NY). All data were tested for normality using the Kolmogorov-Smirnov test. A mixed linear model with Bonferroni-adjusted post hoc

Table 1. Mean Corneal Densitometry Values of Anterior, Central, Posterior and Total Layers Over Annuli of 0 to 2 mm

Location, ϕ 0–2 mm	Mean	Standard Deviation	Range
Anterior layer	20.85	3.02	15.80–31.50
Center layer	13.14	1.61	10.60–18.00
Posterior layer	10.43	1.66	6.90–14.50
Total cornea	14.81	1.85	12.40–21.30

ϕ , annulus; mm, millimeter.

comparisons was used to analyze the differences in the corneal densitometry values in different locations. Pearson's correlation tests were performed to examine the correlations between the scale values, which fit a normal distribution. Spearman's correlation tests were used to determine the correlations between data with a skewed distribution or ranked ordinal data. $P < 0.05$ was considered statistically significant.

Results

The corneal densitometry values over the annulus of 2 to 6 mm followed a skewed distribution. The mean corneal densitometry values of each layer over the 0 to 2 and 2 to 6 mm annulus are listed in [Tables 1](#) and [2](#). The main corneal tomographic data and corneal deformation parameters are listed in [Tables 3](#) and [4](#), respectively.

Corneal Densitometry

A significant difference in the distribution of the densitometric values ([Fig. 1](#)) was detected between the anterior (first 120 μm of the corneal thickness) and posterior (last 60 μm of the corneal thickness) layers over the 0 to 2 and 2 to 6 mm annulus ($F = 308.258$, $P < 0.001$). Bonferroni post hoc comparisons revealed

Table 2. Mean Corneal Densitometry Values of Anterior, Central, Posterior, and Total Layers Over Annuli of 2 to 6 mm

Location, ϕ 2–6 mm	Mean	Standard Deviation	Range
Anterior layer	18.00	2.28	15.00–26.80
Center layer	11.58	1.45	9.40–15.80
Posterior layer	10.46	1.43	8.30–14.30
Total cornea	13.34	1.60	11.10–18.90

Table 3. Corneal Tomographic Parameters of Study Participants Using Pentacam HR

Parameters	Mean	Standard Deviation	Range
K1 (D)	46.63	5.06	39.60–59.80
K2 (D)	49.98	6.08	40.90–68.00
Km (D)	48.15	5.32	40.30–63.70
Kmax (D)	56.25	9.41	41.80–88.10
CCT (μm)	495.3	37.7	413.0–604.0
TCT (μm)	477.0	44.0	369.0–583.0
ACE (μm)	23.9	15.3	0.0–76.0
PCE (μm)	50.1	28.9	0.0–150.0

K1, Flat Keratometry; K2, Steep Keratometry; Km, Mean Keratometry; CCT, Central Corneal Thickness; PCE, Posterior Central Elevation; D, diopter; μm , micron.

that the corneal densitometry value of the anterior cornea over the 0 to 2 mm annulus (anterior 0–2 mm layer) was significantly higher (post hoc $P < 0.001$) than that over the 2 to 6 mm annulus (anterior 2–6 mm layer).

Correlation Between the Densitometric and Tomographic Parameters

Figure 2A demonstrates that the maximum keratometry (Kmax) values significantly correlated with the densitometry values obtained from the anterior layer over the 0 to 2 mm ($R = 0.373$, $P = 0.001$) and 2 to 6 mm ($R = 0.276$, $P = 0.016$) annulus, while Figure 2B shows that the thinnest corneal thickness (TCT) values significantly correlated with the densitometry values of the anterior 0 to 2 mm ($R = -0.331$, $P = 0.003$), anterior 2 to 6 mm ($R = -0.234$, $P = 0.042$), central 0 to 2 mm ($R = -0.256$, $P = 0.026$), and total 0 to 2 mm ($R = -0.230$, $P = 0.045$) layers. Moreover, Figure 2C indicates that the anterior corneal elevation (ACE) values remarkably correlated with the densitometry values of the anterior 0 to 2 mm ($R = 0.392$, $P < 0.001$), anterior 2 to 6 mm ($R = 0.323$, $P = 0.004$), central 0 to 2 mm ($R = 0.232$, $P = 0.043$), total 0 to 2 mm ($R = 0.244$, $P = 0.033$), and total 2 to 6 mm ($R = 0.241$, $P = 0.036$) layers. In addition, Figure 2D illustrates that the posterior corneal elevation (PCE) values considerably correlated with the densitometry values of the anterior 0 to 2 mm ($R = 0.450$, $P < 0.001$), anterior 2 to 6 mm ($R = 0.323$, $P = 0.004$), total 0 to 2 mm ($R = 0.260$, $P = 0.023$), and total 2 to 6 mm ($R = 0.267$, $P = 0.020$) layers.

Table 4. Corneal Deformation Parameters of Study Participants Measured on Corvis ST

Deformation Parameters	Mean	Standard Deviation	Range
AT1 (ms)	6.88	0.30	6.29–7.71
ATh (ms)	16.61	0.53	15.25–17.79
AT2 (ms)	21.80	0.42	20.65–22.56
AL1 (mm)	1.88	0.29	1.24–2.56
AL2 (mm)	1.59	0.40	0.63–2.15
AV1 (m/s)	0.17	0.03	0.11–0.24
AV2 (m/s)	-0.29	0.05	-0.44 to -0.19
IOP (mmHg)	14.11	2.68	4.77–21.00
biOP (mmHg)	15.29	2.63	5.41–22.80
PD (mm)	4.99	0.26	4.06–5.57
R (mm)	5.16	0.77	2.90–6.68
DA (mm)	1.16	0.12	0.87–1.54
CCT (μm)	494.8	37.1	415–614
DeA (mm)	1.02	0.12	0.66–1.37
DAR	5.66	1.35	3.60–13.00
IR	12.47	2.17	8.90–18.40
ARTh	228.91	79.85	83.00–421.50
SP-A1	61.14	20.21	15.90–123.50
BAD-D	8.03	4.87	0.05–23.67
CBI	0.93	0.18	0.00–1.00
TBI	0.94	0.20	0.01–1.00

AT1, Applanation Time (time 1); ATh, Applanation Time (highest); AT2, Applanation Time (time 2); AL1, Applanation Length (time 1); AL2, Applanation Length (time 2); AV1, Applanation Velocity (time 1); AV2, Applanation Velocity (time 2); IOP, intraocular pressure; biOP, biomechanically corrected IOP; PD, peak distance; R, radius of concave curvature; DA, deformation amplitude; CCT, central corneal thickness; DeA, deflection amplitude; IR, integrated radius; ARTh, Ambrósio's relational thickness; SP-A1, stiffness parameter at first applanation; BAD-D, Belin/Ambrósio enhanced ectasia display; CBI, Corvis biomechanical index; TBI, tomography and biomechanical index; ms, millisecond; mm, millimeter; m/s, meter per second; mmHg, millimeters of mercury (1mmHg, 133.32 Pascals).

Correlation Between the Corneal Densitometry and Corneal Biomechanical Properties

The SP-A1 value significantly correlated with the densitometry values of the anterior 0 to 2 mm ($R = -0.397$, $P < 0.001$), anterior 2 to 6 mm ($R = -0.331$, $P = 0.004$), central 0 to 2 mm ($R = -0.306$, $P = 0.007$), central 2 to 6 mm ($R = -0.228$, $P = 0.048$), posterior 2 to 6 mm ($R = -0.243$, $R = 0.035$), total 0 to 2 mm ($R =$

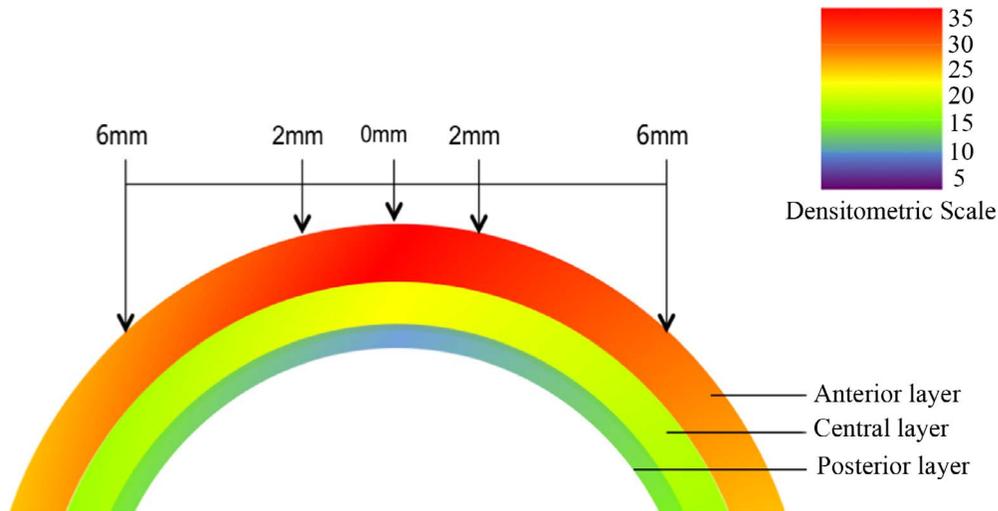


Figure 1. The densitometric distribution from the anterior to the posterior layers over the annuli of 0 to 2 and 2 to 6 mm of a cornea with keratoconus.

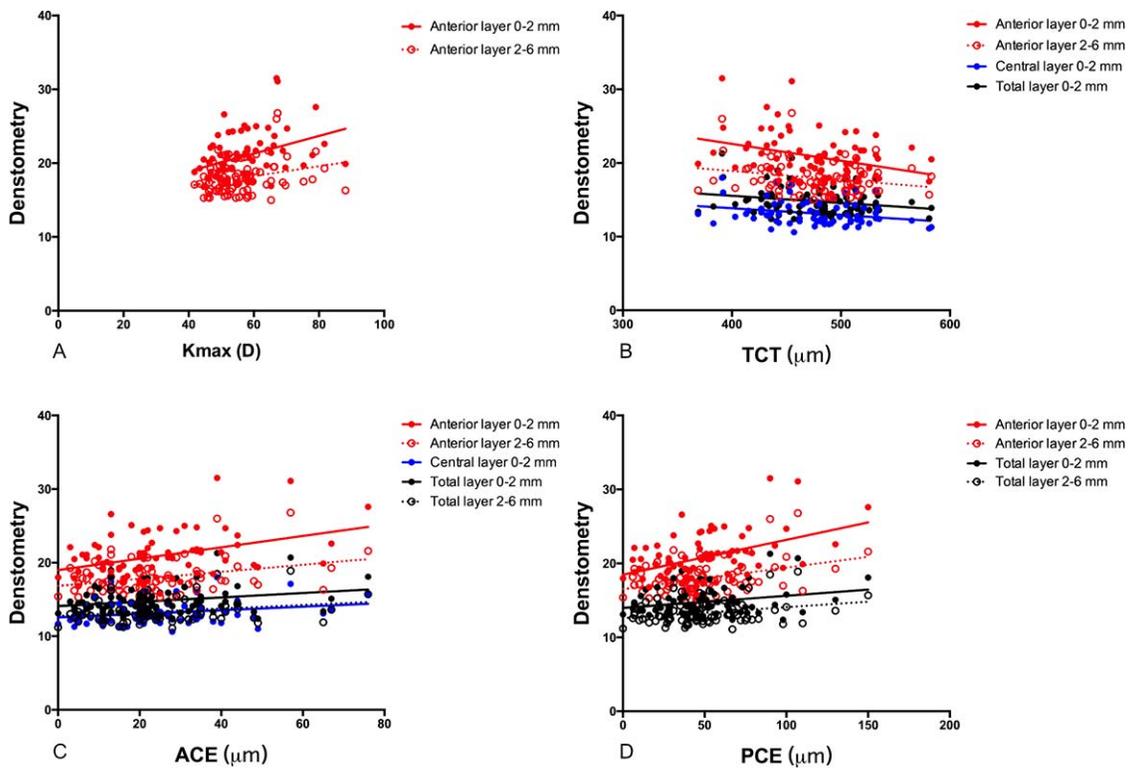


Figure 2. (A) The correlations between the Kmax and corneal densitometry values obtained in the anterior layer over the annuli of 0 to 2 and 2 to 6 mm ($R = 0.373$, $P = 0.001$, and $R = 0.276$, $P = 0.016$, respectively). (B) The correlations between the thinnest corneal thickness values and the corneal densitometry values of the anterior 0 to 2 mm ($R = -0.331$, $P = 0.003$), anterior 2 to 6 mm ($R = -0.234$, $P = 0.042$), central 0 to 2 mm ($R = -0.256$, $P = 0.026$), and total 0 to 2 mm ($R = -0.230$, $P = 0.045$) layers. (C) The correlations between the anterior corneal elevation values and the corneal densitometry values of anterior 0 to 2 mm ($R = 0.392$, $P < 0.001$), anterior 2-6mm ($R = 0.323$, $P = 0.004$), central 0 to 2 mm ($R = 0.232$, $P = 0.043$), total 0 to 2 mm ($R = 0.244$, $P = 0.033$), and total 2 to 6 mm ($R = 0.241$, $P = 0.036$) layers. (D) The correlations between the posterior corneal elevation values and the corneal densitometry values of anterior 0 to 2 mm ($R = 0.450$, $P < 0.001$), anterior 2 to 6 mm ($R = 0.323$, $P = 0.004$), total 0 to 2 mm ($R = 0.260$, $P = 0.023$), and total 2 to 6 mm ($R = 0.267$, $P = 0.020$) layers.

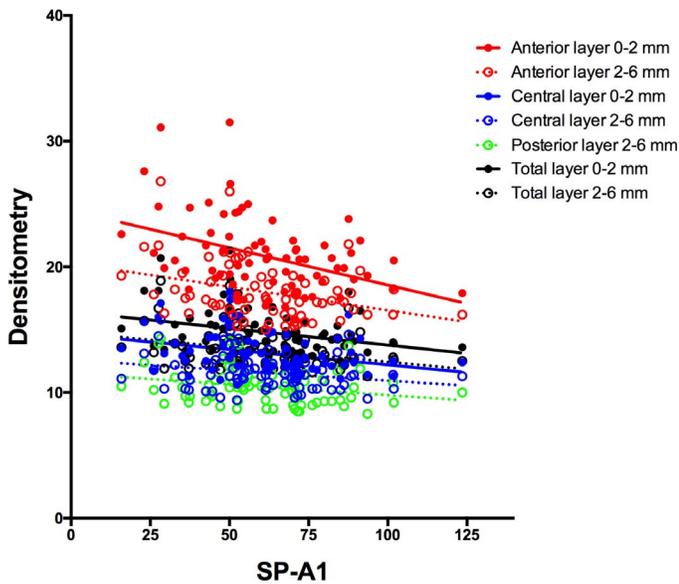


Figure 3. The correlations between the stiffness parameter-applanation time 1 values and the corneal densitometry values obtained in the anterior layer over the annuli of 0 to 2 and 2 to 6 mm, the central layer over the annuli of 0 to 2 and 2 to 6 mm, the posterior layer over the annuli of 2 to 6 mm, and the total layer over the annuli of 0 to 2 and 2 to 6 mm (anterior 0–2 mm, $R = -0.397$, $P < 0.001$; anterior layer 2–6 mm, $R = -0.331$, $P = 0.004$; central layer 0–2 mm, $R = -0.306$, $P = 0.007$; central layer 2–6 mm, $R = -0.228$, $P = 0.048$; posterior layer 2–6 mm, $R = -0.243$, $R = 0.035$; total layer 0–2 mm, $R = -0.291$, $P = 0.011$, and total layer 2–6 mm, $R = -0.295$, $P = 0.010$, respectively).

-0.291 , $P = 0.011$), and total 2 to 6 mm ($R = -0.295$, $P = 0.010$) layers (Fig. 3).

Discussion

Corneal densitometry, which also is known as corneal backscatter, relates to corneal transparency and is influenced by changes in corneal histology.¹³ It was first measured using a slit-lamp photometer with a pin-light attachment.¹⁴ Scheimpflug cameras allow for objective evaluation of the densitometry.¹⁵ It is noteworthy that for normal eyes, the corneal densitometry decreases from the anterior to posterior layers of the cornea. However, it does not show any relationship with the corneal keratometry.¹⁶ We observed that the distribution of the corneal densitometry values was similar to that of normal eyes. However, unlike normal eyes, the densitometry values of the anterior 0 to 2 and 2 to 6 mm layers significantly correlated with the Kmax values.¹⁶ In addition, we also noticed that the densitometry values of the anterior 0 to 2 mm, anterior 2 to 6 mm, and

total 0 to 2 mm layers correlated with the thinnest corneal thickness, anterior corneal elevation, and posterior corneal elevation. This indicated that the severity of keratoconus may be correlated with the elevation of the corneal densitometry values, especially in the anterior layer. Elevated corneal densitometry also has been reported in the pathogenesis of various ocular surface disorders, which may compromise the corneal transparency, including keratitis,¹⁷ endothelial abnormality,¹⁸ and pseudoexfoliation syndrome.¹⁹ Misalignment of the corneal collagen has been noted in keratoconus.⁴ Further, periodic acid–Schiff-positive nodules, Z-shaped cracks caused by ruptures in the Bowman’s layer,²⁰ and wound healing reactions, which triggers fibronectin degeneration in the extracellular matrix,²¹ may be the key causes related to the compromised corneal transparency, leading to an increase in the densitometry values.

SP-A1 is a parameter related to corneal rigidity. It is defined as the ratio of the pressure loading (imposed by the air pulse) on the cornea to the displacement of the corneal apex (from the undeformed state to the first applanation). The SP-A1 value has been reported to be lower in thin than in normal corneas.¹⁰ In our study, the SP-A1 values were negatively correlated with the corneal densitometry values. This implies that, among patients with keratoconus, increased corneal densitometry values may indicate compromised corneal stiffness. Molecular biology studies have reported that enzyme activation has a key role in the degradation of the corneal stroma and in corneal thinning, thus affecting corneal stiffness.²² An increased anterior and posterior surface elevation at the thinnest point of the cornea leads to the formation of a cone as well as an increase in the corneal keratometry.^{23,24} The progressive increase in corneal irregularities, decrease in corneal thickness, and steeping of corneal curvature might underlie the correlations between corneal densitometry, SP-A1, and Kmax.

The limitations of our study are as follows. Firstly, the sample size was small. Secondly, a comparative group with normal eyes was absent. However, our main purpose was to investigate the potential correlations between the densitometric and biomechanical parameters in keratoconic eyes rather than to compare the difference in the densitometry values between patients with keratoconus and the normal population. Thirdly, the randomly enrolled patients with keratoconus were not classified based on the location of the cone apex. This might have affected

the distribution of the corneal densitometry over the entire cornea. Further studies are needed to determine the difference in distribution of the corneal densitometry among patients with keratoconus with different types of cones.

In conclusion, we showed that the corneal densitometry values may correlate with the severity of keratoconus and the SP-A1 values in keratoconus eyes. The increased corneal densitometry values may allow the compromised corneal biomechanics in keratoconus to be predicted.

Acknowledgments

Supported in part by the National Natural Science Foundation of China for Young Scholars (Grants 81600762 and 81500753), the National Natural Science Foundation of China (Grants 81570879 and 81770955), and the Project of Shanghai Science and Technology (Grants 17411950200 and 17411950201).

Disclosure: **Y. Shen**, None; **T. Han**, None; **V. Jhanji**, None; **J. Shang**, None; **J. Zhao**, None; **M. Li**, None; **X. Zhou**, None

*Yang Shen and Tian Han contributed equally to this work and should be considered as equal first authors.

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