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Diagnostic value of various noninvasive indexes in the diagnosis of chronic hepatic fibrosis

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Abstract. – OBJECTIVE: Hepatic fibrosis is a repair response to chronic liver injury. This study evaluated the diagnostic value of various noninvasive indicators for hepatic fibrosis in patients with chronic liver disease.

PATIENTS AND METHODS: 95 patients with liver biopsy were enrolled in this study. Routine clinical and laboratory examinations were collected, including age, sex, blood routine, biochemistry, serum fibrosis, and FibroTouch. APRI and FIB4 scores were calculated. The patients were grouped according to liver pathological staging to analyze the correlation between the fibrosis with serum fibrosis, APRI, FIB4 score, and FibroTouch. The receiver operator characteristics of S2, S3, and S4 were analyzed to calculate the area under the curve (AUC).

RESULTS: No statistical difference was found on age, ALT, AST, GGT, BMI, TG, CHOL, and Glu ($p > 0.05$). Liver stiffness measurement (LSM), APRI, FIB4, PCIII, CIV, LN, and HA exhibited statistical significance ($p < 0.05$). Further correlation analysis showed that PCIII, IV-C, LN, APRI, LSM, and FIB4 were positively correlated with the stage of hepatic fibrosis ($p < 0.05$). ROC curve analysis demonstrated that LSM and FIB4 revealed good predictions of various stages of fibrosis in chronic liver disease with AUC greater than 0.7. The AUC of LSM in the diagnosis of liver cirrhosis (S4) reached 0.908. Its accuracy was influenced by liver inflammation.

CONCLUSIONS: The LSM value in FibroTouch showed high coincidence rate with hepatic fibrosis staging. It is a valuable noninvasive method for assessing the progression of hepatic fibrosis in chronic liver disease.

Key Words:
Transient elastic wave detection, Hepatic fibrosis, Liver stiffness, Cirrhosis.

Introduction

Fibrosis refers to the diffuse over deposition of extracellular matrix in the liver. It is the repair response of various causes of chronic liver injury[1]. Not timely treatment may progress to decompensated cirrhosis and appear various end-stage liver disease complications[2]. Early hepatic fibrosis is a reversible process after active treatment[3]. Therefore, the early diagnosis of hepatic fibrosis has an important clinical significance for clinic. For a long time, the diagnosis of hepatic fibrosis depends on liver biopsy, which is limited by multiple deficiencies, such as trauma, difficult to repeat biopsy, and other complications[4]. Up to now, there is no uniform and reliable serological or imaging method for the diagnosis of hepatic fibrosis. Different degree of fibrosis and different characteristics of causes make diverse sensitivity and specificity of the related indexes. The scholars have tried to explore the noninvasive diagnostic model of hepatic fibrosis, such as hepatic fibrosis serological indicators, APRI and FIB4 index, and transient elastography[5]. It has gradually become a trend to use multiple serological and clinical indicators, and transient elastography to establish a noninvasive diagnostic model to determine the degree of fibrosis. Serum PCIII, IV-C, LN, and HA are the serological indicators used for the assessment of hepatic fibrosis[6]. PCIII reflects the synthesis of intrahepatic type III collagen, and its serum content is consistent with the degree of hepatic fibrosis[7]. IV-C mainly exists in the blood vessels and bile duct basement membrane of normal liver with high sensitivity[8]. LN mainly resides in the basement membrane of intrahepatic bile duct, blood vessels, and lymph vessels in the liver[9]. HA is synthetized by interstitial cells and reflects the liver endothelial cell function and damage[10]. APRI is a noninvasive diagnostic model of hepatic fibrosis proposed by Wai et al[11]. Sterling suggested FIB-4 index evaluation system, which is featured as simple, easy to obtain, and widely application[12]. As a mature noninvasive examination, elastography shows a high diag-

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nostic value to the obvious hepatic fibrosis and cirrhosis[13]. This study integrated these models to verify their clinical values for the diagnosis of hepatic fibrosis in chronic liver disease.

Patients and Methods

Patients

68 patients with chronic hepatitis B and 27 patients with other liver diseases between Nov 2015 and Nov 2016 were enrolled from Taizhou People's Hospital. They included 9 cases with fatty liver, 16 cases with autoimmune liver disease, and 2 cases with alcoholic hepatitis. The mean age was 43.1 ± 1.2 (25-66) years old, while the male patients were 69. No patients received antiviral or anti-hepatic fibrosis drug treatment. Patients with pregnancy, cancer, or other diseases were excluded. All patients received liver pathological and serum examinations.

The study protocol was approved by the Research Ethics Committee of Taizhou People's Hospital, and all patients gave their informed consent before study commencement.

Methods

Laboratory Inspection

Alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), blood glucose (Glu), triglyceride (TG), and total cholesterol (CHOL) were tested by automatic biochemical analyzer. Platelet (PLT) was detected by automatic blood cell analyzer. Type III procollagen (PCIII), type IV collagen (CIV), laminin (LN), and serum hyaluronic acid (HA) were detected by radioimmunoassay (RIA).

FibroTouch Detection Method

The patient was at supine position with hands laced behind head to expand the intercostal space. An image-guided probe was selected to detect the organization through the 7^{th}, 8^{th}, or 9^{th} intercostal space avoiding the cysts, nodules, and blood vessels in the liver tissue. Operating standard: The probe was kept perpendicular to the skin surface. The pressure indicator showed the appropriate location (between green and red). M waveform intensity distributed uniform. The detection started when the A waveform was linear and repeated for 10 times. The median was treated as the final result.

Hepatic Histology Examination

The patient received routine liver biopsy and liver puncture ultrasound positioning before surgery. The patients were treated by Japanese TSK16 G liver puncture needle to obtain the liver sample. The mean length of the specimen was 1.5 (1.5-2.0) cm with the number of portal area ≥ 6. The specimens were fixed with 10% formaldehyde solution and routinely sliced. After stained by hematoxylin-eosin, mesh (Gorden-Sweet method) Masson trichrome, and collagen fibers, the sample was observed under the optical microscope. Hepatic fibrosis was staged according to Scheuer classification criteria, score 0: no fibrosis; S1: fibrosis enlargement in the portal area and confined to the sinus and lobular; S2: fibrosis around the portal area with fibrous septum formation, lobular structure was reserved; S3: fibrous septum associated with lobular structure disorder, no cirrhosis; S4: cirrhosis.

Calculation Method

APRI = AST (U/L) / PLT ($\times 10^9$/L) × 100; FIB4 = [age (yrs) × AST (U/L)] / [PLT ($\times 10^9$/L) × ALT (U/L) $^{1/2}$].

Statistical Analysis

SPSS19.0 statistical software (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for data processing. The measurement data were presented as x ± s and compared by ANOVA. The correlation data were analyzed by using Spearman's rank correlation analysis. The evaluation of diagnostic performance was performed by the receiver operator characteristics (ROC) on MedCalc 11.4 statistical software (Ostend, Belgium).

Results

Hepatic Fibrosis Staging

According to the criteria, there were 19 cases in S0, 28 cases in S1, 5 cases in S2, 12 cases in S3, and 31 cases in S4.

Indicators Comparison in Patients with Different Hepatic Fibrosis Stages

No statistical difference was found on age, ALT, AST, GGT, BMI, TG, CHOI, and Glu ($p > 0.05$). Liver stiffness measurement (LSM), APRI, FIB4, PCIII, IV-C, LN, and HA exhibited statistical significance ($p < 0.05$). LSM and APRI gradually elevated following the increase of hepatic

Table I. Index comparison in patients with different hepatic fibrosis stages.

Item	S1	S2	S3	S4	S5
APRI	1.06 ± 0.20	0.75 ± 0.09*	1.06 ± 0.33*#	1.57 ± 0.52*#&	1.66 ± 0.30*#&@
LSM	6.80 ± 1.86	6.44 ± 2.25*	6.23 ± 1.67*#	6.84 ± 2.16*#&	8.97 ± 1.96*#&@
ALT	77.68 ± 10.46	82.93 ± 13.95	88.60 ± 52.68	96.17 ± 21.49	61.84 ± 8.24
AST	55.11 ± 6.9	53.61 ± 9.07	64.20 ± 11.92	63.00 ± 11.55	57.97 ± 4.05
GGT	116.26 ± 42.52	84.75 ± 19.26	123.8 ± 44.70	60.75 ± 15.371	88.94 ± 8.78
TG	3.30 ± 0.41	3.10 ± 0.31	1.79 ± 0.66	3.92 ± 0.44	3.28 ± 0.24
CHOL	2.46 ± 0.42	2.05 ± 0.26	4.58 ± 0.67	2.64 ± 0.54	2.65 ± 0.37
BMI	23.11 ± 0.68	24.63 ± 0.61	25.32 ± 1.46	24.42 ± 0.71	25.23 ± 0.80
FIB4	4.36 ± 0.69	3.92 ± 0.45*	3.99 ± 0.47*#	6.14 ± 0.40*#&	6.88 ± 0.48*#&@
PCIII	27.09 ± 2.14	26.68 ± 1.43*	24.91 ± 5.5*#	36.42 ± 3.98*#&	52.24 ± 6.61*#&@
IVC	26.91 ± 2.42	28.02 ± 2.12*	27.04 ± 5.47*#	35.31 ± 4.56*#&	51.49 ± 5.65*#&@
LN	19.19 ± 2.42	18.29 ± 2.69*	13.40 ± 4.72*#	10.37 ± 1.97*#&	57.9 ± 14.24*#&@
HA	68.05 ± 7.21	106.65 ± 25.91*	91.05 ± 13.26*#	83.4 ± 13.16*#&	124.33 ± 23.74*#&@

$p < 0.05$, compared with S1; #$p < 0.05$, compared with S2; &$p < 0.05$, compared with S3; @$p < 0.05$, compared with S4.

fibrosis degree from S2. FIB4 demonstrated no statistical significance under S2 ($p > 0.05$), while upregulated following the increase of hepatic fibrosis degree from S3 ($p < 0.05$) (Table I).

Correlation Analysis of Indicators with the Pathological Staging of Hepatic Fibrosis

According to liver pathology, PCIII, IV-C, LN, APRI, LSM, and FiB4 were positively correlated with the stage of hepatic fibrosis ($p < 0.05$). On the contrary, HA and BMI failed to show significant correlation with hepatic fibrosis staging ($p > 0.05$). Spearman correlation analysis revealed that the correlation coefficient of APRI, PCIII, IV-C, LN, LSM, and FiB4 with hepatic fibrosis staging was 0.258, 0.428, 0.440, 0.299, 0.731, and 0.438, respectively.

ROC Curve Analysis of Indicators on the Degree of Hepatic Fibrosis

ROC curve analysis demonstrated that LSM and FIB4 exhibited good predictions of various stages of fibrosis in chronic liver disease with AUC greater than 0.7. Their AUCs for the diagnosis of liver cirrhosis in S4 were 0.908 and 0.777, respectively, with specificity at 96.9% and 62.5%, and sensitivity at 71% and 87.1%. The AUC of PCIII, IV-C, and LN was 0.711, 0.754, and 0.739, with specificity at 92.2%, 54.7%, and 71.09%, and sensitivity at 48.4%, 87.1%, and 71%, respectively. APRI was insensitive to hepatic fibrosis in early stage. Its AUC for the diagnosis of liver cirrhosis was 0.642, with specificity at 60.95 and sensitivity at 71% (Table III, Figure 1-3).

Table II. Correlation analysis of indicators with the pathological staging of hepatic fibrosis.

Item	Correlation coefficient	p
PCIII	0.428	< 0.01
IV-C	0.440	< 0.01
LN	0.299	< 0.01
HA	0.190	> 0.05
BMI	0.172	> 0.05
APRI	0.258	< 0.05
LSM	0.731	< 0.01
FIB4	0.438	< 0.01

ROC Curve Analysis of FibroTouch in the Diagnosis of Hepatic Fibrosis in Autoimmune Liver Disease

ROC curve analysis exhibited good prediction of FibroTouch in hepatic fibrosis staging in autoimmune liver disease with AUC larger than 0.7. Its AUC in the diagnosis of liver cirrhosis in S3 and S4 was 0.979 with sensitivity at 100% (Table IV).

Analysis of Influence Factors in LSM

LSM value was treated as the dependent variable to perform multiple linear stepwise regression analysis. ALT, AST, and fat attenuation were correlated with LSM ($p < 0.05$), whereas liver stiffness values were associated with the degree of attenuation ($p < 0.05$). Gender, age, and BMI exhibited no impact on LSM ($p > 0.05$) (Table V).

Discussion

Fibrous hyperplasia is a repair response to repeated or persistent chronic causes. Liver in-

Table III. Diagnostic value analysis of indicators on hepatic fibrosis.

Model	LV-Stage	AUC	Criterion	95% CI	*p*-value	SE	SP5
PCIII	S2	0.687	43.25	0.584-0.778	0.000	39.6	97.9
	S3	0.743	38.36	0.643-0.827	0.000	48.8	90.4
	S4	0.711	43.25	0.609-0.799	0.000	48.4	92.2
IV-C	S2	0.710	40.97	0.608-0.799	0.000	43.7	93.6
	S3	0.745	27.31	0.645-0.829	0.000	81.4	59.6
	S4	0.754	27.31	0.654-0.836	0.000	87.1	54.7
LN	S2	0.568	17.12	0.462-0.669	0.256	64.6	57.4
	S3	0.598	17.12	0.492-0.697	0.1	67.4	57.7
	S4	0.739	19.15	0.639-0.824	0.000	71	71.9
APRI	S2	0.645	0.38	0.540-0.741	0.01	100	29.8
	S3	0.644	0.38	0.540-0.740	0.01	100	26.9
	S4	0.642	0.74	0.537-0.738	0.01	71	60.9
LSM	S2	0.901**	9.1	0.822-0.953	0.000	91.7	74.5
	S3	0.929▲▲	9.2	0.857-0.971	0.000	95.3	75
	S4	0.908♦♦	14.1	0.831-0.958	0.000	71	96.9
FIB4	S2	0.755	6.2	0.655-0.838	0.001	54.17	85.11
	S3	0.782▲	5.11	0.684-0.860	0.001	83.33	66.04
	S4	0.777♦	5.13	0.679-0.856	0.001	87.1	62.5

**$p < 0.01$, LSM compared with other indicators in S2; ▲$p < 0.05$, FIB4 compared with LSM in S4; ▲▲$p < 0.01$, LSM compared with other indicators except FIB4 in S4; ♦$p < 0.05$, FIB4 compared with LSM in S4; ♦♦$p < 0.01$, LSM compared with other indicators except FIB4 in S4.

flammation or necrosis can lead to continuous hepatic fibrosis. From the clinical and pathological changes, several chronic liver diseases, especially chronic viral hepatitis, hepatic fibrosis is the inevitable stage of chronic liver disease to cirrhosis. The diagnosis of hepatic fibrosis depends on liver biopsy, which is limited by traumatism, difficult to repeat, and certain complications[14].

In the serum markers of hepatic fibrosis, fibroblasts increased following hepatic fibrosis, resulting in PCIII synthesis increase and degradation reduction. When the basement membrane was damaged or changed, the content of serum type IV collagen increased. LN exists in the intrahepatic bile duct, blood vessels, and lymphatic basement membrane. HA is a kind of glycosaminoglycan produced in stromal cells, thus widely presents in connective

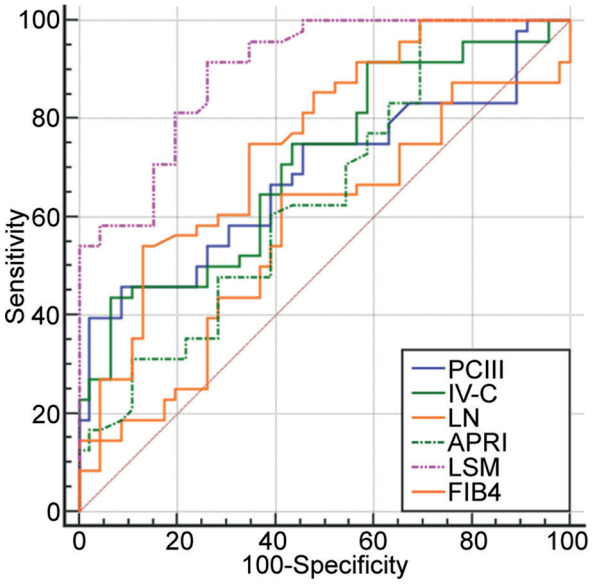

Figure 1. ROC of indicators in S2.

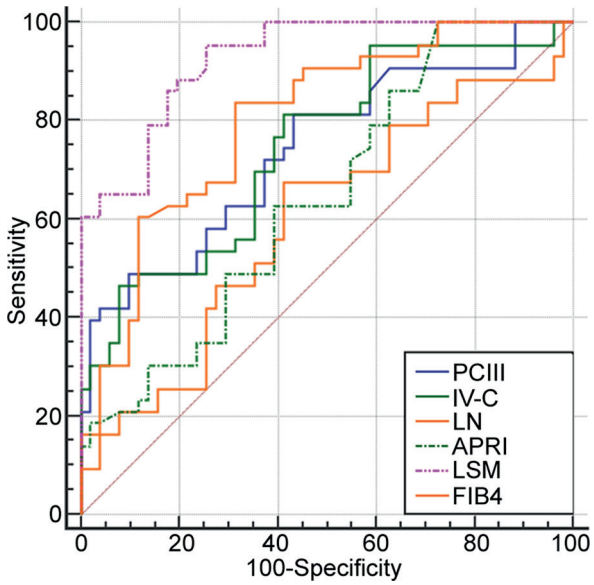

Figure 2. ROC of indicators in S3.

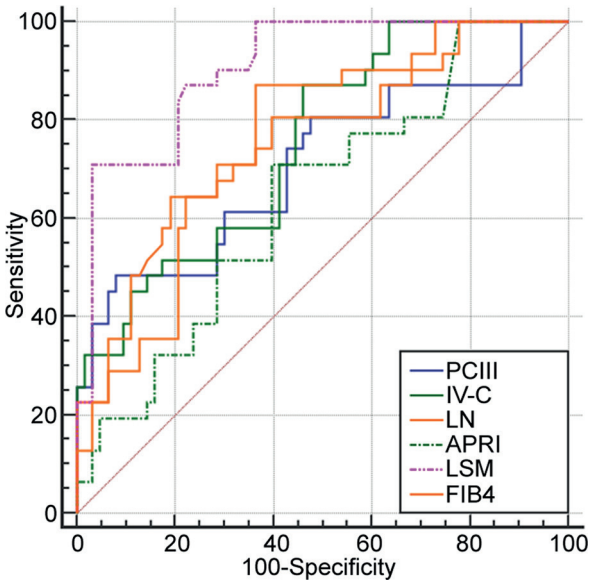

Figure 3. ROC of indicators in S4.

tissue, skin, synovial fluid, and vitreous body that can accurately reflect the liver endothelial cell function, the amount of liver fiber, and liver cell damage. They are commonly used in the clinic to assess hepatic fibrosis[15-17]. This study showed that the four indicators were significantly different in the different stages of fibrosis, of which PCIII, IV-C, and LN were closely associated with pathological liver staging. HA can reflect hepatic fibrosis to a certain extent, while it is insensitive to hepatic fibrosis in early stage, thus cannot accurately estimate the degree of hepatic fibrosis or replace liver biopsy.

APRI is a simple indicator in the diagnosis of hepatic fibrosis as containing only two commonly used clinical indicators. It was found that the AUROC of APRI in diagnosis of significant hepatic fibrosis and early liver cirrhosis was 0.80 and 0.89, respectively[18]. However, our results demonstrated that the correlation coefficient of APRI with hepatic fibrosis staging was 0.258, and no statistical difference was observed for APRI index of each hepatic fibrosis. ROC curve analysis showed that its AUC on S2, S3, and S4 was 0.645, 0.644, and 0.642, resulting in poor diagnostic value. Wai et al[11] also confirmed that the value of APRI index was limited to predict hepatitis B hepatic fibrosis, and cirrhosis of the liver is limited. It may be caused by the fact that AST both reflect hepatic fibrosis and inflammation, while PLT count showed a large overlap between slight and severe hepatic fibrosis. Moreover, other important clinical factors (such as age) were not included. The AUROC of APRI in diagnosis of severe and early stage hepatic fibrosis were only 0.678 and 0.683, showing the low diagnostic value.

FIB-4 index system includes ALT, AST, PLT, and age. It obtains good effect in the prediction of hepatic fibrosis together with hepatitis C virus and human immunodeficiency virus infection, thus can replace liver biopsy in most patients[19]. In this study, we compared the results of FIB-4 and liver biopsy. We found that the correlation coefficient between FIB-4 and liver pathology was significantly higher than that of APRI. The AUC value of FIB-4 was higher than 0.7 in hepatic fibrosis over S2, with

Table IV. The diagnostic value of FibroTouch in hepatic fibrosis of autoimmune liver disease.

LV-Stage	AUC	Criterion	95% CI	*p*	SE	SP
S2	0.933	6.9	0.692-0.998	0.000	100	80
S3	0.979	10.4	0.759-1	0.000	100	91.67
S4	0.979	10.4	0.759-1	0.000	100	91.67

Table V. Multiple factor analyses of LSM.

	Model	B	Std	Beta	*t*	*p*	95% CI
Gender	-1.301	1.126	-0.116	-1.155	.251	-3.540	0.937
Age	-0.052	0.048	-0.108	-1.079	0.284	-0.147	0.044
ALB	-0.324	0.104	-0.335	-3.134	0.002	-0.530	-0.119
ALT	-0.054	0.016	-0.698	-3.445	0.001	-0.085	-0.023
AST	0.071	0.026	0.570	2.749	0.007	0.020	0.122
BMI	0.257	0.135	0.189	1.902	0.061	-0.012	0.526
FAP	0.025	0.010	0.257	2.548	0.012	0.006	0.045

high sensitivity. However, its prediction on fibrosis staging was limited and needs another model for judgment.

FibroTouch shares same principle and diagnosis cutoff with Fibroscan in detecting liver stiffness. The difference is that the former tests instantaneous elasticity based on the two-dimensional ultrasound positioning, whereas latter's success rate is affected by obesity, intercostal space, liver inflammation and necrosis, and fatty change[20]. Image guidance can avoid the gallbladder, blood vessels, and other factors that affect the outcome of hepatic fibrosis. Therefore, it will help to select the appropriate location for liver fiber scan to improve the detection success rate and accuracy. This work suggested that FibroTouch exhibited high consistency with FIB-4, APRI, and liver biopsy and, thus, it had a high diagnostic value on severe hepatic fibrosis and early-stage liver cirrhosis. The mean value of FibroTouch increased with the exacerbation of hepatic fibrosis, indicating that FibroTouch elasticity was affected by the pathological stage of liver. Its reliability was markedly higher than that of FIB-4, APRI, and hepatic fibrosis serum index. However, no statistical difference was found on severe hepatic fibrosis and liver cirrhosis. In the analysis of influencing factors, it was shown that the elasticity of liver cirrhosis was not affected by age and body weight, but by inflammation and fatty degree. However, the samples of hepatic fibrosis in our investigation were few; so, to the accuracy of the results still need to be confirmed by a large sample size study. At present, elastic imaging is mainly used for fibrosis detection in chronic hepatitis B, hepatitis C, and other diseases. There is still lack of report about its application in autoimmune liver disease and other chronic liver disease. It was shown that the technology can effectively shorten the diagnosis time and reduce misdiagnosis of hepatic fibrosis[21]. This study revealed that the use of elastic imaging to quantitatively analyze autoimmune liver disease is equally reliable to assess the degree of hepatic fibrosis, with accuracy rate more than 80% in the severe hepatic fibrosis and liver cirrhosis evaluation or more, indicating that elastic imaging is worth of clinical promotion.

Conclusions

PCIII, IV-C, LN, Fibrotouch, FIB-4, and APRI have a high degree of consistency with hepatic fibrosis and can be used to assess the severity of hepatic fibrosis. Fibrotouch presented better diagnostic accuracy on the degree of hepatic fibrosis than the other three kinds of serum diagnostic mode. It can reduce the need for about 25% of liver biopsy, but is still affected by liver inflammation and fatty degree. Further in-depth exploration is needed to obtain better model to predict the degree of hepatic fibrosis in chronic hepatitis.

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Disclosure of Conflict of Interest

The authors declare no competing financial or commercial interests in this manuscript.

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