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ORIGINAL ARTICLE

Evaluation of Ocular Biomechanical Indices to Distinguish Normal from Keratoconus Eyes

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ABSTRACT

Purpose: To compare and assess the ability of pressure-derived parameters and corneal deformation waveform signal-derived parameters of the ocular response analyzer (ORA) measurement to distinguish between keratoconus and normal eyes, and to develop a combined parameter to optimize the diagnosis of keratoconus.

Materials and methods: One hundred and seventy-seven eyes (177 patients) with keratoconus (group KC) and 205 normal eyes (205 patients; group N) were included. One eye from each subject was randomly selected for analysis. Patients underwent a complete clinical eye examination, corneal topography (Humphrey ATLAS), tomography (Pentacam Oculus) and biomechanical evaluations (ORA Reichert). Differences in the distributions between the groups were assessed using the Mann-Whitney test. The receiver operating characteristic (ROC) curve was used to identify cutoff points that maximized sensitivity and specificity in discriminating keratoconus from normal corneas. Logistic regression was used to identify a combined linear model (Fisher 1.0).

Results: Significant differences in all studied parameters were detected ($p < 0.05$), except for W2. For the corneal resistance factor (CRF): Area under the ROC curve (AUROC) 89.1%, sensitivity 81.36%, specificity 84.88%. For the p1area: AUROC 91.5%, sensitivity 87.1%, specificity 81.95%. Of the individual parameters, the highest predictive accuracy was for the Fisher 1.0, which represents the combination of all parameters (AUROC 95.5%, sensitivity 88.14%, specificity 93.17%).

Conclusion: Waveform-derived ORA parameters displayed greater accuracy than pressure-derived parameters for identifying keratoconus. Corneal hysteresis (CH) and CRF, a diagnostic linear model that combines different parameters, provided the greatest accuracy for differentiating keratoconus from normal corneas.

Keywords: Keratoconus, Cornea, Biomechanical indices, Applanation, Waveform.

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INTRODUCTION

The cornea is a tissue with viscoelastic properties. Alterations in its stromal structure are intimately related to its biomechanical behavior.[1] The commercial ocular response analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY, USA) utilizes a dynamic bidirectional applanation process to quantify corneal biomechanical properties *in vivo* and to determine intraocular pressure (IOP).[2]

There has been increased interest in evaluating corneal biomechanics. The ORA records corneal inward and outward applanation after delivering a metered collimated air pulse and provides an indication of the viscosity and elastic properties of the cornea. Corneal hysteresis (CH) and the corneal resistance factor (CRF), which are the corneal biomechanical metrics generated by the ORA, have been the subjects of several recent publications.[3,4]

Luce presented data (Luce D, ORA waveform analysis and beyond. Presented at: American Society of Cataract and Refractive Surgery Annual Meeting, April 3 to 8, 2009; San Francisco, California) indicating that waveform parameters provided from the ORA signal may be more sensitive than CH or the CRF in discriminating abnormal corneas. The differences in the signal morphology between the two eyes led to the conclusion that the corneas are biomechanically distinct.[5]

The purpose of this study was to evaluate and compare the ORA parameters between patients with keratoconus and healthy control individuals. In addition, we assessed the effect of analysis of all ORA parameters together.

MATERIALS AND METHODS

The study constituted a comparative case series. The research followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Federal University of São Paulo, Brazil (protocol 2012/10). The purpose of the study was explained to all subjects, who gave informed consent before inclusion. Patients were evaluated sequentially from December, 2010 through December, 2011. Demographic and clinical data were obtained, including date of birth, gender and self-reported race or ethnicity.

Each subject underwent a comprehensive ophthalmologic examination, which included a medical history review, best corrected visual acuity, slit-lamp and funduscopic examinations, Placido disc topography (Humphrey ATLAS; Carl Zeiss Meditec, Dublin, CA, USA), Pentacam tomographic evaluation (Oculus, Wetzlar, Germany), and ORA measurements (Reichert Ophthalmic Instruments).

Keratoconus was defined using the Amsler-Krumeich classification.[6] A normal eye had no ocular pathology, previous ocular surgery or relevant refractive error. One eye randomly selected from 177 consecutive patients with clinical bilateral keratoconus was retrospectively included (group KC). The control group included one eye randomly selected from 205 age-matched patients from a database of normal patients considered good candidates (group N). Keratoconus cases with a history of corneal surgery or with extensive corneal scarring were excluded from the study.

According to the Amsler-Krumeich classification of the severity of keratoconus, 120 eyes (67.8%) were classified as grade I, 37 (20.9%) as grade II and 20 (11.3%) as grade III.

The ORA determines corneal biomechanical properties using an applied force displacement relationship. A precisely metered air pulse is delivered to the eye, causing the cornea to move inward, past applanation and into slight concavity. Milliseconds after the initial applanation, the air pump generating the air pulse is shut off, and the pressure applied to the eye decreases in an inverse time, symmetrical fashion. As the pressure decreases, the cornea passes through a second applanated state while returning from concavity to its normal convex curvature. Energy absorption during rapid corneal deformation delays the occurrence of the inward and outward applanation signal peaks, resulting in a difference between the applanation pressures. This difference between the inward and outward motion applanation pressures is CH, which indicates viscous damping in the cornea and reflects the capacity of corneal tissue to absorb and dissipate energy. The CRF is a measure of the cumulative effects of both the viscous and elastic resistance encountered by the air jet while deforming the corneal surface, being an indicator of the overall resistance of the cornea. The CRF was derived empirically to maximize its correlation with the central corneal thickness. It can be considered as weighted by the elastic resistance, because of its stronger correlation with the central corneal thickness than with CH. Although CH and the CRF are related, they can in some cases differ significantly, and each provides distinct information about the cornea.

Using the new ORA software (version 3.00), 37 new parameters were calculated based on the waveform of the ORA signal. Six further keratoconus-specific parameters are incorporated in the latest update to the ORA device. These are: The keratoconus match index (KMI–KC score), and the keratoconus match probability (KMP–KC normal, K suspect, KC mild, KC moderate and KC severe).

Linear discriminant analysis (LDA), and the related Fisher's linear discriminant (Fisher 1.0), are methods used in statistics, pattern recognition and machine learning to identify a linear combination of features that characterizes or separates two or more classes of objects or events. The resulting combination may be used as a linear classifier or, more commonly, for dimensionality reduction before later classification.

Statistical analyses were performed using BioEstat 5.0 (Instituto Mamirauá, Amazonas, Brazil) and Med-Calc 11.1 (MedCalc Software, Mariakerke, Belgium). The nonparametric Mann-Whitney U test (Wilcoxon rank-sum test) was used to assess variable distributions between the keratoconic and normal cornea groups.

Receiver operating characteristic (ROC) curves and the areas under the ROC curves (AUROCs) were calculated for all parameters to determine the overall predictive accuracy of the tests. The standard error of the AUROC was assessed by the DeLong method.[7] The binomial exact method was used to calculate the confidence interval (CI) for the AUROC. Nonparametric pairwise comparisons were performed to determine the significance of differences between AUROCs, using the Hanley-McNeil method[8] to calculate standard errors. Values of $p < 0.05$ indicated statistical significance.

RESULTS

Single eyes randomly selected from 205 patients with normal, unoperated eyes and 177 patients with bilateral keratoconus were included. In the normal and keratoconic groups, the average patient ages were 34.0 ± 10.9 years (range: 12.0-78.1 years) and 30.2 ± 10.8 years (range: 16.1-63.0 years) respectively.

Significant differences were found between normal (group N) and keratoconic (group KC) eyes for all parameters (Mann-Whitney U test, $p < 0.05$) with the exception of the w2 parameter ($p = 0.0491$; Table 1). CH was 8.36 ± 1.63 mm Hg (range: 13.60-3.90 mm Hg) in group KC and 10.66 ± 1.71 mm Hg (range: 15.90-6.20) in group N ($p < 0.0001$). The corneal resistance factor was 7.35 ± 2.05 mm Hg (range: 20.90-3.00) in group KC and 10.56 ± 1.98 mm Hg (range: 16.10-6.00) in group N ($p < 0.0001$). The p1 area was 1,938.32 ± 869.33 (range: 4,849.13-278.19) in group KC and 3,864.45 ± 1,231.35 (range: 10,147.64-1,382.00) in group N ($p < 0.0001$). The KMI (KC score) was 0.07309 ± 0.379904 (range: 2.043 to –0.0747) in group KC and 0.805224 ± 0.394059 (range: 1.806 to –0.111) in the group N ($p < 0.0001$). The KMP (KC normal) was 5.870056 ± 15.92811 (range: 100 to 0) in group KC and 50.37561 ± 37.55337 (range: 100 to 0) in group N ($p < 0.0001$). The Fisher 1.0 was –0.90739 ± 0.40433 (range: 0.862008 to –2.16366) in group KC and 0.057053 ± 0.402856 (range: 1.079689 to –1.2191) in group N. These data are summarized in Table 1.

All parameters had higher values in group N with the exception of path 1, 2, 11, and 21, aplhf and KMP

Table 1: ORA parameters measured in normal and keratoconus eyes

	NL					KC			
	MED	*DESVPAD*	*MAIOR*	*MENOR*	*p-value*	*MED*	*DESVPAD*	*MAIOR*	*MENOR*
IOPg	15.26	3.69	27.30	6.90	<0.0001	11.09	4.09	41.20	3.10
IOPcc	15.49	3.36	26.80	7.40	<0.0001	14.38	3.55	36.60	3.90
CRF	10.57	1.99	16.10	6.00	<0.0001	7.36	2.06	20.90	3.00
CH	10.66	1.71	15.90	6.20	<0.0001	8.37	1.63	13.70	3.90
KC score	0.81	0.39	1.81	–0.11	<0.0001	0.07	0.38	2.04	–0.75
KC normal	50.38	37.55	100.00	0.00	<0.0001	5.87	15.93	100.00	0.00
KC suspect	32.37	24.54	68.00	0.00	<0.0001	20.10	21.75	68.00	0.00
KC mild	15.13	17.64	65.00	0.00	<0.0001	36.30	18.89	65.00	0.00
KC moderate	2.00	5.99	48.00	0.00	<0.0001	25.35	19.96	57.00	0.00
KC severe	0.13	0.85	9.00	0.00	<0.0001	12.38	20.07	94.00	0.00
aindex	9.20	1.05	10.00	5.35	<0.0001	7.65	2.39	10.00	1.18
bindex	9.43	1.11	10.00	0.48	<0.0001	8.04	2.59	10.00	0.21
p1area	3864.45	1231.35	10147.64	1382.00	<0.0001	1938.32	869.33	4849.13	278.19
p2area	2525.99	791.87	4610.50	762.31	<0.0001	1268.27	687.44	6213.70	112.56
aspect1	19.49	5.90	39.31	7.77	<0.0001	12.99	6.77	45.00	1.03
aspect2	20.40	9.33	55.02	4.52	<0.0001	13.70	10.30	51.03	1.01
uslope1	66.28	29.40	187.17	17.64	<0.0001	41.90	26.57	172.00	4.47
uslope2	88.89	41.46	239.13	14.68	<0.0001	53.13	40.79	196.88	1.75
dslope1	28.81	8.67	60.83	11.55	<0.0001	20.62	12.16	102.50	1.30
dslope2	27.28	13.75	84.80	5.59	<0.0001	19.72	15.96	96.38	1.13
w1	21.90	2.62	30.00	15.00	0.00	20.68	5.64	43.00	6.00
w2	18.30	4.20	34.00	8.00	0.05	18.10	7.53	40.00	6.00
h1	418.61	110.03	651.00	171.00	<0.0001	242.97	95.68	530.44	44.26
h2	344.40	107.01	615.56	147.00	<0.0001	195.43	100.20	545.81	20.24
dive1	352.90	140.58	614.50	17.50	<0.0001	204.05	100.76	516.00	9.25
dive2	276.28	108.57	552.75	25.00	<0.0001	150.40	84.15	427.63	5.00
path1	21.94	3.81	36.44	10.08	<0.0001	28.02	8.00	54.86	13.92
path2	25.60	6.46	56.18	11.57	<0.0001	31.53	10.17	65.43	13.86
mslew1	112.80	39.99	239.50	40.75	<0.0001	73.63	34.14	214.50	8.75
mslew2	133.36	54.52	332.75	25.75	<0.0001	85.84	50.75	255.00	11.25
slew1	66.09	29.94	187.17	16.38	<0.0001	46.08	26.12	172.00	4.63
slew2	88.90	41.45	239.13	12.50	<0.0001	57.16	39.18	196.88	2.50
aplhf	1.32	0.29	2.40	0.80	<0.0001	1.68	0.45	3.80	0.90
p1area1	1665.86	629.61	5350.00	542.00	<0.0001	800.14	395.48	2468.63	117.75
p2area1	1093.73	371.50	2142.25	240.88	<0.0001	533.95	302.38	2663.28	28.22
aspect11	25.95	9.21	66.25	10.11	<0.0001	19.10	10.64	63.84	1.02
aspect21	28.26	13.71	71.47	4.56	<0.0001	19.63	14.68	85.06	1.88
uslope11	63.93	30.32	181.38	11.56	<0.0001	44.51	27.00	164.38	4.75
uslope21	72.96	34.82	200.25	11.29	<0.0001	47.77	35.95	177.50	0.00
dslope11	44.97	17.93	121.92	14.10	<0.0001	34.21	20.07	110.50	1.23
dslope21	45.00	25.58	170.50	5.79	<0.0001	32.57	25.66	127.00	2.43
w11	11.28	2.25	18.00	5.00	<0.0001	9.87	3.66	29.00	4.00
w21	9.13	2.74	23.00	3.00	<0.0001	8.16	3.53	22.00	3.00
h11	279.07	73.36	434.00	114.00	<0.0001	161.98	63.78	353.63	29.51
h21	229.60	71.34	410.38	98.00	<0.0001	130.29	66.80	363.88	13.49
path11	31.83	7.65	57.88	11.71	<0.0001	39.54	11.23	69.00	16.70
path21	35.78	9.51	68.60	14.59	<0.0001	42.14	13.20	86.81	17.11
Fisher1.0	0.06	0.40	1.08	–1.22	<0.0001	–0.91	0.40	0.86	–2.16

Significant differences were found between normal and keratoconic eyes for all parameters (Mann-Whitney U test, $p < 0.05$) with the exception of w2 ($p = 0.05$).

(KC mild, KC moderate, and KC severe). Both the corneal-compensated IOP (IOPcc) and the Goldmann-correlated IOP (IOPg) were significantly different between the groups. Although the average group N IOPcc was 15.49 mm Hg and that of group KC was 14.37 mm Hg, the difference was significant ($p < 0.0001$).

The AUROC was >0.85 for 11 parameters, including the CRF (0.891), but not CH (0.841). The parameters related to the area of the waveform during the second and first applanations gave similar KMI (KC score) and the KMP (KC normal) results of 0.915 and 0.910 respectively.

The parameter that achieved the best results was the Fisher 1.0, with AUROC 0.955, and a sensitivity and specificity of 88.14 and 93.17% respectively. The sensitivity, specificity and AUROC results are shown in Table 2. In the comparison of those parameters with an AUROC > 0.85, the Fisher 1.0 was significantly superior to all others (Table 3).

Table 2: Data summary from ROC curve of new ORA parameters in normal and keratoconic eyes

Parameters	*Criterion*	*Sensitivity*	*Specificity*	*AUROC*	*IC (95%)*
IOPg	12.50	74.01	75.61	0.83	0.786-0.864
IOPcc	14.70	61.02	58.54	0.62	0.566-0.666
CRF	8.60	81.36	84.88	0.89	0.855-0.920
CH	9.40	80.23	74.63	0.84	0.800-0.876
KC score	0.341	81.36	88.29	0.92	0.882-0.941
KC normal	5.00	81.36	87.80	0.91	0.877-0.937
KC suspect	14.00	58.19	66.34	0.64	0.587-0.685
KC mild	18.00	81.36	70.73	0.81	0.764-0.846
KC moderate	3.00	81.36	87.80	0.90	0.868-0.930
KC severe	0.00	61.58	96.10	0.80	0.752-0.835
aindex	9081.00	61.58	70.24	0.70	0.648-0.742
bindex	9708.00	59.32	60.00	0.65	0.602-0.700
p1area	2814789.00	87.01	81.95	0.92	0.882-0.941
p2area	1626.375	80.23	88.29	0.91	0.876-0.936
aspect1	16211.00	71.19	69.76	0.78	0.731-0.817
aspect2	15317.00	68.93	70.24	0.73	0.677-0.769
uslope1	43.7	64.97	77.07	0.76	0.712-0.800
uslope2	65.50	68.93	69.27	0.75	0.706-0.795
dslope1	25.917	74.58	63.41	0.75	0.699-0.789
dslope2	19.286	63.84	75.12	0.70	0.646-0.741
w1	21.00	59.32	55.61	0.60	0.553-0.654
w2	17.00	53.11	57.07	0.55	0.498-0.600
h1	365813.00	90.40	67.32	0.89	0.849-0.915
h2	241.875	74.58	83.41	0.84	0.804-0.879
dive1	297.25	81.36	70.24	0.81	0.763-0.844
dive2	184.50	72.32	80.98	0.82	0.781-0.860
path1	23.29	70.06	68.29	0.75	0.701-0.791
path2	26473.00	64.97	64.88	0.69	0.639-0.734
mslew1	87.50	71.75	71.22	0.79	0.740-0.825
mslew2	92.50	66.67	76.10	0.76	0.710-0.798
slew1	48.821	64.97	71.71	0.71	0.666-0.759
slew2	70563.00	69.49	66.34	0.73	0.684-0.775
aplhf	1.40	69.49	70.24	0.76	0.712-0.800
p1area1	1189.75	85.88	80.49	0.90	0.870-0.931
p2area1	751.875	83.05	83.90	0.90	0.865-0.928
aspect11	20.15	61.02	74.15	0.71	0.658-0.751
aspect21	19147.00	61.02	72.20	0.71	0.659-0.753
uslope11	47125.00	61.58	65.37	0.69	0.643-0.738
uslope21	47583.00	64.41	77.56	0.73	0.679-0.771
dslope11	36.25	61.02	66.83	0.68	0.627-0.723
dslope21	32214.00	61.58	61.46	0.67	0.624-0.721
w11	10.00	59.32	66.83	0.65	0.597-0.695
w21	8.00	63.28	59.02	0.63	0.577-0.677
h11	231.75	85.31	71.22	0.89	0.849-0.915
h21	161.25	74.58	83.41	0.84	0.804-0.879
path11	34784.00	62.15	70.24	0.70	0.656-0.750
path21	36901.00	61.02	60.00	0.64	0.590-0.688
Fisher1.0	90.49	88.14	93.17	0.96	0.929-0.973

The AUROC was greater than 0.85 for 11 parameters. The parameter that achieved the best results was Fisher1.0 with AUROC 0.96, 88.14% sensitivity and specificity of 93.17%

Table 3: Pairwise comparison of ROC curves

	KC score	*KC mod*	*KC Nl*	*p1area*	*p2area*	*h1*	*p1area1*	*p2area1*	*h11*	*Fisher1.0*
CRF	0.1522	0.5052	0.2405	0.2141	0.2878	0.785	0.5144	0.642	0.785	<0.0001
KC score		0.0102	0.0813	0.9883	0.6149	0.0274	0.4423	0.1253	0.0274	<0.0001
KC mod			0.1075	0.4032	0.5185	0.2228	0.9317	0.7834	0.2228	<0.0001
KC Nl				0.7542	0.9443	0.0677	0.6515	0.2875	0.0677	<0.0001
p1area					0.7343	0.0058	0.0093	0.3164	0.0058	0.0001
p2area						0.1489	0.7047	0.0448	0.1489	0.0003
h1							0.1258	0.4156	10.000	<0.0001
p1area1								0.7773	0.1258	<0.0001
p2area1									0.4156	<0.0001
h11										<0.0001

DISCUSSION

Corneal hydration, corneal thickness regional variation and collagen fibril orientation and distribution determine corneal biomechanics.[9-12] Additionally, the variation in biomechanical measurements may be due to age.[13] Therefore, both groups consisted of patients of similar ages.

Keratoconic corneas should applanate slightly earlier and respond to a slightly lower rate of air pressure, which has also been reported in forme fruste keratoconus.[5] Therefore, for corneas with keratoconus, lower values were found for most parameters.[3, 14,15] However, our data showed that some parameters derived from the waveform signal; i.e. path 1, 2, 11, 21 and aplhf, were higher in patients with keratoconus. What makes these parameters higher in keratoconus? These parameters are related either to the absolute value of the path lengths around the peaks (path 1, 11, 2 and 21) or to the irregularity of the waveform region between the peaks (aplhf). Multiple oscillations of the waveform may reflect the characteristics of an ectatic cornea.[5] Our study confirms the results for this condition, and should be taken into consideration in future clinical evaluations.

In terms of the pressure-derived parameters, the CRF was better than CH, with AUC CRF = 0.891 compared to AUC CH = 0.841. These results confirm those of a previous study[16] and may be related to findings that suggest that the CRF correlates best with the optical aberrations of keratoconus.[17]

Although CH and the CRF were significantly different between the two groups, there was an overlap, which limits the use of these parameters in isolation, as described previously.[3,18] The parameters related to the signal waveform may better distinguish keratoconus from normal corneas than those derived from pressure parameters (Luce D. ORA waveform analysis and beyond. Presented at the American Society of Cataract and Refractive Surgery Annual Meeting, April 3 to 8, 2009; San Francisco, California).

Our data demonstrate that the parameters derived from the areas under the first and second peaks were better than the traditional parameters.[19] With AUCs of 0.915 and 0.910, they exceeded the parameters CH and CRF (AUCs 0.841 and 0.891 respectively). Interestingly, the KMI and KMP indices achieved results similar to those derived from the areas under the first and second peaks, with AUCs of 0.910 and 0.915 respectively.

Of all parameters, the best was the Fisher 1.0. Its AUC of 0.955 exceeded those of either the pressure- or single-waveform–derived parameters as well as from the KMI and KMP. Why does this parameter provide such a high combined sensitivity and specificity? This increase in the AUC suggests that among the ORA parameters; there are some that do not clearly differentiate keratoconus from normal corneas when used independently, the performance of which are improved significantly when combined with other parameters.[20] Figure 1 shows the ROC curves of the Fisher 1.0, p2area, which is the best parameter-derived signal, and CRF, which is the best parameter derived from the pressure. Figure 2 shows the difference between the result obtained with the Fisher 1.0 and CH, which is the classic parameter.

The parameters of the ORA evolve. Firstly, the pressure derivatives, which consider the biological and biomechanical properties in addition to the geometric features (topography and pachymetry). From the signal curve, we noted that these data relevant provided information. Here the parameters were derived from the signal waveform, in particular the p1area and p2area. This develops further with KMI and KMP, but gives similar results.

Enhanced assessment was achieved with the Fisher 1.0, which is an analysis of the combination of all parameters.

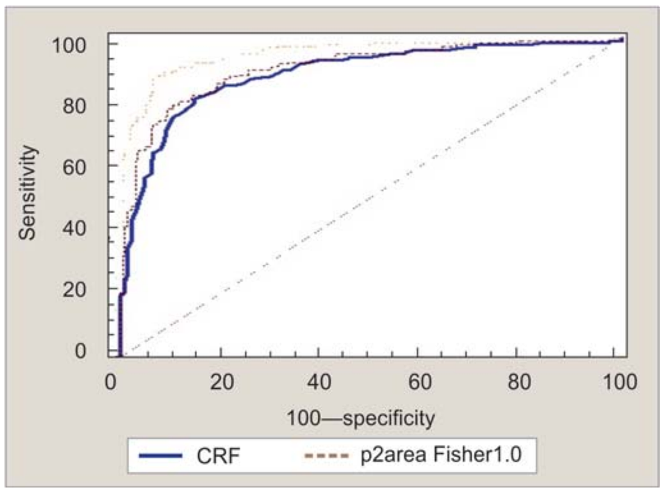

Fig. 1: Combined ROC curves for CRF, p2area and Fisher1.0

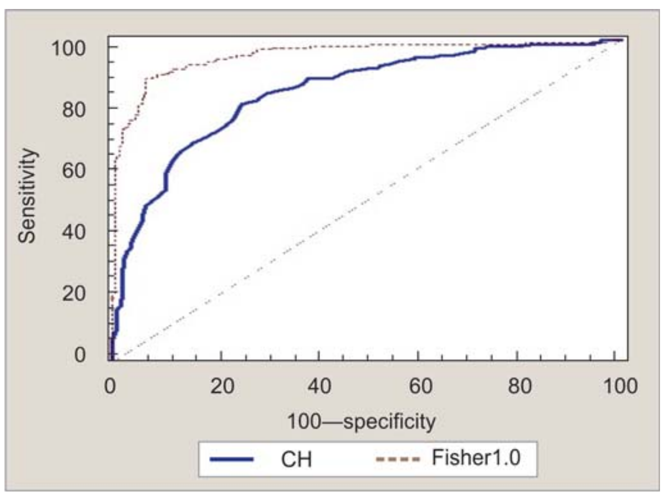

Fig. 2: Combined ROC curves for CH and Fisher1.0

Future studies of this combined analysis in other populations should be performed.

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