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ScienceDirect

Procedia Computer Science 126 (2018) 482–489

Procedia Computer Science

www.elsevier.com/locate/procedia

International Conference on Knowledge Based and Intelligent Information and Engineering Systems, KES2018, 3-5 September 2018, Belgrade, Serbia

Multi-expert analysis and validation of objective vascular tortuosity measurements

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Abstract

The retinal vascular tortuosity is a commonly used parameter for the early diagnosis of several diseases that affects the circulatory system. The manual analysis of fundus images for the tortuosity characterization is a time-consuming and subjective task that presents a high inter-rater variability. Thus, automatic image processing methods allow the efficient computation of objective and stable parameters for the issue. The validation of these methods is crucial to ensure an objective and reliable environment for the retinal experts. This paper describes a multi-expert analysis that measures the clinical performance as well as a validation procedure of the computational tortuosity module of the Sirius framework, a computer-aided diagnosis platform for analyzing retinal images.

Keywords: Retinal circulation; vascular tortuosity; fundus images; computer-aided diagnosis; image analysis;

1. Introduction

The use of medical imaging has raised significantly during the last years over all the levels of the health care systems. Given the increasing availability of medical capture devices, the number of improved health care protocols based on image analysis is growing considerably for the clinical decision-making process. This entails the challenge of dealing with massive amounts of information from large medical image databases in an useful and reliable way for the medical practice. Additionally, the interpretation of medical images by the clinical experts is a tedious and time-consuming task that presents a low repeatability because of the subjective perception of the data, the inter and intra-observer agreement, or the significant variability of the retinal images. Therefore, the use of computer-based systems that cover the management and analysis of medical images by an objective and accurate procedure is highly desirable for diagnostic and treatment purposes.

Among the medical imaging procedures, retinal image analysis presents a significative clinical relevance given its potential for the noninvasive diagnosis of several diseases. The function and morphology of the retina make possible a direct noninvasive observation of the circulatory system, allowing, thereby, the diagnosis of both ocular

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10.1016/j.procs.2018.07.282

diseases, such as glaucoma or macular degeneration, as well as systemic diseases, such as diabetic retinopathy or multiple sclerosis, among others [1]. Considering the great interest of analyzing the eye fundus, Sirius [2] (System for the Integration of Retinal Images Understanding Services) was presented as a computer-aided diagnosis system for the analysis of retinal images. Sirius provides several image processing services for the early diagnosis and disease monitoring that are organized as independent modules. Therefore, one of the modules consists of a fully automatic computation of the arterio-venous ratio (AVR) [3], a relevant parameter related to the vascular risk associated with hypertension. Another module is focused on the detection of microaneurysms [4], which are round microscopic red points corresponding to capillary breaks produced in the initial stages of the diabetic retinopathy. A third module is in charge of measuring the vascular tortuosity of the retinal blood vessels, which is defined as a non-smooth appearance of the vessel course [5,6]. This module incorporates four different retinal tortuosity metrics of reference. The first metric included in the tortuosity module, proposed by Hart *et al.* [7], is the most intuitive and widely used measure. It computes the tortuosity of a vessel by examining how long the curve is relative to its chord length. Another of the metrics included in the module has been proposed by Grisan *et al.* [8]. This approach also considers the times that a vessel curves by splitting each vessel in n segments of constant-sign curvature and then combining the evaluation of such segments. The third tortuosity metric implements the proposal of Trucco *et al.* [9], that measures the vessel skeleton curvature. Finally, the module includes the metric proposed by Onkaew *et al.* [10], which also incorporates a improved chain-code algorithm to compute the curvature.

In order to ensure an objective an reliable environment to support the clinical decision-making process, the different modules of the Sirius framework must be validated in the basis of the expert knowledge. In this sense, Pose *et al.* [11] presented a clinical validation for the AVR prognostic value, as computed in Sirius. Subsequently, Ortega *et al.* [2] performed a validation of this module in several real environments involving different health care systems. In addition to this, posterior evaluations of the vessel width measurement incorporated in Sirius were carried out in the DRIVE and the REVIEW databases [12,13]. With regard to the tortuosity module, the considered metrics were validated on the basis of datasets that were manually annotated by the authors or by one or two experts as much. Moreover, these works used different methods for the arterio-venous tree extraction, so that it is difficult to define a reliable comparison to establish the most accurate tortuosity metric. Sánchez *et al.* [5,6] conducted a draft validation of these metrics using a common technique to extract the whole arterio-venous tree in a preliminary dataset with retinal images that were previously classified as tortuous / non-tortuous. However, a validation considering a higher number of ophthalmologists that ensures a consolidated criteria that covers the entire expert knowledge would be highly desired for diagnostic and treatment purposes.

There is no standard guide for the characterization of the vascular tortuosity, so that the clinical experts, based on their experience, analyze the appearance and changes in and around the retinal vessels. The perception of abnormal signs related to the tortuosity is highly subjective and, thereby, there is a significant disagreement among the clinical experts. In the work herein described, a multi-expert validation of the tortuosity module of the Sirius framework is proposed. The validation procedure was performed in the basis of the clinical knowledge of five experts covering the different medical profiles of the ophthalmological services of the health care systems, from the head of the service to resident physicians. Regarding the tortuosity rating, a four-grade scale from non-tortuous to severe tortuosity was initially considered, being complemented with non-tortuous / tortuous and asymptomatic / symptomatic binary classifications. First, the inter-rater reliability was analyzed in order to assess the consistency of the expert criteria for the tortuosity characterization as well as the suitability of the different scales for the clinical practice. According to this analysis, the sets of experts with the best consensus were set as reference for the validation of the prognostic performance of the computational measurements. Among the different computational metrics included in the tortuosity module of the Sirius framework, the simplest and most widely used metric, presented in [6], was considered for being compared with these sets of experts and, therefore, evaluate if its prognostic performance is similar to the experts performance.

This paper is organized as follows: Section 2 describes the dataset and details the tortuosity metric and the procedure for multi-expert validation. Next, Section 3 details the performed experiments and discusses the obtained results and, finally, Section 4 presents the conclusions and possible future work.

2. Materials and Methods

2.1. Dataset

The used dataset is composed of 60 retinal images of patients that were diagnosed with any diabetes grade varying from non visible signs of abnormal vascular course to severe tortuosity. There is no objective standard guide for the quantitative measurement of the retinal vascular tortuosity. In the clinical practice, the experts commonly analyze the vessel appearance and their changes in and around the vessels in order to assess its degree of vascular tortuosity. The perception of these signs is mainly based on the experience of the clinician. In order to cover the entire spectrum of the expert knowledge, a group of five experts belonging to different levels of an ophthalmological service, from the head to resident physicians, is considered for the rating procedure. This way, the manual characterization of the retinal vascular tortuosity incorporates assessments at different levels of expertise and medical profiles.

With regard to the grading of the retinal vascular tortuosity, a qualitative four-grade scale that comprises none, mild, moderate, and severe tortuosity degree is initially used. The manual rates provided by the set of experts $E = \{E_1, E_2, .., E_5\}$ according to this scale in a totally blind process for the whole dataset are summarized in Table 1.

Table 1. Retinal vessel tortuosity rated by 5 different experts during a totally blind process using a four-grade scale.

	0:none	**1:mild**	**2:moderate**	**3:severe**
E1	34	19	7	0
E2	10	29	20	1
E3	21	22	17	0
E4	20	25	12	3
E5	31	18	11	0

In order to assess the suitability of the tortuosity levels for the clinical practice, two binary classifications obtained by different groupings of the grades were also considered. Therefore, the tortuous / non-tortuous binary classification is obtained by grouping mild, moderate and severe tortuosity in the same class in order to discriminate between retinal images with any level of tortuosity against those with no sign of anomalies in their constituting vessels. On the other hand, considering that mild tortuosity is a common anomaly that does not present clinical symptoms whereas moderate and severe tortuous vessels can lead to serious risks that should be treated[14], the binary classification asymptomatic / symptomatic is defined by grouping none and mild grades in one class and moderate and severe grades in the other class.

2.2. Automatic measurement of the retinal tortuosity

Health retinal blood vessels usually follow a straight or slightly curved paths. However, in the presence of vascular diseases, the vessels tend to dilate and become tortuous, presenting an abnormal curvature, non-smooth appearance, or turns and twists throughout their course. Vascular tortuosity can be focal, only affecting to a small region, or global, involving the whole retinal vascular tree. Some representative examples of non-tortuous and tortuous blood vessels are shown in Fig. 1.

The tortuosity module included in the Sirius framework takes a color retinal image as input (see Fig. 2 (a)) and compute its global vascular tortuosity measurement according to different tortuosity metrics of reference. To this end, the first step consists of extracting the arterio-venous tree and, after that, splitting it into its constituent vessels. For this purpose, a crease-based method[15,16] is applied, first, to extract the retinal blood vessels. This procedure follows the idea that the vessels can be considered as ridges or valleys in the retinal image. This way, the Multi Local Set of Extrinsic Curvature enhanced by the Structure Tensor (MLSEC-ST) operator is applied to extract the vessels by detecting peaks and valleys depending on the intensity at each point of the retinal image (see Fig. 2 (b)). After this, the centerline of a maximum of $1px$ width is extracted for each vessel by applying a thinning process[17]. Then, the arterio-venular tree is decomposed into its constituent vessels by means of an edge tracking algorithm. Finally, a smoothing process is locally applied to the vessel point coordinates with the aim of discarding the discrete effect of the pixel representation. Therefore, the resulting vessel segments are used for the objective tortuosity computation (see Fig. 2 (c)).

The most widely used tortuosity measurements found in the literature are based on analyzing how long the vessel is in relation to its chord length, providing, thereby, a measure of the deviation from a straight vessel course[18,19,7]. Among the metrics included in the tortuosity module of the Sirius framework, the proposal described in Hart *et al.*[7] follows the aforementioned idea. Therefore, this representative proposal is selected for this analysis since it is a metric of reference that provides a simple and direct tortuosity computation by using an intuitive mathematical definition close to the expert perception. It is calculated as follows:

$$\tau = \frac{L_c}{L_x} - 1 \tag{1}$$

where L_c is the arc length obtained from the counting of all the points that form the vessel, from the start to the end, and L_x is the length of the corresponding chord, this is, the euclidean distance between the two ends of the vessel. This metric is zero for straight vessel segments and takes increasing positive values the more tortuous the vessels are.

Given the tortuosity measurements of all the vessels composing the arterio-venous tree, the tortuosity corresponding to the entire retina is obtained from the weighted average of all the vessel tortuosity values. For this purpose, the final tortuosity is computed from each vessel tortuosity proportional to its arc length by applying the compositionality property of the Hart measure in (1), defined as:

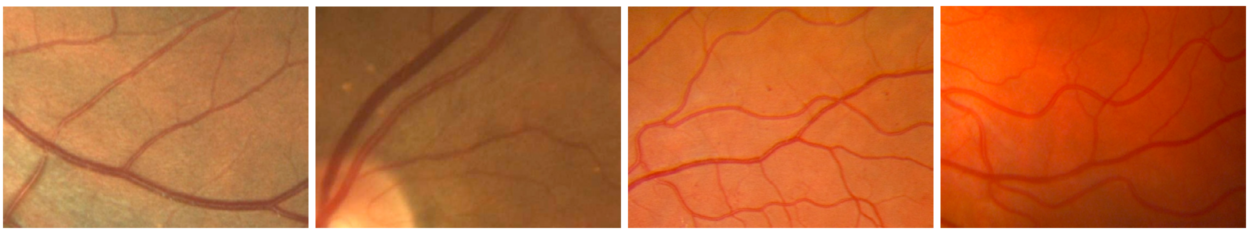
$$\tau(c1, c2) = \frac{[L_{c1}\tau_{c1} + L_{c2}\tau_{c2}]}{L_{c1} + L_{c2}} \tag{2}$$

where L_{ci} is the arc length of the vessel and ci and τ_{ci} is the tortuosity value obtained from Eq. 1 for that vessel. This way, the total retinal tortuosity measurement is within the range of the tortuosity values of its constituent vessels[8]. This measurement may be interpreted as a tortuosity density allowing, thereby, the comparison between retinal images at different scales.

2.3. Inter-expert agreement analysis

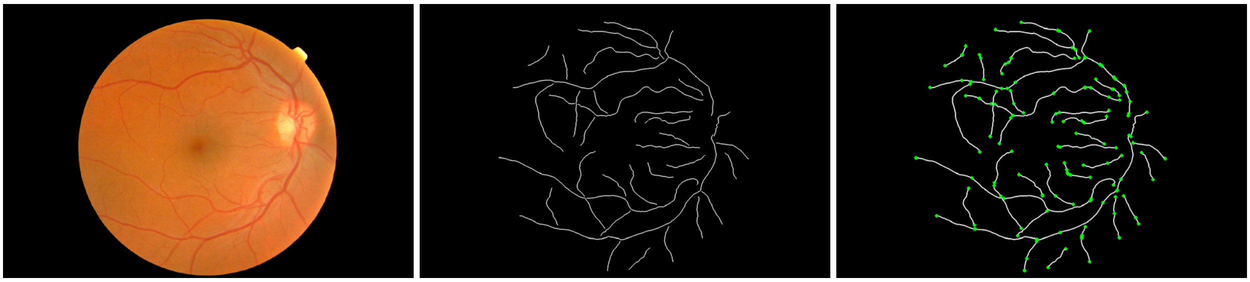
The agreement between experts in the manual characterization of the retinal vascular tortuosity is analyzed in order to assess the maturity and consistency of the clinical criteria. For this purpose, an overall comparison is performed including all the manual rates for the entire dataset provided by the five experts that cover the full spectrum of clinical profiles. This comparison is carried out in base of the percentages of retinal images with full consensus and with four, three or at least two expert coincidences in the four-grade scale. Additionally, the coincidences among experts are also analyzed for the tortuous / non-tortuous and asymptomatic / symptomatic binary classifications with the aim of determining the suitability of the different classifications for the clinical practice.

Furthermore, in order to assess the correlation between the expert perception and the computational measurements, the sets of experts with maximum consensus are set as reference. To this end, Fleiss-Kappa indexes[20] are computed to measure the inter-rater reliability for the set of all experts E and for all the combinations of three and four experts considering the four-grade scale as well as the tortuous / non-tortuous and asymptomatic / symptomatic binary classifications.



(a) (b) (c) (d)

Fig. 1. Retinal images with (a & b) non-tortuous and (c & d) tortuous blood vessels.



(a) (b) (c)

Fig. 2. Retinal vessel extraction. (a) Original retinal image. (b) Arterio-venous tree segmentation. (c) Ends of each vessel of the segmented vascular tree.

2.4. Multi-expert validation of the computational measurement analysis

On the basis of the inter-expert agreement analysis, the prognostic performance of the computational tortuosity measurement and its correlation with the clinical perception are evaluated. For this purpose, the tortuous / non-tortuous and the asymptomatic / symptomatic binary classifications are set as target predictions. Then, a ROC analysis was performed by building the curves from the reciprocal relation between sensitivity and specificity computed for all the possible threshold values in the computational metric[21]. This way, the computational measurement can be evaluated against each of the expert predictions. Similarly, the performance of each expert against the others can be evaluated by means of the same ROC analysis. In this case, only one point in the ROC space was obtained, so that the curve was built from this point and the two endpoints of the ROC space.

In order to extend these analysis against sets of several experts, combined ROC curves were built by averaging the curves related to each expert. Therefore, $\overline{ROC}(\tau, \{E_1, .., E_n\})$ represents the averaged ROC curve resulting from combining all the curves between the tortuosity metric τ and each of the experts from E_1 to E_n. In the same way, $\overline{ROC}(E_1, \{E_2, .., E_n\})$ corresponds to the averaged curve between E_1 and each expert from E_2 to En.

Given a set of experts E, the ROC curves $\overline{ROC}(E_i, E \setminus E_i)$ and their equivalents $\overline{ROC}(\tau, E \setminus E_i)$ are computed for each expert in the set E. The comparison of the AUC values of the equivalent curves allows to evaluate the correlation between the prognostic performance of the computational tortuosity measurement and the expert perception.

3. Results

3.1. Inter-expert agreement results

The overall comparison among all the manual rates in the entire dataset for the four-grade scale as well as for the non-tortuous / tortuous and the asymptomatic / symptomatic binary classifications is summarized in Table 2. It presents the percentages of retinal images with full consensus among all the experts and the cases where there are four or at least three experts that agree in their labels. These results show that there is a high inter-rater variability, specially for the four-grade scale. Regarding the binary classifications, the experts present a higher agreement in the discrimination between asymptomatic / symptomatic retinal images since this differentiation is more familiar, being close to the clinical practice due to the need for treatment and monitoring of the symptomatic cases, whereas the distinction between non-tortuous / tortuous is more related to the theoretical definition of the vascular tortuosity.

Table 3 includes the Fleiss-Kappa indexes for the best combinations of experts sorted in descending order by the asymptomatic / symptomatic classification since, as said, it provided a higher agreement. An standard characterization for these indexes assumes excellent agreement for values greater than 0.75, poor agreement for values below 0.40, and values between 0.40 and 0.75 as fair to good agreement[22]. Considering this characterization, the four-grade scale provides very low rates whereas the agreement increases in the binary classifications, specially between asymptomatic / symptomatic tortuosity.

These results suggest that there is not enough consistency in the expert criteria for grading on the basis of four different qualitative grades. However, grouping several grades in the same class that represents meaningful clinical conditions facilitates the rating. The asymptomatic / symptomatic binary classification presents the higher inter-expert agreement, reaching good Fleiss-Kappa indexes for some combinations of experts. Besides this, the symptomatic class is associated with significant risks and the need for proper medical treatment, so that asymptomatic / symptomatic presents better suitability to the clinical practice.

3.2. Multi-expert validation of the computational measurement results

According to the results obtained for the inter-expert agreement analysis, the four-grade scale is discarded for the correlation with the computational measurement given the poor agreement among the experts. Regarding the binary classifications, the set of experts with higher Fleiss-Kappa indexes are selected for validating the prognostic performance of the computational measurement. Thus, the set $E_A = \{E3, E4, E5\}$ and the set $E_B = \{E1, E4, E5\}$ are set as reference for the non-tortuous / tortuous and the asymptomatic / symptomatic binary classifications, respectively. Figure 3 (a) shows the ROC curves $\overline{ROC}(E_i, \underline{E_A} \setminus E_i)$ and their equivalents $\overline{ROC}(\tau, \underline{E_A} \setminus E_i)$ for each expert in E_A. Similarly, Fig. 3 (b) shows the ROC curves $\overline{ROC}(E_i, E_B \setminus E_i)$ and their equivalents $\overline{ROC}(\tau, E_B \setminus E_i)$ for each expert in E_B.

The graphs show that even among the experts with more consensus for each binary classification, the agreement is higher for the asymptomatic / symptomatic case, with Area Under the Curve (AUC) values placed between 0.85 and 0.91, whereas the AUC values for the non-tortuous / tortuous binary classification were between 0.78 and 0.81. This suggests that the experts follow a more unified criteria to identify the cases that require a treatment or clinical intervention. Regarding the computational tortuosity measurement, the prognostic performance is below of the experts performance, especially for the asymptomatic / symptomatic binary classification. The selected metric is based on the simplest mathematical approach for an objective tortuosity measurement, giving an idea of the deviation of the vessel in relation to a straight course. Though this underlines the idea of vascular tortuosity, the experts in the basis of their experience, consider a larger amount of properties. Thus, the computational metric offered a satisfactory performance, despite it is relatively differentiated from the experts performance.

Table 2. Inter-expert agreement in the four-grade scale, and the non-tortuous / tortuous (0 / 1-2-3) and asymptomatic / symptomatic (0-1 / 2-3) binary classifications.

% images	**4-grade**	**0 / 1-2-3**	**0-1 / 2-3**
5 experts	11.7	38.3	63.3
4 experts	50.0	73.3	78.3
3 experts	90.0	–	–

Table 3. Fleiss-Kappa for different sets of experts in four-grade, non-tortuous / tortuous and asymptomatic / symptomatic.

E1	**E2**	**E3**	**E4**	**E5**	**4-grade**	**0 / 1-2-3**	**0-1 / 2-3**
•			•	•	0.35	0.47	**0.55**
•		•		•	0.34	0.42	0.50
•		•	•	•	0.33	0.45	0.49
•	•		•	•	0.25	0.34	0.49
	•		•	•	0.27	0.36	0.48
•		•	•		0.25	0.36	0.48
•	•		•		0.17	0.27	0.48
	•	•	•		0.24	0.34	0.47
	•	•	•	•	0.29	0.41	0.46
•	•	•		•	0.26	0.32	0.46
		•	•	•	0.36	**0.54**	0.45

4. Conclusions

The analysis of the retinal vascular tortuosity presents a considerable potential for the early diagnosis of several vascular and systemic diseases so that a reliable quantitative measurement is crucial to support the clinical decision-making process. However, there is not a precise and standard definition of the vascular tortuosity, and consequently, its manual characterization is a subjective task with a high variability.

This work describes a procedure for the multi-expert analysis and validation of the computational tortuosity module of the Sirius framework. This validation included the participation of a group of five different experts covering the different clinical profiles of a ophthalmological service, thus yielding a full representation of the expert knowledge. These experts rated a dataset of 60 retinal images in a totally blind process according to a qualitative four-grade scale from non-tortuous to severe tortuosity. Besides this scale, the non-tortuous / tortuous and the asymptomatic / symptomatic binary classifications were added by grouping the different grades in classes that represent clinical situations of meaningful relevance.

The inter-rater agreement was evaluated in order to assess the consistency of the clinical criteria for the tortuosity characterization. In addition to this, the four-grade scale and the binary classifications were also analyzed to determine their suitability to the clinical practice. The results that were obtained from this analysis suggests that there is no enough consistency in the criteria for grading according the four-grade scale. However, the binary classifications resulting from grouping the grades provide a more reliable representation of the clinical perception.

Among the different approaches included in the tortuosity module of the Sirius framework, it was selected a metric that provides a simple and direct tortuosity computation by measuring the deviation of each vessel in relation to a straight course. It is a metric of reference widely used that mathematically defines the intuitive idea of the retinal vascular tortuosity as perceived by the experts. According to the analysis of the inter-expert agreement, the four-grade scale was discarded given the poor correspondence between experts, whereas the non-tortuous / tortuous and the asymptomatic / symptomatic binary classifications were set as target predictions for validating the prognostic performance of the computational metric. Therefore, the sets of experts with maximum consensus were selected for each binary classification and a ROC analysis was performed to compare the computational measurement against the experts performance for both classifications. The results shows that there are differences between the computational metric and the expert perception, since the experts, based on their experience, consider additional properties that are not included in the automated metric.

The low rates of agreement extracted from this analysis highlight a need for further clarification on the criteria among experts, so that future work includes a process to unify criteria and re-labeling the dataset. Regarding the computational measurement, the prognostic performance achieved acceptable values, despite that it does not reached

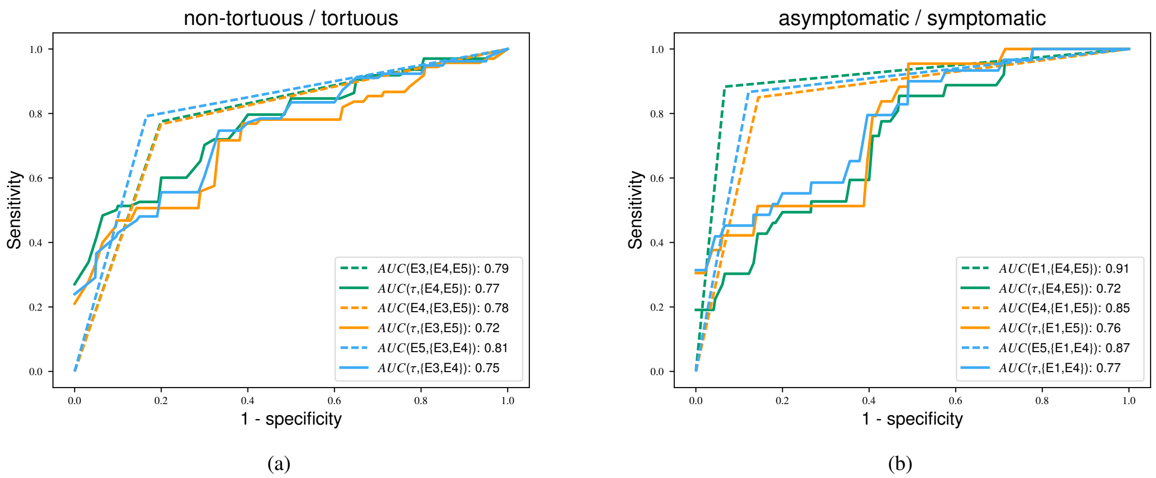


Fig. 3. ROC curves of the comparison of the manual and computational retinal vascular tortuosity measurements. (a) Non-tortuous / tortuous binary classification. (b) Asymptomatic / symptomatic binary classification.

the rates obtained by the experts since it is related to the simplest approach for the tortuosity analysis. Thus, the multi-expert validation will be extended to the remaining tortuosity metrics and new parameters will be analyzed in order to improve the results.

Acknowledgements

This research has been economically supported by the Instituto de Salud Carlos III, Government of Spain and FEDER funds of the European Union through the PI14/02161 and the DTS15/00153 research projects and by the Ministerio de Economía y Competitividad, Government of Spain through the DPI2015-69948-R research project. Also, this work has received financial support from the European Union (European Regional Development Fund - ERDF) and the Xunta de Galicia, Centro singular de investigación de Galicia accreditation 2016-2019, Ref. ED431G/01; and Grupos de Referencia Competitiva, Ref. ED431C 2016-047.

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