A predictive screening tool to detect diabetic retinopathy or macular edema in primary health care: construction, validation and implementation on a mobile application

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The most described techniques used to detect diabetic retinopathy and diabetic macular edema have to be interpreted correctly, such that a person not specialized in ophthalmology, as is usually the case of a primary care physician, may experience difficulties with their interpretation; therefore we constructed, validated and implemented as a mobile app a new tool to detect diabetic retinopathy or diabetic macular edema (DRDME) using simple objective variables. We undertook a cross-sectional, observational study of a sample of 142 eyes from Spanish diabetic patients suspected of having DRDME in 2012-2013. Our outcome was DRDME and the secondary variables were: type of diabetes, gender, age, HbA1c, foveal thickness and visual acuity (best corrected). The sample was divided into two parts: 80% to construct the tool and 20% to validate it. A binary logistic regression model was used to predict DRDME. The resulting model was transformed into a scoring system. The area under the ROC curve (AUC) was calculated and risk groups established. The tool was validated by calculating the AUC and comparing expected events with observed events. The construction sample (n=106) had 35 DRDME (95% CI: 24.1-42.0%), and the validation sample (n=36) had 12 DRDME (95% CI: 17.9-48.7%). Factors associated with DRDME were: HbA1c (per 1%) (OR=1.36, 95% CI: 0.93-1.98, p=0.113), foveal thickness (per 1 µm) (OR=1.03, 95% CI: 1.01-1.04, p<0.001) and visual acuity (per unit) (OR=0.14, 95% CI: 0.00-0.16, p<0.001). AUC for the validation: 0.90 (95% CI: 0.75-1.00, p<0.001). No significant differences were found between the expected and the observed outcomes (p=0.422). In conclusion, we constructed and validated a simple rapid tool to determine whether a diabetic patient suspected of having DRDME really has it. This tool has been implemented on a mobile app. Further validation studies are required in the general diabetic population.

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13   INTRODUCTION

14   Diabetes mellitus is prevalent worldwide and its most important ophthalmological complications

15   are diabetic retinopathy and diabetic macular edema (Jeganathan, Wang & Wong, 2008;

16   International Diabetes Federation, 2013). The main consequences of these disorders are possible

17   loss of vision and blindness (Jeganathan, Wang & Wong, 2008). Considering that these

18   conditions can be treated in their initial stages it is important to diagnose them as early as

19   possible and thus prevent the dire consequences (No authors listed, 1991; No authors listed,

20   1995).

21   The Valencian Community, an autonomous Mediterranean region in southeast Spain, has

22   a population of some 5 million (Instituto Nacional de Estadística, 2014). A diabetic patient in

23   this Community is mainly controlled by the primary care team, who refer the patient to the

24   ophthalmological specialist when the patient reports sudden loss of visual acuity, is suspected of

25   having macular edema, proliferative retinopathy, advanced retinopathy is shown on non-

26   mydriatic retinography screening or there is evidence of cataracts (Generalitat Valenciana:

27   Conselleria de Sanitat, 2006). This protocol is based on relevant scientific literature to treat

28   diabetic retinopathy and maculopathy, for both primary health care and ophthalmology services.

29   Thus, the diabetic patient has the diabetic retinopathy monitored independently of its severity. It

30   is regularly managed by the primary care physician during its early stages and by

31   ophthalmologists in more severe cases (Generalitat Valenciana: Conselleria de Sanitat, 2006).

32   The most described techniques used to detect diabetic retinopathy are non-mydriatic

33   retinography and biomicroscopy of the retina (No authors listed, 1991; Baeza et al., 2009; Ryan

34   et al., 2013), and those used to detect diabetic macular edema include biomicroscopy,

35   angiography and optical coherence tomography (No authors listed, 1995; Ryan et al., 2013).

36   However, most of these tests have to be interpreted correctly, such that a person not specialized

37   in ophthalmology, as is usually the case of a primary care physician, may experience difficulties

38   with their interpretation, as this is subjective. Accordingly, we undertook a study in the

39   Valencian Community aimed at constructing and validating by means of a mathematical model a

40   tool to detect diabetic retinopathy and diabetic macular edema using simple objective variables,

41   which would therefore present no interpretation difficulties. In addition, as the mathematical

42   model requires arithmetic operations, the tool has been implemented on a mobile app. The results

43   of this study, therefore, provide a simple tool to help primary care services determine whether a

44   diabetic patient needs to be referred to the ophthalmological specialist.

45

46   METHODS

47   *Study population*

48   The population study involved diabetic patients followed by the ophthalmological service of the

49   General University Hospital of Elche (Valencian Community, Spain). These patients are referred

50   from the primary health care services, according to the protocol (Generalitat Valenciana:

51   Conselleria de Sanitat, 2006).

52   *Study design and participants*

53   This cross-sectional, observational study was undertaken in a sample of diabetic patients referred

54   to the ophthalmological service of the General University Hospital of Elche by the primary care

55   teams between October 2012 and June 2013 and who were willing to participate. The sampling

56   procedure consisted of randomly selecting one day each week (not always the same day) and

57   recruiting all the diabetic patients who attended that day, by means of linear systematic

58   sampling. A patient was considered to have diabetes if the diagnosis had been made by a

59   physician (ICD9-MC 250.X). Patients were excluded if they had dementia, high myopia or

60   another macular disorder, had had vitreoretinal surgery, a cataract operation during the previous

61   3 months, had received laser treatment in the macular area or panphotocoagulation, or were

62   taking anti-angiogenic drugs.

63   *Variables and measurements*

64   The main outcome variable was the presence of at least treatable diabetic retinopathy (severe,

65   very severe or proliferating (Ryan et al., 2013)) or diabetic macular edema (DRDME). The

66   diagnosis of these two disorders was made by clinical ophthalmological examination of the

67   retina by indirect ophthalmoscopy and biomicroscopy of the central retina with a Topcon slit

68   lamp, model SL-8Z (Topcon Corporation; Tokyo, Japan) using a 78 diopter lens (78D aspheric

69   lens. Volk Optical Incorporated Company; Mentor, OH) and indirect ophthalmoscopy with a

70   28D lens by an expert retinal ophthalmologist. Macular edema was defined as the presence of

71   hard exudates or localized retinal thickening within a distance of 500 μm from the fovea, and the

72   degree of diabetic retinopathy was defined according to the ETDRS study (No authors listed,

73   1991). The secondary variables were type of diabetes, gender, age (years), glycated hemoglobin

74   (HbA1c) (%), foveal thickness (μm) and visual acuity (best corrected). The source of information

75   for data concerning the type of diabetes, hypertension, dyslipidemia, gender, smoking, age and

76   HbA1c was the clinical history. Best corrected visual acuity was obtained using the Snellen

77   scale. The foveal thickness was obtained at the central area by dilating the pupil with a drop of

78   tropicamide and measuring with spectral domain optical coherence tomography (Topcon 3D

79   OCT 2000; Topcon Corporation®, Itabashi, Tokyo, Japan). The images were acquired by 512

80   horizontal linear scans and 128 vertical scans, centered on the fixation point making a 6x6 square

81   3D pattern. The mean retinal thickness was calculated automatically by the software of the

82   device. We measured a 6 mm diameter area, centered on the fovea, thereby using for the study

83   the central 1000 μm area (the central circle).

84   *Sample size*

85   The construction sample involved data from 106 patients, of which 35 had DRDME. To contrast

86   an area under the ROC curve (AUC) different to 0.5, assuming a 95% confidence level and

87   expecting to find an AUC of 0.9, the contrast power was nearly 100%. Using the same

88   parameters in the validation sample (36 patients, 12 with DRDME), we obtained a contrast

89   power of 97.17% (Hanley & McNeil, 1982).

90   *Statistical methods*

91   The quantitative variables are reported as means and standard deviations, and the qualitative

92   variables as absolute and relative frequencies. All the analyses were done with a significance of

93   5% and the confidence interval was calculated for each relevant parameter. The complete sample

94   was divided into two parts. One part (80%) to construct the predictive model and the other part

95   (20%) to validate the model constructed.

96   Construction: we used a binary logistic regression model to predict DRDME using the

97   most clinically relevant variables, taking into account that we could only use a maximum number

98   of explanatory variables in the model (10 observations of our outcome for each explanatory

99   variable). The resulting model was transformed into a scoring system using the method of the

100   Framingham study (Sullivan, Massaro & D'Agostino, 2004). The ROC curve was calculated and

101   we constructed groups based on the probabilities of the model: low (<25%), medium (25-50%),

102   high (50-75%) and very high (≥75%).

103   In the validation sample the AUC was calculated and the observed events compared with

104   the expected events of the model using the X^2 test. No calculations were made of the classical

105   indicators of a diagnostic test, such as sensitivity, specificity, predictive values and likelihood

106   ratios, as the test constructed does not indicate a single value (positive or negative) but rather a

107   probability of DRDME associated with each score. Accordingly, differences were studied

108   between the expected (given by the predictive model) and the observed events to determine

109   whether the reality corresponded to what was indicated by the model. On the other hand,

110   calculating the AUC indicates the discriminating power of our model. A similar methodology

111   has been used in other studies (Palazón-Bru et al., 2015).

112   *Mobile application*

113   The models were implemented on a mobile application for the operating systems Android and

114   iPhone (see Supplemental Note S1). This application is free to download from any of the stores.

115   Its name is *Diabetic retinopathy predictor*.

116   *Ethical consideration*

117   The study was approved by the Ethics Committee of the General Hospital of Elche. All the

118   patients signed the informed consent document. The study was undertaken in accordance with

119   the basic principles of the World Medical Association Declaration of Helsinki and complied with

120   the norms described in the European Union guidelines for good clinical practice.

121

122   RESULTS

123   Table 1 shows the information for the two samples. In the Construction sample (n=106) there

124   were 35 cases of DRDME (95% CI: 24.1-42.0%) (retinopathy alone, 8; macular edema alone, 9;

125   both disorders, 18). In the Validation sample (n=36) there were 12 cases of DRDME (95% CI:

126   17.9-48.7%), of which 6 had both disorders, 3 just macular edema and 3 just retinopathy. For the

127   other characteristics, in both samples there was a majority of type 2 diabetes (76.5-85.7%), an

128   older mean age (62.8-63.4 years), high HbA1c (7.7-7.9%), visual acuity of 0.7 and mean foveal

129   thickness between 261.2 and 285.2 µm. No significant differences were found between the two

130   samples (p: 0.117-0.886).

131   The factors associated with DRDME (Table 1) were: HbA1c (per 1%) (OR=1.36, 95%

132   CI: 0.93-1.98, p=0.113), foveal thickness (per 1 µm) (OR=1.03, 95% CI: 1.01-1.04, p<0.001)

133   and visual acuity (per unit) (OR=0.14, 95% CI: 0.00-0.16, p<0.001). The scoring system with its

134   risk groups created from these factors is shown in Fig. 1. In the model we selected the three most

135   clinically relevant variables, as we had 35 outcomes in our sample (Alasil et al., 2010; Buabbud,

136   Al-latayfeh & Sun, 2010; Hermann et al., 2014; Varma et al., 2014; Palazón-Bru et al., 2015).

137   In the Validation sample (Fig. 2) the AUC was 0.90 (95% CI: 0.75-1.00, p<0.001). No

138   significant differences were found between the expected outcomes and the observed outcomes

139   (p=0.422) (Fig. 3).

140

141   DISCUSSION

142   This study constructed an innovative tool able to determine whether a diabetic patient has

143   diabetic retinopathy or diabetic macular edema, and who should therefore be referred to a

144   specialist in ophthalmology. The model uses easily obtained variables and the calculation can be

145   done easily and simply using a mobile application.

146   A literature search revealed no such multifactor models determining the likelihood of

147   presenting DRDME, so that it is not possible to compare our model overall. However, we can

148   make independent comparisons with the factors obtained. We found greater complications with

149   higher levels of Hb1Ac and a greater foveal thickness, and a lower likelihood of DRDME as the

150   visual acuity decreased. These particular findings are consistent with others (Alasil et al., 2010;

151   Buabbud, Al-latayfeh & Sun, 2010; Hermann et al., 2014; Varma et al., 2014).

152   This study constructed and validated a tool to enable the physician to discriminate

153   between those patients who should be referred to an ophthalmologist and those who do not need

154   to be. Thus, the primary care physician should carry out regular control examinations to assess

155   the possible need for referral. A patient found to be in the High or Very High group should be

156   referred to the specialist, as the associated likelihood of DRDME is very high. On the other hand,

157   if a patient is found to be in the Medium or Low groups (<3 points), the primary care physician

158   should control the patient. A model such as the one explained herein generally presents certain

159   difficulties in its use, as the model is usually complex and requires a certain time to do the

160   calculation. However, our model uses very simple variables that, once introduced into the mobile

161   application, give the likelihood of the outcome. Finally, a nursing professional who receives

162   adequate training (use of the apparatus and measurement of visual acuity) could also use the

163   proposed model and thus reduce the workload of the primary care physician.

164   In some regions optical coherence tomography is not used in primary health care.

165   Nevertheless, consideration could be given to its use in order to improve the screening of

166   referable retinopathy. This tool, though, is expensive, so it is not feasible to include it at all

167   health centers. An instrument could, though, be purchased for each health care area (each area

168   covers various health care centers), and diabetic patients suspected as having referable

169   retinopathy could attend this particular center to undergo the test described here. This method

170   would reduce the possible cost considerably. Another possibility would be the use of a mobile

171   unit that could rotate between the various health centers. This would help to integrate our

172   predictive model into usual clinical practice, with the idea being to refer to the specialist services

173   just those patients who really need it. Additionally, the inclusion of optical coherence

174   tomography in primary health care could enable other macular disorders to be monitored, as this

175   device can provide greater information about the macula. The resulting information, though,

176   should be interpreted by an ophthalmologist, whereas the foveal thickness is a completely

177   objective measure that can be interpreted with the other clinical parameters of our model by a

178   healthcare professional working in the area of primary care. Finally, this study could be

179   undertaken by other healthcare systems with different referral criteria, with the idea of reducing

180   the proportion of patients who really need to be referred to the specialist ophthalmological

181   services yet still following their own protocols.

182   *Strengths and limitations of the study*

183   The main strength of this study concerns its novel way to construct and validate a scoring system

184   to help primary care physicians take decisions about referring a diabetic patient to the

185   ophthalmological specialist. Additionally, the factors used in the model are obtained objectively,

186   so they do not have to be interpreted, as is the case with retinography.

187   Although the sample size may seem small, it is sufficient for the aims of the study

188   (constructing and validating the model), as the contrast power was greater than 95%, whereas

189   this is generally 80-90%. There are, too, non-significant variables in the model constructed.

190   However, as in other studies, we have to consider that we are evaluating the model overall and

191   not variable by variable, that is the goodness of fit (likelihood ratio test=53.4, p<0.001;

192   Nagelkerke R^2=0.583) and the AUC in the validation sample (0.90) (Palazón-Bru et al., 2015).

193   As this model was validated in diabetic patients who had already been referred to the specialist,

194   further studies are needed in the general diabetic population to determine if it is applicable as a

195   screening test for all diabetic patients when they attend their primary health care center (selection

196 bias). These would study the probabilities of DRDME with our scoring system, as the general

197 population would have a low prevalence of this macular disorder. On the other hand, concerning

198 measurement bias, all the measurements were taken using calibrated devices and in accordance

199 with current guidelines. Finally, we did not include other variables in the model that could have

200 influenced DRDME, such as the duration of the disease. This particular variable was not

201 assessed because the clinical history does not record it and the patient knows the duration of the

202 disease only approximately. This could therefore cause an information bias, which is why it was

203 not included in this study. Nevertheless, even without this variable the predictive model had an

204 AUC of 0.90, which equates to a great discriminating power.

205

206 CONCLUSION

207 This study constructed and validated a predictive model based on a scoring system to determine

208 whether a diabetic patient referred to the specialist has DRDME. This model can be used to

209 reduce the volume of patients referred to the ophthalmological services from primary health care

210 centers. Nevertheless, further studies should be undertaken to determine whether the model is

211 applicable as a screening test in the general diabetic population.

212

213 ACKNOWLEDGMENTS

214 We thank Ian Johnstone for help with the English language version of the manuscript.

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268

Scoring system to predict diabetic retinopathy and diabetic macular edema.

Foveal thickness (μm)	Points
<200	0
200-249	1
250-299	2
300-349	3
350-399	4
≥400	5

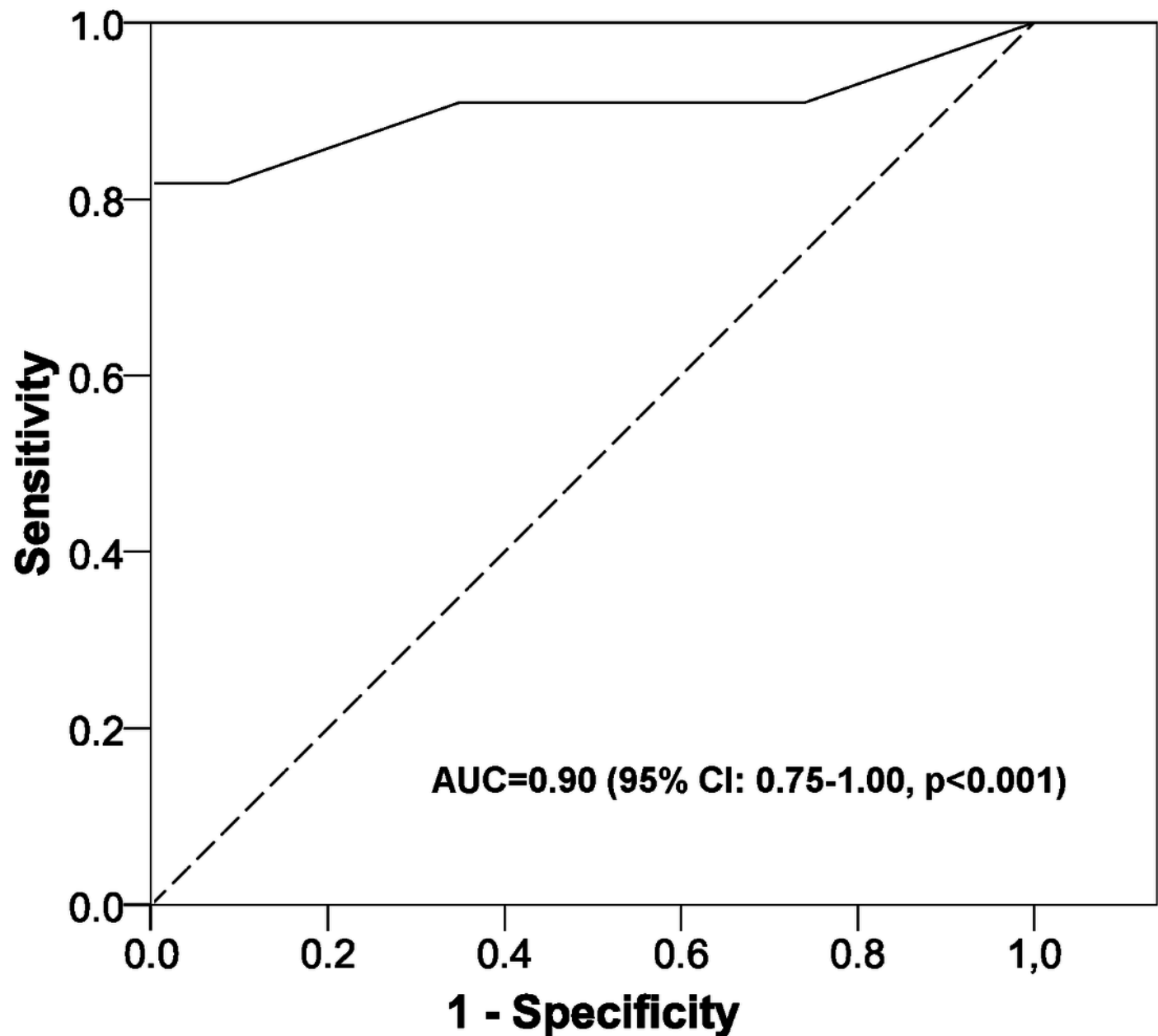
HbA1c (%)	Points
<8	0
≥8	1

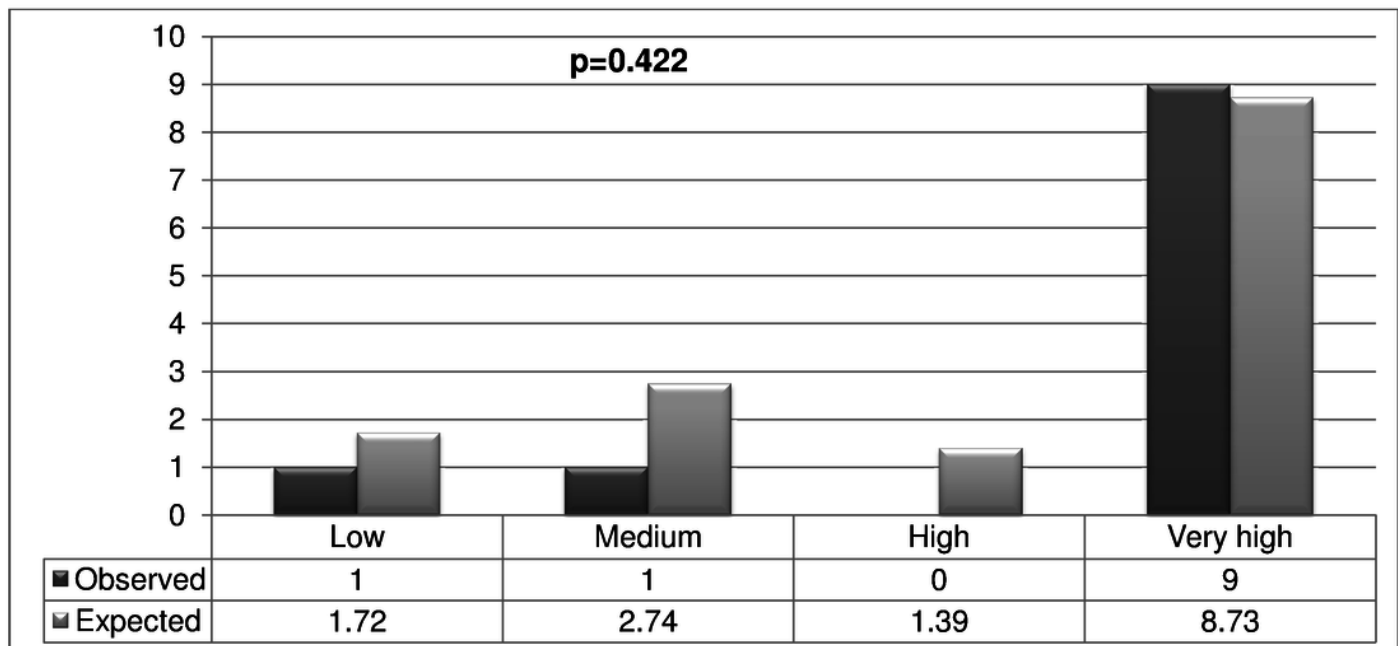
Visual acuity	Points
0.9-1	0
0.6-0.8	1
0.3-0.5	2
0.0-0.2	3

Points Sum	Risk (%)
Low (0-2)	1.45-15.35
Medium (3)	39.15-39.20
High (4)	69.55-69.60
Very high (≥5)	≥89.05

Area under the ROC curve of the scoring system.

AUC, area under the ROC curve; CI, confidence interval.

Figure: ROC curve with axes Sensitivity (y-axis) and 1 - Specificity (x-axis). AUC=0.90 (95% CI: 0.75-1.00, p<0.001)

3

Validation of the scoring system.

Descriptive characteristics and analysis for diabetic retinopathy or macular edema in diabetic patients from a Spanish region. 2012-2013 data.

Abbreviations: Adj. OR, adjusted odds ratio; CI, confidence interval; DM, diabetes mellitus; DRDME, diabetic retinopathy or diabetic macular edema; N/A, not applicable; N/M, not in the model. n(%), absolute frequency (relative frequency); x±s, mean ± standard deviation. Goodness-of-fit: likelihood ratio test=53.4, p<0.001; Nagelkerke R^2=0.583.

Variable	Construction sample n=106 n(%)/x±s	Validation sample n=36 n(%)/x±s	p-value	Adj. OR for DRDME (95% CI)	p-value
DRDME	35(34.7)	12(33.3)	0.886	N/A	N/A
DM Type 2	90(85.7)	26(76.5)	0.207	N/M	N/M
Female gender	52(49.1)	20(55.6)	0.500	N/M	N/M
Age (years)	63.4±14.4	62.8±16.8	0.847	N/M	N/M
HbA1c (%)	7.7±1.5	7.9±1.8	0.643	1.36 (0.93-1.98)	0.113
Foveal thickness (μm)	261.2±71.3	285.2±95.1	0.117	1.03 (1.01-1.04)	<0.001
Visual acuity	0.7±0.3	0.7±0.3	0.689	0.14 (0.00-0.16)	<0.001