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Computed and subjective blue scleral color analysis as a diagnostic tool for iron deficiency

Hervé Lobbes

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UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE
pour le
DIPLOME D'ÉTAT DE DOCTEUR EN MÉDECINE
par

LOBBES, Hervé, Bertrand, Antoine

Présentée et soutenue publiquement le 4 juillet 2019

Computed and subjective blue scleral color analysis as a diagnostic tool for iron deficiency.

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Dédicaces aux membres du jury :

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Liste des abréviations :

BMI: Body Mass Index

BP: Blue Percentile

CPP: Comité de Protection des personnes.

CRP: C-reactive protein.

HGA: Homogentisic Acid.

ID: Iron deficiency.

IQR: Inter-Quartile Range.

LR: Likelihood Ratio.

NPV: Negative Predictive Value.

OI: Osteogenesis Imperfecta.

PPV: Positive Predictive Value.

ROC: Receiver operating characteristic.

SF: Serum Ferritin.

TPS: Transferrin Percent Saturation.

WHO: World Health Organization.

1. Introduction:

Iron deficiency (ID) is the world's most common form of nutritional deficiency (1), with a prevalence ranging from 4.5% to 18% in most recent studies in the US (2). ID remains the most common cause of anemia (3), with an annual incidence of 7.2-13.96 per 1000 person-years in Europe (4). ID leads to disability through impairment of cognitive function (5), functional capacity and quality of life (6,7), and it can be improved by iron supplementation. Consequently, ID is a major issue for practitioners in primary care.

ID diagnosis is based on serum ferritin level which is the most specific and sensitive test (8,9) with a cut-off $\leq 30 \mu\text{g/L}$ or $\leq 100 \mu\text{g/L}$ in cases of ID accompanied by inflammation. Clinical findings depend on the depth and speed of onset of the anemia. Most findings are common to all types of anemia (mucosal pallor, fatigue, headache and tachycardia) (10) but some manifestations are deemed to be specific to ID. Indeed, iron is involved in multiple functions of epithelial cells, which are characterized by their high turn-over. As such, various mucocutaneous manifestations are reported to be caused by ID such as skin dryness and roughness, mild alopecia, atrophic glossitis or koilonychia (11).

Among these signs, blueish coloration of the sclera was first described in 1908 by Osler in iron-deficient malnourished teenagers. Since then, sporadic reports have been published, indicating the diagnostic potential interest of blue sclera in ID (12). In the late 1980s, Kalra et al (13,14) published two studies claiming that blue sclera was a highly sensitive and specific sign of ID. These findings were later confirmed by Clemente et al (15) and Kotsev et al (16). In both studies, assessment of the blueish coloration of the sclera relied on subjective appreciation by independent physicians, who were asked to grade the color as absent, equivocal, definite or striking. Blue sclera can be associated with other conditions such as collagen diseases, for example in osteogenesis imperfecta, but these conditions are less common than ID.

Despite these encouraging results, the use of blue sclera has only rarely been reported and its assessment could be a simple diagnostic tool for ID in primary care. Therefore, we aimed to determine the real value of the blueish tint in the sclera for the diagnosis of ID, through subjective and computed analyses of eye images obtained using a smartphone.

2. Patients and methods:

2.1 Ethics

We conducted a pragmatic prospective monocentric study in Clermont-Ferrand University Hospital. In line with French regulations, ethical approval was obtained from the International Review Board “CPP Sud EST VI”, reference number 2019/CE02. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Recommendations.

2.2 Patients

The inclusion criteria were: patients aged ≥ 18 -years, with:

- Suspicion of ID:
 - clinical suspicion supported for example by pruritus, fatigue, pallor, tachycardia, restless leg syndrome, glossitis.
 - biological suspicion defined by microcytic hypochromic anemia with low reticulocyte count.
- Biological assessment of serum iron stores by at least one of the following biological analyses: serum ferritin (SF) or Transferrin Percent Saturation (TPS).

Exclusion criteria were medical history of Marfan or Ehler Danlos syndrome, scurvy or osteogenesis imperfecta, or eye surgery or injury.

2.2 Analysis of eye image

A preliminary two-step study was conducted using the first nine patients to enroll (17). First, a smartphone application was created using OpenCV library to provide a repeatable image acquisition using multiple time exposure. We decided to use a smartphone device (Google Nexus 5X®) instead of a powerful professional camera because the aim was to allow widespread use of this diagnostic tool. The smartphone application allowed us to anonymize the pictures and to collect clinical and biological data for each patient. Automated color correction and automatic white balance of the camera were disabled. To measure the “true” color of a picture, we used a white reference provided by a color-checker (X-rite®), which placed by the physician next to the eye, to take a picture including both the eye and white patch of the color-checker. Second, post-processing software was created to analyze the blue color of the sclera. To obtain High Dynamic Range pictures, images with multiple time exposures were merged into a single image. Finally, the software analyzed the percentage of each color (red, green and blue) in scleral pixels after white correction.

The pictures were taken by the same physician throughout the study. Exposure conditions were standardized: the patient sat next to a window, in natural daylight. There was no direct contact with the patient, so the process was completely non-invasive.

Three independent physicians who were blinded to the presence or absence of ID subjectively assessed the blueish coloration of the sclera in anonymized pictures. The sequence of evaluation was randomized for each physician. Blue color was evaluated as: 1 (absent), 2 (equivocal), 3 (definite) and 4 (striking).

Clinical data (age, sex, height, weight, Body-Mass-Index = BMI) and biological data were collected at the same time. Iris color was graded as light (grey, green, blue) or dark.

2.3 Outcome assessment

ID was defined as stated by Camaschella and colleagues (18) by one of the following criteria:

- SF \leq 30 $\mu\text{g/L}$ or \leq 100 $\mu\text{g/L}$ in case of inflammatory syndrome (elevation of C-reactive protein).
- TPS \leq 16% and SF \leq 300 $\mu\text{g/L}$.

Subjective blue color of the sclera was defined by a sign graded as definite or striking. We also used the definition used in previous studies in that at least two physicians had to state that the sign as definite or striking (13–16).

Objective blue color was measured by computer analysis as the percentage of blue color in the 25% most blue pixel in the area of interest, which can be interpreted as a Blue Percentile (BP) in the analyzed pixels.

We used three methods to delineate the area of interest of the sclera:

- Automated method: the sclera is automatically recognized by the software and the whole sclera is analyzed. This method is termed Full-Sclera (FS).
- Semi-automated method: the physician selects the bluest area of the sclera to allow the software to delineate a small area of pixels with the same color characteristics. This method is termed Semi-Automated Sclera (SAS).
- Manual method: the analyzed area of sclera is manually delimited by the physician who delineates the bluest area of the sclera. This method is termed Manual Sclera (MS).

2.4 Statistical analysis

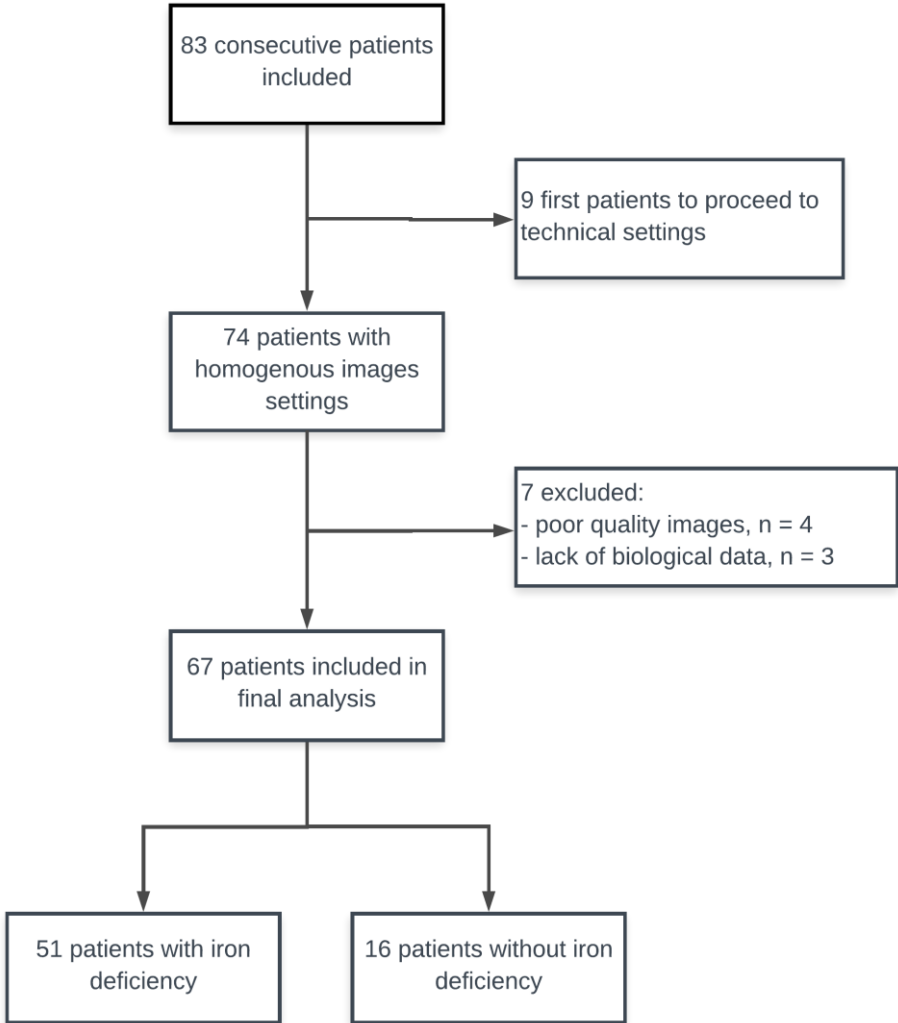
Because we conducted an exploratory study, no calculation of power or number of subjects could be made. All statistical analyses performed using Stata version 13 (StataCorp, College Station, TX, USA), for a two-sided type I error at 5%. The categorical parameters were expressed as numbers and percentages, whereas the quantitative variables were described as mean \pm standard deviation or median with [interquartile range], according to the statistical distribution. Normality was studied using the Shapiro-Wilk test. The inter-rater reliability and agreement with the gold standard were evaluated using Lin's concordance coefficient for quantitative variables and Fleiss's κ coefficient for categorical data. The results were studied according to the usual rules defined in literature (19): 0.00-0.20 (poor agreement), 0.21-0.40 (fair agreement), 0.41-0.60 (moderate agreement), 0.61-0.80 (good agreement) and > 0.80 (very good agreement). Then, the between-group comparisons (ID vs. no ID: NID) were performed using the following statistical tests: Student's t -test or Mann-Whitney test if the assumptions of the t -test were not met (normality, and homoscedasticity as identified by the Fisher-Snedecor test) for quantitative variables and χ^2 test or if necessary, Fisher's exact test for categorical variables. Statistical analyses were completed by analyzing the Receiver Operating Characteristic (ROC) curve to determine the most appropriate threshold to predict ID, for each method: FS, SAS and MS. The optimal threshold was determined according to usual indexes reported in medical literature (Youden, Liu and efficiency). Then, sensitivity, specificity and predictive values were estimated and expressed with 95% confidence interval.

3. Results:

From November 2014 to July 2018, 83 consecutive inpatients were enrolled in the study. As previously stated, we adjusted the technical settings on the camera to provide adequate picture quality using the first nine patients to enroll.

During the second phase, we tested 74 patients using the same procedure for shooting and the same camera settings. We excluded seven patients: four were excluded because of poor picture quality (blurred images, over- or underexposed images) and three because of a lack of data regarding iron stores. A total of 67 patients were included in the final analysis.

Figure 1: flowchart.



3.1 Inclusion characteristics

Baseline characteristics are shown in **Table I**. Male:female ratio was 0.8 in the overall population and was significantly lower in the ID group (0.59) than in the NID group (2.2). Mean age was significantly higher in the ID group ($p = 0.01$). Overall, 52/67 (77.6%) patients had anemia (hemoglobin ≤ 12 g/dL for women, ≤ 13 g/dL for men): 46/51 in the ID group and 6/16 in the NID group.

Table I: Baseline characteristics of the population.

	All (n = 67)	ID (n = 51)	NID (n = 16)
Male (%)	30 (44%)	19 (37%)	11 (68%)
Mean age (yr)	59.9 \pm 20.1	63.1 \pm 20.3	49.6 \pm 16.4
BMI (kg/m ²)	26.2 \pm 7.3	26.7 \pm 7.8	24.5 \pm 5.6
Dark iris, n (%)	43 (64%)	35 (68%)	8 (50%)
Hemoglobin (g/dL)	10.3 \pm 2.5	9.7 \pm 2.1	12 \pm 3
No. of patients with anemia (male)	52 (22)	46 (19)	6 (3)
Mean corpuscular volume (fL)	84.4 \pm 8.5	82.4 \pm 7.8	90.5 \pm 8
Platelet count (G/L)	255 \pm 116	267 \pm 113	217 \pm 119
Ferritin (μ g/L)	28.5 [16;75]	20.5 [11;34]	244.5 [111.7;440.7]
TPS (%)	9.6 [6;38.5]	8 [6;11]	40 [32.5;54]
Fibrinogen (g/L)	4.2 \pm 1.8	4.2 \pm 1.6	4.2 \pm 2.8
C-reactive protein (g/L)	9.6 [2.9;37.5]	13.5 [3.5;43]	2.9 [2.9;9]

Data are expressed as mean \pm standard deviation or as median [interquartile range].

3.2 Physician assessment of blue sclera color

We first compared physician assessments of sclera color and iron stores (ID or NID) (Table II). Blue color of the sclera was defined for each physician by a sign graded as definite or striking.

Table II: Subjective assessment of blue sclera and iron stores by physician.

		NID (n = 16)	ID (n = 51)
Physician 1	Blue (%)	5 (31.25)	31 (60.78)
	No blue (%)	11 (68.75)	20 (39.22)
Physician 2	Blue (%)	3 (18.75)	23 (45.09)
	No blue (%)	13 (81.25)	28 (54.91)
Physician 3	Blue (%)	1 (6.25)	15 (29.41)
	No blue (%)	15 (93.75)	36 (70.59)

We found a significant association between subjective blue color assessment of the sclera by physician 1 and the diagnosis of ID ($p = 0.03$, $\chi^2 = 4.27$), whereas there was a non-significant trend for physicians 2 ($p = 0.05$, $\chi^2 = 3.56$) and 3 ($p = 0.05$ by Fisher's exact test due to the small sample size). Subjective analysis of blue color was not influenced for any of the physicians by iris color ($p = 0.28$, $p = 0.37$ and $p = 0.44$ respectively), sex ($p = 0.58$, $p = 0.23$, $p = 0.50$) or by the presence of anemia ($p = 0.22$, $p = 0.08$, $p = 0.07$, respectively).

Sensitivity was low: 60.8% [CI95: 46.1;74.2%] for physician 1, 45.1% [CI95: 31.1;59.7%] for physician 2 and 29.4% [CI95: 17.5;43.8%] for physician 3. Specificity was 68.8% [CI95: 41.3;89%] for physician 1, 81.3% [CI95: 54.4;96%] for physician 2 and 93.8% [CI95: 69.8;99.8%] for physician 3. Positive predictive value (PPV) was 86.1% [CI95: 70.5;95.3], 88.5% [CI95: 69.8;97.6%] and 93.8% [CI95: 69.8;99.8] for physicians 1, 2 and 3 respectively. Negative predictive value (NPV) was low: 35.5% [CI95: 19.2;54.6%], 31.7% [CI95: 18.1;48.1%] and 29.4% [CI95: 17.5;43.8%] for physicians 1, 2 and 3, respectively. Positive likelihood ratio (LR) was 1.95 [CI95: 0.91;4.16], 2.41 [CI95: 0.83;6.97] and 4.71 [CI95: 0.67;32.9] for physicians 1, 2 and 3, respectively.

When we used the definition of blue sclera found in previous studies (**Table III**), we found no significant association between blue sclera and ID ($p = 0.09$). This result could be linked to a poor inter-rater reliability, as shown by the Fleiss's κ value which was between 0.09 and 0.23. Sensitivity was 51% [CI95: 36.6;56.2%], specificity was 93.8% [CI95: 69.8;99.8%], PPV was 96.3% [CI95: 81;99.9%] and NPV 37.5% [CI95: 22.7;54.2%]. Positive LR was 8.16 [CI95: 1.2;55.5].

Table III: Subjective assessment of blue sclera and iron stores (3 physicians together).

	NID (n = 16)	ID (n = 51)
Blue (%)	1 (6.25)	26 (50.98)
No-blue (%)	15 (93.75)	25 (49.02)

3.3 Computed analysis of blue color

The correlation between the three methods of computed sclera color analysis was excellent, as shown by the Pearson correlation test: $r = 0.929$ (FS vs. MS), $r = 0.927$ (FS vs SAS) and $r = 0.945$ (MS vs. SAS). We found no effect of iris color on computed results of sclera color analysis via any of the three methods (FS: $p = 0.68$; MS: $p = 0.88$; SAS: $p = 0.94$)

Computed results of blue color analysis are shown in **Table IV**. Blue color seemed to be higher in ID than in NID subjects for all three methods, but the difference reached significance only for the MS method ($p = 0.04$, FS method: $p = 0.12$ and SAS method: $p = 0.05$).

Table IV: Computed blue color assessment in ID and NID subjects. Results are presented as mean \pm SD blue percentile (BP).

	NID (n = 16)	ID (n = 51)
FS (BP)	29.18 \pm 4.31	31.07 \pm 3.33
MS (BP)	29.12 \pm 3.53	31.24 \pm 3.39
SAS (BP)	29.03 \pm 3.87	31.19 \pm 3.29

For physicians 1 and 3, the MS-computed blue color was significantly higher in patients with blue sclera (graded as definite or striking) compared to patients without blue sclera ($p = 0.002$ and $p < 0.001$ respectively, **Table V**). For physician 2, the difference did not reach statistical significance ($p = 0.33$).

Table V: MS computed blue color by physician. Results are presented as mean \pm SD blue percentile.

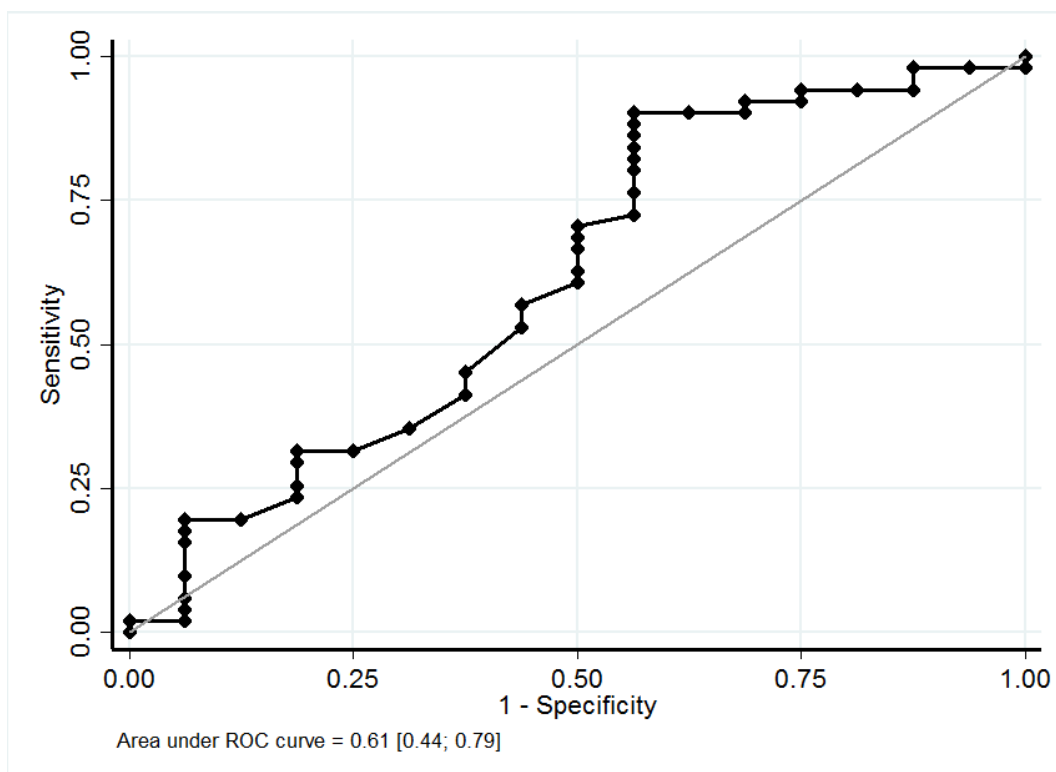
	Physician 1	Physician 2	Physician 3
No blue	29.27 \pm 4.19	30.42 \pm 3.93	30.01 \pm 3.93
Blue	32 \pm 2.17	31.23 \pm 2.75	33.03 \pm 1.93

3.4 ROC curves for computed blue color

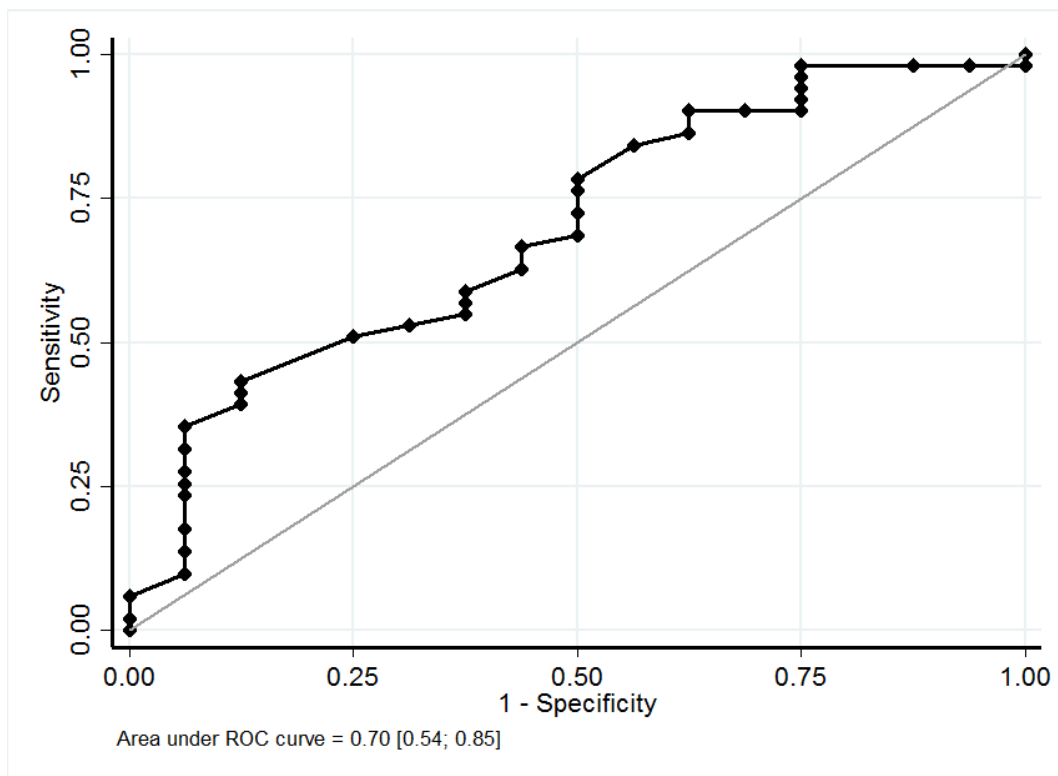
For the detection of ID, the ROC curve with the FS method (Figure 2A) showed a sensitivity of 90.2% [CI95: 78.6;96.7%], a specificity of 43.8% [CI95: 19.8;70.1%], PPV of 83.6% [CI95: 71.2;92.2%] and NPV of 58.3% [CI95: 27.7;84.8%] with a threshold of 27.6 (Youden index). The MS method (Figure 2B) showed a sensitivity of 78.4% [CI95: 64.7;88.7%], a specificity of 50% [CI95: 24.7;75.3%], PPV of 83.3% [CI95: 69.8;92.5%] and NPV of 42.1% [CI95: 20.3;66.5%] with a threshold of 29.1 and the highest area-under-the-curve of 0.7 [CI95: 0.54;0.85]. The SAS method (Figure 2C) showed a sensitivity of 84.3% [CI95: 71.4;93%], a specificity of 50% [CI95: 24.7;75.3%], PPV of 84.3% [CI95: 71.4;93%] and NPV of 50% [CI95: 24.7;75.3%] with a threshold of 28.9.

Figure 2: ROC curves for computed blue color.

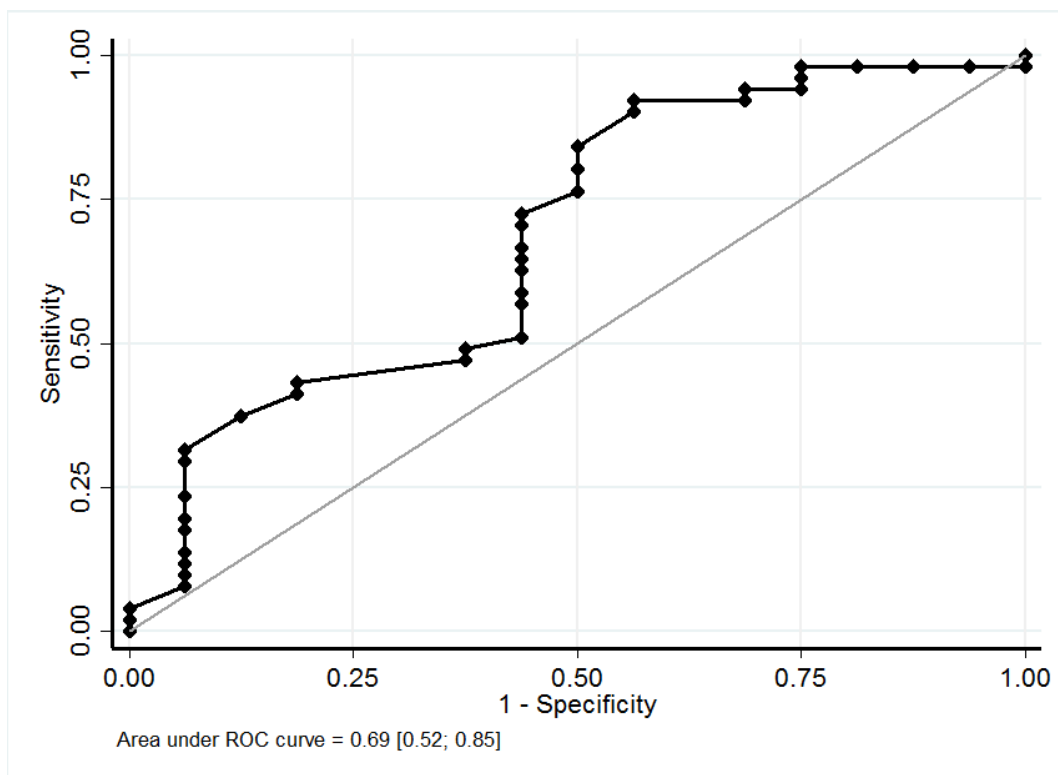
2A: FS method.



2B: MS method.



2C: SAS method.



4. Discussion:

To our best knowledge, ours is the first attempt to provide an objective measurement of blue sclera as a diagnostic tool for ID. We proceeded to a two-step study. First, we evaluated subjective blue color assessment by three well-trained physicians who were blinded to the results of iron-store analysis. Our results are at odds with previously published work (13). In our study, PPV was high (86.1-93.8% depending on the physician) but sensitivity and specificity were low. One explanation could be the difference in inclusion criteria. We included patients based on clinical or biological suspicion of ID, while previous studies included patients with and without suspicion of anemia or ID. Furthermore, assessment of blue color was different in our study, to ensure blindness of the physicians: color assessment was undertaken on anonymized pictures in our study while it was live in previous studies. Second, we applied a computer analysis of blue scleral color. Noticeably, the blue color was higher in patients graded with blue sclera by physicians and in ID. Results were contradictory depending on the methodology used to delineate the sclera. The best results were obtained with the MS method, but specificity was poor with the three methods.

Blue coloration of the sclera can be found in a wide variety of conditions. For example, antibiotic treatment by minocycline is known to induce blue pigmentation of teeth, ears and sclera (20) which is also found in alkaptonuria, a rare autosomal-recessive disorder leading to an accumulation of homogentisic acid (HGA) in connective tissues which induces blueish coloration (21). None of our patients had a history of prolonged minocycline therapy or of symptoms consistent with alkaptonuria (osteoarthritis and dark urine). We did not measure HGA in urine, therefore diagnosis of alkaptonuria cannot be ruled out in our patients although the rarity of this disease makes this hypothesis highly unlikely (22). Other rare inherited conditions with connective tissue abnormalities can also be associated with blueish discoloration of the sclera, such as: Ehlers-Danlos syndrome (23), Marshall-Smith syndrome

(24), Loeys-Dietz syndrome (25), De Barsy syndrome (26) or Mevalonic Aciduria (27). The best-known and most frequent alternate diagnosis of blue sclera due to genetic disorder is osteogenesis imperfecta (OI) (28): mutations in *COL1A1* or *COL1A2* genes lead to quantitative or qualitative defects in type 1 collagen inducing bone fragility. Notably, none of our patients had a history of multiple bone fractures or dysmorphic features.

Electron microscopy of sclera tissues from OI patients revealed reduced collagen thickness of collagen fibers indicative of immature collagen, which is more translucent than normal collagen. This feature could explain the blueish coloration by making the blood vessels and underlying uveal pigment more visible (29,30). To the best of our knowledge, such a study in ID patients has not been conducted but the same hypothesis can be proposed to explain the blue coloration in our patients. Collagen structure of the sclera is composed of 90% type I collagen fibers (31) whose synthesis requires non-heme iron prolyl-4-hydroxylase (32). We postulate that ID leads to impaired synthesis of type I collagen fibers reducing sclera thickness and resulting in blueish coloration. This hypothesis could be easily verified through non-invasive measurement of the sclera by anterior-segment optical coherent tomography (33).

Blue coloration of the sclera in our study was assessed in a similar way to previous studies of this feature in ID patients (13–16). In OI, blue coloration was graded by comparison of commercial scale of blue color. The grades ranged from 8 (bluest grade) which was a 50% dilution of the hue of a 4 year-old patient suffering with OI, to 1 (almost white) by 50% dilution between each grade (34). In our study, physicians graded the blue color in comparison with an absolute white color provided by a color-checker (X-Rite®), but the inter-rater reliability was poor. Any attempt to increase the complexity of the grading might reduce even furthermore the extent of agreement between the assessors. Interestingly, iris color affected neither the assessment of the physician nor the computed analysis of the sclera color.

Finally, the small size of our population meant that we could not performed an analysis according to ethnicity. Furthermore, we could not evaluate the impact of the severity of ID nor its duration. Further studies should focus on improvement of blue detection to enhance specificity. Improvement of this innovative method could provide a simple diagnostic tool for ID for physicians involved in primary care.

Conclusion :

Physician assessment of blue sclera has a good PPV for the diagnosis of ID in subjects with clinical or biological suspicion of ID. However, sensitivity and specificity are poor, and the inter-rater agreement is low. Interestingly, iris color affected neither the assessment of the physician nor the computed analysis of the sclera color. Computed analysis provides encouraging results: blue color was higher in ID than in NID, but the diagnostic value depended on the methodology used to delineate the sclera. Further studies should focus on the improvement of blue detection to enhance specificity. The improvement of this innovative method could provide an easy handling diagnosis tool of great interest for primary care physician in ID diagnosis.

La valeur prédictive positive de la couleur bleue de la sclère est élevée pour le diagnostic de carence martiale chez des sujets présentant des signes cliniques ou biologiques évocateurs. Cependant, la sensibilité et la spécificité sont faibles tout comme le niveau d'accord inter-observateur. De façon intéressante, la couleur de l'iris n'influe pas sur l'évaluation subjective ou informatisée de la couleur de la sclère. Les résultats obtenus par analyse informatique de la couleur de la sclère sont encourageants : un taux de bleu plus élevé est retrouvé chez les sujets présentant une carence martiale mais la valeur diagnostique de cette mesure dépend de la méthode de délimitation de la sclère. Augmenter la détection de la quantité de bleue devrait permettre d'améliorer la spécificité de ce signe. L'amélioration de cette méthodologie innovante pourrait fournir à terme un outil intéressant chez les praticiens de premier recours pour le diagnostic de carence martiale.

Clermont-Ferrand, le
Pierre CLAVELOU
Doyen – Directeur

Clermont-Ferrand, le 17/05/19
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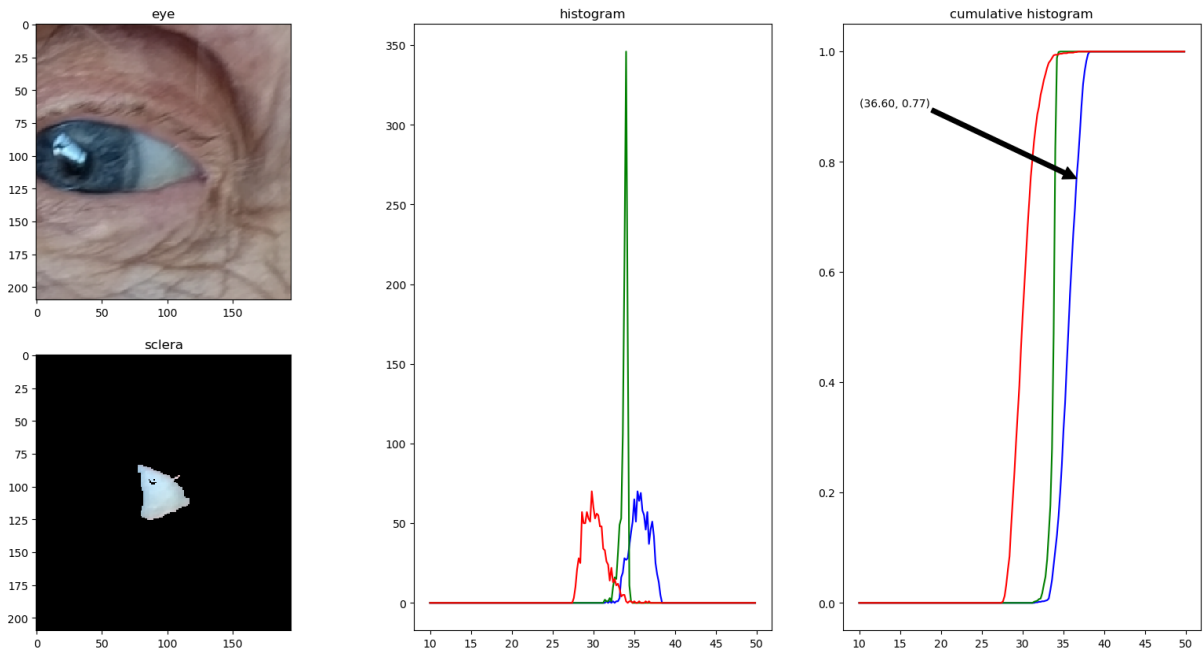
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Annexes :

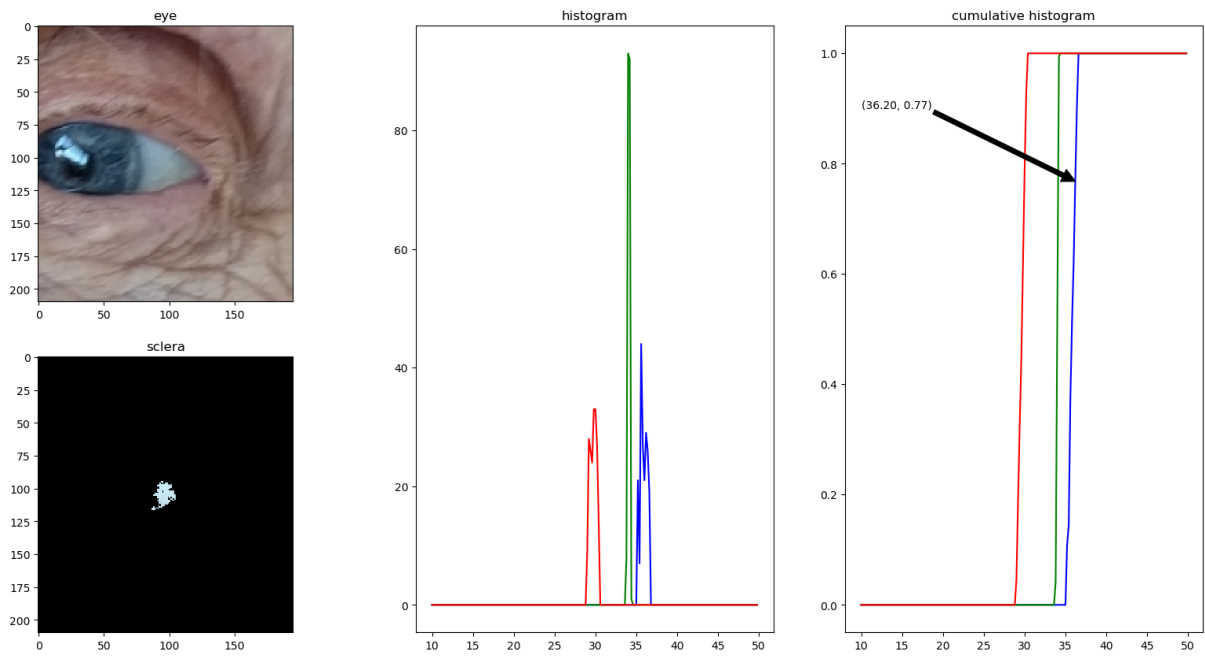
Annexe 1 : Picture of eye and color-checker (X-Rite®) for physician assessment of blue sclera.



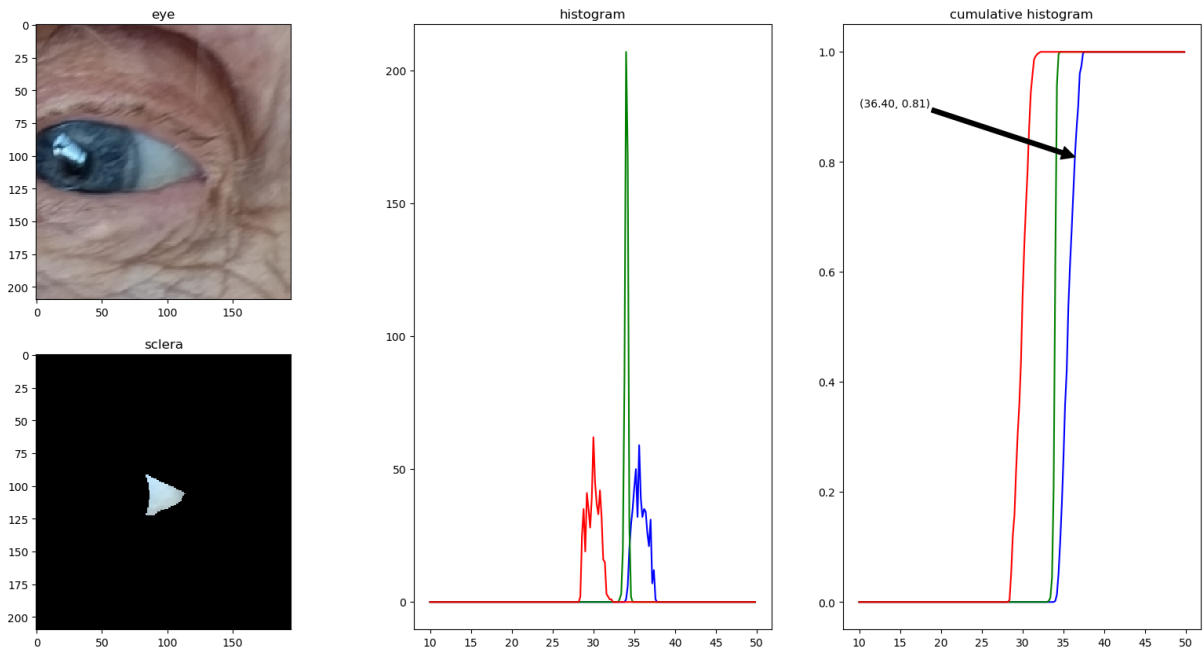
Annexe 2: Computed analysis of blue sclera (FS method).



Annexe 3 : Computed analysis of blue sclera (SAS method).



Annexe 4: Computed analysis of blue sclera (MS method).



Serment d'Hippocrate :

(conseil national de l'ordre des médecins)

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, des raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me sont confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

Serment d'Hippocrate :

En présence des MAÎTRES de cette faculté et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

Étude de la couleur bleue de la sclère pour le diagnostic de carence martiale : analyse clinique et informatisée.

Introduction : la carence martiale (CM) est fréquente en soins primaires. Les signes cliniques sont pauvres : le diagnostic repose sur le dosage de la ferritine sérique. La présence d'une sclère bleue serait un signe sensible et spécifique de CM. Notre objectif était d'évaluer la valeur diagnostique de ce signe pour le diagnostic de CM.

Méthodes : une photographie par smartphone des yeux de 74 patients suspects de CM était réalisée de façon standardisée. Trois médecins indépendants évaluaient en aveugle la couleur de la sclère sur les images anonymisées. Une analyse informatisée déterminait le percentile de bleu dans les pixels de la sclère. La CM était définie par une ferritine $\leq 30 \mu\text{g/L}$ ($100 \mu\text{g/L}$ en cas de syndrome inflammatoire).

Résultats : 67 patients (56% de femmes) étaient inclus dans l'analyse finale (âge moyen 59.9 ± 20.1 ans). 51 patients présentaient une CM. La présence d'une sclère bleue était significativement associée à la CM pour l'évaluateur 1 ($p = 0.03$) avec une sensibilité de 60.8% [IC95: 46.1;74.2], une spécificité de 68.8% [IC95: 41.3;89%] et une valeur prédictive positive de 86.1% [IC95: 70.5;95.3]. Une tendance non significative ($p = 0.05$) était observée pour les autres évaluateurs. L'analyse informatisée montrait un percentile de bleu plus élevé chez les patients avec CM ($p = 0.04$). L'aire sous la courbe de la courbe ROC était de 0.7 [IC95: 0.54;0.85], donnant une sensibilité de 78.4% [IC95: 63.7;88.7] et une spécificité de 50% [IC95: 24.7;75.3]. L'évaluation clinique et informatisée n'étaient influencées ni par le sexe, la couleur de l'iris ou la présence d'une anémie.

Conclusion : la présence d'une sclère bleue a une forte valeur prédictive positive pour le diagnostic de CM. L'analyse informatisée est bien corrélée à l'évaluation clinique. L'amélioration de cette méthode permettrait de proposer un outil intéressant pour le diagnostic de la CM.

Mots clés :

Carence martiale.
Sclère bleue.
Diagnostic clinique
Analyse informatisée

Computed and subjective blue scleral color analysis as a diagnostic tool for iron deficiency.

Introduction: Iron deficiency (ID) is common in primary care and its diagnosis requires measurement using ferritin due to its non-specific clinical presentation. Blue sclera is described as a specific and sensitive sign of ID but there are few reports of this in the literature. We aimed to determine the diagnostic value of blue sclera for the diagnosis of ID.

Methods: We enrolled a total of 74 patients suspected of having ID in a tertiary medical center. Pictures of their eyes were taken using a smartphone under similar daylight. Three independent physicians who were blinded from iron stores, graded the scleral color in anonymized pictures. A computer analysis of the picture yielded the blue percentile (BP) of the sclera. ID was defined where ferritin $\leq 30 \mu\text{g/L}$ ($100 \mu\text{g/L}$ in case of inflammatory syndrome).

Results: Final analysis included 67 patients (mean age 59.9 ± 20.1 -year) with a male:female ratio of 0.8. Fifty-one patients had ID. Subjective blue scleral color was associated with ID for physician 1 ($p = 0.03$) with low sensitivity 60.8% [CI95: 46.1;74.2], specificity 68.8% [CI95: 41.3;89%] and high positive predictive value 86.1% [CI95: 70.5;95.3]. A non-significant trend was observed for other physicians ($p = 0.05$). Inter-rater reliability was poor (*Fleiss's* κ 0.02-0.23). Computer analysis of the pictures showed higher BP in the ID group ($p = 0.04$). The area-under-the-curve of receiver-operating-characteristics curve was 0.7 [CI95: 0.54;0.85]. Sensitivity was 78.4% [CI95: 63.7;88.7], specificity was 50% [CI95: 24.7;75.3] with a threshold of 29.1. Assessment of blue sclera was not influenced by iris color, sex or anemia.

Conclusion: Clinical assessment of blue sclera has good positive-predictive value for ID diagnosis. Computer analysis showed encouraging results correlated to clinical assessment. Improvement of this innovative method could provide simple diagnostic tool for ID diagnosis in primary care.

Mots clés :

Iron deficiency
Blue sclera
Diagnostic tool
Computer analysis