The Infantile Hemangioma Referral Score: A Validated Tool for Physicians

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abstract

OBJECTIVES: Infantile hemangiomas (IHs) are common; some cases require timely referral and treatment to prevent complications. We developed and validated a reliable instrument for timely and adequate referral of patients with IH to experts by nonexpert primary physicians.

METHODS: In this multicenter, cross-sectional, observational study, we used a 3-stage process: (1) development of the Infantile Hemangioma Referral Score (IHReS) tool by IH experts who selected a representative set of 42 IH cases comprising images and a short clinical history, (2) definition of the gold standard for the 42 cases by a second independent committee of IH experts, and (3) IHReS validation by nonexpert primary physicians using the 42 gold standard cases.

RESULTS: A total of 60 primary physicians from 7 different countries evaluated the 42 gold standard cases (without reference to the IHReS tool); 45 primary physicians evaluated these cases using the IHReS questionnaire, and 44 completed retesting using the instrument. IHReS had a sensitivity of 96.9% (95% confidence interval 96.1%–97.8%) and a specificity of 55.0% (95% confidence interval 51.0%–59.0%). The positive predictive value and negative predictive value were 40.5% and 98.3%, respectively. Validation by experts and primary physicians revealed substantial agreement for interrater reliability and intrarater repeatability.

CONCLUSIONS: IHReS, a 2-part algorithm with a total of 12 questions, is an easy-to-use tool for primary physicians for the purpose of facilitating correct and timely referral of patients with IH. IHReS may help practitioners in their decision to refer patients to expert centers.

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Drs Léauté-Labrèze, Baselga Torres, Weibel, Boon, El Hachem, and Troilius Rubin created the Infantile Hemangioma Referral Score tool, selected the 42 clinical cases for validating the tool (stage 1), and validated the study design; Drs van der Vleuten and Roessler participated in the validation of the gold standard (stage 2); and all authors discussed and validated the study results (including the choice of the threshold), reviewed and validated the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Some infantile hemangiomas require treatment to prevent complications. Treatment is more effective in the proliferative phase, and referral delays require shortening. A validated, reliable instrument for timely expert referral is needed for optimal care of patients with infantile hemangiomas.

WHAT THIS STUDY ADDS: The Infantile Hemangioma Referral Score is an easy-to-use algorithm with good intrinsic properties. Validation by experts and primary physicians reveals substantial agreement for interrater reliability and intrarater repeatability. The Infantile Hemangioma Referral Score can assist physicians in selecting patients requiring expert-center referral.

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Infantile hemangiomas (IHs) are the most common tumors of infancy. They have the unique ability to involute after proliferation, often leading primary care providers (PCPs) to assume they will resolve without intervention or consequences. However, a subset of IHs rapidly develop complications, resulting in pain, functional impairment, or permanent disfigurement, which merit consideration for medical treatment.[1–3]

Physical deformities secondary to IHs can have a negative impact on health-related quality of life, social functioning, and emotional and psychological well-being, both on children affected by this vascular tumor and on their parents.[4,5] Consequently, nonexpert primary physicians (eg, physicians with no specific IH expertise) need to determine which IH lesions require referral to specialists to minimize complications.[1,2] Early assessment of the severity of the IH is essential to evaluate the need for early appropriate treatment of these lesions to reduce potential complications.[2,6] Indeed, the timing of therapy is critical in severe IH because early treatment during the proliferative phase will result in higher response rates, and therefore improve outcomes.[7,8]

Many authors have already emphasized the importance of early referral of high-risk IH to multidisciplinary vascular anomaly centers with experienced subspecialists, especially because the discovery of the effectiveness of propranolol for IHs has led to changing treatment decisions in IHs, with more frequent and earlier treatment.[1,9] Unfortunately, clinical studies have revealed that despite the fact that most IH growth is completed at ~5 months of age, infants are often referred at a later age.[10]

Consequently, there is a strong request from primary care physicians to provide them with a tool to support the identification of potentially problematic IHs that should be referred to expert centers. IH experts from 8 European countries developed the Infantile Hemangioma Referral Score (IHReS) screening tool, which consists of a quick and easy-to-use questionnaire. In the current study, we report the development and validation of the IHReS tool for use by nonexpert primary care physicians.

METHODS

Study Design

This multicenter, cross-sectional, observational study was conducted in 3 stages (Table 1). In stage 1, the IHReS questionnaire was developed, and a set of IH clinical cases were selected. In stage 2, an independent committee of experts classified the set of cases to define the gold standard, and the instrument criterion validity was assessed. In stage 3, the tool was validated by assessment of the selected clinical cases by nonexpert primary physicians and an independent committee of experts through a 3-step process all accessed via a dedicated Web site.

Questionnaire Development and Selection of Clinical Cases

The IHReS tool was developed by the Infantile Hemangioma European Task Force (IHETF). The referral questionnaire consisted of 12

TABLE 1 Stages of the Study To Validate the IHReS Tool for Use by Primary Physicians

	Development of the IHReS	Step 1: Classification of the SRC	Step 2: Completion of the IHReS Questionnaire for the SRC	Step 3: Completion of the IHReS Questionnaire for the SRC a Second Time (Test-Retest)
Stage 1: IHETF	Initial design of the questionnaire and clinical cases selection	—	—	—
Stage 2: independent board of experts	—	Gold standard definition	—	—
Stage 3: independent board of experts	—	—	Criterion validity (Fleiss' κ) Construct validity (factor analysis) Internal consistency (Cronbach's α) Interrater agreement (Fleiss' κ)	Intrarater agreement (Cohen's κ)
Stage 3: primary physicians as investigators	—	Usual practice assessment before IHReS (added value of the IHReS)	Internal consistency (Cronbach's α) Interrater agreement (Fleiss' κ) Intrinsic properties (sensitivity, specificity, PPV, NPV, ROC analysis, *J*)	Intrarater agreement (Cohen's κ)

SRC, selected reference cases; —, not applicable.

questions and a 2-part algorithm (Fig 1). Referral to a specialist was considered as mandatory if at least 1 of the 6 questions in part 1 was ticked "Yes," and/or if the composite score for questions 7 to 12 in part 2 was superior to a threshold to be defined. Patients not to be referred are actively monitored by the primary care physician for IH evolution and complications, if any. The task force also selected a set of 42 IH reference images (Supplemental Figs 3–44), which were representative of common cases seen by primary physicians. A brief description of each clinical case (including the age and sex of the child and the date of IH onset and evolution) accompanied the 42 images.

A second group of 9 international experts independently classified the set of 42 IH reference images. Expert referral decisions for all 42 cases were considered as the gold standard case definitions, which were used for subsequent validation.

Validation of IHReS

Internal validation and reliability assessment of the tool were performed by evaluation of the 42 selected clinical cases by both the 9-member independent international expert panel and the 60 nonexpert primary physicians (pediatricians and/or general practitioners) from 7 European countries (France, Switzerland, Belgium, Spain, Italy, Germany, and the Netherlands) using a 3-step process.

The initial judgment (step 1) of the 9-member independent expert panel, before accessing the IHReS questionnaire, was used to define the gold standard for the 42 selected reference cases. For the 42 cases, each member of the expert panel had to independently evaluate whether the patient should be referred to an expert center or actively monitored. The majority position was defined as the gold standard. The initial judgment (step 1) of the 60 nonexpert primary physicians, before accessing the IHReS questionnaire, was made as an assessment of standard clinical practice without reference to any tool. In step 1, nonexpert primary physicians made a subjective assessment to refer or actively monitor each of the 42 cases according to their own (and limited) IH experience. This step was to evaluate the gap between expert and nonexpert (naive) assessments and to evaluate how using the IHReS would improve the evaluation. By using the same assessments (refer or actively monitor), completion of the IHReS questionnaire for the 42 selected reference cases was then performed in step 2 by 8 members of the independent expert panel (1 expert panel member was unable to participate) and 45 of the nonexpert primary physicians (15 primary physicians were excluded because of nonresponse or missing values) to compare the results by using the tool to the "gestalt" assessments in step 1. To establish intrarater reliability, retesting (step 3) was conducted 2 weeks later by the same 8 independent experts and 44 of the nonexpert primary physicians (Table 1).

Results from the nonexpert primary physicians were assessed for internal consistency by using Cronbach's α (a measure of how closely related the set of items is as a group belonging to the same concept), which was calculated from pairwise correlations between items. Interrater reliability, which is used to determine the strength of agreement between a fixed number of raters when assigning categorical ratings to a number of items or classifying items, was measured by Fleiss' κ coefficient; intrarater repeatability, which is used to measure the degree of agreement among repeated administrations of a diagnostic test performed by a single rater, was assessed by using Cohen's κ coefficients. Further details and interpretations for reliability measures are provided in the Supplemental Information; a statistical analysis summary is provided in Table 1. Moreover, the construct validity (the extent to which items on the questionnaire adequately cover the same concept) was assessed by a higher-order factor analysis (Supplemental Information).

End Points

Classification performance of the IHReS was assessed by calculation of the sensitivity (the ability of the scale to correctly classify an IH as requiring referral to an expert center; as a probability, the closer the value is to 1, the better the sensitivity), specificity (the ability of the scale to correctly classify an IH as only requiring active monitoring; as a probability, the closer the value is to 1, the better the specificity), positive predictive value (PPV), and negative predictive value (NPV). Results (sensitivity versus 1 − specificity) were plotted on receiver operating characteristic (ROC) curves, and the Youden index (*J*) measure was calculated for different cutoff values of the questionnaire score. Sensitivity and specificity are 2 dual values, meaning that as the sensitivity increases, the specificity decreases and vice versa. The choice of the IHReS threshold score driving the referral decision acts as a cursor between the 2 values. The ROC curve plots the sensitivity according to 1 − specificity for different values of the threshold score, thereby allowing one to find the optimal cut point resulting in the best combination of sensitivity and specificity (the point on the curve closest to the upper left corner, the Youden index, being maximal at this location). Further details and definitions of statistical measures are provided in the Supplemental Information.

Statistics

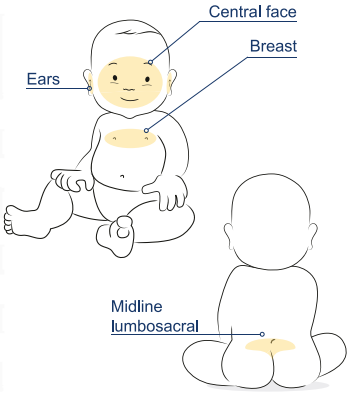
SAS software (version 9.4; SAS Institute, Inc, Cary, NC) was used for

IHReS

To answer the 6 questions below, tick **"Yes"** or **"No."**

Infant's name .....
Age .....
Hemangioma onset __ / __ / __
Expert center .....

Complications or potential risk of complications (ulceration, visual compromise, feeding difficulties, stridor)	◯ Yes	◯ No
Central face and/or **ears**	◯ Yes	◯ No
Breast (in girls)	◯ Yes	◯ No
Midline lombosacral	◯ Yes	◯ No
Size ≥4 cm (focal or segmental)	◯ Yes	◯ No
Number of hemangiomas ≥5	◯ Yes	◯ No



If at least 1 of the previous situations is ticked "Yes," please refer the patient to an expert center.

If you ticked "No" to all questions, please fill in the table on the next page.

Note: In the case of multiple IHs, the score should be done for each IH.

IHReS

For each parameter, tick **"Yes"** or **"No."**

The total score is the sum of the scores from each parameter below.

Parameters	Items			Score Please consider only the highest score for each parameter
Location of hemangioma	Other facial areas than those mentioned previously	◯ Yes ◯ No	If yes: 3 points *(if no: 0 point)*	◯ 3 ◯ 2 ◯ 0
	Neck, diaper area, scalp	◯ Yes ◯ No	If yes: 2 points *(if no: 0 point)*	
Size of the biggest hemangioma	≥1 cm on other facial area than those mentioned previously	◯ Yes ◯ No	If yes: 3 points *(if no: 0 point)*	◯ 3 ◯ 2 ◯ 0
	2 to 4 cm on other body area than those mentioned previously	◯ Yes ◯ No	If yes: 2 points *(if no: 0 point)*	
Current child age and growth of hemangioma	The infant is <2 months	◯ Yes ◯ No	If yes: 3 points *(if no: 0 point)*	◯ 3 ◯ 2 ◯ 0
	The infant is ≥2 and ≤4 months, with an evident growth within the last 2 weeks	◯ Yes ◯ No	If yes: 2 points *(if no: 0 point)*	
			Total	

Score ≥4: please refer the patient to an expert center.
Score <4: the patient is not to be referred and should be monitored. The score will be done at every visit.

The final decision to refer the patient to an expert centre is up to the physiciab and the parents.

FIGURE 1
IHReS.

all statistical analyses. The type I risk (α) was defined as .05 for all tests. Sample size calculations were based on the target sensitivity and specificity, as described by Buderer.[11] Calculations revealed that ~20 physicians were needed to estimate, with a 95% level of confidence, the sensitivity and specificity of the IH score with an absolute precision of ≤5%. Details and definitions of statistical measures are provided in the Supplemental Information.

Ethics Approval

All patients signed an informed consent form for the use of their photographs for publication in medical journals.

RESULTS

Validity Measures

Regarding criterion validity, individual experts assessed the 42 gold standard cases using the IHReS tool and correctly made 37 (88.1%) recommendations for specialist referral. The type I error rate was 11.9%, with 5 gold standard no referral cases (ie, requiring active monitoring) assessed by experts using the tool as needing referral. The type II error rate was 0%, with no gold standard referral case assessed by experts as not needing referral.

The unidimensionality of the questionnaire (defined as the existence of 1 dominant factor underlying the data) was confirmed by the higher-order factor analysis (Supplemental Information). The practical indices of the adjustment (comparative adjustment index and nonstandardized adjustment index) were acceptable (0.9123 and 0.8588, respectively; see Bentler comparative fit index and Bentler-Bonett nonnormed index in Table 2). Parameters of the model are reported in Table 2. Given the different indicators, the model was well adjusted, which means that the composite score from item responses can be grouped into 1 overall score (Supplemental Information).

Reliability Measures

Normalized Cronbach's α, a measure of internal consistency, was 0.51 (poor) for nonexperts. Substantial agreement was observed for expert interrater reliability, with Fleiss' κ values for step 1 (expert judgment related to clinical practice), step 2 (use of IHReS), and step 3 (IHReS retesting) of 0.60, 0.66, and 0.73, respectively. A total of 60 nonexpert primary physicians evaluated each of the 42 gold standard cases (without reference to the IHReS tool; step 1). In step 2, 45 of these physicians evaluated these cases using the IHReS questionnaire, and 44 physicians completed retesting using the instrument (step 3).

For primary physicians, there was moderate agreement for interrater reliability at step 1 (ie, standard clinical practice; Fleiss' κ = 0.56) and step 2 (Fleiss' κ = 0.55) but substantial agreement for IHReS retesting in step 3 (Fleiss' κ = 0.64). Regarding repeatability, in the test-retest assessment, Cohen's κ coefficient values revealed substantial agreement in intrarater repeatability for both experts (0.77) and primary clinicians (0.71).

ROC Analysis

The ROC analysis for varying threshold scores revealed that a score of 5 was optimal, with a sensitivity of 89.5% (95% confidence interval [CI] 88.0%–91.1%) and a specificity of 69.5% (95% CI 65.8%–73.2%). The PPV and NPV were 48.1% and 95.4%, respectively. The Youden index was 0.59. The weighting assigned to questions 7 to 12 was varied to optimize sensitivity and specificity. Increasing the weighting of question 11 from 2 to 3 improved the discriminatory power of the IHReS, producing a sensitivity of 94.8% (95% CI 93.7%–95.9%), with a PPV of 46.1%, and a specificity of 65.0% (95% CI 61.2%–68.8%), with an NPV of 97.5%, for a threshold ≥5.

After reviewing the discrepant cases, and to not miss relevant cases, we finally considered a threshold ≥4 with a sensitivity of 96.9% (95% CI 96.1%–97.8%), with a PPV of 40.5%, and a specificity of 55.0% (95% CI 51.0%–59.0%), with an NPV of 98.3% (see Discussion). The Youden index was 0.52 (Fig 2).

DISCUSSION

The IHReS was developed as a simple, rapid, easy-to-use tool to assist nonexpert primary physicians in their decision to refer patients with IH to expert centers. Timely and appropriate referral to expert centers should reduce complications in patients and residual lesions after involution of the IH. An electronic version of the IHReS is available for access by nonexpert physicians, along with sample training cases, at www.ihscoring.com.

Overall, the IHReS instrument had good intrinsic properties, with a sensitivity of ~97% and a specificity of 55%. Validation by experts and primary physicians revealed substantial agreement for interrater reliability and intrarater repeatability. The type I and type II error rates for expert assessment of the referral tool were 11.9% and 0%, respectively. Of these, the type II error, which recommended active monitoring rather than referral, was clinically more important.

On the basis of an IHReS score <4, our recommendation is that patients should not be referred to a specialist but that they should be monitored, with the IHReS score repeated at every subsequent clinic visit. Although the general purpose of the IHReS tool is to increase awareness among nonexpert physicians regarding the need to conduct regular and active monitoring because of the natural and unpredictable evolution of IHs, rather than having a passive

TABLE 2 Higher-Order Factor Analysis: Parameters of the Final Model

	Summary of Adjustments		
	Criteria To Be Met in the Higher-Order Factor	Required	Obtained
Absolute index	Ratio of χ^2/degrees of freedom	<5	7.6
Absolute index	Pr is greater than χ^2	Not significant (not often the case)	<0.0001
Absolute index	SRMR	<0.05	0.0429
Absolute index	GFI	>0.8	0.9767
Economy index	Adjusted GFI	>0.8	0.9557
Economy index	RMSEA estimate	At ~0.05 or at least <0.08; the lower the RMSEA, the better the model	0.056
Economy index	Lower bound of the CI RMSEA at 90%	—	0.0503
Economy index	Upper bound of the CI RMSEA at 90%	—	0.0619
Incremental index	Akaike information criterion	The lowest possible among the models tested	385.6065
Incremental index	Bentler CFI	>0.9	0.9123
Incremental index	Bentler-Bonett nonnormed index	>0.9	0.8588

CFI, comparative fit index; GFI, goodness-of-fit index; RMSEA, root mean square error of approximation; Pr, χ2 test *P*; SRMR, standardized root mean square residual; —, not applicable.

waiting attitude (ie, "Nothing to do, it will disappear spontaneously"), there is currently no specific guideline or consensus on how and how frequently to conduct monitoring. A group of European experts has proposed the following general rule for estimating the frequency of monitoring visits: the frequency of monitoring visits (in weeks) is equal to the age of the infant (in months).[12] However, this recommendation has not been validated by clinical data and, at present, cannot be proposed as a formal rule. The important lesson here is to acknowledge that lesions in the rapid-growth phase can quickly become functionally or cosmetically problematic and that reassessment performed only at well-child visits may not be sufficient. As part of the ongoing monitoring process, PCPs may invite patients with IH to e-mail photographs of their lesions, or contact the office at regular intervals, particularly if certain findings (ie, early ulceration or thickening of previously superficial lesions) become evident.

Other purpose-made instruments for IHs have been described: the Hemangioma Activity Score, which scores the proliferative activity of IH[13]; the Hemangioma Severity Scale (HSS), which measures disease

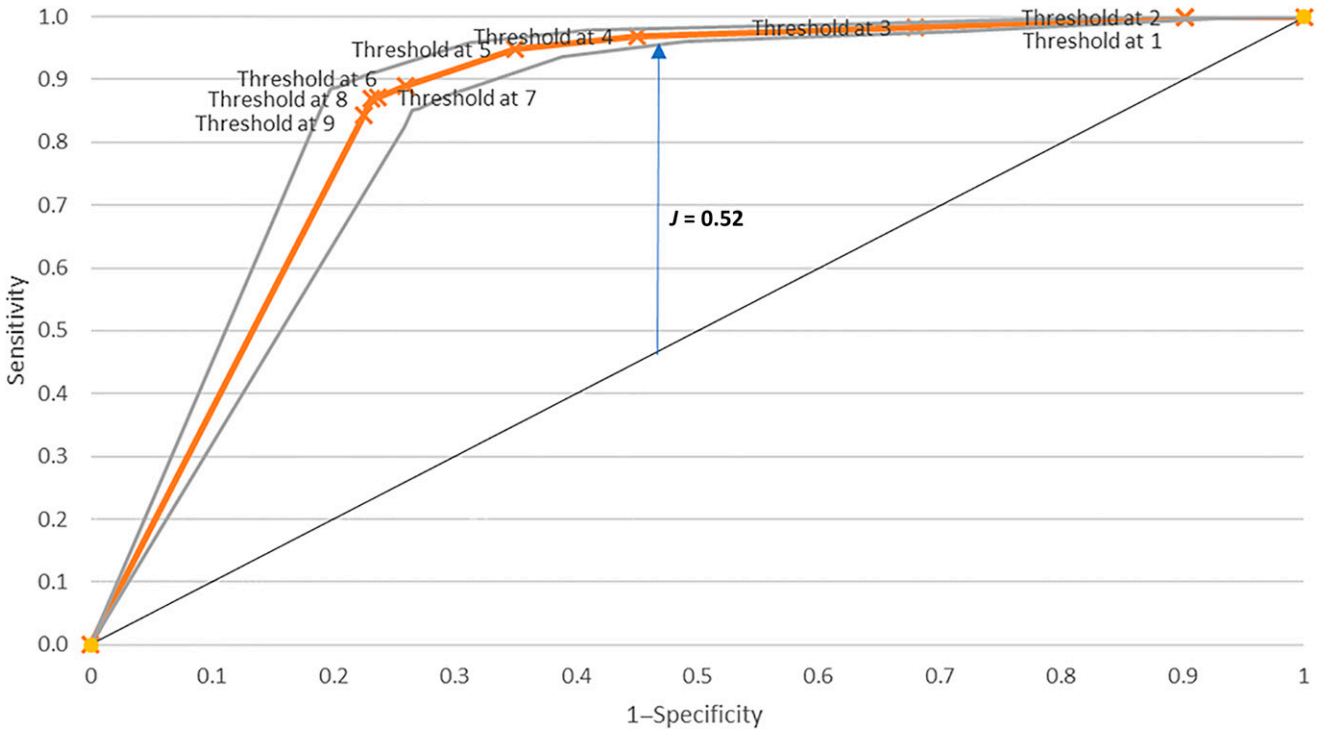


FIGURE 2
ROC analysis for varying IHReS threshold scores. Gray lines denote 95% CIs.

severity[14]; and the Hemangioma Dynamic Complication Scale, which measures IH complications for longitudinal use.[14] A comparison of the Hemangioma Activity Score and HSS tools revealed that observer intraclass correlation coefficients were comparable but that the HSS was a less reliable tool for disease severity assessment because scores often remained unchanged despite clinical improvement of the IH.[15] Furthermore, although the HSS was used to assist IH treatment decisions or referral, the cutoff values used for decision-making were inconsistent.[16,17]

The current study had some limitations. One of the constraints of conducting a real-world observational study was that the representativeness of the participating physicians was potentially limited, restricting generalizability. This is reflected in the fact that although private-practice physicians who participated in the validation of the score were recruited from several countries, recruitment was limited only to those who agreed to participate, and, with the exception of France, all were pediatricians. Because cases were not selected on the basis of a predetermined severity, there is a possibility of selection bias. However, no case was a priori rejected from the sample of cases. Cases were rejected only in the absence of parental consent to use photographs, because of poor photograph quality, or if cases were similar. In such situations, we checked that retained cases covered the vast majority of cases commonly seen in our clinical practices to ensure that no typical case of IH was missing. Additionally, regarding the selection of cases, selection based on a predetermined severity score was not judged as appropriate. For example, some small focal hemangiomas could be scored as not severe, whereas the purpose of the IHReS tool is to alert a PCP to refer their patient to an expert center because of the potential risk of that kind of hemangioma. The first 6 questions in the IHReS represent cases that a PCP must not miss referring because of the potential associated risks. The second set of 6 questions represents the complexity of IHs and should alert a PCP that other conditions should be taken into consideration. Consequently, we did not want to select only evident cases, based on predetermined severity, but retain all cases, even the less obvious ones. There were also limitations associated with the use of a set of patient photographs to determine the gold standard cases. Because there was no consensus regarding the sensitivity and specificity values that were considered acceptable to validate a classification questionnaire, the results of the study should be interpreted carefully. For the present questionnaire, it was hypothesized that minimum values for sensitivity and specificity of 85% and 60%, respectively, should be acceptable; however, these values can vary depending on the intent of the test, the context of testing, or the prevalence of the disease in the group tested. Considering the purpose of the score, and to provide an efficient triage of patients without missing important cases, we decided to lower the IHReS cutoff threshold to 4 (from 5). This optimization of the score cutoff threshold increased the sensitivity of the IHReS to 96.9% (from an initial sensitivity of 89.5%), with an acceptable specificity of 55%. Further research with a larger sample of real-word IHs should be used to assess whether outcomes arising from this study can be generalizable.

CONCLUSIONS

The IHReS tool is an easy-to-use tool aimed at primary physicians with the purpose of facilitating correct and timely referral of patients with IH. It consists of a 2-part algorithm and a total of 12 questions. IHReS may help practitioners in their decisions to refer patients to expert centers identify children who require early treatment.

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ABBREVIATIONS

CI: confidence interval
IH: infantile hemangioma
IHETF: Infantile Hemangioma European Task Force
IHReS: Infantile Hemangioma Referral Score
HSS: Hemangioma Severity Scale
NPV: negative predictive value
PCP: primary care provider
PPV: positive predictive value
ROC: receiver operating characteristic

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POTENTIAL CONFLICT OF INTEREST: Dr Léauté-Labrèze is a consultant and clinical trial investigator for Pierre Fabre and is a member of the Infantile Hemangioma European Task Force (IHETF) and received consultant fees. Dr Baselga Torres is a consultant and speaker for Pierre Fabre, is a member of the IHETF and received consultant fees, is a consultant for Ferrer and Sanofi, is the founder and consultant for Vanthera, and is a speaker for Almirall. Dr Weibel is member of the IHETF and received consultant fees; she is a consultant and speaker for Sanofi, MEDA, Merz, Permamed, and La Roche Posay (L'Oréal) and the principal investigator in clinical trials with AbbVie, Novartis, Eli Lilly, and Pfizer. Dr Boon is member of the IHETF and received consultant fees and has relationships with the following companies: Deciphera Pharmaceuticals, Inc (Waltham, MA), Venthera, Inc (Palo Alto, CA), and Pfizer, Inc (Ixelles, Belgium) (sirolimus or VASE study). Dr El Hachem is member of the IHETF and received consultant fees. Dr van der Vleuten is a member of the IHETF and received consultant fees. Dr Roessler is a consultant for Pierre Fabre, is a member of the IHETF and received consultant fees, is a consultant for SOBI, and has received research grants from Pfizer and travel grants from Roche. Dr Troilius Rubin is a member of the IHETF and received consultant fees.

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