# Screening for infantile hepatic hemangioma in patients with cutaneous infantile hemangioma: A multicenter prospective study

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***Background:*** Abdominal ultrasonography has been proposed to screen for infantile hepatic hemangioma (IHH) in patients with multiple cutaneous infantile hemangiomas (IHs).

***Objectives:*** The aim of this study was to establish the optimal cutoff point for the number of cutaneous IHs needed to screen for IHH.

***Methods:*** We performed a prospective, multicenter study to screen for IHH in patients younger than 9 months who had multiple cutaneous IHs ($n \geq 3$) on ultrasonography. For comparison, a group of patients with 1 or 2 focal cutaneous IHs was also recruited.

***Results:*** In total, 676 patients with at least 3 cutaneous IHs and 980 patients with 1 or 2 focal cutaneous IHs were enrolled. Thirty-one patients were found to have IHH. A higher number of cutaneous IHs was associated with an increased risk of IHH ($R = 0.973$; $P < .001$). Receiver operating characteristic curve analysis showed that 5 cutaneous IHs was the optimal cutoff point to screen for IHH, with an area under the curve of 0.872 ($P < .001$; 95% confidence interval, 0.789-0.955).

***Limitations:*** This was an uncontrolled study.

***Conclusions:*** Screening for IHH is recommended in patients younger than 9 months who present with 5 or more cutaneous IHs. (J Am Acad Dermatol 2021;84:1378-84.)

***Key words:*** cutoff point; infantile hemangioma; infantile hepatic hemangioma; multiple; screening.

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Infantile hepatic hemangioma (IHH) is the most common hepatic tumor in infancy. IHH can be classified into 2 subtypes: multiple and diffuse. IHHs can have varied presentations.[1,2] Many multiple IHHs are clinically silent and self-limiting, whereas others may become symptomatic and rapidly proliferate within the first few months of life. Unidentified or untreated multiple IHHs may proliferate and evolve into diffuse IHHs. Patients with diffuse IHHs are more likely to have serious complications, including hypothyroidism, abdominal compartment syndrome, and congestive heart failure.[3] Therefore, prompt initiation of treatment in patients with IHH is occasionally indicated.

It is well known that the presence of multiple cutaneous infantile hemangiomas (IHs) could be associated with IHH.[4] Ultrasonography screening for IHH in patients with multiple cutaneous IHs may allow for earlier treatment and closer surveillance before life-threatening progression occurs, preventing complications and reducing mortality.[5] The American Academy of Pediatrics published clinical practice guidelines for the management of IHs in 2015 and updated these in 2019.[6,7] The guidelines stated that clinicians should screen for IHH in infants younger than 6 months of age who present with 5 or more cutaneous IHs.[6] However, there is a shortage of large, prospective validations of this recommendation. In addition, there is debate about the number of cutaneous IHs that should serve as the ultrasonography screening threshold or cutoff point.[4,8,9] The objective of this study was to determine the incidence of IHH in patients with multiple cutaneous IHs and estimate the optimal cutoff point for ultrasonography screening for IHH.

**CAPSULE SUMMARY**

- Multiple cutaneous infantile hemangiomas could be associated with infantile hepatic hemangioma.
- A higher number of cutaneous infantile hemangiomas was associated with an increased risk of infantile hepatic hemangioma.
- Abdominal ultrasonography is recommended for infants younger than 9 months of age who present with 5 or more cutaneous infantile hemangiomas.

## METHODS

### Study design and participants

This was a prospective, multicenter study measuring the incidence of IHH in patients with cutaneous IHs. This trial was conducted as a collaboration among 5 tertiary referral centers. The study protocol was approved by the ethics committee on medical research of each participating site. All procedures followed the study protocol and were conducted according to the Declaration of Helsinki. The patients' parents or guardians gave written informed consent before enrollment. The study has been registered at www.clinicaltrial.gov (NCT03331744).

The inclusion criteria were as follows: age of 0 to 9 months and presence of clinically confirmed multiple cutaneous IHs ($n \geq 3$). The exclusion criteria included a personal history of IHH and a diagnosis of other vascular anomalies. For comparison, 980 patients aged 2 to 9 months with 1 or 2 focal cutaneous IHs were randomly selected by cluster sampling from participant sites.

### Definitions

All cutaneous IHs were categorized according to the classification system of the International Society for the Study of Vascular Anomalies (www.issva.org). Multifocal IHHs were defined as multiple masses separated by normal hepatic parenchyma. Diffuse IHHs were characterized by the extensive replacement of hepatic parenchyma with innumerable centripetally enhancing lesions. Focal hepatic hemangiomas were the hepatic form of cutaneous congenital hemangiomas. Individuals with these congenital hepatic hemangiomas were excluded from the analysis.[2,10]

### Measurement and screening program

Before the examination, the patients' parents who opted for enrollment completed a questionnaire to provide demographic, prenatal history, family history, and medical history information. The numbers of cutaneous IHs were recorded. When patients had more than 1 cutaneous IH, detailed information was obtained for the most clinically important hemangioma (typically the largest lesion). All included patients were initially assessed for IHH-related symptoms (eg, hepatomegaly and abdominal distension) through physical examinations.

The main outcome was incidental IHH. IHH was assessed through abdominal ultrasonography by accredited sonographers at each participant site. The features of IHH on ultrasonography examination were hyperechoic or hypoechoic nodules with abnormal vascular channels. If ultrasonography was performed before 1 month of age and the result was negative, the patient was followed up until the next

*Abbreviations used:*

CI: confidence interval
IH: infantile hemangioma
IHH: infantile hepatic hemangioma
MRI: magnetic resonance imaging
OR: odds ratio
ROC: receiver operating characteristic

screening ultrasonography, which was performed at 2 months of age. If IHHs were detected by screening ultrasonography, the individuals required further abdominal magnetic resonance imaging (MRI) to confirm and assess the IHHs. The MRI scans were examined independently by 2 radiology specialists. The number of IHHs, extent of IHH, liver size, and arteriovenous shunting were assessed.

### Diagnosis of disorders associated with IHH

Electrocardiogram, echocardiogram, full blood count, liver and renal function, coagulation function, thyroid function, and alpha fetoprotein examinations were performed in infants with IHHs.

### Study visits and management

For patients with IHH, study visits were scheduled at enrollment and at 1, 4, 12, 24, 36, and 48 weeks after enrollment or if there was any specific need after enrollment. Patients with IHHs with symptoms (eg, hepatomegaly), complications (eg, hypothyroidism), large lesions (maximum diameter ≥ 3.0 cm), and lesion progression received a recommendation to undergo oral propranolol treatment. A prescription for propranolol was also required in patients with problematic cutaneous IH (eg, impaired function, cosmetic reasons, or ulceration and/or bleeding). Propranolol was administered in a progressive schedule up to 2.0 mg/kg per day, as previously described.[11,12] Levothyroxine was needed in patients with hypothyroidism. Physical examination, routine laboratory tests, and ultrasonography were performed during protocol visits and in between visits if needed. Follow-up MRI was performed after 6 and 12 months of propranolol treatment.

### Statistical analysis

For analysis, we divided the patients into 5 groups depending on the number of cutaneous IHs: (1) 1 or 2 cutaneous IHs; (2) 3 or 4 cutaneous IHs; (3) 5 to 9 cutaneous IHs; (4) 10 to 30 cutaneous IHs; and (5) more than 30 cutaneous IHs. The chi-square test or Fisher's exact test was used to analyze categorical data. The Student *t* test and Mann-Whitney *U* test were used to analyze continuous variables, where appropriate. Correlations between variables were tested by a nonparametric Spearman rank correlation test. To determine the optimal cutoff point for the number of cutaneous IHs that best predicts the presence of IHH, the sensitivity and specificity were calculated by using receiver operating characteristic (ROC) curve analysis. The Youden index was used to evaluate the ideal cutoff point for screening IHH and was calculated by using the following formula: Youden's index = sensitivity + specificity − 1. Statistical analyses were conducted with SPSS 23.0 for Windows (SPSS Inc). *P* values less than .05 were considered statistically significant.

## RESULTS

### Participants

The participants were enrolled from January 2015 to December 2018. Among 1762 patients assessed for eligibility, 106 were excluded. A total of 1656 individuals met the inclusion criteria and were ultimately enrolled in the study. The demographic and clinical characteristics are shown in Table I. There were 431 male and 1225 female infants, with a male to female ratio of 1:2.84. The mean age at enrollment was 3.1 months. In total, 676 patients had at least 3 cutaneous IHs.

### Detection of IHHs and comorbidities

Abdominal ultrasonography was the first imaging modality in all cases. A total of 31 patients were found to have IHH. All 5 subgroups were found to be associated with IHH (Table II, Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/dnv7jkz95t.1). In these 31 patients, physical examination showed that 3 (9.7%) had IHH-related symptoms, including hepatomegaly (3/3), abdominal distention (1/3), malnutrition (1/3), and failure to thrive (1/3). Subsequent MRI scans showed that the hepatic hemangioma lesions ranged from 0.8 to 6.5 cm in diameter. One patient had diffuse IHH, and the remaining patients had multifocal IHHs. Hepatic arteriovenous shunting and intrathoracic hemangioma were observed in 1 patient with multifocal IHH.

Consumptive hypothyroidism was observed in 3 (9.7%) patients, with serum thyroid-stimulating hormone levels ranging from 13.6 to 68.0 mIU/L. Among these 3 patients, 1 patient had diffuse IHH. Two patients had multifocal IHH with lesion sizes larger than 5.0 cm. Both patients were older than 6 months at diagnosis (6.5 and 7.0 months, respectively). Hypertrophic cardiomegaly (1/31), pulmonary hypertension (1/31), anemia (2/31), and liver dysfunction (1/31) were also observed (Table III).

**Table I.** Demographic and clinical characteristics

| Characteristics | With IHH (n = 31) | Without IHH (n = 1625) | Total (n = 1656) | *P* value* |
|---|---|---|---|---|
| Patients | | | | |
| Sex, n (%) | | | | .978† |
| Male | 8 (25.8) | 423 (26.0) | 431 (26.0) | |
| Female | 23 (74.2) | 1202 (74.0) | 1225 (76.0) | |
| Age, months | | | | .508‡ |
| Mean (SD)‡ | 3.0 (1.6) | 3.1 (1.0) | 3.1 (1.0) | |
| Gestational age, n (%) | | | | .578§ |
| Born at term | 5 (16.1) | 201 (12.4) | 206 (12.4) | |
| Born prematurely | 26 (83.9) | 1424 (87.6) | 1450 (87.6) | |
| Cutaneous IHs | | | | |
| Morphologic subtype, n (%) | | | | .476‖, |
| Localized | 29 (93.6) | 1570 (96.6) | 1599 (96.6) | |
| Indeterminate | 2 (6.5) | 47 (2.9) | 49 (3.0) | |
| Segmental | 0 (0) | 8 (0.5) | 8 (0.5) | |
| Description, n (%) | | | | .444‖ |
| Superficial | 26 (83.9) | 1442 (88.7) | 1468 (88.6) | |
| Mixed | 4 (12.9) | 166 (10.2) | 170 (10.3) | |
| Deep | 1 (3.2) | 17 (1.0) | 18 (1.1) | |
| Lesion size,¶ $cm^2$, median (IQR) | 4.2 (0.6-15.5) | 3.9 (0.8-16.8) | 3.9 (0.6-16.8) | .871# |

*IH*, Infantile hemangioma; *IHH*, infantile hepatic hemangioma; *IQR*, interquartile range; *SD*, standard deviation.
*Patients with IHH compared to patients without IHH.
†*P* value was calculated with the chi-square test.
‡*P* value was calculated with an independent-sample Student *t* test.
§*P* value was calculated with Fisher's exact test.
‖*P* value was calculated with the Pearson chi-square test.
¶The lesion sizes (surface areas) were recorded by using hemispheric measurements. A soft tape measure was draped over the hemangioma, and the longest diameter and a measurement perpendicular to it were noted to obtain a measurement in $cm^2$.
#*P* value was calculated with the Mann-Whitney *U* test.

**Table II.** Incidence of IHH in patients with cutaneous IH

| Characteristics | With IHH (n = 31) | Without IHH (n = 1625) |
|---|---|---|
| Cutaneous IHs, n (%) | | |
| 1 | 3 (0.5) | 610 (99.5) |
| 2 | 0 (0) | 367 (100.0) |
| 3 | 1 (0.3) | 322 (99.7) |
| 4 | 2 (1.4) | 142 (98.6) |
| 5 | 2 (4.8) | 40 (95.2) |
| 6 | 4 (10.0) | 36 (90.0) |
| 7 | 3 (7.5) | 37(92.5) |
| 8 | 2 (7.4) | 25 (92.6) |
| 9 | 3 (15.8) | 16 (84.2) |
| ≥10 and ≤30 | 7 (24.1) | 22 (75.9) |
| >30 | 4 (33.3) | 8 (66.7) |

*IH*, Infantile hemangioma; *IHH*, infantile hepatic hemangioma.

### Higher numbers of cutaneous IHs confer a greater risk of IHH

No significant differences were noted in sex, age at recruitment, or gestational age between patients with IHHs and those without IHHs ($P > .05$). There was no significant difference in the incidence of IHH between patients with 1 or 2 cutaneous IHs and those with 3 or 4 cutaneous IHs (0.3% vs 0.6%; $P = .395$; odds ratio [OR], 0.475; 95% confidence interval [CI], 0.095-2.362). However, the incidence of IHH was higher in patients with 5 to 9 cutaneous IHs than in those with fewer than 5 cutaneous IHs (8.3% vs 0.4%; $P < .001$; OR, 21.833; 95% CI, 8.271-57.636). Similarly, a higher incidence of IHH was noted in patients with 10 to 30 cutaneous IHs than in those with 5 to 9 cutaneous IHs (24.1% vs 8.3%; $P = .011$; OR, 3.500; 95% CI, 1.273-9.622). The incidence of IHH was also higher in patients with more than 30 cutaneous IHs than in those with 10 to 30 cutaneous IHs (33.3% vs 24.1%), although the difference was not significant ($P = .701$; OR, 1.571; 95% CI, 0.361-6.842).

Changes in the incidence of IHH were compared with the number of cutaneous IHs. Higher numbers of cutaneous IHs were associated with a greater risk of IHH (Spearman: $R = 0.973$; $P < .001$). However, no significant association between the number of cutaneous IHs and the number of IHHs was identified (Spearman: $R = 0.129$; $P = .488$).

**Table III.** Clinical features of 31 patients presenting with IHH

| Case | Sex | Age at diagnosis, mo | Number of cutaneous IHs | Maximum size of the cutaneous IHs, cm | Number of IHHs | Maximum size of the IHHs, cm | Major sign, symptoms, and/or complications |
|---|---|---|---|---|---|---|---|
| 1 | Female | 3.5 | 1 | 2.5 | 8 | 2.0 | — |
| 2 | Female | 3.0 | 1 | 3.0 | ≥10 and ≤30 | 1.5 | — |
| 3 | Male | 5.0 | 1 | 1.5 | 3 | 1.8 | — |
| 4 | Female | 6.5 | 3 | 3.5 | 4 | 5.5 | Hypothyroidism |
| 5 | Female | 3.0 | 4 | 2.5 | ≥10 and ≤30 | 2.5 | — |
| 6 | Male | 2.0 | 4 | 2.0 | 9 | 1.2 | — |
| 7 | Female | 4.0 | 5 | 4.5 | >30 | 1.0 | — |
| 8 | Female | 1.5 | 5 | 2.0 | 4 | 0.8 | — |
| 9 | Male | 4.0 | 6 | 1.5 | ≥10 and ≤30 | 2.6 | Hepatomegaly, hypertrophic cardiomegaly, pulmonary hypertension, anemia, liver dysfunction |
| 10 | Female | 7.0 | 6 | 3.0 | ≥10 and ≤30 | 1.5 | — |
| 11* | Female | 2.0 | 6 | 2.5 | 7 | 1.3 | — |
| 12 | Female | 1.5 | 7 | 1.0 | 8 | 2.2 | — |
| 13 | Female | 2.6 | 7 | 3.0 | ≥10 and ≤30 | 1.8 | — |
| 14 | Female | 2.0 | 7 | 2.0 | 6 | 2.0 | — |
| 15 | Female | 3.0 | 7 | 2.0 | 8 | 2.0 | — |
| 16 | Female | 2.0 | 8 | 1.2 | ≥10 and ≤30 | 1.5 | — |
| 17 | Female | 1.5 | 8 | 1.5 | 4 | 1.0 | — |
| 18 | Male | 3.0 | 8 | 2.0 | ≥10 and ≤30 | 1.6 | — |
| 19 | Female | 7.0 | 9 | 1.5 | 5 | 6.5 | Hepatomegaly, hypothyroidism |
| 20 | Female | 3.0 | 9 | 1.8 | 9 | 1.4 | — |
| 21 | Male | 1.2 | ≥10 and ≤30 | 1.2 | ≥10 and ≤30 | 2.2 | — |
| 22 | Male | 3.0 | ≥10 and ≤30 | 1.2 | ≥10 and ≤30 | 1.0 | — |
| 23 | Male | 2.0 | ≥10 and ≤30 | 2.5 | 9 | 1.5 | — |
| 24 | Female | 1.5 | ≥10 and ≤30 | 1.2 | ≥10 and ≤30 | 1.2 | — |
| 25 | Female | 2.0 | ≥10 and ≤30 | 1.8 | 6 | 2.0 | — |
| 26 | Female | 3.5 | ≥10 and ≤30 | 1.0 | >30 | 2.2 | Hepatomegaly, abdominal distention, malnutrition, failure to thrive, hypothyroidism, anemia |
| 27 | Female | 3.0 | ≥10 and ≤30 | 1.2 | 3 | 1.5 | — |
| 28 | Female | 3.0 | >30 | 1.0 | 8 | 1.6 | — |
| 29 | Male | 1.5 | >30 | 0.8 | ≥10 and ≤30 | 2.0 | — |
| 30 | Female | 2.0 | >30 | 1.0 | 7 | 1.0 | — |
| 31 | Female | 2.0 | >30 | 1.2 | ≥10 and ≤30 | 2.5 | — |

*IH*, Infantile hemangioma; *IHH*, infantile hepatic hemangioma.
*Patient 11 had ultrasonography performed at 21 days of age, with negative findings, but was subsequently diagnosed with IHH at the time of the 2-month ultrasonography.

### Optimal cutoff point for cutaneous IHs to screen for IHH

To further inspect the prognostic accuracy and diagnostic potential of the numbers of cutaneous IHs in predicting IHH, we performed an ROC curve analysis. The area under the ROC curve was 0.872 ($P < .001$; 95% CI, 0.789-0.955), indicating that the logistic model had good discrimination between patients who developed IHH and those who did not (Fig 1). The Youden index for the number of

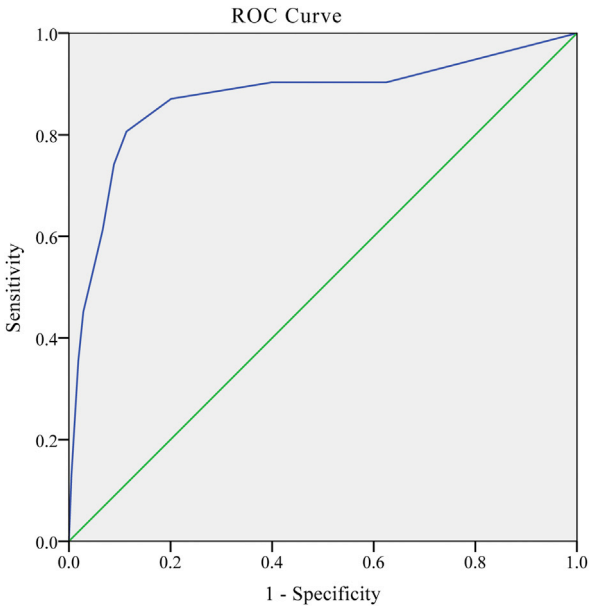


**Fig 1.** Receiver operator characteristic (ROC) curve for the cutoff point to screen for infantile hepatic hemangioma. The 45° line represents the ROC curve with an area under the curve of 0.5. The area under the curve is 0.872.

cutaneous IHs was highest at 4.5 (index = 1.693, sensitivity = 80.6%, specificity = 11.3%). Therefore, the cutoff point for the number of cutaneous IHs was set at 5 to screen for IHHs.

### Follow-up and outcomes

Five patients received propranolol treatment for IHH. In these 5 patients, 3 who had consumptive hypothyroidism received short-term combination treatment with levothyroxine. Four patients with IHH received propranolol treatment for their cutaneous IHs. In all of these 9 patients treated with propranolol, symptom relief and/or lesion reduction were noted within 4 weeks after treatment. For untreated patients, abdominal ultrasonography was performed at the scheduled visits until involution of IHH was observed (involution typically began at 12 to 18 months of age). All patients experienced good results on follow-up.

## DISCUSSION

Because many small lesions are unidentifiable and asymptomatic, the true incidence of IHH remains unknown.[1,3] Several previous studies have suggested that the presence of segmental cutaneous IH might be a marker for underlying hepatic involvement.[4,13] Subsequent reports have suggested that it was the number of cutaneous IHs rather than the hemangioma size that was the useful marker for IHHs.[9] However, the prevalence of IHH in patients with focal cutaneous IHs is unknown. In the present study, we provided evidence that the frequency of IHH in patients presenting with 1 to 2 focal cutaneous IHs was extremely low. In addition, the results of our prospective study showed that increased numbers of cutaneous IHs were associated with increased risks of IHH. Remarkably, patients with 10 or more cutaneous IHs had an annual risk of 24.1% to 33.3% for developing IHH.

Despite a lack of randomized data, several retrospective studies provided evidence on the benefits of IHH screening.[11,14,15] Rialon et al[5] found that patients with IHH detected through screening were less likely to develop serious clinical symptoms and complications and had reduced mortality. From a practical point of view, ultrasonography is the most cost-effective, noninvasive, and well-tolerated imaging tool for screening patients with cutaneous IH. Previous studies evaluating the cutoff point to screen for IHH in smaller cohorts and retrospective studies have yielded conflicting results. In these studies, cutoff points were set at 5, 6, or 10 cutaneous IHs.[4,5,8,9] These cutoff points were not selected on the basis of standard statistical methods, such as ROC curves. Until now, only 1 previous prospective study on ultrasonography screening for IHH has been reported. However, only 50 patients with 1 to 4 cutaneous IHs were recruited in that study.[9] In the present study, we recruited a larger number patients with 1 to 4 cutaneous IHs. Our findings emphasize that patients with fewer than 5 cutaneous IHs should not be overlooked, because some of these patients had IHH. In addition, previous studies were weakened by not excluding congenital hepatic hemangiomas. IHHs are histologically, biologically, and behaviorally distinct from congenital hepatic hemangiomas, which are present and fully formed at birth.[10]

Accurate information on the effectiveness of screening ultrasonography is needed to provide guidance on whether widespread screening ultrasonography would be a beneficial strategy. In the present study, we calculated the Youden index to establish the cutoff point to screen for IHH. The cutoff point for the number of cutaneous IHs was set at the highest Youden index. Our prospective study showed that a cutoff point of 5 cutaneous IHs was preferable. Our results suggest that screening for IHH in patients with fewer than 5 cutaneous IHs is not necessary.

In the present study, patients identified by ultrasonography screening had a 12.9% chance of having hypothyroidism. Diffuse IHH and large (maximum diameter of ≥5.0 cm) multifocal IHH appeared to be predictors of hypothyroidism. It was noted that

hypothyroidism developed not only in patients younger than 6 months of age but also in patients older than 6 months. It is also worth mentioning that the sizes of IHH in 2 patients who were older than 6 months were relatively large, and both of these patients had hypothyroidism at the time of detection. The growth of cutaneous IH is not linear. Cutaneous IH with a deep component can continue to grow until approximately 9 to 12 months of age.[16] Considering that IHH-related complications (e.g., hypothyroidism) and IHH growth may extend beyond 6 months of age, we recommend screening for patients with 5 cutaneous IHs up to 9 months of age. Nonetheless, we are not in a position to conclude that screening patients aged 0 to 9 months rather than 0 to 6 months leads to a significant improvement in the overall outcome of patients with IHH. Further studies are needed to establish if such a screening program using these criteria will ultimately have an impact on the outcome of patients with IHH.

Despite international recommendations, some patients with multiple cutaneous IHs do not undergo screening.[14] One major reason for the underuse of IHH screening may be that nonexpert primary physicians (eg, physicians with no specific IH expertise) fail to order screening for children with known multiple cutaneous IHs. Nonexpert primary physicians may lack knowledge about the benefits of screening.[14] In children with a positive screening result, further evaluation with MRI and other examinations (eg, thyroid function tests and echocardiography) may be required to identify potential complications. Referrals for high-risk IHH that are growing or potentially life threatening should be considered urgent.[6,17]

## CONCLUSIONS

Increased awareness of IHH screening will allow for earlier diagnosis and potential curative treatment. The results from this prospective, multicenter study propose a screening algorithm for children at high risk for developing IHH. Abdominal ultrasonography is recommended for children younger than 9 months of age who present with 5 or more cutaneous IHs.

### Conflicts of interest

None disclosed.

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