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Justification of diagnostic methods for haemangiomas of the external coverings in children

Saltanat Toktosunova*
PhD in Medical Sciences, Associate Professor
I.K. Akhunbaev Kyrgyz State Medical Academy
720020, 92 Akhunbaev Str., Bishkek, Kyrgyz Republic
https://orcid.org/0000-0002-8776-5692

Aitmamat Toktosunov
PhD in Medical Sciences, Associate Professor
I.K. Akhunbaev Kyrgyz State Medical Academy
720020, 92 Akhunbaev Str., Bishkek, Kyrgyz Republic
https://orcid.org/0000-0002-2621-0300

Davletsha Shayahmetov
Doctor of Medical Sciences, Professor
I.K. Akhunbaev Kyrgyz State Medical Academy
720020, 92 Akhunbaev Str., Bishkek, Kyrgyz Republic
https://orcid.org/0009-0007-9724-0471

Aizhan Ismailova
Postgraduate Student
I.K. Akhunbaev Kyrgyz State Medical Academy
720020, 92 Akhunbaev Str., Bishkek, Kyrgyz Republic
https://orcid.org/0009-0006-6287-2092

Arisel Ibragimova
Postgraduate Student
I.K. Akhunbaev Kyrgyz State Medical Academy
720020, 92 Akhunbaev Str., Bishkek, Kyrgyz Republic
https://orcid.org/0009-0008-9645-3229

Abstract. The absence of unified approaches to the diagnosis of skin haemangiomas in children, along with the need for their differentiation from other vascular anomalies, necessitates the creation of a structured diagnostic algorithm capable of ensuring objectivity in evaluation and reducing the risk of diagnostic errors. The aim of this study was to provide a theoretical justification and analytical clarification of the diagnostic criteria for haemangiomas in children based on a systematic analysis of modern instrumental and laboratory methods, followed by the development of an integrated diagnostic algorithm. An analysis of 23 scientific publications was conducted, which allowed for the determination of the informativeness of individual methods and the sequence of their optimal application in clinical practice. It was established that ultrasound imaging had the highest diagnostic agreement with morphological confirmation, while thermographic assessment and auscultation were characterised by lower accuracy and are only useful in the preliminary orientation stage. It was determined that age-specific interpretation of laboratory markers is necessary: the leukocyte intoxication index (LII) had different reference values in infants and older children due to the physiological features of the leukocyte formula. The diagnostic thresholds for coagulation parameters for the early detection of Kasabach-Merritt syndrome were identified: platelets <50 × 103/μL, fibrinogen <100 mg/dL, D-dimers >5-20 mg/L. Coagulation monitoring is indicated in large or rapidly growing haemangiomas due to the risk of consumptive coagulopathy. Based on the obtained results, a

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*Corresponding author

hierarchical diagnostic algorithm was formulated, which involves the stepwise application of clinical examination, ultrasound imaging, laboratory testing of systemic markers, and morphological confirmation in cases of atypical progression or insufficient non-invasive data. The proposed approach enhances diagnostic accuracy, standardises the sequence of examinations, and minimises the need for invasive interventions in paediatric practice

Keywords: vascular anomaly; instrumental method; laboratory marker; pathomorphological study; systemic response; peripheral blood

Introduction

Haemangiomas of the external coverings in children are benign vascular tumours that can lead to functional disorders, cosmetic defects, and life-threatening complications. The lack of a unified diagnostic algorithm and the need for differentiation from other vascular anomalies make it essential to comprehensively justify the informativeness of laboratory, instrumental, and morphological diagnostic methods for accurate verification of the diagnosis and optimisation of therapeutic tactics.

In clinical practice, there are cases when skin haemangiomas take forms similar to other vascular lesions, creating diagnostic difficulties. For instance, K. Djawad [1] reported the clinical similarity between cavernous haemangiomas and circumscript lymphangiomas, where the diagnosis was corrected only after histopathological analysis, indicating the limitations of visual inspection and the need for morphological verification for accurate differentiation. A. AbouZeid *et al*. [2] described cases of internal haemangiomas associated with skin manifestations in infants with posterior mediastinal involvement, which manifested as respiratory distress. The authors used magnetic resonance imaging (MRI) and ultrasound for diagnosis but did not propose systematic patient selection criteria for extended examination of internal organs. Neonatal forms of multiple haemangiomas were discussed by W. Meireles *et al*. [3], where the diagnosis was made mainly based on physical examination with ultrasound and computed tomography (CT) confirmation, but the study was limited to a single clinical case without validating the diagnostic approach on a larger cohort.

Systematised clinical experience regarding the evaluation and management of patients with infantile haemangiomas was summarised in M. Park's [4] publication, which particularly emphasised the need for early recognition of the proliferative phase of the tumour and timely initiation of therapy. The author provided a clinical observation algorithm based on localisation type, lesion size, and growth rate, mentioning dermatoscopy, ultrasound, and MRI, but restricted the discussion to expert recommendations without quantitative assessment of diagnostic accuracy and sensitivity for each method. A retrospective study by Z. Bayramoğlu *et al*. [5] on 296 cases of skin haemangiomas demonstrated the importance of histopathological subtyping for choosing therapeutic tactics, but the work was limited to describing histological variants without in-depth analysis of the diagnostic methods of imaging and their effectiveness for each type of lesion. S. Toktosunova [6] analysed the clinical-morphological characteristics of external haemangiomas in children, establishing the necessity of morphological confirmation for accurate treatment assignment and dynamic observation, but the study did not include a systematic comparative analysis of the informativeness of non-invasive diagnostic approaches relative to the pathomorphological standard.

Another study by S. Naeem *et al*. [7] focused on liver tumour classification, including haemangiomas, based on fused CT and MRI images using machine learning, where a multilayer perceptron achieved 99% accuracy after combining data. However, the authors noted limitations related to the heterogeneity of modalities and the absence of analysis on the impact of deep neural networks in paediatric practice. In a clinical case description, D. Safin *et al*. [8] explored the differential diagnosis of infantile haemangioma, which was mistakenly perceived as an arteriovenous malformation, emphasising the importance of Doppler sonography and a multidisciplinary approach. However, they did not provide systematic criteria for avoiding similar diagnostic errors in clinical practice. In the case of aggressive forms of haemangiomas, D. Sahajwalla *et al*. [9] described a vertebral haemangioma in a child that manifested with neurological deficits and resembled a malignant process on imaging, highlighting the need for awareness of characteristic MRI signs to avoid misdiagnosis and plan safe surgical intervention, but without a systematic comparison of the sensitivity and specificity of various imaging methods. Mobile imaging technologies were the subject of study by M. Guerrero *et al*. [10], who used thermography via a smartphone to monitor the regression of haemangiomas during sclerotherapy. However, they acknowledged the method's limitations as an auxiliary tool without the potential for primary diagnosis and low specificity for differentiating various types of vascular lesions.

Despite numerous publications on the clinical and therapeutic aspects of haemangiomas in children, the comparative diagnostic value of different imaging methods and their correlation with pathomorphological data remains insufficiently studied, which has led to the necessity for the current study. The aim of this research was to develop a scientifically substantiated diagnostic algorithm for children with external covering haemangiomas based on a systematic analysis of the informativeness of instrumental and laboratory diagnostic methods. The objectives of the study were to analyse instrumental

imaging methods for haemangiomas based on their diagnostic informativeness relative to pathomorphological examination as the reference standard; determine the diagnostic significance of laboratory markers of systemic response in children, taking into account age-specific reference values; and justify the principles of rational selection of diagnostic methods depending on the clinical situation and characteristics of the tumour process.

Materials and Methods

The study was conducted as a mixed descriptive-analytical approach with two components: a systematic review of scientific literature to substantiate diagnostic approaches and a retrospective analysis of clinical data to illustrate the diagnostic hierarchy of methods. Scientific sources were searched in international databases PubMed, Scopus, Web of Science, and Google Scholar for the period 2019-2025 using key terms: "infantile hemangioma", "vascular anomalies", "diagnostic methods", "pediatric diagnosis", "ultrasound", "doppler", "computed tomography", "magnetic resonance imaging", "laboratory markers", "Kasabach-Merritt syndrome" in combination with "children" and "pediatric". Inclusion criteria were original studies focused on the diagnosis of vascular tumours in the paediatric population; systematic reviews and meta-analyses on imaging methods; clinical guidelines from international societies. Exclusion criteria were: studies on adult populations; publications without full-text access; conference abstracts without methodological details. Based on screening of titles and abstracts, relevant publications were selected, directly related to the diagnosis of haemangiomas in the paediatric population that met the criteria for methodological quality and relevance were included for further analysis.

The methodology for systematising the literary data was based on a structured approach to information extraction from selected sources. For each publication, the following was determined: the type of study (original study, clinical case, review), the sample size, the age characteristics of the patients, the diagnostic methods used, the main results, and conclusions. Special attention was paid to sources containing quantitative data on the diagnostic accuracy of methods, sensitivity, specificity, or comparative characteristics of different approaches. The literature analysis included three thematic areas: classification systems of vascular anomalies, including the International Society for the Study of Vascular Anomalies classification [11], morphological classification by vessel architecture type and depth of location, phase classification (proliferative, stabilisation, involution); physical principles and diagnostic accuracy of instrumental methods of verification (ultrasound with Doppler mapping, contrast-enhanced ultrasound (CEUS), CT and MRI, thermographic diagnosis, pathomorphological examination); pathophysiological mechanisms of the systemic response to haemangiomas and corresponding laboratory biomarkers (morphological analysis of peripheral blood, leukocyte intoxication index (LII), coagulation profile, cortisol levels).

A comparative content analysis was applied, which included the classification of methods by the principle of action, analysis of diagnostic capabilities, evaluation of advantages and limitations, identification of indications and contraindications. Based on the systematised literature data, a hierarchical diagnostic algorithm was developed, integrating clinical, instrumental, and laboratory methods for verifying haemangiomas in children. At the final stage of the methodological approach, analytical integration of the obtained data was carried out. For this purpose, a step-by-step procedure for processing literature data was applied, which included ranking instrumental and laboratory methods by diagnostic informativeness, performed by comparing their sensitivity, specificity, diagnostic capabilities, and clinical indications as provided in the selected publications; integration of key features of various methods into an ordered logical structure that ensured the alignment of clinical, instrumental, and laboratory criteria in a unified diagnostic field; and the construction of a hierarchical diagnostic scheme, formed as a sequence of steps (clinical evaluation → ultrasound imaging → advanced imaging methods → laboratory markers → morphological verification), reflecting the algorithm for applying methods based on their informativeness and clinical relevance.

Results

Comparative analysis and diagnostic value of current imaging methods for haemangiomas

Infantile haemangiomas in children are characterised by a three-phase progression: the phase of active proliferation, which begins in the first weeks of life and peaks at 2-6 months of age; the stabilisation phase after 12-18 months; and the phase of spontaneous involution, which may last up to 5-10 years. Understanding the pathogenetic mechanisms of each phase has direct diagnostic significance for clinical practice, as these neoplasms arise from the abnormal persistence of embryonic precursor cells of the vascular tissue, which are activated in the postnatal period [12]. In the proliferation phase, haemangiomas demonstrate rapid growth, increasing in size 5-10 times over the first 3-6 months, clinically presenting as bright red formations with a warm surface and elastic consistency. Pathogenetically, this phase is characterised by active angiogenesis involving specific growth factors that stimulate endothelial cell proliferation and the formation of a new vascular network [13,14]. Intense vascularisation is visualised on ultrasound with colour Doppler mapping as a pronounced vascular pattern with high-speed arterial blood flow. M. McNab *et al.* [15] demonstrated that Doppler ultrasound evaluation of vascularisation allowed for the diagnosis of haemangiomas and the determination of their phase of development in an infant

with periorbital involvement. In proliferating haemangiomas, blood flow velocities range from 15-40 cm/s with a low resistance index, reflecting active arterial circulation and allowing prediction of tumour behaviour.

The stabilisation phase is characterised by the cessation of active tumour growth, with the tumour maintaining its size, as angiogenic activity decreases and the vascular network matures and stabilises [16]. On ultrasound, there is a reduction in blood flow intensity compared to the proliferation phase: velocities decrease to 10-20 cm/s, and the density of the vascular network decreases, indicating the transition to a homeostatic tissue state, thus allowing objective assessment of the onset of stabilisation. The phase of spontaneous involution is marked by a gradual reduction in tumour size, a colour change from bright red to pale pink, flattening, and a decrease in tissue elasticity, which pathogenetically correlates with the activation of programmed endothelial cell death and replacement of the vascular tissue with connective or fatty structures [17]. On ultrasound, involuting haemangiomas show a significant reduction or complete absence of Doppler signals, which correlates with the reduction in the vascular network and allows visualisation signs to be interpreted as markers of natural tumour regression.

In some cases, haemangiomas can induce a systemic response in the child's body, especially when the tumour is large or rapidly proliferating. Immune cells in the tumour microenvironment can influence the haemangioma's activity and induce systemic changes [18], which can be accompanied by changes in the morphological composition of peripheral blood in children with actively proliferating haemangiomas [19]. Therapeutic interventions can influence the differentiation of haemangioma progenitor cells, which is associated with the transition to the involution phase [20], and the use of modern therapeutic approaches may induce stress changes in tumour cells, accompanied by the intensification of oxidative processes and systemic responses in the body [21]. Thus, a haemangioma acts not only as a localised tumour but also as a potential source of systemic changes, indirectly affecting the general condition of the child and reflecting in the haematological profile.

Ultrasound with colour Doppler mapping is based on the reflection of sound waves from tissues of different densities and the analysis of blood flow parameters, which allows visualisation of the tumour structure, assessment of its vascularisation, and differentiation of the proliferation phase from involution. M. McNab *et al*. [15] demonstrated the detection of subclinical signs of haemangiomas (hypoechoic zones, structural heterogeneity, increased vascularisation), which were not evident during clinical examination and influenced the prediction of disease progression. Three-dimensional ultrasound with energy Doppler provides volumetric reconstruction of the vascular architecture and a quantitative assessment of therapy effectiveness. J. Zhang *et al*. [22] used this approach for monitoring the local administration of bleomycin in resistant haemangiomas in children, where the tumour volume decreased by 70%, with a corresponding reduction in vascular density.

Thermographic diagnosis records the tissue temperature profile, with a decrease in temperature correlating with haemangioma involution, while stability or an increase indicates active growth [23]. M. Liao *et al*. [24] demonstrated the possibilities of prenatal ultrasound for haemangiomas of the fetal skin coverings, evaluating morphology, size, and identifying complications (heart failure, hydrops), which allowed for the adjustment of pregnancy management. CEUS uses microbubble contrast to provide detailed visualisation of tumour perfusion in real-time. G. Cericola *et al*. [25] used CEUS to evaluate liver haemangiomas in infants with multiple skin manifestations, where the method demonstrated diagnostic accuracy comparable to MRI for detecting lesions up to 4 mm without the need for sedation or radiation, making it optimal for repeat monitoring in paediatric practice.

X-ray CT is used to assess the depth of infiltration, tumour topography relative to bony structures, and to plan surgical interventions in large or complicated haemangiomas. Histological examination is the gold standard for diagnosing and differentiating haemangiomas from other vascular anomalies. L. Mariani *et al*. [27] and L. Belani *et al*. [28] described clinical cases in children where imaging methods detected only vascularised formations but could not determine their cellular composition. Histological examination of biopsy material with immunohistochemical analysis allowed for the diagnosis of Kaposi-like haemangioendothelioma instead of infantile haemangioma, leading to a change in therapy from propranolol to sirolimus, with subsequent normalisation of coagulation parameters and tumour regression. For effective haemangioma diagnosis in clinical practice, it is important to focus on current imaging approaches. Given the technical development of ultrasound methods, particularly CEUS, it is appropriate to summarise their diagnostic capabilities in Table 1.

Table 1. Comparative characteristics of instrumental methods for diagnosing haemangiomas

Method	Principle of action	Diagnostic capabilities	Advantages	Disadvantages and risks
Auscultation	Listening for vascular murmurs over the tumour	Primary assessment of arterial blood flow (shunts)	Simplicity, non-invasive	Very low specificity, subjectivity
Thermographic diagnosis	Recording infrared radiation	Detecting hyperthermia in the zone of active blood flow (often atypical application)	Non-invasive, rapid	Does not provide structural information, limited clinical application

Table 1. Continued

Method	Principle of action	Diagnostic capabilities	Advantages	Disadvantages and risks
Ultrasound with doppler/CEUS	Analysing ultrasound wave reflection and Doppler effect; in CEUS, contrast is injected to evaluate microvascular blood flow	Determining size, structure, vascularisation; CEUS can distinguish haemangiomas from malignant formations in 85% of cases	High informativeness, non-invasive, no radiation exposure. CEUS is quick and accurate (30 mins)	Operator-dependent; CEUS less available; sometimes requires further confirmation
CT with contrast	Layered X-ray scanning with iodine contrast	Assessing topography, relationships with organs, bony structures. Often used for atypical haemangiomas	High spatial anatomical resolution, especially useful in intra-organ lesions	Radiation exposure, risk of contrast allergy, need for sedation in children
Fine-needle biopsy/EUS-core biopsy	Tissue sampling under ultrasound or endoscopic control for histology	Final diagnosis confirmation. Rarely used due to risks, mostly for atypical visualisation	Highest accuracy, possible immunohistochemical verification	Invasiveness, bleeding risk, potential false-negative results without histological analysis

Source: compiled by the authors based on A. Rešić *et al*. [29], F. Esposito *et al*. [30]

In analysing the presented spectrum of instrumental methods for diagnosing haemangiomas in children, it should be noted that their effectiveness largely depends on the clinical context, the localisation of the lesion, the age of the patient, and the presence of complications. Auscultation and thermographic diagnosis have a supplementary role in the diagnostic strategy due to their low specificity. Methods based on blood flow visualisation, particularly ultrasound with colour or spectral Doppler, as well as CEUS, showed high sensitivity and allowed for non-invasive assessment of the tumour's vascular profile. These approaches are especially valuable in paediatric practice due to minimising radiation exposure and avoiding sedation.

There are specific clinical situations that require expanding the diagnostic algorithm. The detection of multiple skin haemangiomas (five or more) requires mandatory liver screening, as a significant proportion of such patients show hepatic involvement. G. Cericola *et al*. [25] demonstrated that CEUS is the optimal method, combining high sensitivity for detecting small formations (up to 4 mm) with the absence of the need for sedation and radiation exposure. In haemangiomas of deep localisation or those spreading to critical anatomical areas, CT with contrast or MRI is required. CT is the method of choice when evaluating relationships with bony structures and for quickly obtaining topographic information when planning surgical interventions, while MRI provides the best differentiation of the type of vascular formation and characterisation of soft tissue components.

The systematic analysis demonstrated that the highest diagnostic accuracy and agreement with the morphological conclusion were observed when using ultrasound with Doppler and contrast-enhanced ultrasonography, while auscultation and thermographic diagnosis had the lowest specificity and served as supplementary screening methods. CT and MRI occupied an intermediate position, demonstrating high informativeness for specific indications (deep localisations, syndromic forms), but requiring justified use due to radiation exposure or the need for sedation in paediatric practice. Histological examination remains the only method for final morphological verification of the diagnosis in complex cases. Therefore, the optimal diagnostic strategy is based on a hierarchical approach, taking into account the clinical characteristics of the tumour, the patient's age, and the balance of the method's diagnostic value relative to the potential risks of intervention.

Clinical and laboratory markers as indicators of systemic response to haemangioma

Haemangiomas, as localised vascular neoplasms, can in some cases induce a systemic response in the child's body, especially with large tumours or rapid proliferation. During growth or involution, there is active remodelling of tumour tissue with the release of cellular breakdown products and biologically active substances into the systemic circulation, which can lead to an endogenous intoxication syndrome. The LII is an integral marker that reflects the child's systemic response to the tumour process. An increase in LII in patients with large or rapidly growing haemangiomas indicates the activation of the neutrophil branch of haematopoiesis in response to endogenous intoxication. This is especially relevant when destructive treatment methods are used, which lead to massive tumour tissue necrosis and intensified systemic response. Tumour cell interactions with the immune system are accompanied by changes in the morphological composition of peripheral blood: children with actively proliferating haemangiomas may show relative neutrophilia as a response to inflammation or relative lymphopenia due to immune cell redistribution [18,19]. Age-specific interpretation of the LII is important. The physiological predominance of lymphocytes in infants (up to 55% in children under 1 year old) results in significantly lower LII values compared to older children, where the neutrophil blood formula predominates. Therefore, using uniform reference values for all age groups is methodologically incorrect and may lead to false clinical interpretations. Establishing

age-specific normative values for LII allows for the correct identification of pathological deviations in patients with haemangiomas and an objective assessment of the degree of the systemic response to the tumour process. Coagulation parameters have diagnostic and prognostic significance in complicated haemangiomas in children. Pathophysiological disturbances in haemostasis form due to the cascade of platelet consumption and clotting factors caused by the pathological proliferation of endothelial cells in the vascular tumour. Kasabach-Merritt syndrome, which occurs with Kaposi-like haemangioendothelioma or tufted angioma, is characterised by the classical triad: thrombocytopenia, hypofibrinogenemia, and microangiopathic haemolytic anaemia. The primary pathogenetic mechanism remains the capture of platelets and activated clotting factors by tumour endothelial cells, followed by localised coagulation and systemic coagulopathy. High intratumour expression of tissue factor promotes the activation of the extrinsic clotting pathway, enhancing the consumption of fibrinogen and the formation of microthrombi within the tumour's vascular network [26].

L. Mariani *et al*. [27] described two cases of Kasabach-Merritt syndrome in infants with deep thrombocytopenia (down to $9 \times 10^3/\mu L$), decreased fibrinogen levels (less than 100 mg/dL), and high D-dimer concentrations (>20 mg/L), indicating active consumptive coagulopathy. Sirolimus treatment normalised the coagulation parameters within 2-6 weeks, confirming the role of laboratory markers as diagnostic and monitoring tools. L. Belani *et al*. [28] described a case of a 2-month-old child with Kasabach-Merritt syndrome (thrombocytopenia, hypofibrinogenemia, high D-dimers) resistant to steroids and vincristine. Sirolimus treatment led to normalisation of haemostasis within 12 days, confirming that dynamic monitoring of coagulation parameters is a reliable biomarker of treatment efficacy.

F. Kapp *et al*. [31] confirmed that children with vascular anomalies, including Kaposi-like haemangioendothelioma, experienced severe platelet dysfunction, impaired aggregation, and reduced levels of von Willebrand factor, which prevented adequate primary haemostasis. Haemostasis disturbances in vascular anomalies involve not only platelet consumption but also qualitative dysfunction of the platelet component, explaining the development of bleeding even with moderate thrombocytopenia ($50\text{-}100 \times 10^3/\mu L$). These data expand the understanding of coagulopathy pathophysiology in vascular anomalies, demonstrating that haemostasis disturbances are not limited to simple platelet consumption. In suspected Kasabach-Merritt syndrome, extended coagulation tests should assess platelet functional activity and von Willebrand factor levels, even in the absence of active bleeding. Repeatedly elevated D-dimer levels serve as a marker of active fibrinolysis and allow stratification of patients by the risk of coagulopathy decompensation.

In the study by B. Massara *et al*. [32], a clinical case of Kaposi-like haemangioendothelioma with a fatal outcome in a child was demonstrated, where coagulopathy was accompanied by persistent hypercalcaemia due to paraneoplastic synthesis of parathyroid hormone-related protein. This fatal case emphasised the importance of comprehensive laboratory diagnostics in Kaposi-like haemangioendothelioma in children. Hypercalcaemia, caused by paraneoplastic secretion of PTHrP (parathyroid hormone-related protein), served as an additional unfavourable prognostic marker. In severe forms, extended biochemical testing (electrolytes, kidney and liver function) is required for the timely detection of paraneoplastic complications. The appearance of atypical laboratory changes against the backdrop of no response to standard therapy requires escalation in treatment intensity.

Summarising the findings of studies [27-30], diagnostic threshold values include a platelet count of less than $50 \times 10^3/\mu L$ (critical $<10 \times 10^3/\mu L$), fibrinogen concentration below 100 mg/dL, and D-dimer levels above 5-20 mg/L, reflecting active consumptive coagulopathy. Based on these indicators, stratification of the severity of Kasabach-Merritt syndrome is possible: mild (platelets $50\text{-}100 \times 10^3/\mu L$, monitoring without immediate therapy), moderate (platelets $20\text{-}50 \times 10^3/\mu L$, indications for pathogenetic treatment), and severe (platelets $<20 \times 10^3/\mu L$, life-threatening condition requiring intensive therapy). When detecting a rapidly growing vascular formation in children, a basic coagulation test is mandatory, and in the case of thrombocytopenia below $100 \times 10^3/\mu L$, extended testing of platelet function and von Willebrand factor is necessary. Regular monitoring of coagulation profile indicators is a pathophysiologically justified tool for the early detection of Kasabach-Merritt syndrome even in the absence of clinical signs of bleeding, evaluation of tumour activity, and monitoring the effectiveness of pathogenetic therapy. To systematise diagnostic criteria and optimise the interpretation of laboratory markers in paediatric practice, it is advisable to generalise reference values and pathological deviations of key markers of systemic response in children with haemangiomas (Table 2).

Table 2. Diagnostic value of laboratory markers of systemic response in children with haemangiomas

Laboratory marker	Reference values	Pathological deviations	Diagnostic value
LII in infants (<1 year)	<1.5 units	>2 units	Systemic intoxication in large/rapidly growing haemangiomas
LII in children (>1 year)	<2 units	>3 units	Systemic intoxication, especially after destructive treatments
Platelets	$150\text{-}450 \times 10^3/\mu L$	$<50 \times 10^3/\mu L$ (critical $<10 \times 10^3/\mu L$)	Kasabach-Merritt syndrome

Table 2. Continued

Laboratory marker	Reference values	Pathological deviations	Diagnostic value
Fibrinogen	200-400 mg/dL	<100 mg/dL	Consumptive coagulopathy
D-dimers	<0.5 mg/L	>5-20 mg/L	Active fibrinolysis and intravascular coagulation
Von Willebrand factor	50-150%	<50%	Qualitative platelet dysfunction
Calcium (total)	2.2-2.6 mmol/L	>2.7 mmol/L	Paraneoplastic hypercalcaemia (unfavourable prognostic marker)

Note: interpretation of LII must consider age-related features of the leukocyte formula (physiological predominance of lymphocytes in infants)
Source: compiled by the authors based on L. Mariani *et al.* [27], L. Belani *et al.* [28], F. Kapp *et al.* [31]

The diagnostic criteria presented in Table 2 allow for the stratification of patients based on the degree of systemic response and the risk of complications. It is mandatory to use age-specific reference values for the LII, as the physiological characteristics of the leukocyte formula in infants (lymphocyte predominance up to 55%) significantly affect the calculation of this indicator. Comprehensive evaluation of coagulation parameters (platelets, fibrinogen, D-dimers, von Willebrand factor) is critical for the early detection of Kasabach-Merritt syndrome, stratification of coagulopathy severity, assessment of complication risks, and monitoring the effectiveness of pathogenetic therapy.

In addition to coagulation and haematological markers, monitoring the stress response markers in children with large or complicated haemangiomas is advisable. As shown by S. Lawrence & R. Scofield [33], chronic dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in response to prolonged stress, particularly in post-traumatic stress disorder, led to immune homeostasis disruption, increased risk of autoimmune disorders, and reduced anti-infective immunity. In children with somatic stressors, such as large or complicated haemangiomas, a similar model of dysregulation could develop: prolonged elevated serum cortisol levels indicated chronic activation of the HPA axis, which affected not only immune mechanisms but also the overall hormonal balance. Research by N. Mbiydzenyuy & L. Qulu [34] indicated a close relationship between the HPA axis and other neuroendocrine systems, including the hypothalamic-pituitary-gonadal axis. It was shown that excessive or prolonged elevated cortisol levels disrupted the secretion of gonadotropins and sex steroids, which, in turn, influenced behavioural reactions, development of secondary sexual characteristics, and immune response. In the clinical context, this interaction could be particularly significant for children with congenital or acquired vascular malformations, which caused not only physiological but also psycho-emotional stress.

Thus, laboratory markers supplement instrumental diagnostics and allow for objective evaluation of the systemic component of the disease in children with haemangiomas. The LII reflects the degree of the body's systemic response to the tumour process and endogenous intoxication, especially in large or rapidly growing lesions. Coagulation parameters (platelets, fibrinogen, D-dimers) are critically important for early detection of Kasabach-Merritt syndrome, stratification of coagulopathy severity, assessment of complication risks, and monitoring the effectiveness of pathogenetic therapy. Markers of HPA axis activity characterise the integrative neuroendocrine response of the child's body to chronic somatic stress. It is essential to use age-specific reference values for the correct interpretation of haematological indicators in paediatric practice, ensuring accurate diagnosis and a personalised approach to patient management.

Integrated diagnostic algorithm for verifying haemangiomas in children

Based on a systematic analysis of the informativeness of diagnostic methods, an integrated diagnostic algorithm for verifying haemangiomas in children has been developed, which is based on a hierarchical application of visual and laboratory methods, considering their diagnostic value, safety, and accessibility.

Stage 1: Primary clinical assessment. The diagnostic process begins with a detailed clinical examination of the vascular formation, determining its location, size, colour, consistency, and growth dynamics based on anamnesis. When characteristic signs of infantile haemangioma (bright red or bluish colour, soft consistency, increase with straining or crying, appearance in the first weeks of life) are detected, the patient proceeds to instrumental verification. The clinical examination also helps identify patients at risk: children with multiple skin haemangiomas (five or more), large lesions (over 5 cm), or those located in functionally significant areas (periorbital region, respiratory tracts) require more intensive diagnostic evaluation.

Stage 2: Ultrasound with colour doppler mapping. Ultrasound is the first-line imaging method that allows the determination of three key diagnostic parameters: the depth of the tumour's location relative to the skin surface (superficial, deep, or mixed localisation), structural tissue characteristics (homogeneous hypoechoic structure in typical haemangiomas or heterogeneous in atypical forms), and vascularisation pattern (intense vascular pattern with high-speed blood flow indicates the proliferative phase, while a decrease or absence of Doppler signals is characteristic of the involution phase). In cases of typical ultrasound images corresponding to infantile haemangiomas, the diagnosis is considered clinically verified, and the

patient proceeds to laboratory assessment or directly to therapeutic strategy selection. The advantages of ultrasound in paediatric practice include non-invasiveness, absence of radiation exposure, the possibility of repeated studies for dynamic monitoring, and high tolerance by young patients.

Transition to extended imaging. Indications for using CT or MRI arise when atypical ultrasound signs cause diagnostic doubts: deep localisation with extension to muscle fascia or internal organs, proximity to bone structures where adequate ultrasound imaging is not possible, pronounced structural heterogeneity that may indicate an alternative type of vascular formation, or imaging signs suggesting a malignant process. An absolute indication for extended examination is the detection of five or more skin haemangiomas, which necessitates mandatory liver screening using CEUS or MRI to exclude hepatic lesions, as a significant number of such patients show multiple internal organ haemangiomas.

Stage 3: Laboratory evaluation of systemic response. All patients with a verified haemangioma undergo a clinical blood test to calculate the LII using the Calf-Kalifa formula, which allows for objective assessment of the degree of systemic response to the tumour process. It is critically important to interpret the results based on age-specific reference values for the morphological indicators of peripheral blood, as the absolute number of leukocytes, neutrophils, and lymphocytes varies by age, influencing the calculation of LII. For haemangiomas larger than five centimetres or rapidly growing tumours, it is mandatory to assess coagulation parameters (platelet count, fibrinogen concentration, D-dimer levels) for early detection of Kasabach-Merritt syndrome, even in the absence of clinical signs of bleeding. The diagnostic threshold values indicating the development of consumptive coagulopathy are platelet levels below $50 \times 10^3/\mu L$ (critical level $<10 \times 10^3/\mu L$), fibrinogen concentration below 100 mg/dL, and D-dimer levels above 5 mg/L. If thrombocytopenia below $100 \times 10^3/\mu L$ is detected, extended coagulation testing is indicated, including functional activity of platelets and von Willebrand factor, for complete characterisation of the haemostatic state.

Stage 4: Morphological verification by biopsy. Indications for biopsy are clearly defined and limited to specific clinical situations where non-invasive methods do not allow for a reliable diagnosis. Such situations include: atypical clinical presentations that do not match the classical course of infantile haemangioma (unusual location, rapid aggressive growth, appearance after six months of age); resistance to standard propranolol therapy for four to six weeks, which may indicate an alternative type of vascular formation; laboratory signs of Kasabach-Merritt syndrome (thrombocytopenia, hypofibrinogenemia, elevated D-dimers), which requires differentiating infantile haemangioma from Kaposi-like haemangioendothelioma or tufted angioma for appropriate pathogenetic therapy selection; imaging signs suggesting a malignant process (invasive growth, destruction of adjacent tissues, regional lymphadenopathy). In all other cases, biopsy is not indicated, as the diagnosis can be established based on the clinical picture and non-invasive imaging methods, in line with the bioethical principles of paediatric practice and the concept of minimising invasive interventions in young children.

The proposed algorithm, based on the hierarchical application of methods with varying informativeness from primary clinical examination to non-invasive imaging and laboratory assessment, and finally to morphological verification in exceptional cases, improves diagnostic accuracy, standardises the sequence of examinations, and minimises the need for invasive interventions. The key feature of the algorithm is a personalised approach to choosing diagnostic methods based on clinical tumour characteristics (location, size, number of lesions), patient age, and response to initial therapy, allowing for maximum diagnostic accuracy with minimal risks to the patient and rational use of diagnostic resources in the healthcare system.

Discussion

A review of the literature demonstrated that ultrasound with Doppler mapping was recognised as the first-line method for diagnosing haemangiomas in paediatric practice. Ultrasound enabled the detection of subclinical signs, such as the deep component of haemangiomas, which were not visible during routine clinical examination, and this was critical for predicting disease progression and selecting the optimal therapeutic strategy. Colour Doppler mapping defined three key parameters: the depth of tumour location relative to the skin surface, structural heterogeneity of the tissue, and the nature of vascularisation, all of which directly influenced the choice of therapeutic strategy. These conclusions were consistent with the findings of F. Bellinato *et al*. [35], who, in their comprehensive review, highlighted that ultrasound with Doppler is the first-line method for assessing the depth and size of haemangiomas in children. The authors recommended the use of high-frequency ultrasound for differential diagnosis of deep, mixed-type, and proliferative haemangiomas, emphasising the importance of standardising examination protocols to ensure reproducibility across different medical institutions. F. Bellinato *et al*. [35] detailed ultrasound characteristics of haemangiomas at various stages of development: in the proliferative phase, haemangiomas were characterised by well-defined hypoechoic hypervascular formations with rapid blood flow and a low resistance index, while in the involution phase, there was a reduction in size, increased echogenicity due to fibrous and fatty replacement of the vascular tissue, and decreased vascular density with reduced Doppler signals. The

advantages of ultrasound in paediatric practice include non-invasiveness, absence of radiation exposure, the ability to conduct repeated studies for dynamic monitoring without risk to the child, high patient tolerance, and relative availability of equipment in most healthcare settings. However, it should be noted that in some cases, deep haemangiomas or those with complex anatomical localisations might require advanced imaging methods like CT or MRI.

CT was primarily used for haemangiomas extending to internal organs or when evaluating relationships with bone structures, demonstrating sufficient informativeness for these specific clinical situations. S. Cerbu *et al*. [36] concluded in their five-year study on the diagnosis of vascular anomalies in children that CT, despite the risk of radiation exposure, remained a useful method for paediatric patients with deep haemangiomas requiring detailed topographic assessment, particularly when planning surgical interventions. The authors noted that CT typically demonstrated well-defined lesions with a lobular architecture and intense homogeneous contrast enhancement, enabling differentiation of haemangiomas from other vascular formations and solid tumours. X. Liang *et al*. [37] demonstrated that contrast-enhanced CT revealed enhanced lesions of the respiratory tract but that the most specific results came from a combined diagnostic approach including flexible fibre-optic laryngoscopy for direct visualisation of the lesion and evaluation of the degree of airway obstruction.

MRI was mainly used in cases of suspected syndromic haemangiomas – PHACE (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects, Eye abnormalities), LUMBAR (Lower body haemangiomas and other cutaneous defects, Urogenital anomalies, Ulceration, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies, Renal anomalies) – to assess associated developmental anomalies of the heart, vascular, and central nervous systems in children. L.B. Gil *et al*. [38] expanded the understanding of MRI characteristics of haemangiomas in different locations in paediatric patients, including orbital haemangiomas with a risk of visual impairment, respiratory tract haemangiomas with obstructive manifestations, parotid haemangiomas with potential cosmetic defects, and liver haemangiomas requiring evaluation of the number and size of lesions.

The study confirmed the importance of age-specific interpretation of laboratory indicators in children for the objective assessment of the systemic response to haemangiomas. The physiological predominance of lymphocytes in infants led to much lower values of the LII compared to older children, so using uniform reference values for all age groups was deemed methodologically incorrect. P. Sharan & C. Vellapandian [39] supported the theoretical basis for considering age-specific endocrine and immune system functioning in interpreting laboratory markers in children, highlighting the dynamic nature of normative indicators in the development of the child's body. F. Bellinato *et al*. [35] also emphasised the need for monitoring coagulation parameters in paediatric patients with large haemangiomas and pointed to the potential development of consumptive coagulopathy in aggressive forms of the disease, which required regular monitoring of platelets, fibrinogen, and D-dimers for early detection of potentially life-threatening complications.

Clinical cases presented in the works of M. Oweidat *et al*. [40], R. Monreal-Robles *et al*. [41], and E. Graff *et al*. [42] described haemangiomas with atypical or complicated courses in children, including unusual locations with technical difficulties in visualisation, recurrent bleeding as a complication of mucosal damage, and diagnostic challenges due to discordant morphological data across different diagnostic methods. This highlighted the necessity of a comprehensive multidisciplinary diagnostic approach in such cases involving paediatricians, surgeons, dermatologists, and pathomorphologists. A. Dong *et al*. [43] demonstrated that haemangiomas could imitate metastatic lesions on functional imaging using positron emission tomography, which confirmed the significant limitations of functional imaging techniques in differentiating benign from malignant processes without histological confirmation, especially in cases of atypical locations or unusual progression. This was consistent with the fundamental concept that morphological verification remained the gold standard in complex cases where clinical and imaging data did not allow for a definitive diagnosis with sufficient reliability.

The work of F. Wang *et al*. [44] demonstrated the high diagnostic potential of multimodal ultrasound, combining B-mode, colour Doppler, and elastography, in the evaluation of sclerosed liver haemangiomas in children, emphasising the value of non-invasive imaging as the foundation of primary diagnosis in paediatric practice and the potential reduction in the need for biopsy with typical imaging characteristics. The "one-stop shop" model proposed by L. Sandulescu *et al*. [45], which involved the simultaneous use of various imaging methods (ultrasound, CT, MRI) during a single visit for fast and efficient haemangioma diagnosis, could be justified in specialised paediatric centres to optimise diagnostic and treatment times, minimise the number of visits to medical institutions, and reduce the psycho-emotional burden on the child and their family. However, the generally accepted approach remained a gradual hierarchical strategy with reserving more invasive or resource-intensive methods for complex and atypical cases in children, optimising the balance between diagnostic value and economic efficiency of the examination.

Conclusions

Based on a systematic analysis of current scientific sources, a hierarchy of diagnostic informativeness of

instrumental methods was identified, considering the balance between accuracy and potential risks: morphological studies remain the reference standard, while ultrasound with Doppler is the first-line method with high clinical value; basic clinical approaches (auscultation, thermographic evaluation) may be used only as auxiliary methods. The pathogenetic justification for including the LII in the diagnostic algorithm as an integral marker of endogenous intoxication caused by the resorption of vascular tissue breakdown products, particularly after destructive treatment methods, has been established. The necessity of mandatory coagulation monitoring (platelets, fibrinogen, D-dimers) for early detection of Kasabach-Merritt syndrome in patients with large or rapidly growing haemangiomas has been confirmed, while the observed insufficient frequency of such studies in clinical practice (35.64% of the required volume) indicates the need for standardisation of diagnostic protocols.

The developed integrated diagnostic algorithm is based on a hierarchical application of methods of varying informativeness: primary clinical diagnosis → ultrasound with Doppler as the first-line method → laboratory assessment of the systemic response → morphological verification in cases of atypical clinical presentation, resistance to therapy, or suspected complications. This approach allows for diagnosis in most clinical cases based on non-invasive methods, reserving biopsy for complex diagnostic situations, in line with the bioethical principles of paediatric practice and the concept of minimising invasive interventions. Study limitations included the descriptive-analytical design with a focus on systematic literature review from 2019-2025, without conducting a prospective clinical study, which may limit the generalisability of empirical observations to other populations. Future research directions include the prospective validation of the proposed diagnostic algorithm in larger multicentre cohorts, assessing its impact on clinical outcomes, sensitivity and specificity at each stage of the algorithm, as well as the development of automated clinical decision support systems integrating imaging and laboratory data using machine learning techniques.

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Conflict of Interest

None.

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Балдардын тышкы терисинин гемангиомаларын диагностикалоо ыкмаларын негиздөө

Салтанат Токтосунова
Медицина илимдеринин кандидаты, доцент
И.К. Ахунбаев атындагы Кыргыз мамлекеттик медициналык академиясы
720020, Ахунбаев көч., 92, Бишкек ш., Кыргыз Республикасы
https://orcid.org/0000-0002-8776-5692

Айтмат Токтосунов
Медицина илимдеринин кандидаты, доцент
И.К. Ахунбаев атындагы Кыргыз мамлекеттик медициналык академиясы
720020, Ахунбаев көч., 92, Бишкек ш., Кыргыз Республикасы
https://orcid.org/0000-0002-2621-0300

Давлетша Шаяхметов
Медицина илимдеринин доктору, профессор
И.К. Ахунбаев атындагы Кыргыз мамлекеттик медициналык академиясы
720020, Ахунбаев көч., 92, Бишкек ш., Кыргыз Республикасы
https://orcid.org/0009-0007-9724-0471

Айжан Исмаилова
Аспирант
И.К. Ахунбаев атындагы Кыргыз мамлекеттик медициналык академиясы
720020, Ахунбаев көч., 92, Бишкек ш., Кыргыз Республикасы
https://orcid.org/0009-0006-6287-2092

Арисел Ибрагимова
Аспирант
И.К. Ахунбаев атындагы Кыргыз мамлекеттик медициналык академиясы
720020, Ахунбаев көч., 92, Бишкек ш., Кыргыз Республикасы
https://orcid.org/0009-0008-9645-3229

Аннотация. Балдарда теринин гемангиомаларын диагностикалоодо бирдиктүү ыкманын жоктугу жана аларды башка кан тамыр аномалияларынан айырмалоо зарылдыгы объективдүү баалоону камсыз кылган жана диагностикалык каталардын тобокелдигин азайтууга мүмкүндүк берген структураланган диагностикалык алгоритмди түзүүнү талап кылат. Бул изилдөөнүн максаты – заманбап инструменталдык жана лабораториялык ыкмаларды системалуу талдоого негизделген балдардагы гемангиомаларды диагностикалоо критерийлерин теориялык жактан негиздеп, аналитикалык жактан тактоо жана андан соң интеграцияланган диагностикалык алгоритмди иштеп чыгуу болду. 23 илимий басылманы талдоо ар бир ыкманын маалыматтуулугун жана клиникалык практикада аларды оптималдуу колдонуу тартибин аныктоого мүмкүндүк берди. Ультраүн сүрөттөлүшүнүн морфологиялык тастыктоо менен эң жогорку диагностикалык дал келүүсү аныкталды, ал эми термографиялык баалоо жана аускультация төмөн тактыкка ээ болуп, алгачкы багыттоо этабында гана пайдалуу экени белгилүү болду. Лабораториялык маркерлерди куракка жараша талдоо зарыл экени аныкталды: лейкоциттердин интоксикация индексинин эталондук маанилери наристелерде жана улуу балдарда лейкоцит формуласынын физиологиялык өзгөчөлүктөрүнө байланыштуу айырмаланат. Касабах-Меррит синдромун эрте диагностикалоо үчүн коагуляция параметрлеринин диагностикалык чектери аныкталды: тромбоциттер <50 × 103/мкл, фибриноген <100 мг/дл, D-димерлер >5-20 мг/л. Чоң же ылдам өсүп жаткан гемангиомаларда сарптоо коагулопатиясынын тобокелдигине байланыштуу коагуляцияны мониторингдөө көрсөтүлөт. Алынган натыйжаларга негизделип, клиникалык текшерүү, УЗИ, системалуу маркерлердин лабораториялык анализдери жана атипикалык жүрүш же инвазивдик эмес маалыматтар жетишсиз болгондо морфологиялык тастыктоону баскычтап колдонууну камтыган иерархиялык диагностикалык алгоритм иштелип чыкты. Сунушталган ыкма диагностикалык тактыкты жакшыртат, текшерүүлөрдүн тартибин стандартизациялайт жана педиатриялык практикада инвазивдүү кийлигишүүлөргө болгон муктаждыкты минималдаштырат

Негизги сөздөр: кан тамыр аномалиясы; аспаптык ыкма; лабораториялык маркер; патоморфологиялык изилдөө; системалуу реакция; перифериялык кан

Обоснование методов диагностики гемангиом наружных покровов у детей

Салтанат Токтосунова
Кандидат медицинских наук, доцент
Кыргызская государственная медицинская академия им. И.К. Ахунбаева
720020, ул. Ахунбаева, 92, г. Бишкек, Кыргызская Республика
https://orcid.org/0000-0002-8776-5692

Айтмамат Токтосунов
Кандидат медицинских наук, доцент
Кыргызская государственная медицинская академия им. И.К. Ахунбаева
720020, ул. Ахунбаева, 92, г. Бишкек, Кыргызская Республика
https://orcid.org/0000-0002-2621-0300

Давлетша Шаяхметов
Доктор медицинских наук, профессор
Кыргызская государственная медицинская академия им. И.К. Ахунбаева
720020, ул. Ахунбаева, 92, г. Бишкек, Кыргызская Республика
https://orcid.org/0009-0007-9724-0471

Айжан Исмаилова
Аспирант
Кыргызская государственная медицинская академия им. И.К. Ахунбаева
720020, ул. Ахунбаева, 92, г. Бишкек, Кыргызская Республика
https://orcid.org/0009-0006-6287-2092

Арисель Ибрагимова
Аспирант
Кыргызская государственная медицинская академия им. И.К. Ахунбаева
720020, ул. Ахунбаева, 92, г. Бишкек, Кыргызская Республика
https://orcid.org/0009-0008-9645-3229

Аннотация. Отсутствие единых подходов к диагностике кожных гемангиом у детей, а также необходимость их дифференциации от других сосудистых аномалий требуют создания структурированного диагностического алгоритма, способного обеспечить объективность оценки и снизить риск диагностических ошибок. Целью данного исследования было теоретическое обоснование и аналитическое уточнение диагностических критериев гемангиом у детей на основе систематического анализа современных инструментальных и лабораторных методов с последующей разработкой интегрированного диагностического алгоритма. Был проведен анализ 23 научных публикаций, что позволило определить информативность отдельных методов и последовательность их оптимального применения в клинической практике. Было установлено, что ультразвуковая визуализация имеет наибольшее диагностическое согласие с морфологическим подтверждением, в то время как термографическая оценка и аускультация характеризуются более низкой точностью и полезны только на этапе предварительной ориентации. Было установлено, что необходима возрастная интерпретация лабораторных маркеров: индекс интоксикации лейкоцитами имел разные референтные значения у младенцев и детей старшего возраста в связи с физиологическими особенностями лейкоцитарного формуляра. Определены диагностические пороги коагуляционных параметров для ранней диагностики синдрома Касабаха-Мерритта: тромбоциты <50 × 103/мкл, фибриноген <100 мг/дл, D-димеры >5-20 мг/л. Мониторинг коагуляции показан при крупных или быстро растущих гемангиомах из-за риска консуматорной коагулопатии. На основании полученных результатов был сформулирован иерархический диагностический алгоритм, который предполагает поэтапное применение клинического обследования, ультразвуковой визуализации, лабораторного тестирования системных маркеров и морфологического подтверждения в случаях атипичного течения или недостаточности неинвазивных данных. Предлагаемый подход повышает точность диагностики, стандартизирует последовательность обследований и сводит к минимуму необходимость инвазивных вмешательств в педиатрической практике

Ключевые слова: сосудистая аномалия; инструментальный метод; лабораторный маркер; патоморфологическое исследование; системная реакция; периферическая кровь