Review

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Paediatric hepatocellular adenomas: Lessons from a systematic review of relevant literature

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Summary

Hepatocellular adenomas (HCAs) are rare benign liver tumours. Predisposing factors and complication rates appear to differ among children and adults. In the present study, we aimed to systematically characterise paediatric HCAs and determine their course, complications, and management. Medical history, clinical symptoms, imaging, histopathology, and genetics of children with HCAs were collected through a systematic and comprehensive review of the published literature. A total of 316 children with HCAs were included in the present study. HCAs were diagnosed primarily in girls (59.3%) and at a mean age of 11.5 (range 0-17.7) years. The majority (83.6%) of HCAs occurred in children with predisposing diseases, of which glycogen storage disease was the most common, followed by portosystemic shunts and MODY3 (maturity-onset diabetes of the young type 3). Each of these diseases leads to a well-defined HCA molecular pattern. A significant number of HCAs either bled (24.7%) or transformed (14.8%) over time. HCA transformation was significantly more frequent in children with portosystemic shunts and in β-catenin-mutated HCAs, while haemorrhages were more frequent in children exposed to hormones and those with larger lesions. Management was primarily guided by any predisposing conditions and the number of lesions. Therefore, vascular shunts were closed when possible, while complicated lesions were resected. Liver transplantation has made it possible to treat adenomatosis, as well as any underlying diseases. Progress in understanding genetic and/or malformative contributions, which appear to be significant in paediatric HCAs, have provided insights into tumour pathogenesis and will further guide patient surveillance and management.

Keywords: liver adenoma; children; portosystemic shunt; glycogenosis; HNF1A; hepatocellular carcinoma

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Introduction

Hepatocellular adenomas (HCAs), non-malignant liver tumours, are extremely rare in children, accounting for only 2% of all paediatric liver tumours. Little is known, however, regarding the pathogenesis and natural history of HCAs in this population. Currently, paediatric hepatologists rely on adult guidelines to classify and manage HCAs in paediatric patients. However, early reports have suggested that the predisposing factors are different, and complications are more frequent in children. Consequently, the use of adult guidelines is unlikely to be optimal for predicting disease progression and complications in children.

HCA, with an overall incidence rate of approximately 3/100,000, has been extensively investigated in adults by the French GENTHEP/HCA Network.[1] Women are more prone to developing HCAs (female/male ratio, 8:1), with oral contraceptives being the most frequent risk factor. Adult HCAs are classified into eight molecular types, based on their genotypes and phenotypes.[2,3] HCA type has an impact on patient management and is the major determinant of the risk of malignant transformation or haemorrhage.

Biallelic *HNF1A*-mutated HCAs (H-HCAs) are the most common type of adenoma in adults (34%), and primarily affect women. Immunohistochemical staining of H-HCAs is characterised by marked steatosis and reduced expression of L-FABP (liver fatty acid-binding protein). Inflammatory adenomas (I-HCAs) are observed in older obese individuals or those with a history of chronic alcohol consumption, associated with increased serum inflammatory markers, and characterised by activating somatic mutations in the JAK/STAT pathway,[4] while I-HCA pathology shows positive immunohistochemical staining for inflammatory proteins, serum amyloid A and C-reactive protein. Beta (β)-catenin (*CTNNB1*)-mutated HCAs (B-HCAs) tend to present as a single lesion in young adults and carry a high risk of malignant transformation if the mutation occurs in exon 3 (B^{ex3}-HCA), but not in exon 7-8 ($B^{ex7\text{-}8}$-HCA). Additionally, B^{ex3}-HCAs often show the diffuse and intense expression of glutamine

synthetase, whereas B^{ex7-8}-HCAs only weakly express this protein.[5] Some HCAs combine inflammatory and β-catenin features ($B^{ex3\ or\ ex7-8}$I-HCA). Sonic hedgehog-activated HCAs (Sh-HCAs), which are caused by the *INHBE*/*GLI1* fusion, occur in obese patients and tend to cause bleeding.[6,7] Finally, unclassified HCAs (U-HCAs, 7%) shared no characteristics with the aforementioned types.[1]

The aim of the present study was to provide a comprehensive summary of the currently available data on HCAs in children, identify specific aetiologic risk factors, and delineate the phenotypes, genotypes, and long-term course of these tumours in paediatric patients. Such a systematic and detailed analysis should identify the criteria for stratifying paediatric patients for appropriate clinical management – those who may require close follow-up and those who are likely to have a favourable outcome. To this end, we performed a systematic search of published literature to obtain as complete a picture as possible of the features of HCAs in children.

Materials and methods

Literature review

We searched PubMed (1946-Dec 2022), Embase (1980-Dec 2022), and the Cochrane Central Register of Controlled Trials (CENTRAL) (from inception-Dec 2022) for relevant articles, using a combination of the following search terms: ["liver cell adenoma" OR "liver adenoma" OR "hepatocellular adenoma"] AND ["children" OR "pediatric"]. All articles were included, regardless of the publication type, although the search was limited to human studies published in English. All patients with paediatric-onset HCAs (age <18 years) were included in the present study. When cases were reported in more than one study, the available data were pooled.

Two of the authors (IS and AL) independently analysed the titles, abstracts, and original articles using predetermined selection criteria. The searches were bolstered by examining the references used in the selection of the publications. Any discrepancies were resolved by consensus.

Data concerning the date of publication, patient epidemiology (sex, age at presentation, and ethnicity), duration of follow-up, personal and family history, biochemistry, imaging data, histopathological findings, treatment, and outcomes were extracted and summarised.

Statistical analysis

Statistical analyses were performed by CB (UCLouvain/Louvain Institute of Data Analysis and Modeling/Statistical Methodology and Computing Service) and by FZ using JMP® Pro (version 15.2.0, Marlow, UK), GraphPad® Prism Software (version 10.1.0, San Diego, CA, USA) and SPSS® (IBM, version 24.0, Chicago, IL, USA). Descriptive data for continuous variables are reported as either mean ± SD and 95% CIs or median with IQR, as appropriate. To compare dichotomous data, we used the chi-squared test with Cook's correction or Fisher's exact test in cases of very small numbers. To compare continuous data, we used the Mann-Whitney rank sum test. Multivariate logistic regression was performed, as appropriate. Since most of the articles included in the present systematic review were case reports, there were no methods to adjust for the multiplicity of inferences or to control for false discovery rates.

Key points

- The majority of HCAs develop in children with predisposing diseases and girls are more likely to be affected.
- Most affected children will develop several HCAs over time.
- Hormone exposure and increasing lesion size confer a significantly increased risk for HCA haemorrhage.
- Portosystemic shunts and β-catenin-mutated HCAs are predisposing factors for malignant transformation.
- Transplantation is a valuable treatment for unresectable or multiple HCAs in patients with an underlying liver disease.

Results

Paediatric HCA – literature review

To obtain a complete depiction of the spectrum of HCAs in children, we systematically reviewed the available literature, which yielded 903 citations (PubMed, n = 542; Embase, n = 361) (Fig. 1, flow diagram). After cross-referencing, 24 additional articles were obtained, with a total of 154 publications finally included in this retrospective case review. Data from 316 children with HCAs were included in the present study (see references and supplementary references).

Epidemiology and clinical presentation

HCA was diagnosed in 316 children at a mean age of 11.5 (SD 4.9; 95% CI 10.8-12.0) and a median age of 12.9 (IQR 9-15; range 0-17.7) years; it affected girls more than boys (156/263; 59.3%) with a preponderance towards the Caucasian ethnicity (37/67; 55.2%) (Table 1 and Table S1). Most children had multiple HCAs at diagnosis (188/316; 59.5%), and 22/61 (36.1%) had liver adenomatosis (>10 HCAs). Children with a single lesion were younger than those with multiple lesions, at 11 (IQR 6-14; range 0-17) *vs*. 14 (IQR 11-16; range 0-17.7) years, respectively (p <0.0001), and were more likely to have sporadic HCAs (35/116 *vs*. 13/165; p <0.0001). Mean lesion size was 7.4 (SD 5.0; 95% CI 6.6-8.2) and median lesion size was 6.5 (IQR 3-11; range 0.6-22) cm. Abdominal pain (42/158; 26.6%) and hepatomegaly (42/159; 26.4%) were the primary clinical signs and symptoms leading to the diagnosis of HCA. Increased liver enzyme levels and/or cholestasis were present in 33/62 (53.2%) and 19/50 (38%) patients, respectively, at the time of the first assessment. Alpha-fetoprotein (AFP) levels were increased in 9/59 (15.3%) patients; six of them (6/9, 66.6%) had imaging and/or histology confirming malignant transformation of HCA.

Risk factors and predisposition for HCA

The majority of patients (245/293; 83.6% - no data available for n = 23) had a personal history of predisposing conditions (Tables S2 and S3A,B), the most prevalent of which were glycogen storage disease (GSD, n = 112/245; 45.7% - especially GSD type 1a), cardiovascular diseases, including portosystemic shunts (PSSs, especially PSS type 2, n = 13, and type 1, n = 8) and right-sided cardiopathies (n = 38/245; 15.5%), endogenous or exogenous hormone exposure (n = 38/245; 15.5%), or maturity-onset diabetes of the young type 3 (MODY3, n = 19/245; 7.8%). Other rare conditions were identified as potential risk factors for HCA, such as polyposis syndromes (familial adenomatous polyposis, n = 6/245, 2.4%; constitutional mismatch repair deficiency

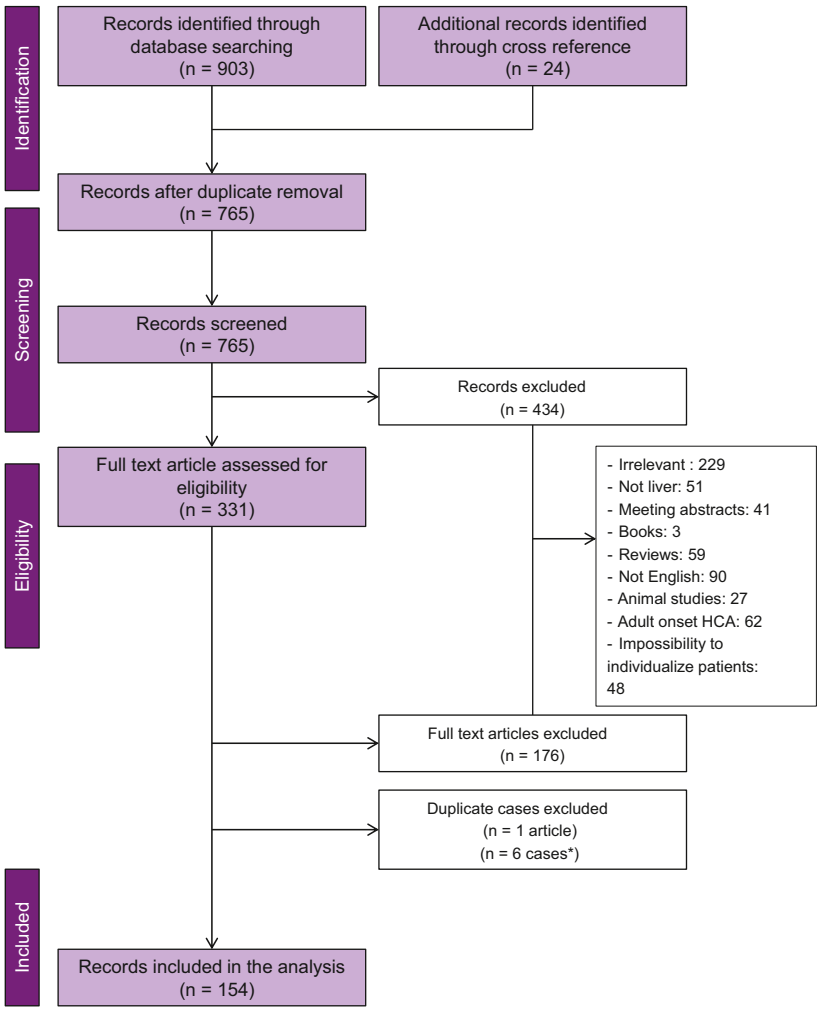

Fig. 1. Flow diagram of the systematic literature case review according to PRISMA guidelines. Adult onset: concerned HCA in adults; animal studies: concerned HCA occurring in animals or animal models; irrelevant: concerned colon adenomatous polyps, liver tumours (without reference to HCA), focal nodular hyperplasia, cystadenoma, cystadenocarcinoma, choledochal cysts; not liver: concerned endocrine gland adenomas; not English: concerned articles published in other languages. HCA, hepatocellular adenoma.

syndrome, n = 3/245, 1.2%) and Wolf-Hirschhorn syndrome (4p partial deletion, n = 3/245, 1.2%). Of note, in patients with Fanconi anaemia (n = 26), the median duration of exposure to androgen therapy before a diagnosis of HCA was as short as 50 (IQR 36-60) months (mean 51.3; SD 25.8; 95% CI 35-67.7).

Immunohistochemistry, imaging features, and genetic background

Histopathological and genetic backgrounds of HCAs were determined in 79/316 (25%) and 10/316 (3.2%) children, respectively.

Overall, 35 (43.2%) lesions were H-HCAs, 21 (25.9%) were B-HCAs, 17 (21%) were I-HCAs, 8 (9.9%) were BI-HCAs, and 3 (3.7%) were U-HCAs, while 6 (7.6%) children had combined lesions of different subtypes (H- and B-HCA, n = 5; and I- and B-HCA, n = 1) in the liver. Sh-HCA, which was described recently, has not yet been identified in children.

HCAs from children with GSD showed positive staining (n = 7/9 patients) for serum amyloid A and C-reactive protein, which are characteristic of I-HCA[1] ($p = 0.003$), one of which additionally overexpressed GS (BI-HCA). The BI-HCA showed a mutation gain in the JAK/STAT pathway effector *IL6ST*, and *CTNNB1* (Tables S2 and S4). Of note, H-HCAs were not observed in children with GSD.

Among children with PSSs (Tables S2 and S4) eight had B-HCAs, seven had H-HCAs, three had BI-HCAs, and one had I-HCA. Interestingly, four children had combined B-HCA and H-HCA phenotypic features (three in separate lesions and one within the same lesion), whereas two other children with B-HCA also expressed inflammatory features (BI-HCA). One case each of H-HCA and B-HCA were sequenced, confirming the presence of two somatic mutations in *HNF1A* in the first and one mutation in *CTNNB1* in the latter.

Patients with MODY3 developed H-HCAs (p <0.0001) characterised by marked steatosis and loss of L-FABP staining at pathology compared to normal adjacent liver parenchyma (n = 14/14). This fatty component enabled H-HCAs to be distinguished from other HCAs on MRI, with the former showing a diffuse signal loss in a T1-weighted chemical shift sequence (n = 3/3). H-HCA sequencing (n = 3) confirmed a biallelic inactivating mutation (germinal and additional somatic) in *HNF1A* in these lesions (Tables S2 and S4).

Table 1. Epidemiologic and clinical data on paediatric HCA.

HCA epidemiology	Overall cohort (N = 316)
Age at diagnosis	Available data n = 248/316
Global cohort	
Median	12.9 years (IQR 9-15; range 0-17.7)
Mean	11.5 years (SD 4.9; 95% CI 10.8-12.0)
<1 year	11 (4.4%)
1–5 years	29 (11.7%)
6–10	43 (17.3%)
11–15	106 (42.7%)
16–<18	59 (23.8%)
Gender	n = 263
Male	107 (40.7%)
Female	156 (59.3%)
Race	n = 67
Caucasian	37 (55.2%)
African	10 (14.9%)
Asian	17 (25.4%)
Hispanic/Latino	3 (4.5%)
Native American/Hawaii/Pacific	0 (0%)
Lesion number	n = 316
Unique	128 (40.5%)
Multiple	188 (59.5%)
Adenomatosis (>10 lesions)	22/61 (36.1%)
Circumstances for HCA discovery	
Symptoms	
Abdominal pain	42/158 (26.6%)
Nausea/vomiting	15/158 (9.5%)
Fatigue	8/158 (5.1%)
Anorexia	2/158 (1.3%)
Pruritus	3/157 (1.9%)
Clinical signs	
Fever	10/157 (6.4%)
Mass/hepatomegaly	42/159 (26.4%)
Weight loss	10/157 (6.4%)
Hypotension, shock	3/157 (1.9%)
Haemorrhage	4/157 (2.6%)
Jaundice	8/157 (5.1%)
Other	
Incidental finding	25/153 (16.3%)
Follow-up predisposing disease	31/155 (20.0%)
Autopsy	14/153 (9.2%)
Biochemistry findings	
Increased CRP	2/5 (40.0%)
Increased liver enzymes	33/62 (53.2%)
Cholestasis	19/50 (38.0%)

CRP, C-reactive protein; HCA, hepatocellular adenoma.

The pheno-genotypes of HCA lesions linked to other conditions are summarised in (Table S2). In children with sporadic HCA, all phenotypes except Sh-HCA were found.

Follow-up, complications, and outcomes

Patients were followed for a median of 4 (IQR 2.0-9.4; range 0-30) years. Although often considered benign in children, HCA was diagnosed or complicated in a significant number of patients because of haemorrhage (41/166; 24.7%), bile duct compression (17/153; 11.1%), or malignant transformation (30/203; 14.8%). Haemorrhage was fatal in four children (4/41; 9.7%) and hepatocellular carcinoma (HCC) in five (5/30; 16.7%) (Table 2).

Among the children with GSD, five (5/40; 12.5%) developed HCC. HCA progressed to HCC after a median duration of 7.5 years. Malignant lesions were significantly larger than HCAs (median size, 10 *vs*. 2.8 cm, respectively; IQR: 1.2-7; $p = 0.03$).

HCA transformation occurred in 12 (12/27; 44.4%) patients with PSSs, one with H-HCA, four with B-HCAs, and two with BI-HCAs. Patients with syndromic PSSs had a significantly higher risk of developing HCC than those with an isolated PSS (8/10 *vs*. 4/17, respectively; $p = 0.006$). Of note, none of the 17 H-HCAs followed in patients with MODY3 were transformed during childhood.

Tumour markers have proven useful in distinguishing HCAs from HCCs. Elevated AFP levels were significantly associated with HCCs ($p = 0.027$). In univariate analysis, transformation was significantly correlated with PSSs (p <0.0001) and B-HCA ($p = 0.0003$). These findings were confirmed by multivariate analysis (odds ratio [OR] for PSSs: 6.4; OR for B-HCA: 9.7) (Tables 2 and 3).

Haemorrhage was observed significantly more frequently in sporadic cases than predisposed patients (p <0.001). Overall, in the univariate analysis (Table 2), hormone exposure ($p = 0.003$), sporadic HCA ($p = 0.003$), and larger lesion size ($p = 0.0006$) were risk factors for HCA haemorrhage; however, in the multivariate analysis, only HCA size (OR 2.5) and hormone exposure (OR 5.9) were significant (Table 3).

Management of historic paediatric HCA cohort

The therapeutic approach to HCA was primarily guided by the patient's underlying condition(s). Medical management is the first step in metabolic control in children with GSD. Twenty-four children with GSD and HCA were initially followed up, and in about half (7/12), the HCAs increased in size and/or number over time, while 3/12 remained stable in size. Lesion resection was the first-line treatment in 17 patients, while radiofrequency ablation was performed in one. Ultimately, 16 children underwent orthotopic liver transplantation (OLT), which successfully treated HCA and stabilized their metabolic conditions.

Adenomas arising in the context of PSSs were managed by shunt closure in eight patients, resulting in lesion regression in 2/6 cases, while 4/6 continued to grow. In seven patients, the HCA was resected, and in another seven, OLT was the first-line treatment. Six patients underwent observation initially (median follow-up duration 4 years; IQR 2-7.4), but in four patients, the lesions increased in size during this period. Resection was then proposed in 2/4 patients, while OLT was performed in the other 2/4 patients.

Among patients who developed HCA during hormone exposure, the reduction or discontinuation of hormone therapy was proposed in 19 patients, which led to tumour regression in two patients and resolution in 11, while follow-up data were unavailable for the remaining six. HCA resection or ablation was proposed as the first-line treatment in seven patients, while two underwent OLT, one in the setting of HCA-related haemorrhage and the other due to diffuse adenomatosis.

Among the patients with HCA and MODY3, nine underwent initial lesion resections, while four were followed up clinically.

In paediatric patients without risk factors, resection was performed in 26 patients and embolization in one, while OLT was performed in two; one owing to transformation and the other for an unexplained reason. Of the seven patients who were followed up (mean follow-up 5 years; IQR 1-10.5), 1/3 remained stable while 2/3 had growing nodules.

Discussion

HCAs predominantly develop in children with predisposing conditions that largely predict the HCA phenotype (Fig. 2). By reviewing data from previously reported cases, we improved our understanding of the characteristics and mid-term outcomes of paediatric HCAs. The present comprehensive analysis should

Table 2. Univariate analysis of the global HCA cohort for haemorrhage and malignant transformation.

	Transformation (available data n = 203/316)			Haemorrhage (available data n = 166/316)		
	Yes (n = 30, 14.8%)	No (n = 173, 85.2%)	*p* value	Yes (n = 41, 24.7%)	No (n = 125, 75.3%)	*p* value
Age (years)	9.4	11.2	**0.046**	11.9	10.8	n.s.
Mean (SD; 95% CI)	(4.9; 7.6-11.3)	(5.3; 10.4-12)		(4.1; 10.6-13.2)	(5.5; 9.8-11.8)	
Gender, male/total (%)	14/29 (48.3%)	57/155 (36.8%)	n.s.	10/39 (25.6%)	46/115 (40%)	n.s.
HCA size (cm)	8.8	7.9	n.s.	11.1	7.5	**0.0006**
Mean (SD; 95% CI)	(4.2; 6.7-11)	(5.1; 6.9-8.9)		(4.5; 9.4-12.9)	(4.7; 6.4-8.5)	
Underlying disease						
PSS and right-sided cardiopathies	12	15	**<0.0001**	2	20	n.s.
GSD	5	35	n.s.	3	26	n.s.
Hormones	3	19	n.s.	10	9	**0.003**
MODY3	0	17	n.s.	4	12	n.s.
Sporadic	3	43	n.s.	17	25	**0.003**
Type of adenoma						
H-HCA	4	30	n.s.	4	26	n.s.
B-HCA	11	17	**0.0003**	2	23	n.s.
BI-HCA	2	2	n.s.	0	7	n.s.
I-HCA	2	23	n.s.	1	22	n.s.
U-HCA	2	1	n.s.	1	2	n.s.

B-HCA, β-catenin-mutated HCA; BI-HCA, β-catenin-mutated/inflammatory HCA; GSD, glycogen storage disease; HCA, hepatocellular adenoma; H-HCA, *HNF1A*-mutated HCA; I-HCA, inflammatory HCA; MODY3: maturity-onset diabetes of the young; PSS, portosystemic shunt; U-HCA, unclassified HCA.
Descriptive data for continuous variables are reported as mean ± SD and 95% CIs. To compare dichotomous data, we used the chi-squared test with Cook's correction or Fisher's exact test in cases of very small numbers. To compare continuous data, we used the Mann-Whitney rank sum test.
Significant results have been highlighted in bold.

Table 3. Multivariate analysis of the global HCA cohort for haemorrhage and malignant transformation.

	Transformation			Haemorrhage		
	p value	Odds ratio	95% CI	*p* value	Odds ratio	95% CI
Age	n.s.			n.s.		
Male gender	n.s.			n.s.		
HCA Size	n.s.			**0.0034**	**2.5**	**1.4-4.4**
Underlying disease						
PSS	**<0.0001**	**6.4**	**2.6-15.9**	n.s.		
GSD	n.s.			n.s.		
Hormones	n.s.			**0.015**	**5.9**	**1.5-23.1**
MODY3	n.s.			n.s.		
Sporadic	n.s.			n.s.		
Type of adenoma						
H-HCA	n.s.			n.s.		
B-HCA	**0.0004**	**9.7**	**2.4-39.1**	n.s.		
BI-HCA	n.s.			n.s.		
I-HCA	n.s.			n.s.		
U-HCA	n.s.			n.s.		

B-HCA, β-catenin-mutated HCA; BI-HCA, β-catenin-mutated/inflammatory HCA; GSD, glycogen storage disease; HCA, hepatocellular adenoma; H-HCA, *HNF1A*-mutated HCA; I-HCA, inflammatory HCA; MODY3: maturity-onset diabetes of the young; PSS, portosystemic shunt; U-HCA, unclassified HCA.
Significant results have been highlighted in bold.

guide clinicians in the management of patients with HCA and pave the way for further research on these lesions.

According to the results of the present review, HCAs affected girls more than boys. Lesions were diagnosed from birth, but their onset peaked during adolescence. Although the clinical signs and symptoms of HCA are specific, and elevated liver enzymes and/or cholestasis are inconsistent, these features lead to further imaging investigations and diagnosis of HCA.

Most paediatric HCAs develop in children with underlying genetic diseases, liver vascular anomalies, or post-hormone exposure. Although the correlation between certain predisposing diseases/medications and HCAs is undeniable, the roles of other exceptional associations remain unclear. Due to the congenital nature of most risk factors, paediatric patients are significantly more likely to develop multiple adenomas over time. Therefore, the incidental discovery of multiple adenomas should prompt further investigations to rule out predisposing diseases, and the diagnosis of predisposing diseases should lead to surveillance for HCAs.

In most children, the underlying disease predicts the lesion phenotype, of which six molecular types have been identified: B-HCA; I-HCA; BI-HCA; H-HCA; BH-HCA; and U-HCA. Although data on genotype-phenotype correlations are limited, each of these phenotypes has been shown to be linked to mutations in specific signalling pathways. Sh-HCA has not been described in children, and very little data are available on the subtyping of B-HCAs into B^{ex3}-HCA and $B^{ex7\text{-}8}$-HCA, which may be due to the limited use of genetic testing.

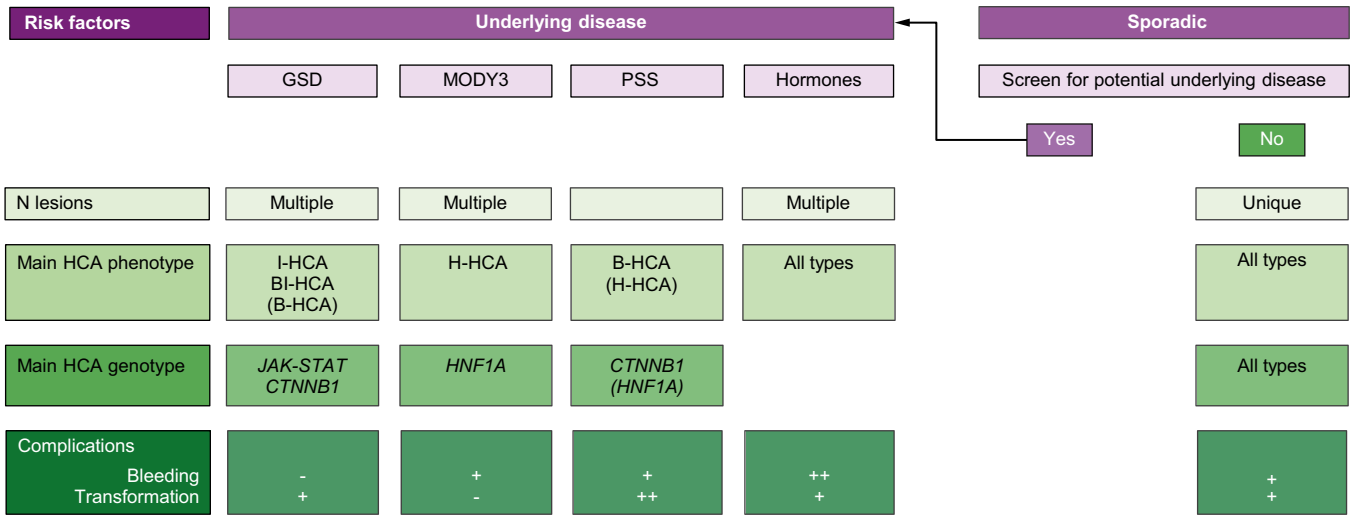

Fig. 2. Risk factors and associated HCA characteristics in children. B-HCA, β-catenin-mutated HCA; BI-HCA, β-catenin-mutated/inflammatory HCA; PSS, portosystemic shunt; GSD, glycogen storage disease; HCA, hepatocellular adenoma; H-HCA, *HNF1A*-mutated HCA; I-HCA, inflammatory HCA; MODY3: maturity-onset diabetes of the young; U-HCA, unclassified HCA.

In children with GSD, HCA is predominantly phenotyped as I-HCA. Disease genotype and environmental factors, such as high fat and sugar intake, appear to be important drivers of the development of HCA and HCC in patients with GSD.[8] Studies in mice have shown that HCAs develop when glucose-6-phosphatase activity is severely impaired (<3%).[9] Furthermore, altered glucose and lipid metabolism in patients with GSD have been shown to impair autophagy, induce endoplasmic reticulum stress, and dysregulate apoptosis, ultimately predisposing patients to the development of HCA and HCC.[8] Furthermore, HCAs occurring in patients with GSD belong to different molecular subgroups, with the exception of H-HCAs, as described previously.[10]

Children with PSSs predominantly developed B-HCA, followed by H-HCA or a combination of both HCA types in the same liver, or even within the same lesion. Although intratumoral *HNF1A* mutations have been described as exclusive to *CTNNB1*,[1] the intertumoral heterogeneity of *HNF1A* and *CTNNB1* has occasionally been described in adult HCAs.[11] Although the available data are limited in the population of the present study, consistent with the descriptions of Laumonier *et al.*,[12,13] H-HCAs are recognisable on MRI by diffuse and homogeneous signal loss on chemical shift sequences owing to a large lesional fat component, whereas B-HCAs have no recognisable features on imaging. The imaging characterisation of HCAs in patients with PSSs is challenging because decreased portal perfusion and increased arterial flow can alter enhancement dynamics. However, the association between portal deprivation and HCA development remains poorly understood. Epidemiological studies have shown that patients with PSS type I are more likely to develop HCAs than those with PSS type II,[14] suggesting an important role of portal deprivation in the pathophysiology of HCAs. Abnormal portal blood flow impairs nutrient absorption, hormone metabolism, waste metabolism and clearance.[15] Secondly, studies in mice have shown that PSSs induce changes in the vascular morphology of the liver, such as portal space arterialisation and sinusoid hyperplasia.[16] Both of these mechanisms promote cell growth and proliferation.

Patients with MODY3 and constitutional biallelic mismatch repair deficiency develop H-HCAs carrying biallelic mutations or polycytosine C8-microstallite instability in *HNF1A*,[17] respectively. The large fatty component allows H-HCAs to be recognised on MRI by diffuse and homogenous signal loss in the chemical shift sequences.[12] In cell models, *HNF1A* mutations have been shown to alter liver and oestrogen metabolism, increase the expression of growth factors, receptors, and cell cycle regulators, and stimulate angiogenesis. These effects promote liver cell proliferation and HCA formation.[18] Clinical studies in a cohort of patients with MODY3 failed to establish a correlation between the development of HCA and metabolic control, although specific mutations, such as p.Gly292*fs, appear to be over-represented.[19]

Steroids, oxcarbazepine, androgens, or oestrogens significantly predispose children to developing HCAs. Further studies are needed, however, to better delineate HCA phenotypes in these patients. From a mechanistic point of view, it has been shown in zebrafish that oestrogens promote liver cell proliferation by activating the PI3K/AKT/mTOR pathway.[20] Androgens promote liver carcinogenesis in cell lines by activating the WNT-pathway.[21] The antiepileptic drug oxcarbazepine increases the risk of developing HCAs by increasing serum androgen levels.[22] In Fanconi anaemia, the oncogenic effect of hormone exposure adds to the tumorigenic effect of the altered DNA damage response.

Ultrasound is the first-line imaging modality used for diagnosis, screening, and follow-up in children. HCAs present as well-delimited solid masses, and ultrasound has certain limitations, including small lesion size, isoechoic HCAs, and heterogeneous background liver. Contrast-enhanced MRI and ultrasound (CEUS) can help clarify the characteristics of a lesion. HCAs generally appear as hypersignals on T2W sequences, enhance early after contrast injection, and show progressive washout. Laumonier *et al.*[12,13] showed for the first time that lesion composition characteristics could help discern the different subtypes of HCA using MRI or CEUS. Indeed, sinusoidal dilatation associated with I-HCA leads to a marked hypersignal on T2W sequences, with delayed and persistent enhancement of

the lesion on MRI. On CEUS, strong centripetal enhancement and peripheral linear vascularity during the arterial phase, as well as central washout during the late venous phase, were specific for I-HCA. However, owing to their large fatty component, H-HCAs are recognisable on MRI by a diffuse, homogenous signal dropout on chemical shift sequences, moderate arterial enhancement, and contrast washout during the delayed phase. On CEUS, H-HCAs appear as homogeneous, hyperechoic masses. Despite limited data, the behaviours of H-HCAs and I-HCAs on MRI in children are similar to these descriptions. Unfortunately, there were no distinguishing features for the other HCA types. One important caveat is that well-differentiated HCCs strongly enhance during the arterial phase and may retain contrast during the venous and delayed phases;[23] therefore, it is difficult to distinguish them with certainty from HCA. Additionally, the enhancement characteristics of lesions may be altered by PSSs.

Haemorrhage and malignant transformation are two important complications of HCAs. In the paediatric population in the present study, we showed that HCAs occurring in children exposed to hormones, as well as large HCAs, present a significant risk of bleeding. The pathophysiological mechanisms underlying HCA haemorrhage are not fully understood. Transformation occurred in 14.8% of HCAs, significantly more than the 4–8% described in the adult HCA literature.[1] Future prospective studies, however, are required to confirm these findings. Furthermore, HCAs occurring in children with PSSs and B-HCAs are significantly more prone to transformation. Although data on the evolution of HCAs in children with PSSs are limited, transformation appears to occur preferentially in B-HCA lesions and in children with syndromic PSS. Mutations in *CTNNB1* are important drivers of liver cell proliferation. Mutations in this gene have been associated with the development of HCA and HCC. Rebouissou *et al.*[24] have shown that an exon3 mutation results in a stronger activation of β-catenin than an exon7-8 mutation, and thus confers a higher risk for transformation. Positive AFP levels suggest HCA transformation, and differentiating HCAs from HCCs using pathology or imaging can be difficult. Rapid lesion growth and early arterial contrast uptake, followed by rapid washout on MRI, are suggestive of malignancy.[25] Biopsy of the largest mass, which is thought to be most likely to harbour malignant features, and the adjacent normal liver tissue may prove useful to better approach the benign or malignant nature of the lesion.

The therapeutic approach to HCA, as described in the historical literature cohort, was guided by the underlying disease, HCA-related complications, and the location and number of lesions. Shunt closure led to a reduction in the size or even resolution of the HCA in 2/4 patients with PSSs, while dose reduction or discontinuation of hormone therapy proved beneficial, allowing tumour regression or even resolution in exposed patients. The decision to resect an HCA or perform a transplant was guided by the number of lesions (single lesions tended to be resected when possible), location, and ability to simultaneously treat the underlying disease.

Unfortunately, the retrospective nature of the present study detracted from the quality of the data. A substantial number of articles have reported cases of HCA based on histological features before in-depth studies of the HCA phenotype were published. Medical records and bibliographic reports were often incomplete, and we could not exclude reporting bias, particularly as cases of complicated HCAs could have been overreported, whereas patients with smaller lesions were not diagnosed or described. Uncertainty about the nature of the lesion, complications, and patient history may also have influenced management decisions. Nevertheless, we believe that the present systemic review will pave the way for larger, well-needed, prospective multicentre studies to further refine the predisposing factors, genetic background, tumour-driving mutations, risk of complications, and management of children with HCAs.

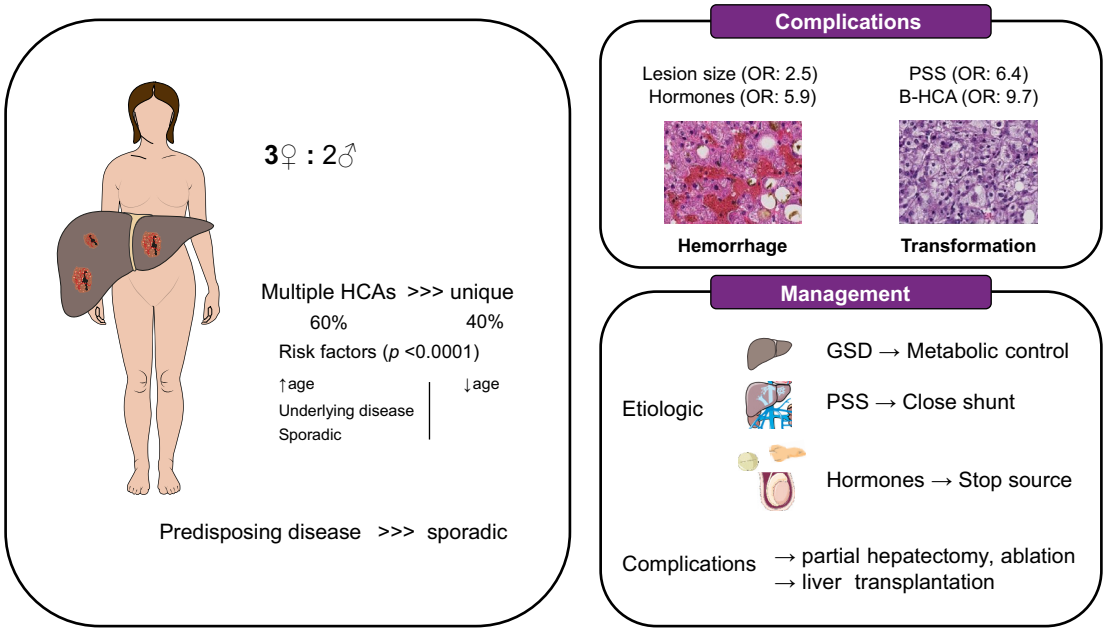

Fig. 3. Summary of study findings. B-HCA, β-catenin-mutated HCA; GSD, glycogen storage disease; HCA, hepatocellular adenoma; OR, odds ratio; PSS, portosystemic shunt.

HCAs in children affect a greater number of girls than boys and occur primarily in patients with predisposing diseases. Due to the congenital nature of most risk factors, paediatric patients are significantly more likely to develop multiple adenomas over time. Although HCAs are benign, many patients develop complications. Patients with large HCAs and those exposed to hormones were at a significant risk of bleeding, whereas HCAs arising in PSSs and B-HCAs were prone to transformation (Fig. 3). Therefore, precise phenotyping and tailored surveillance are essential for proper management of HCAs. The management of uncomplicated HCAs is personalised according to the underlying conditions: optimisation of metabolic control; restoration of portal flow; and suppression of hormone exposure. Patients with larger lesions, B-HCAs, or complicated HCAs should undergo resection or transplantation.

Abbreviations

AFP, alpha-fetoprotein; B-HCA, β-catenin-mutated HCA; BI-HCA, β-catenin-mutated/inflammatory HCA; CEUS, contrast-enhanced ultrasound; GSD, glycogen storage disease; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; H-HCA, *HNF1A*-mutated HCA; I-HCA, inflammatory HCA; MODY3, maturity-onset diabetes of the young type 3; OLT, orthotopic liver transplantation; OR, odds ratio; PSSs, portosystemic shunts; Sh-HCAs, sonic hedgehog-activated HCAs; U-HCA, unclassified HCA.

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Conflict of interest

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Authors' contributions (CRediT Recommendations)

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Supplementary data

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Author names in bold designate shared co-first authorship

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