Research Square

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Real-World Study of Hepatic Hemangioma at a Single Center – Data From 2008 to 2017

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Keywords: hepatic hemangioma, epidemiology, surgery, complications, risk factors

Posted Date: November 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-111320/v1

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Abstract

Objective: The objective of the present study was to investigate the clinical and epidemiological characteristics of hepatic hemangioma (HH) and the risk factors for complications associated with HH resection in a single center experience.

Materials and methods: Clinical data of 5,266,670 outpatients and 246,419 individuals who were physically examined between 2016 and 2017 were used to evaluate epidemiological profiles of HH. A total of 1,981 patients hospitalized with HH between January 1, 2008 and January 1, 2018 were examined to identify relevant features associated with surgery.

Results: The study found that HH was similar in male and female incidence, mostly at the age of 40, and the tumor was usually single and mostly located in the right lobe of the liver. No serious postoperative complications occurred, and the method of HH resection was related to the occurrence of postoperative complications.

Conclusion: HH is a common benign disease of the liver. There are certain distribution rules in age, tumor size, and location, and laparoscopic HH resection that can reduce postoperative complications.

Introduction

Hepatic hemangioma (HH) is one of the most common solid benign tumors in the liver. HH has previously been detected in autopsy specimens, with a detection rate ranging from 0.4–20% due to lack of observable clinical symptoms[1]. The number of patients diagnosed with HH has increased with the development and application of imaging examination techniques, and the improvement of national health awareness. Previous studies have revealed that HH is prevalent in females (male to female ratio: 5:1), and in 30 to 50-year-olds[1, 2]. Studies have reported that estrogen can promote proliferation and migration of vascular endothelial cells and form capillary-like structures. For example, pregnancy and oral contraceptives can increase the levels of progestin and estrogen in the body, leading to the growth of hemangiomas, which may be associated with the pathogenesis of HH in women[3, 4].

Presently, the etiology of HH remains unknown and it is generally believed that HH is a vascular malformation caused by excessive growth of abnormal differentiation of blood vessels during embryonic development, rather than a true tumor. Patients with HH are predominantly asymptomatic and are usually identified during routine physical examinations or other viscera disease imaging examinations. Moreover, most tumors are small and relatively stable, with no effect on liver function. Therefore, most patients do not exhibit observable clinical symptoms or abnormal biochemical examination results. Patients with a large HH (> 4 cm) may exhibit no clinical symptoms or present different symptoms or complications, such as abdominal pain, nausea, fever, jaundice, vomiting, and spontaneous or traumatic rupture[5–8]. Thrombus formation within a giant HH can cause thrombocytopenia and eventually lead to coagulation dysfunction (Kasabanch – Merritt syndrome)[9].

Currently, a variety of treatment options for HH exist, including observation, non-surgical treatment, and surgical intervention. A definite diagnosis is required because the tumor is often small when detected. Although, some researchers suggest that most HHs do not require treatment, and routine follow-up and imaging observations should be conducted every 6 months or annually to assess tumor progress[10–12]. Treatment should be administered in the case of HHs with unclear diagnosis, rapid growth, high risk of tumor rupture, and observable symptoms[13–15]. Treatment options include drug therapy, interventional therapy, radiofrequency ablation, surgical resection, and liver transplantation. However, presently, big data research on the epidemiological characteristics of HH is lacking, and an integrated understanding of the indications and methods of interventions in HH does not exist. The purpose of this study was to investigate the clinical epidemiological characteristics of HH in a real clinical setting in a single center at the First Affiliated Hospital of Guangxi Medical University, to identify the complications that patients develop after HH resection, and to explore related risk factors.

Materials And Methods

General information

A retrospective descriptive method was adopted to analyze the medical records of patients diagnosed with HH in outpatient and physical examination centers of the First Affiliated Hospital of Guangxi Medical University between 2016 and 2017, and individuals diagnosed with HH in inpatient centers between January 1, 2008 and January 1, 2018. The present study met the requirements of the Declaration of Helsinki. Patients and their families signed written informed consent, and the study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.

Inclusion and exclusion criteria

The inclusion criteria included the following: (1) clinical diagnosis of HH and (2) all patients who received tumor resection and postoperative pathology to confirm HH.

The exclusion criteria were as follows: (1) patients with incomplete crucial clinical data records (e.g., loss of surgical records, medical records), (2) patients with HH who did not require a surgical intervention were excluded from the operation due to the existence of other underlying liver diseases (such as primary, focal nodular hyperplasia, intrahepatic bile duct stones, etc.) (Figure 1).

Follow-up visits

The patients were followed up using a hospital information system (HIS), hospital outpatient system, and telephone calls. The follow-up time was calculated on a monthly basis from the date of surgery to June, 2019. Patient outcomes included cure, residual, relapse, among others.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables conforming to normal distribution were expressed as mean±standard deviation (SD), data not conforming to normal distribution were expressed as median (quartile), and classified variables were expressed as percentages (cases). Univariate analyses were performed using non-parametric tests and related factors grouped according to data types, while multiple factors were analyzed using ordered logistic regression analysis. $P<0.05$ was considered statistically significant.

Results

Data was collected from outpatient and physical examination centers between 2016 and 2017, and the total number of outpatients was 5,266,670, with a HH incidence rate of 0.089%. HH incidence rate in males was 0.040% and that of females was 0.049%, and majority were aged between 41 and 60 years. A total of 246,419 individuals who were physically examined were included in the study, and the incidence rate of HH was 1.217%, with males having an incident rate of 0.707% and that of females was 0.510%; majority were aged between 21 and 40 years. Further analyses of data for the physical examination group revealed that the males were 1,743 (58.1%) and the females were 1,257 (41.9%). The median age of patients with HH was 40 (16–87) years, maximum diameter of the tumor was 1.3 (0.4–9.9 cm) cm, tumor was predominantly located in the right lobe of the liver, and single occurrence was prevalent. With reference to the analysis of clinical liver hemangioma among the Chinese population, surgery patients mainly □ type b, c, and □ □ type a, and mainly for check-up crowd □ □ type a and type a. In relation to the hospitalized population, the number of male and female patients was similar and the number of patients diagnosed increased in both sexes. Most patients were aged between 41 and 60 years (Figs. 2 and 3, Tables 1 and 2).

Table 1
Physical examination of HH population data

Variables		**NO./%**
Sex		
(n = 3000)	Male	1743/58.1%
	Female	1257/41.9%
Age(year)		40(16–87)
(n = 3000)	≤ 20	6/0.2%
	21–40	1587/52.9%
	41–60	1229/41%
	> 60	178/5.9%
Tumor size(cm)		1.3(0.4–9.9)
(n = 2979)	≤ 5 cm	2923/98.12%
	> 5 cm	56/1.88%
Tumor location		
(n = 2353)	Left lobe	210/8.9%
	Right lobe	1889/80.3%
	Left and right lobes	254/10.8%
The number of tumor		
(n = 2986)	Single	2643/88.5%
	Multiple	343/11.5%

n = Number of persons with complete information

Table 2
Clinical classification of HH

Clinical classification	Pattern of manifestation	Number of tumors	Tumor diameter or sum of diameters or tumor volume	Surgery patients	Physical examination crowd
□a	Single	1	< 5 cm	29	2601
□b	Single	1	5 ~ 10 cm	85	38
□c	Single	1	> 10 cm	48	0
□a	Multiple	2 ~ 5	< 10 cm	47	316
□b	Multiple	2 ~ 5	10 ~ 20 cm	25	23
□c	Multiple	2 ~ 5	> 20 cm	0	0
□a	Diffuse	> 5	≤ 50% Liver volume	0	0
□b	Diffuse	> 5	> 50% Liver volume	0	0

In the present study, 234 patients underwent resection for liver hemangioma, which included 70 cases (29.9%) of males and 164 cases (70.1%) of females. The median age of patients who underwent surgery was 44 (38–50) years, of which the proportion of patients aged 41–60 years was 61.54%. A total of 144 patients had an average tumor size of 8 cm (0.5–25 cm), and lesions in 110 cases (47.0%) occurred in the right lobe of the liver, lesions in 81 cases (34.6%) occurred in the left lobe of the liver, 162 cases (69.2%) of liver lesions were single-shot, 72 cases (30.8%) were frequent lesions, 39 cases (16.7%) were a combination of hepatitis B. HH was detected in most patients by examination (125 cases = 53.4%), and the primary clinical manifestation was upper abdominal pain (93 cases = 39.7%). The primary surgical methods employed were laparotomy (153 cases = 65.4%), laparoscopy (64 cases = 27.4%), small-scope liver resection (206 cases = 88.0%), and exfoliation (5 cases = 2.1%). The median operative time was 200 min (137.7–278.3 min), and the median intraoperative blood loss was 400 ml (150–800 ml). Most of the patients (155 cases = 66.2%) did not receive intraoperative blood transfusion; transfusion volume was 100–800 ml in 36 cases (15.4%) and > 800 ml in 43 cases (18.4%). Based on the Clavien-Dindo classification of postoperative complications, 16 (6.8%) patients experienced grade □ complications and 4 (1.7%) patients experienced grade □ complications. The incidence of postoperative International Study Group of Liver Surgeries (ISGLS) complications was 11.966%, 0.427%, 3.846% and 2.137%, respectively. No postoperative biliary fistula or death occurred among the patients. Postoperative pathological types were spongiform hemangioma that was recorded in 224 cases (95.7%), capillary hemangioma recorded in 3 cases (1.3%), sclerosing hemangioma recorded in 2 cases (0.9%), and other types recorded in 5 cases (2.1%) (Fig. 4, Tables 3 and 4).

Table 3
Preoperative data

Variables	No./%
Age(Median age)	44
≤ 20	13/5.56%
21–40	61/26.07%
41–60	144/61.54%
> 60	16/6.84%
Sex	
Male	70/29.9%
Female	164/70.1%
Clinical symptoms	
exist	122/52.1%
without	112/47.9%
Clinical feature	
Abdominal mass	4/1.7%
Examination revealed	125/53.4%
Epigastric discomfort	93/39.7%
Waist pain	6/2.6%
Other	6/2.6%
Diagnostic methods	
Contrast-enhanced ultrasonography	1/0.4%
Enhanced computed tomography	209/89.3%
Magnetic resonance imaging	11/4.7%
Enhanced Magnetic resonance imaging	10/4.3%
Ultrasound	3/1.3%
Tumor size	8(0.5–25)
≤ 8 cm	138/59.0%
> 8 cm	96/41.0%
Distribution of tumor	

Variables	No./%
Right lobe	110/47.0%
Left lobe	81/34.6%
Left and right lobes	43/18.4%
Tumor number	
Single	162/69.2%
Multiple	72/30.8%
Tumor site	
Liver parenchyma	179/76.5%
Under the liver capsule	55/23.5%
Viral hepatitis B	
exist	39/16.7%
without	195/83.3%
Liver status	
Cirrhosis	3/1.3%
Normal	231/98.7%
Preoperative laboratory examination	
WBC(10 ~ 9/L)	6.25(4.98–6.72)
Hb(g/L)	123(112.8-135.4)
PLT(10 ~ 12/L)	226.9(196.7–272.0)
AST(U/L)	20(16–25)
ALT(U/L)	17(14–24)
TBil(μmol/L)	10(7.2–12.5)
DBil(μmol/L)	2.8(2.1–3.7)
AFP(ng/ml)	0.9(0.9-1)
Surgical indications	
Tumor grows fast	24/10.3%
Obvious clinical symptoms	43/18.3%
Women planning to become pregnant with large subcapsular hemangioma	1/0.4%

Variables	No./%
Patient psychological factors	102/43.6
Combined with spontaneous rupture bleeding or accident	14/6.0%
Emergency treatment for life-saving treatment	1/0.4%
Unclear diagnosis	49/20.9%

Table 4
Intraoperative and postoperative data

Variables	**No./%**
Treatment Modality	
Laparoscopic	64/27.4%
Laparoscopic conversion	17/7.3%
Open resection	153/65.4%
Hepatectomy method	
Small-range hepatectomy (≤ 3 liver segments)	206/88.0%
Extensive hepatectomy (> 3 liver segments)	23/9.9%
Stripping technique	5/2.1%
Regular hepatectomy	
Yes	45/19.2%
No	189/80.8%
Hepatic portal blockade	
Pringle	104/44.4%
Hemi-hepatic block	34/14.5%
Continuous hepatic artery occlusion	2/0.9%
Selective portal vein branch occlusion	5/2.1%
Other	56/23.9%
Without blocking	33/14.1%
Operation time	200(137.7-278.3)
Blood loss(ml)	400(150–800)
Blood transfusion(ml)	
None	155/66.2%
100–800	36/15.4%
> 800	43/18.4%
Surgical complications	
Bleeding	20/8.5%

n = Number of persons with complete information

Variables	No./%
Infection	80/34.2%
Bile leak	0
Pleural fluid	15/6.4%
Fever	79/33.8%
Abdominal pain	37/15.8%
Other	3/1.3%
Dindo grade	
□	115/49.1%
□	99/42.3%
□a	16/6.8%
□b	0
□a	1/0.4%
□b	3/1.3%
□	0
ISGLS Bleeding grade	
A	9/3.8%
B	5/2.1%
C	0
ISGLS Grade of liver failure	
A	29/12.4%
B	3/1.3%
C	0
Pathological type	
Capillary Hemangioma	3/1.3%
Sclerosing Hemangioma	2/0.9%
Cavernous Hemangioma	224/95.7%
Other	5/2.1%

n = Number of persons with complete information

Variables	No./%
Symptom improvement	
Improve	95/40.6%
No change	90/38.5%
Deterioration	3/1.3%
Lack of clarity	46/19.7%
Hospital stay (days)	16(12–19)
Tumor recurrence	
Yes	3/1.3%
No	181/77.4%
Residual	6/2.6%
Unknown	44/18.8%
First review time	1(1–3)n = 191
First review of tumor size	1.5(1-3.5)n = 11
n = Number of persons with complete information	

The reasons for surgery among the patients were analyzed and classified. A total of 24 patients received surgical treatment due to continuous tumor growth and 11 patients with complete data were followed up, and tumor growth rate calculated. The median follow-up time was 56 (11–132) months, and median tumor growth rate was 0.055 (0.019– 0.08) cm per month. Continuous tumor enlargement was observed in patients older than 30 years (Fig. 5).

After the Clavien-Dindo classification of surgical complications, logistic regression analyses, single-factor analyses and multiple factors in the single factor analyses of clinical symptoms were conducted. The results of the analyses revealed that maximum tumor diameter (cm) and blood loss increased (ml), blood transfusion volume (ml) increased, the length of time (day), tumor distribution: left/right liver, liver door blocking methods: Pringle maneuver has/other methods, as well as the treatment: laparoscopic/open associated with complications. Multivariate analyses revealed that treatment was significantly correlated with postoperative complications ($P < 0.05$), which was a risk factor for postoperative complications (Table 5).

Table 5
Logistic regression analysis of the risk of Clavien-Dindo complications

		Univariate analysis			Multifactor analysis	
Variables	OR	95% CI	P	OR	95% CI	P
Increased clinical symptoms	1.8	1.15–4.06	0.011			
The maximum diameter of the tumor increased(cm)	1.49	1.04–2.13	0.028			
Increased blood loss(ml)	1.47	1.08–1.99	0.014			
Increased blood transfusions(ml)	1.6	1.16–2.2	0.04			
Increased hospital stay(d)	4.83	2.92–7.97	0.001	3.55	2.07–6.1	0.001
Tumor distribution: Left lobe/right lobe	2.42	1.37–4.29	0.02			
Hepatic portal blockade method: Pringle/ Others	2.39	1.04–5.04	0.039			
Treatment: Laparoscopy/Open resection	0.12	0.06–0.25	0.001	0.18	0.08–0.38	0.001

Discussion

HH is the most prevalent benign tumor of the liver, and its incidence is second to that of hepatic cyst. Previous studies have revealed that the incidence of HH in the general population is 5–20%[16–18]. Statistical analyses of data extracted from the physical examination reports of 670,000 healthy individuals in China revealed that the incidence of HH was approximately 1.5%, and the male to female ratio was approximately 1.3:1. The age group with a high incidence of HH was 40–60 years, accounting for 58%[19]. Kamyab et al. conducted abdominal ultrasound examination of 1,985 patients among the Iranian population, and the results revealed that the prevalence of HH was 2.04%, which was higher in females (2.26%) than in males (1.7%) and the age distribution of the disease was predominantly 40–50 years[20]. In addition, a study conducted by Duxbury et al. revealed that the prevalence of HH was higher in females than in males (female: male ratio = 5:1), and the average age was 50 years[2]. Mocchegiani et al. conducted a retrospective analysis of 83,181 abdominal CT or MRI records of patients who visited the radiology department over a 7-year period, and the study results revealed that the prevalence of HH was 2.5%[21]. Guang-chuan et al. conducted a retrospective analysis of 818 patients with HH who were treated at a health facility from 2003 to 2011 and the results revealed that the number of patients with HH increased annually, and distribution of patients with HH among the different age groups varied between male and female patients. The proportion of patients aged 41–60 years was the highest[22]. However, liver hemangioma is a benign disease, thus does not draw attention in some patients, and this could result in missed diagnoses. Incomplete electronic medical records due to the heavy work load of clinical doctors also result in missed diagnoses of patients. Real-world studies provide a broad inclusion criteria and limited exclusion criteria, and non-randomly selected interventions for real conditions and intentions of patients with larger sample sizes. The present study adopted a retrospective analysis design to identify the true clinical and epidemiological characteristics of single center experience HH. Retrospective analyses of outpatient and physical examination data between 2016 and 2017 revealed that the prevalence rate of HH in the outpatient population was 0.089%, with males accounting for 0.040% and females accounting for 0.049%, and the ages of patients ranged between 41 and 60 years. The prevalence of HH was 1.217% in the healthy population, with males having an incidence rate of 0.707% and females 0.510%, and the ages of participants ranged between 21 and 40 years. The high number of healthy individuals among a sick population when compared to the outpatient population could be associated with the continuous improvement in the living standards and health awareness of individuals. Furthermore, the observation could be attributed to the fact that outpatients consider the disease as a guide and only a few patients receive liver imaging examinations, but generally lower than the figures reported in previous studies. With reference to the age of outpatients and inpatients with HH, the patients were all aged 41–60 years, which was consistent with the age group in previous studies. However, the physical examination group was younger, with ages ranging from 21 to 40 years, which could be associated with the characteristics of the included population.

A few studies have revealed that female patients are more likely to develop HH than male patients, and high estrogen levels during pregnancy and long-term use of contraceptives can promote the growth of HH[23–26]. Conversely, a few studies have revealed that HH is not associated with the history of menstruation, reproduction, or contraceptive use[27]. In addition, no statistically significant difference was observed in the occurrence and development of HH between males and females, and HH prevalence in both sexes increased[28, 29]. Wang et al. established that the trend exhibited by tumors in women was associated with age and was consistent with the varying estrogen levels[30]. Tumor diameter in women increased with age and subsequently decreased. Vascular malformation caused by excessive vascular development or abnormal differentiation is the primary cause of liver hemangioma, and estrogen is largely degraded and inactivated in the liver. Presently, the mechanism of action between estrogen and liver hemangioma is still unclear; therefore, further research is required to investigate underlying mechanisms. The present study established that the number of male and female patients among outpatients and inpatients was similar, whereas the number of male patients was higher than that of female patients in the check-up population. The observation was contrary to the findings of recent studies, but a reason explaining the high number of males is unknown. This could be associated with factors identified in previous studies, such as using surgical patients as research objects, exclusion of a healthy population, and a very small sample size.

Based on the distribution of HH locations, the current research results revealed that the right lobe of the liver is mostly in the left lobe of the liver. A study by Wahab et al. that evaluated 144 patients with giant HH revealed that the right lobe of the liver accounted for 64.6% of multiple lesions, the left lobe of the liver accounted for 28.5% of multiple lesions, and the left lobe of the liver accounted for 6.9% of multiple lesions; among which, 88.9% were single lesions and 11.2% were multiple lesions[31]. Yoon et al. evaluated 115 patients with HH and established that the right lobe of the liver was more common than the left lobe of the liver[32]. A previous analysis of 818 cases of HH at the First Affiliated Hospital of Guangxi Medical University revealed that the lesions were predominantly located in the right lobe of the liver (57.2%), followed by the left lobe of the liver (27.2%), with lesions located in multiple lobules accounting for 15.6%[22]. Lesions in the right lobe of the liver among the 234 patients who underwent surgical resection accounted for 47%, lesions in the left lobe of the liver accounted for 34.6%, and lesions in multiple lobes accounted for 18.45% of the cases; single lesions accounted for 69.2% and multiple patients accounted for 30.8% of the cases. The number and location of hemangiomas could be associated with blood supply and anatomy of the liver.

Most patients with HH did not exhibit clinical symptoms. However, patients with tumors larger than 5 cm could present clinical symptoms[15]. Abdominal pain is a common clinical manifestation, especially discomfort in the right upper quadrant; other clinical symptoms are not specific. Abdominal distension can occur in patients with tumors > 10 cm[15, 33], and tumors located at different parts of the liver can cause compression of adjacent organs or tissues, consequently causing other clinical symptoms. If the pressure on the bile duct can cause obstructive jaundice, then the pressure on the portal vein can lead to intrahepatic, pre-hepatic, and other types of portal hypertension. Furthermore, pressure on the stomach can result in decreased appetite and abdominal distension after an early meal saturated with fats. Some patients may present with fever, dyspnea, heart failure, hemophilia, and other rare symptoms[34–37]. A large hemangioma of the liver could lead to Kasabach-Merrit syndrome (thrombocytopenia, disseminated intravascular coagulation, and systemic bleeding), which is manifested in laboratory disorders caused by multiple factors, leading to severe complications and pose a huge threat to a patient's life. In the current study, the incidence of Kasabach-Merrit syndrome in tumors > 15 cm was 0.3–26%[15, 38]. Another severe complication is spontaneous or traumatic rupture of the tumor (mostly seen in peripheral and exogenous giant HH), and the risk of rupture has been demonstrated to be extremely low (0.47%)[21]. The research results of a previous study conducted at the First Affiliated Hospital of Guangxi Medical University revealed that most patients (510 cases = 62.3%) with HH were identified by accidental examination during hospitalization, while 174 (21.3%) cases of HH were detected by physical examination, and only 134 cases (16.4%) exhibited clinical symptoms, predominantly abdominal discomfort and pain[22]. The proportion of patients with an abdominal mass was 1.7%, patients with upper abdominal discomfort accounted for 39.7% of the cases, which was second to 53.4%, and lumbar pain accounted for 2.6% of the cases, which were consistent with the results of previous studies.

In relation to the clinical classification of HH, relevant previous studies have revealed that the diameter and number of tumors form a critical basis for clinical classification, especially the diameter of tumors. Previously, an integrated classification standard in foreign reports did not exist, and a diameter of 4 cm was largely recommended as the cut-off point for tumor classification, while most domestic scholars recommended a diameter of 5 cm as the cut-off point for classification[31, 39]. Based on tumor diameter, HH was classified into three grades by the Chinese hepato-biliary and pancreatic expert group: (1) small hemangioma (diameter < 5.0 cm), (2) large hemangioma (diameter of 5.0–9.9 cm) and (3) giant hemangioma (diameter ≥ 10.0 cm), and most patients with tumor diameters < 5.0 cm did not exhibit clinical symptoms. Therefore, the consensus is to classify tumors based on their clinical manifestations and characteristics, diameters, numbers, and pathology[19]. The patients who underwent surgical and physical examination in this study were classified in accordance with the domestic consensus of clinical classification. The surgical patients mainly had large and giant hemangiomas, while the physical examination group mainly had small hemangiomas. Precise diagnosis and classification are the crucial preconditions that could guide appropriate treatment of patients with HH, and tumor diameter can be used as one of the indicators of classification and treatment.

Currently, the most controversial treatment indicator is prophylactic treatment of HH. In a previous study that involved 236 patients with a median follow-up time of 48 (3–26 months) months, 61% of the patients exhibited increased tumor size and peak growth rate, and patients with tumors ranging between 8 and 10 cm exhibited an increase in tumor size at a rate of 0.80 ± 0.62 cm per year[14]. In another study involving 123 patients over the age of 30 years, the mean linear size of hemangiomas increased by 5% or more in 39.3% of the patients. The average annual linear growth rate for all lesions was 0.03 cm, and that of 5% or more was 0.19 cm[40]. A previous study on 534 cases of patients with a median follow-up time of 18 months (14 to 22 months) revealed that tumor diameters increased in 215 cases (40.3%), decreased in 217 cases (40.6%), and did not change in 102 cases (19.1%). Strikingly, the researchers established that tumor diameter increased with increase in age between different genders in patients with hemangiomas aged 40 years; hemangioma in male patients over 40 years of age increased gradually, whereas hemangioma in female patients exhibited a relatively decreasing trend[30]. In this study, only 24 patients (10.3%) received surgical resection due to rapid tumor growth and 11 patients with complete follow-up data were assessed to calculate tumor growth rate. The median follow-up time was 56 (11–132 months) months and the median growth rate was 0.055 (0.019–0.08 cm) cm per month. Tumor mass in patients older than 30 years exhibited a trend of continuous and gradual enlargement. Most hemangiomas in individuals from a healthy population were small (< 5 cm), as well as the primary tumor. Therefore, tumor enlargement during follow-up should be closely monitored rather than administering aggressive treatment, and prophylactic surgical resections should be discouraged.

With the current advances in medical technology, the safety of elective resection of benign liver tumors is relatively similar to that of a major intra-abdominal surgery. Moreover, the rapid development of laparoscopic surgery confers the advantages of minimally invasive surgery in treatment. However, liver hemangioma surgery still has certain surgical risks and complications[32, 41]. Wahab et al. evaluated 144 patients with giant HH and established that 32 (22.2%) patients had postoperative complications, 20 (8.3%) had G I complications of the Clavien-Dindo classification, 7 (4.9%) had G II complications, 12 (8.3%) had G III complications, and 1 (0.7%) had G V complications[31]. In a previous study by Miura et al., 241 patients with hepatic hemangioma who underwent surgery were evaluated and the findings revealed that a total of 14 patients (5.7%) experienced postoperative complications of grade III and above based on the Clavien-Dindo classification, 2 (0.8%) patients died and 3 (1.2%) patients experienced life-threatening complications within 30 days after surgery[38]. In the present study, the incidence of grade A and Grade B complications of ISGLS[42] liver function was 11.966% and 0.427%, respectively while the incidence of grade A and Grade B bleeding complications of ISGLS postoperative hemorrhage[43] was 3.846% and 2.137%, respectively. No patients had postoperative biliary fistula and no perioperative death was recorded. A total of 16 patients (6.8%) experienced grade III complications[44] and 4 (1.7%) patients experienced grade IV complications of the Clavien-Dindo classification system.

In this study, univariate analyses of complications after Clavien-Dindo classification of hepatectomy were performed, and the results of the analyses revealed that clinical symptoms, maximum tumor diameter, blood loss, blood transfusion volume, length of hospital stay, tumor distribution, hepatic portal blockade, and treatment were correlated with postoperative complications. Furthermore, sequential logistic regression analyses revealed that treatment was a significant factor influencing postoperative complications. By contrast, Dong et al. evaluated 190 patients with HH and the results revealed that the size of HH was not an independent factor influencing postoperative complications[45]. Previous studies have revealed that perioperative blood transfusion is a crucial factor influencing postoperative complications and death after hepatectomy[46−48]. Perioperative blood transfusion affects the prognosis of patients, postoperative recovery of liver function, and increases the incidence of postoperative complications. Increased hemorrhage and coagulation abnormalities caused by delayed postoperative recovery of liver function could still occur despite of the existence of intraoperative hepatic portal occlusion. A few patients require perioperative blood transfusion therapy, and allogeneic blood transfusion can lead to immunosuppression, inflammatory reactions, postoperative infections, and other complications[49], which in turn affect postoperative recovery of patients.

HH is a tumor that originates from the mesoderm and comprises of a single layer of flattened endothelial cells and cavities filled with blood, which is mainly supplied by the hepatic artery. HHs can be classified into capillary hemangiomas and cavernous hemangiomas[50]. Pathologists have classified HHs into sclerosing hemangiomas, vascular endothelial cell tumors, capillary hemangiomas, cavernous hemangiomas, and other subtypes based on the fiber content of the tumor tissues, and cavernous hemangiomas are the most common type[19]. The pathological types of HHs in 234 patients evaluated in the present study included 224 cases (95.7%) of cavernous hemangioma, 3 cases (1.3%) of capillary hemangioma, 2 cases (0.9%) of sclerosing hemangioma, and 5 cases (2.1%) of other types of hemangiomas.

Nevertheless, the present study adopted a retrospective study design, which had a few limitations. The data used for analyses only covered a two-year period in relation to the epidemiological survey; therefore, variation in the overall incidence of HH should be validated using large sample sizes to carry out big data epidemiological survey. In addition, the lack of uniform standards in imaging reports resulted in the loss of crucial information of some patients with HH. The time span was long and a certain deviation in postoperative complication statistics could be observed with the improvement of surgical techniques. A high rate of loss to follow-up occurred because HH is a benign disease.

Conclusion

HH is a common benign disease of the liver with similar prevalence rates in both outpatients and inpatients aged between 40 and 60 years. Most of the males in the physical examination group were female, and most were aged between 21 and 40 years. A median tumor had a maximum diameter of 1.3 (0.4–9.9) cm; most lesions were located in the right lobe of the liver and were predominantly single lesions. Treatment and length of hospital stay of patients with HH were associated with the occurrence of complications after tumor resection, with a statistically significant difference ($P < 0.05$). Treatment and length of hospital stay were related risk factors for postoperative complications in patients with HH.

Abbreviations

AFP Alpha Fetoprotein

ALT Alanine Transaminase

AST Aspartate aminotransferase

CT Computed Tomography

DBil Direct Bilirubin

Hb Hemoglobin

HH Hepatic Hemangioma

MRI Magnetic Resonance Imaging

PLT Platelet

RFA Radiofrequency ablation

TAE Transcutaneous Arterial Embolization

TBil Total Bilirubin

WBC White blood cells

Declarations

Availability of data and materials

The data and materials used to support the findings of this study are available from the corresponding author upon request.

Ethical Statement

The study was approved by the Ethics Review Committee of the First Affiliated Hospital of Guangxi Medical University.

Consent for publication

We obtained the patients' or legal representative's consent for publication of this study.

Competing interests

The authors declare no potential conflicts of interest.

Funding

This study was funded by the National Nature Science Foundation of China (Grant No. 81560535). Natural Science Foundation of the Guangxi Province of China
(Grant No. 2018 GXNSFBA138013). Guangxi Key R&D Program (GKEAB18221019), and Guangxi Key Medical and Health research project (Z2010018).

Authors' Contributions

Tao Peng designed the study. Yongfei He collected clinical data ,interpreted the results and wrote the article. Guangzhi Zhu, Hao Su, Xiwen Liao, Chengkun Yang,Yongguang Wei, Zhongliu Wei, Tianyi Liang, Shutian Mo and Zijun Chen collected clinical data. Zili Lv contributed to conducted pathological typing. Chuangye Han contributed to guidance writing. Tao Peng edited and funding the article. All authors discussed the results, and approved the final version of the manuscript.

Acknowledgments

The authors thank the Medical Records Information Section and the Computer Centre for their assistance.

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Figures

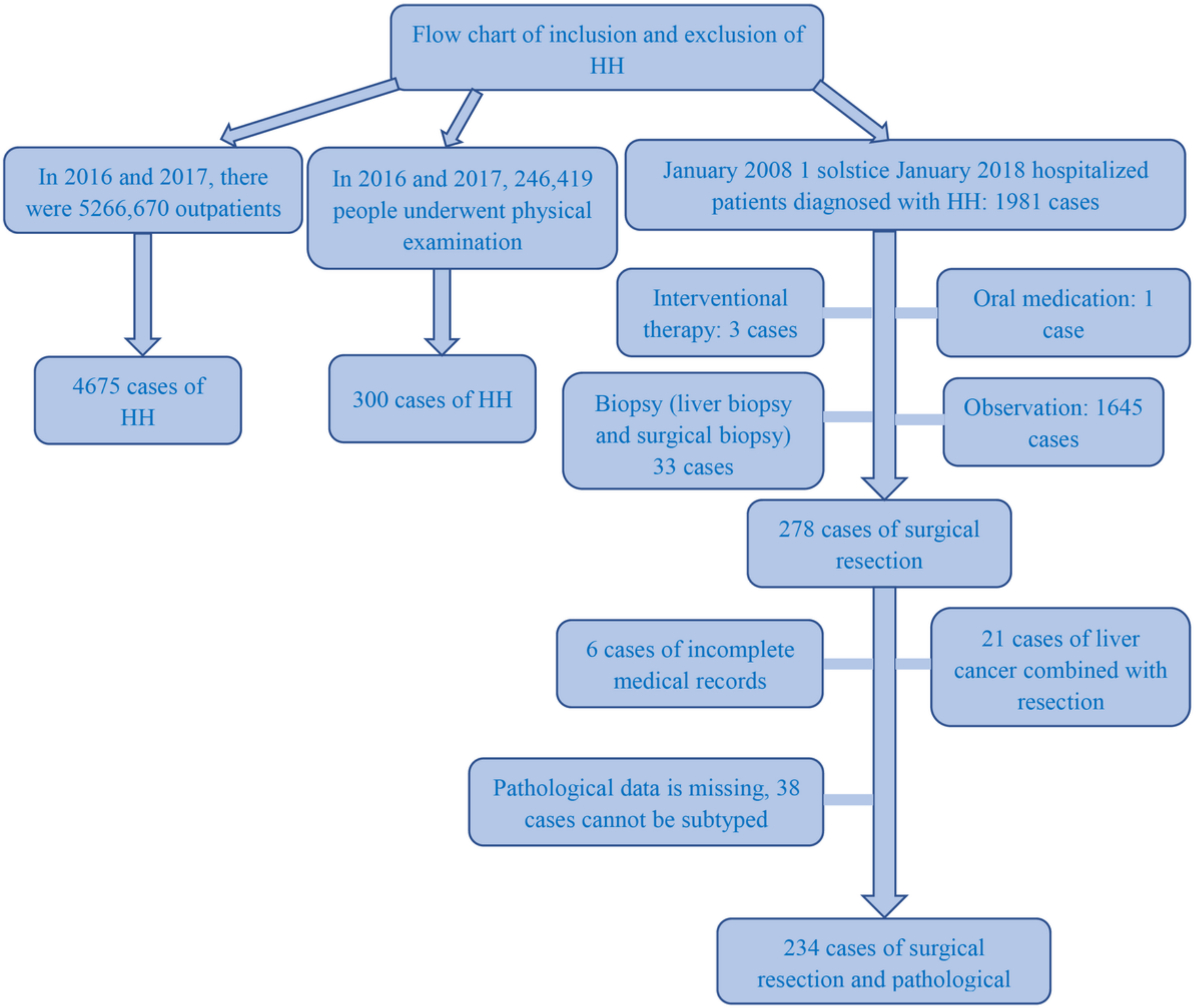
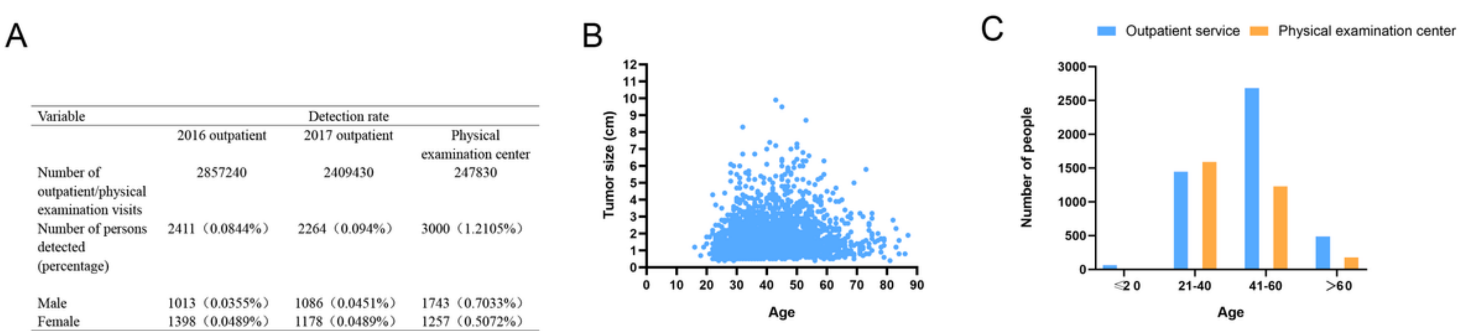


Figure 1

Flow chart of patient inclusion and exclusion



Variable	Detection rate		
	2016 outpatient	2017 outpatient	Physical examination center
Number of outpatient/physical examination visits	2857240	2409430	247830
Number of persons detected (percentage)	2411（0.0844%）	2264（0.094%）	3000（1.2105%）
Male	1013（0.0355%）	1086（0.0451%）	1743（0.7033%）
Female	1398（0.0489%）	1178（0.0489%）	1257（0.5072%）

Figure 2

Data of outpatient and physical examination patients. A, Detection rate of HH in outpatient and physical examination. B, Age distribution of HH in outpatient and physical examination. C, Age and tumor size distribution of HH in the physical examination population

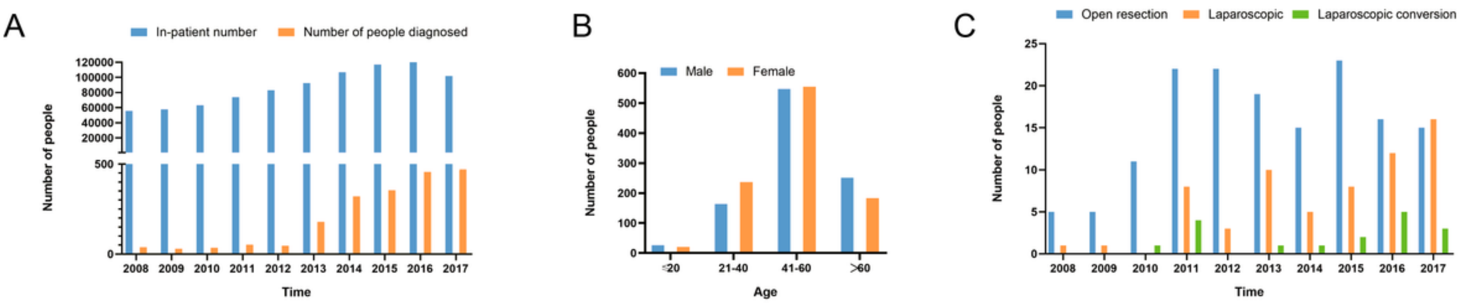


Figure 3

Data on HH in inpatients. A, Diagnosis of hospitalized patients and HH from 2008 to 2017. B, Age distribution of HH in inpatients. C, Changes of surgical methods for HH.

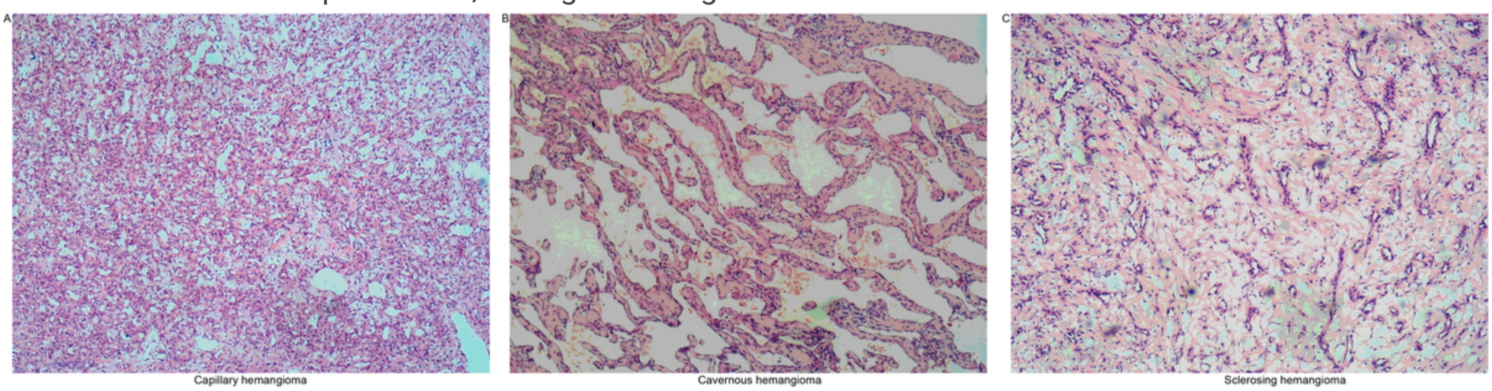
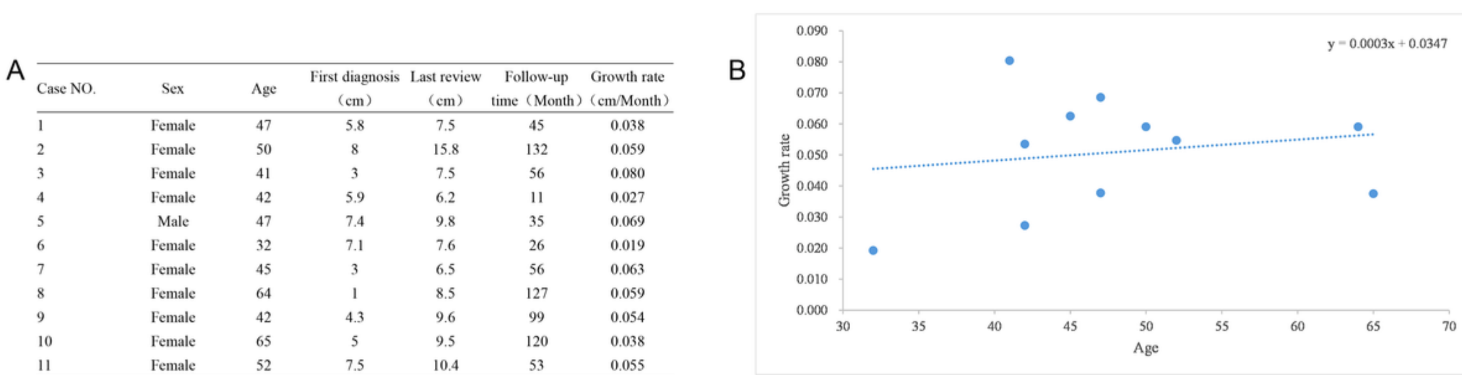


Figure 4

Pathological type of HH.



Case NO.	Sex	Age	First diagnosis (cm)	Last review (cm)	Follow-up time (Month)	Growth rate (cm/Month)
1	Female	47	5.8	7.5	45	0.038
2	Female	50	8	15.8	132	0.059
3	Female	41	3	7.5	56	0.080
4	Female	42	5.9	6.2	11	0.027
5	Male	47	7.4	9.8	35	0.069
6	Female	32	7.1	7.6	26	0.019
7	Female	45	3	6.5	56	0.063
8	Female	64	1	8.5	127	0.059
9	Female	42	4.3	9.6	99	0.054
10	Female	65	5	9.5	120	0.038
11	Female	52	7.5	10.4	53	0.055

Figure 5

Relationship between tumor growth rate and age. A, Follow-up data on the rate of tumor growth in patients with HH. B, Linear relationship between tumor growth rate and age in patients with HH.