Differentiation and management of hepatobiliary mucinous cystic neoplasms: a single centre experience for 8 years

Junhao Zheng
Zhejiang University School of Medicine Sir Run Run Shaw Hospital https://orcid.org/0000-0002-3688-1239
Jingwei Cai
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Mubarak Ali Kirih
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Junjie Xu
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Liye Tao
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Yuelong Liang
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Xu Feng
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Jing Fang
Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Xiao Liang (**srrshlx@zju.edu.cn**)
https://orcid.org/0000-0002-9423-9201

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Abstract

Background

Hepatobiliary mucinous cystic neoplasms (H-MCNs) are quite rare cystic neoplasms in the liver. The management and prognosis between the hepatic simple cyst (HSC) and H-MCNs are adverse, and the differential diagnosis of H-MCNs remains big challenging. This study aimed to present our experience in the management of H-MCNs and provide a preoperative H-MCNs risk prediction nomogram to differentiating H-MCNs from HSC.

Methods

29 patients diagnosed with H-MCNs and 75 patients diagnosed with HSC between June 2011 and June 2019 at Zhejiang University, School of medicine, Sir Run-Run Shaw Hospital, were reviewed in this study. Demographic and clinicopathological variables were analyzed.

Results

US, CT, and MRI could accurately diagnose only 3.4%, 46.1%, and 57.1% of H-MCNs, respectively. After univariate analysis and multivariate logistic regression analysis, the variables significantly associated with H-MCNs were enhancement after contrast ($p = 0.009$), tumour located in the left lobe ($p = 0.02$) and biliary ductal dilation ($p = 0.027$). An H-MCN risk predictive nomogram constructed by these factors and serum CA199 level showed excellent discrimination (areas under the receiver operating characteristic curve were 0.940) and agreement calibration between predicted probability and actual probability.

Conclusion

Among patients with the H-MCNs, the location of the tumour, enhancement in CT scan, and biliary ductal dilation are significantly independent risk factors. The reasonable treatment of H-MCNs is radical resection. Using our nomogram could facilitate screening and identification of patients with liver cystic lesions.

Background

with the development of the radiography technique and the increasing frequency of routine health examination, more and more cystic lesions of the liver had been discovered through these years. It was reported that about 20% of ordinary people have liver cystic lesions.[1] The most majority of these lesions are hepatic simple cysts (HSC), a kind of common benign cysts of the liver. HSC is a benign cystic lesion that grows up by inches, and most of the HSC require no treatment or just fenestration. However, there are other two more aggressive lesions in the liver, called intrahepatic biliary cystadenomas (IBC) and intrahepatic biliary cystadenocarcinoma (IBAC). IBC and IBAC are estimated to occupy less than 5% of the liver cysts.[2, 3] IBC was first reported by Henter et al. in 1887.[4] In 1958, Emre described IBC as a liver cystic neoplasm with the pathological feature of “ovarian-like stroma(OS).”[5] By the year of 2010, the World Health Organization (WHO) redefined that the OS is the requirement for the diagnosis the cystadenoma both in liver and pancreas, and uniformly rename the IBC and IBAC as hepatobiliary mucinous cystic neoplasms (H-MCNs).[6, 7]

Although H-MCNs were defined by the new standard, the preoperative diagnosis of H-MCNs remains quite tricky. Notably, even the equipment of diagnosis have been improving quite a lot, such as contrasted-enhanced ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI), the differential diagnosis for H-MCNs and HSC was still a big challenge.[8] IBC has a malignant potential to transform into IBAC in 20–30% patients, and the rate of recurrence is much higher than HSC after fenestration therapy.[9] Because the biological characteristics and treatment strategies between these two diseases are quite different, the accurate preoperative diagnosis of H-MCNs is of great significance. This study aimed to present our experience in the diagnosis and management of H-MCNs under the new WHO classification. Meanwhile, we developed and validated a predictive model to enhance the diagnostic accuracy between H-MCNs and HSC, and display the model with a nomogram.

Methods

Patient and Data

We retrospectively reviewed the data of patients who underwent surgical treatments and pathologically diagnosed as H-MCNs with the WHO 2010 new standard between June 2011 and June 2019 at Zhejiang University, School of medicine, Sir Run-Run Shaw Hospital. A total of 29 patients diagnosed with H-MCNs by at least two experienced pathologists were included in this study. Besides, clinical data of 75 patients with HSC between June 2011 and June 2019 were randomly collected to compare the characteristics with the H-MCNs. The patients with other liver neoplasms, missing or incomplete data, nonoperative treatment, or these who weren't diagnosed in histology were excluded from the study. (Fig. 1)

Clinical and demographic variables, including age, gender, clinical symptoms, duration of symptoms, serum tumour markers, liver function, were obtained from medical records. Information about the preoperative imaging findings of US, CT, and MRI was reviewed. Radiological features like enhancement after contrast, multilocular cyst, septa, calcification, biliary ductal dilatation were collected. The surgical approaches, operation time, and bleed loss were reviewed from operation records. Tumour size was obtained from the pathological reports, which is defined as the longest diameter of the tumour. If the size was not mentioned in pathological reports, we referred to the most recently preoperative cross-sectional imaging report. The presence of OS was the requirement to diagnosis the H-MCNs in histology. This retrospective study was approvaled by the Ethics committee of Sir Run Run Shaw Hospital.

Statistical Analysis

Continuous variables were displayed as the mean ± standard deviation or medians with ranges. Categorical variables were presented as numbers and percentages. We used student's t-test or Mann–Whitney U test to compare continuous variables, and chi-square or Fisher's exact test to compare categorical variables among different groups. The subgroup was set by the cut-off value according to the receiver operating characteristic curve analysis reported by Wang et al.[10]

The univariate analysis was used to analyze the relationship of preoperative clinical characteristics and imaging features between HSC and H-MCN. Variables with statistical significance were further enrolled in the multivariate logistic analysis. We incorporated the variables significantly independent in multivariate logistic analysis or significantly in clinical practice to construct a preoperative H-MCNs risk prediction nomogram. Bootstraps with 1,000 resamples were used to validate the calibration of the nomogram. And we used receiver operating characteristic curve analysis and concordance Index (C-index) to assess the model discrimination. A P-value of less than 0.05 was deemed as statistical significance. All of the statistical analysis was conducted by SPSS (ver 23.0, USA) and R software (ver 3.5.3, USA).

Result

Demographic, clinical characteristics, preoperative image outcome, and treatment

From June 2011 to December 2018, 29 patients diagnosed as H-MCNs in histology underwent surgical treatment in our institution, including 4 cases of IBAC. The images of US, CT, MRI, and corresponding histology were displayed in Fig. 2. Their demographics and clinical characteristics were presented in **Supplement A**. The median age of the patients were 53 years (range, 47–62). A majority of patients were female (69%). Half of the patients initially complained about abdominal pain (48.3%); the median duration of symptoms was 48 months (range, 0.3–240 months). Interestingly, although the left part of the liver is much smaller than the right, most of the lesions (79.3%) were located on the left.

Preoperative image examination and treatment characteristics between H-MCNs and HSC were shown in Table 1. Although most of the patients with H-MCNs underwent US, only 1 (3.4%) patient was accurately diagnosed by the US. Whereas, among the patients with HSC, the accuracy of the US was 90.4%. In the H-MCNs group, 26 and 14 patients respectively underwent CT and MRI, 12 (46.1%), and 8 (57.1%) of the patients were accurately diagnosed as H-MCNs by CT and MRI. The diagnostic accuracy of CT and MR was much higher in the patients with HSC. In our institution, half (50%) of the patients with H-MCNs were performed a laparoscopic operation, and all (100%) of the patients with HSC were in laparoscopy. About the type of surgery, the operative intervention included cyst resection (34.5%) and partial liver resection (65.5%); 3 patients were initially performed fenestration, then concerted to radical operation because intraoperative frozen section examination suggested that the lesion may be H-MCNs. Compared with the H-MCNs group, most of the patients with HSC (96%) underwent fenestration; 3 patients (4%) were performed radical resection due to misdiagnosing as H-MCNs. A total of 4 patients (14.2%) with H-MCNs and one patient with HCS suffered a postoperative complication.

Table 1
Image examination and treatment between hepatobiliary mucinous cystic neoplasms and hepatic simple cyst.

	H-MCNs (n = 29)	HSC (n = 75)
Preoperative imaging, x/n † (%)		
Ultrasound (US)	1/29(3.4)	66/73(90.4)
contrast computed tomography (CT)	12/26(46.1)	62/67(92.5)
Magnetic resonance imaging (MRI)	8/14(57.1)	6/8(75)
Surgery, n (%)		
Fenestration	0(0)	72(96)
Tumor resection	10(34.5)	2(2.7)
Partial liver resection	19(65.5)	1(1.3)
Surgical approach, n (%)		
Laparoscopy	14(48.3)	75(100)
Open	15(51.7)	0(0)
Estimated blood lost, median (IQR)	200(100–300)	10(5-13.75)
Operation time, median (IQR)	169(213–288)	55(45–90)
complication, n (%)		
Abdominal bleeding	1(3.6)	0(0)
Bile leakage	2(7.1)	0(0)
Incisional infection	1(3.6)	0(0)
Pleural effusion	0(0)	1(1.3)

H-MCNs: hepatobiliary mucinous cystic neoplasms; HSC: hepatic simple cyst.

†X: diagnose accurately by the equipment; n: the number of the patient who have done the examination.

Comparison of demographic and clinical characteristic between patients with H-MCNs and HSC

During the study period, a total of 104 patients who had liver cyst lesions and underwent surgical treatment were included. Preoperative demographics and clinical characteristics of H-MCNs and HSC were displayed in Table 2. Twenty-three variables were used to be tested as potential predictors of H-

MCNs in liver cystic lesions. In univariate analysis, eight preoperative variables including abdominal pain, fever, duration of the symptom, serum CA19-9 elevation, enhancement after contrast, biliary ductal dilation, septa were significantly different ($p < 0.05$) between the group of H-MCNs and HSC. These statistically significant predictors were included in further analysis by using a multivariable logistic regression model. On multivariable analysis (Table 3), with the reported as odds ratio (95%CI), enhancement after contrast (12.1[2.11–100]), lesion located in the left of the liver (11.0[1.71–121]), biliary ductal dilatation (9.80[1.46–92.2]) were independently associated H-MCNs. And the elevation of serum CA19-9 (5.21[1.02–31.9], $p = 0.053$) was a nearly significantly independent factor. Then, we conducted collinearity diagnosis for these independent risk factors, the variance inflation factor was 1.11, 1.03, 1.20, and 1.06, respectively, which means that there is no collinearity among these four factors, and the model composed of these four variables would be robust.

Table 2
Clinical and imaging feature of the patients with the hepatic liver lesion.

	H-MCNs (n = 29)	**HSC (n = 75)**	***p*-value**
Demographics			
Age,mean(SD), yr			0.068
> 60	9 (31.0)	40 (53.3)	
≤ 60	20 (79.0)	35 (46.7)	
Sex, n (%)			0.463
Female	20 (69.0)	57 (76.0)	
Male	9 (31)	25 (24)	
Symptom, n (%)			
Abdominal pain	14 (48.3)	19 (25.3)	**0.024**
Abdominal fullness	7 (24.1)	10 (13.3)	0.181
fever	4 (13.8)	0 (0)	**0.005**
Jaundice	2 (6.9)	0 (0)	0.076
Weight loss	1 (3.4)	0 (0)	0.275
Duration of the symptom (month)	1 (0.133-240)	60 (0.1–360)	**< 0.001**
Liver function			
AST (IQR), U/l	23 (13–38)	20 (18–23)	0.273
ALT (IQR), U/l	20 (13.5–31.5)	17 (14–22)	0.101
Total bilirubin (IQR), mg/dl	13.4 (11.2–16.2)	12.3 (10–16)	0.730
Serum tumor markers			
CA 19–9 (U/mL), n (%)			**0.001**
> 20	18 (64.3)	15 (27.3)	
≤ 20	10 (35.7)	40 (72.7)	
CEA (ng/mL), n (%)			0.469
> 5	2 (7.1)	2 (2.7)	
≤ 5	26 (92.9)	54 (72.0)	

†Imaging features were collected based on abdominal contrast CT or abdominal contrast MRI.

	H-MCNs (n = 29)	HSC (n = 75)	*p*-value
CA 12–5 (U/mL), n (%)			0.117
> 20	6 (20.7)	5 (9.1)	
≤ 20	22 (75.9)	50 (90.9)	
AFP (ng/ml), n (%)			0.598
> 10	2 (7.1)	2 (3.6)	
≤ 10	26 (92.9)	54 (96.4)	
Imaging feature †, n (%)			
Biliary ductal dilation	17 (58.6)	4 (5.3)	**< 0.001**
Multilocular cyst	17 (58.6)	26 (83.9)	0.109
Enhancement after contrast	20 (69.0)	11 (14.7)	**< 0.001**
septa	13 (44.8)	12 (16.0)	**0.002**
calculous	10 (34.5)	2 (2.7)	**< 0.001**
Calcification	2 (6.9)	12 (16.0)	0.223
cyst size (cm), median (IQR)	8.5 (3.7–12.3)	9.1 (7.8–11.0)	0.131
Location of the cyst, n (%)			**< 0.001**
Left	23 (79.3)	22 (29.2)	
Right	3 (10.3)	39 (58)	
Both	3 (10.3)	14 (18.7)	

†Imaging features were collected based on abdominal contrast CT or abdominal contrast MRI.

Table 3
Multivariate statistical analyses of Clinical characteristics in HSC and H-MCNs.

	OR (95%CI)	p-value
Abdominal pain	3.71 (0.572–29.8)	0.178
Fever	NA	0.995
Duration of the symptom	0.97 (0.985-1.00)	0.600
CA199	5.21 (1.02–31.9)	0.053
Enhancement after contrast	12.1 (2.11–100)	0.009 **
Intrahepatic location		
right	-	-
left	11.0 (1.71–121)	0.020 *
both	7.56 (0.871-108)	0.087
Biliary ductal dilation	9.80 (1.46–92.2)	0.027 **
septa	2.89 (0.455–20.3)	0.260
OR: odds radio; CI: confidence interval.		

Based on the result of multivariate statistical analysis, these four individual predictive factors were incorporated in a preoperative prediction model. We display the model as a preoperative H-MCNs risk prediction nomogram (Fig. 3).

Validation of Nomogram

To validate the discrimination of the prediction model, we created a ROC curve of the nomogram (Fig. 4A), and display a C-index of 0.940,suggesting that this prediction has excellent discrimination. The calibration validation of the model was conducted by the calibration plot by bootstrapping with 1,000 resamples (Fig. 4B). The predicted probability of the nomogram was good agreement with the actual probability.

Discussion

With the improvement of the abdominal radiological technique, more liver cystic lesions were discovered during these years. However, most majorities of cysts are HSC which is a benign disease and often no harmful to the body.[11] IBC and IBAC are rare liver cystic tumours that were redefined as H-MCNs by WHO 2010 with the presence of an ovarian-like stoma (OS), occupying only 5% of liver cystic lesions.[3, 6, 7] H-MCNs are much more aggressive than HSC. BAC tends to transform into IBAC at about 20%.

Meanwhile, it can lead to cholangitis, intestinal obstruction, peritonitis after rupturing, or other complex complications.[12–14] Thus,the treatment between HSC and H-MCNs is extremely diverse, and the accurate diagnosis of H-MCNs and HSC is of great significance. However, for the lack of specific biochemical markers and imaging features, the diagnosis of H-MCNs was still challenging. To improving the differential diagnosis between H-MCNs and HSC, some researchers make their effects on finding some statistical differences on markers. [8, 11, 15, 16]. Due to a relatively rare quantity of H-MCNs, these small-sample studies can hardly find significant features to differentiate these two lesions. Labib et at. found that H-MCNs often combined with single cyst;[15] Koffron et at. found that cystic fluid CA19-9 and CEA level are useful in differentiating H-MCNs and HSC;[16] while Choi et at. reported that cystic analysis of CA19-9 and CEA have no help to diagnose H-MCNs. Up to now, the imaging examination is the most effective method to diagnose H-MCNs, although there is no reliably specific radiographic feature. [9] In a word, the data on the diagnostic feature of H-MCNs remains scarce, and few studies about IBC and IBAC were based on the new classification of H-MCNs with the requirement of a present of OS.[3–5, 7, 9, 17, 18]

In our study, a total of 29 H-MCNs with the presence of OS were included to analyze. Major of H-MCNs occurred in women (20/29, 69%), particularly younger age women (≤ 60 year,79%), which is consistent with the previous study.[8, 15] However, there were no significant differences in age and sex between H-MCNS and HSC, indicated that sex and age were not useful to distinguish these two diseases. Some patients of H-MCNs would complain about abdominal pain (14/29, 48.3%), fever (4/29,13.8%), jaundice (2/29,6.9%) and other symptoms, the symptom of fever was significantly higher than that of HSC, which could be explained that the H-MCNs originate from some congenitally aberrant bile ducts and could lead to cholangitis.[18, 19] The presence of bile duct dilation in imaging also supported this viewpoint.

There are many studies compared the tumour markers between HSC and H-MCNs.[8, 15, 16, 20] Choi et at. found that serum tumour marker of CA19-9 was elevated in the H-MCNs but not reached a significant difference from HSC. In our study, when adjusted cut-off value to 20 U/ml, serum CA19-9 was a nearly independent factor to predict H-MCNs. Other tumour markers like CEA, CA12-5, AFP were not able to differentiate these two diseases, which are consistent with previous researches[20]. Cyst fluid tumour markers analysis of H-MCNs remains controversial and needs more extensive sample sizes study to verify.[8, 15]

Up to now, the radiographic examination was the primary tool to diagnose H-MCNs, although with a high misdiagnosis rate. [21] We gathered the information (Table 1.) to find that only about half of patients with H-MCNs could be accurately diagnosed by the CT (12/26,46.1%) and MRI (8/14,57.1%), while the US was nearly no help to diagnose H-MCNs (1/29,3.4%). The characteristic features of H-MCNs are often solitary, large, thick-wall, multilocular cystic with internal septation and calcification.[10, 21] However, not all lesions simultaneously possess all of these characteristics, and some of HSC could also be described similarly, which made H-MCNs difficultly diagnosed accurately by radiography. In the current study, enhancement after contrast, septa, biliary ductal dilation were significantly associated with H-MCNs compared with HSC. What was interesting is that most lesions of H-MCNs (23/29,79.3%) were located in the left lobe of the liver, bur the normal right lobe of the liver is much bigger than the left. We also found the location of the lesion had a significant difference between H-MCNs and HSC. The mechanism of that need to be further explored.

The distinguish of H-MCNs and HSC preoperatively was crucial to the therapeutic plan. The treatment of HSC is usually fenestration or unroofing. Several patients misdiagnosed as H-MCNs could be performed radical excision and get unnecessary surgical trauma. In our institution, almost all of the fenestration surgery could be conducted by laparoscopy, and majors of patients could discharge in one or two days after the operation. However, because of the high rate of recurrence and the potential of malignant transformation, patients with H-MCNs were recommended to undergo radical resection, such as complete cyst resection or anatomical liver resection, even a liver transplant.[9, 22, 23] It was reported that complete cyst resection of H-MCNs could bring to long-term survival and a low rate of recurrence.[9, 24] According to a multi-institutional study, if the H-MCNs were performed fenestration, the recurrence could reach 48.6%, and might enhance the risk of malignant-transformation.[9]

Since the preoperative diagnosis of H-MCNs remain quite difficult, and the treatment of H-MCNs and HSC is extraordinarily different, it is essential to establish a preoperative diagnosis model to enhance the ability to differentiate H-MCNs and HSC. Therefore, we created a diagnosis nomogram that facilitates accurate identification and screening of H-MCNs before the operation. Although many kinds of literature have investigated factors to distinguish H-MCNs and HSC, to our knowledge, no study has incorporated these independent risk factors to create a diagnosis model.[8, 15, 20] Nomogram is a visualized tool that could vividly display the logistic regression model and help to make clinical decisions. In our nomogram, three factors (Enhancement after contrast, intrahepatic location, and biliary dilation) were significantly associated with H-MCNs in multivariate logistic regression analysis and a nearly significant factor (serum CA19-9 level greater than 20 U/ml) were included. This was the first nomogram that could calculate the probability of H-MCNs in liver cystic lesions. The advantages of the nomogram were that it provides individualized risk assessment in a dynamic manner, and all the factors included are routinely reached in clinical practice. By utilizing this nomogram, the patients with a high probability of H-MCNs would be recommended to undergo a complete resection or a frozen section examination during the operation to get a better survival and a low rate of recurrence.

There were some limitations to this study. First, this was a retrospective study based on Sir Run run Shaw hospital electronic medical records with a relatively small simple. Second, the data of this study were collected in a single institution. Before the full acceptance of this nomogram, it is desirable to validate this result from other institutions. Third, because whether the cystic fluid tumour marker level can help in the diagnosis of H-MCNs remain controversial, and not all of the liver cystic lesion patients were routinely performed aspiration paracentesis, we didn’t include fluid tumour marker level as a predictive factor. Lastly, other specific markers to estimate H-MCNs might further improve the accuracy of this diagnosis prediction model.

Conclusion

H-MCNs were rare cystic tumour of the liver, which is difficulty in differentiation. Enhancement after contrast, located in the left lobe of the liver and biliary ductal dilation, are significantly independent factors to distinguish between H-MCNs and HSC. The H-MCNs risk predictive nomogram provides an accurate probability of H-MCNs risk in liver cystic patients and helps to make the clinical decision.

Abbreviations

H-MCNs hepatobiliary mucinous cystic neoplasms

HSC hepatic simple cyst

IBC intrahepatic biliary cystadenomas

IBAC intrahepatic biliary cystadenocarcinoma

OS ovarian-like stroma

WHO World Health Organization

US ultrasound

CT computed tomography

MRI magnetic resonance imaging

C-index concordance Index

Declarations

Ethics approval and consent to participate

This study was approvaled by the Ethics committee of Sir Run Run Shaw Hospital. All of the participants signed the consent of the study.

Consent for publication

Consent for publication has been pbtained from individuals who might be identified from data or images included in this publication

Availability of data and material

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Competing interests

All authors have none competing interest to declare.

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Authors' contributions

X. L: Study/Protocol design;

JH. Z, JW.C, M. A. K: Data collection and management;

JW. C, JJ. X, LY. T, J. F: Data analysis;

JH. Z: Writing the manuscript.

YL. L, X. F, JJ. X, M. A. K: Reviewing and revising the manuscript.

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Figures

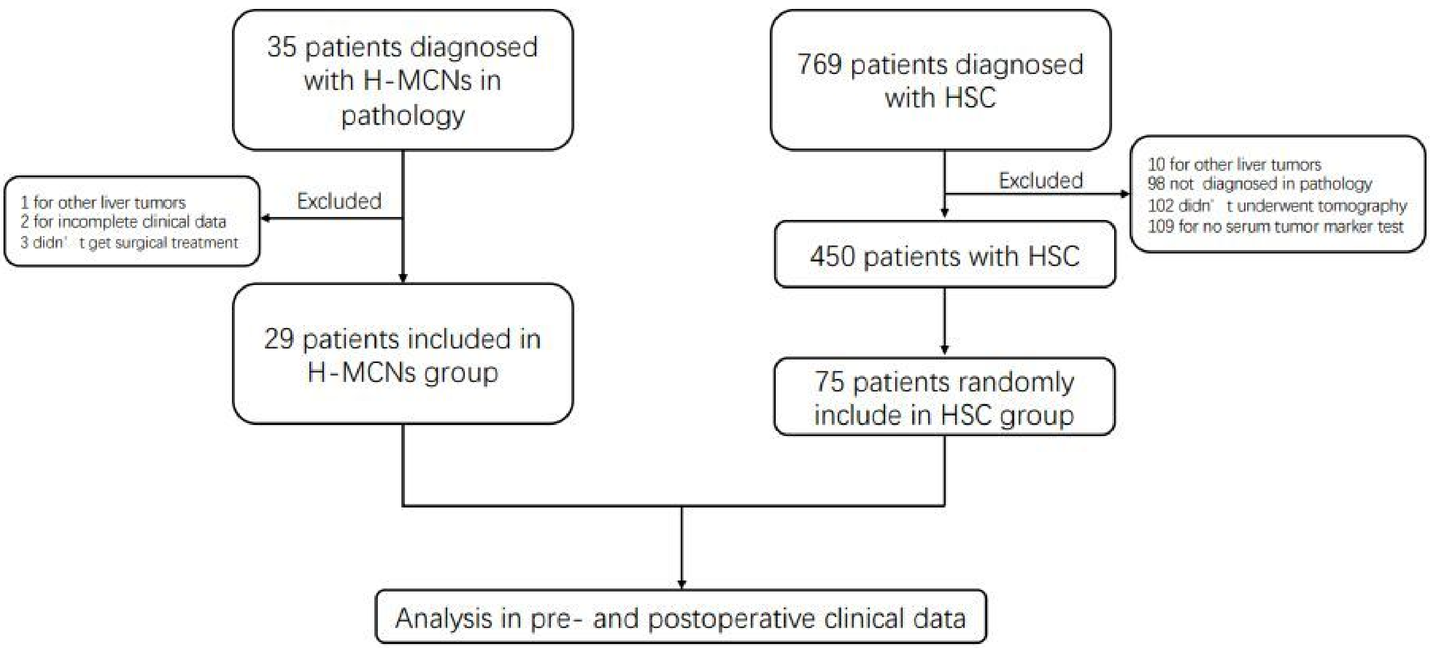

Figure 1

Flowchart of patient selection

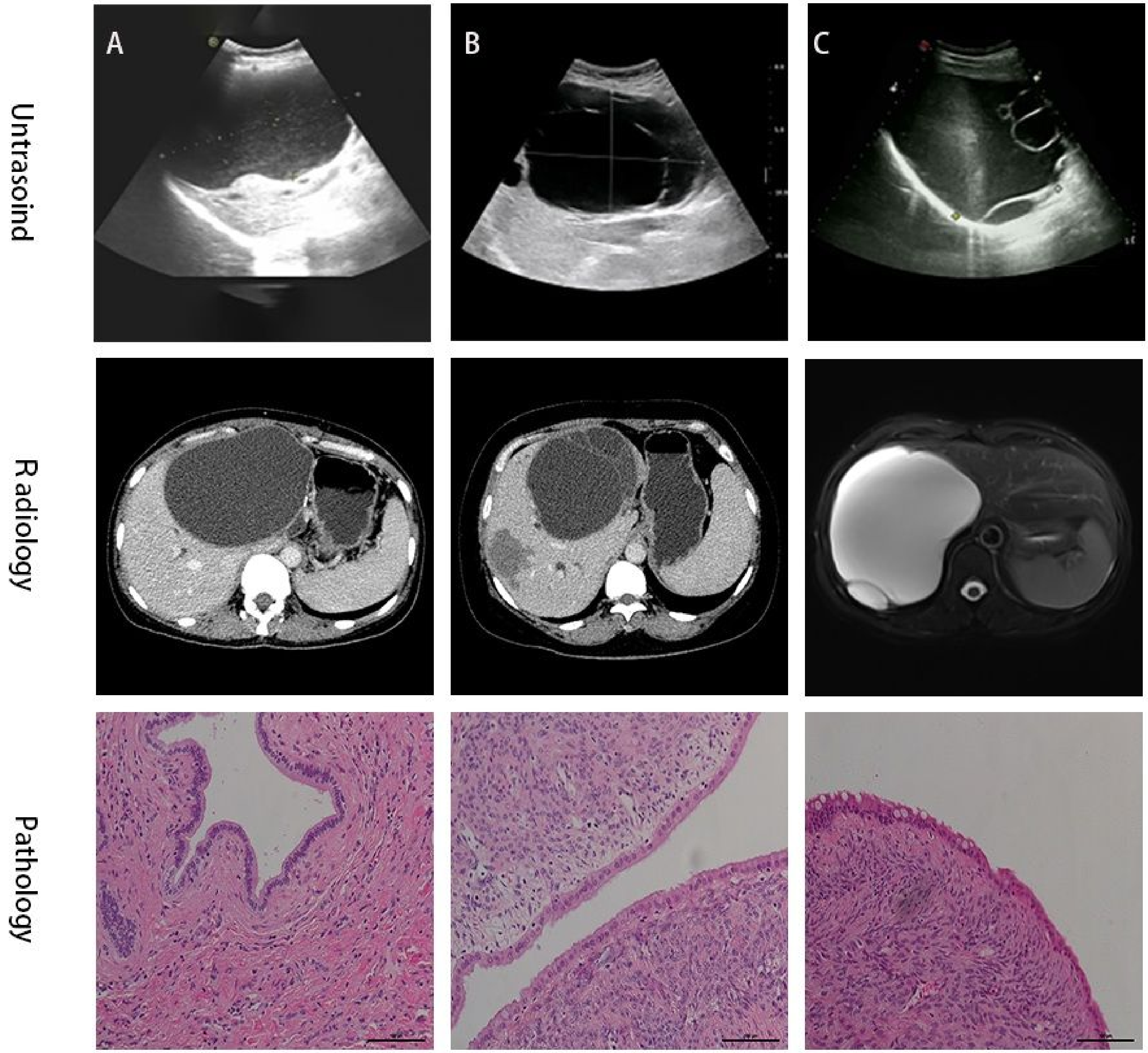

Figure 2

Photos of contrast CT, MRI, and the pathological section of patients with hepatobiliary mucinous cystic neoplasm (H-MCNs). (Heamatoxy-lin & eosin, x40) Patient A was a 47-year-old woman who had been discovered the liver cystic lesion with no symptom for 8 years. Three years ago, she underwent laparoscopic left lateral hepatic lobectomy in her local hospital. But two years later, she was found a 17cm cystic tumor in the liver again. We performed the laparoscopic left hemihepatectomy and caudate lobectomy for her. Patient B was a 39 years old woman who had been discovered “hepatic simple cyst” for 10 years. Two years ago, she was diagnosed as the hepatic simple cyst and underwent liver cyst fenestration in another hospital. The postoperative pathological report showed the lesion was H-MCNs but wasn’t performed further treatment. She admitted to our hospital for abdominal pain for two months.

The US, CT images were showed above. We performed a laparoscopic liver cystic tumor resection and T-tube drainage for her. Patient C was a 51 years old woman who admitted to our hospital due to being discovered a liver cystic lesion for ten years. Two years ago, she was performed fenestration, but the cyst still grew up gradually. By MRI picture, we can see a big cyst in the right lobe of the liver with septa. The corresponding histology (Haematoxylin and eosin staining) pictures showed OS and mucinous epithelial lining. All of those three patients were alive with no recurrence when the latest followed up.

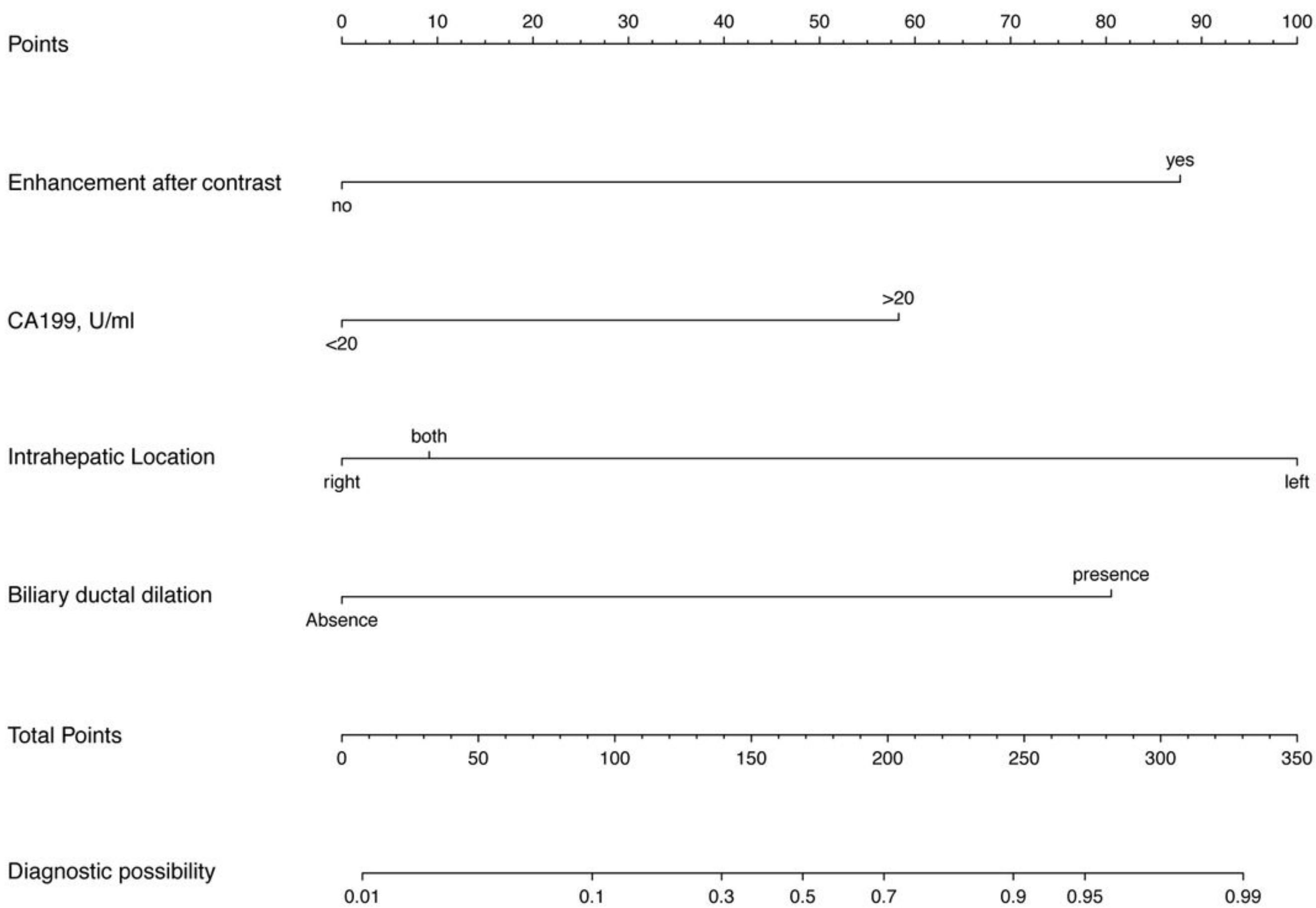

Figure 3

A nomogram to estimate the possibility of H-MCN in liver cystic lesions. To use this nomogram, find the position of the variables on the corresponding axis, draw a vertical line to the points axis to get the points of the variable. Calculate the total points of all variables and draw a line from the corresponding total points axis to the possibility axis to get the probability of the H-MCNs.

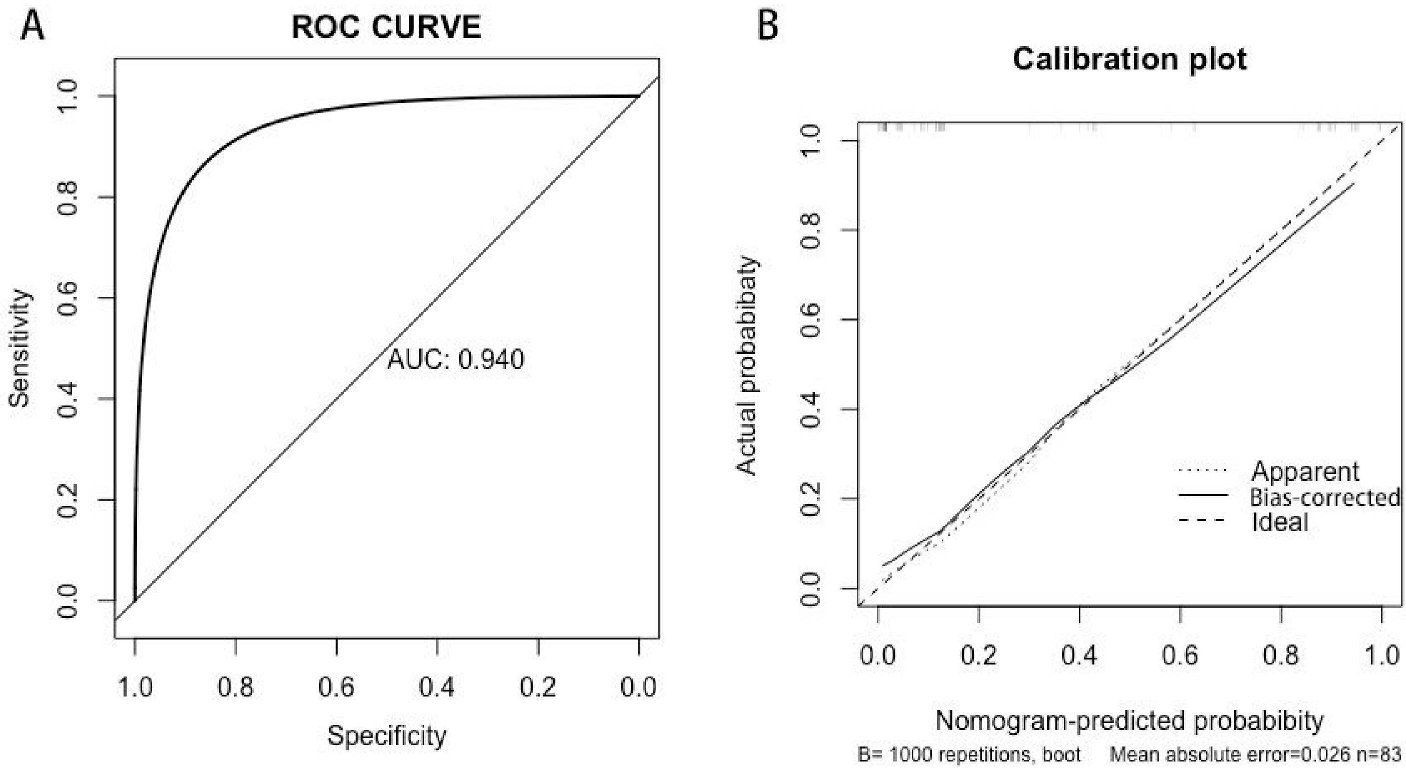

Figure 4

A ROC curve of the H-MCNs prediction nomogram. The ROC curve of the model showed excellent discrimination (C-index=0.940). Figure 4. B Calibration plot for predicting the probability of H-MCNs in the hepatic cystic lesion. The predicted probability of the nomogram was good agreement with the actual probability.

Supplementary Files

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- SupplementA.docx