Inflammatory and multiple hepatocellular adenoma are associated with a higher BMI

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ABSTRACT

Aim: To identify patient and lesion characteristics associated with the occurrence of single or multiple hepatocellular adenoma (HCA)

Patients and methods: Using a tertiary centre database, we retrospectively collected information on patient and lesion characteristics, management and follow-up of all patients with HCA included between 2001 and 2016. Patients were classified into three groups; patients with a single HCA, 2–9 HCA and at least 10 HCA

Results: A total of 458 patients were diagnosed with HCA, including 121 (26.4%) with single HCA, 235 (51.3%) with 2–9 HCA and 102 (22.3%) with at least 10 HCA. Significant differences in the mean BMI were found, with the highest BMI in patients with more than 10 HCA ($P < 0.05$). The mean BMI was significantly higher in patients with inflammatory HCA compared with steatotic HCA (31 vs. 26, respectively, $P < 0.05$). Steatotic HCA were more often single lesions (22/55, 40%), whereas patients with inflammatory HCA were often diagnosed with multiple lesions (122/166, 73%).

Conclusion: Our series show a significantly higher BMI and frequency of inflammatory HCA in patients with multiple HCA compared with single HCA.

INTRODUCTION

A validated molecular and pathological classification of hepatocellular adenoma (HCA) was introduced by Bioulac-Sage et al. [1]. This classification identifies HCA with a different clinical outcome [1-2]. One subgroup of steatotic HCA lacks the expression of the liver-fatty-acid binding protein and has a very low risk of bleeding or malignant proliferation (H-HCA, 35–50%) [3]. A second subgroup includes inflammatory HCA (IHCA) (I-HCA, 45–50%), a subtype that is at risk of having a β-catenin mutation associated with an increased risk of malignant transformation and bleeding [4]. A third subgroup is characterized by a β-catenin mutation (β-HCA, 15–18%). Finally, a group is being defined as unclassified as it does not show any specific features or mutations (U-HCA, 10%) [1] [5-6].

All these different subtypes may present as a solitary lesion on imaging. A small minority of patients with HCA presents with liver adenomatosis (LA), defined by Flejou et al. [7] as the presence of more than 10 adenoma lesions in an otherwise normal liver parenchyma. Only several case reports and small case series with patients with more than 10 HCAs have been described [8]. However, as estimation of the exact number of HCAs appears to be difficult, the term liver adenomatosis has been replaced by multiple HCAs [3]. Multiple HCAs have been described to be present in ~50% of all HCA.

Studies describing risk factors of HCA are mainly based on analysis of a solitary HCA and include the long-term use of oestrogen-containing oral contraceptives, female sex and obesity [4] [9-10]. It has yet to be studied whether risk factors for multiple HCA differ from single HCA.

It may be questioned whether patients with multiple HCAs must be treated according to the same guidelines as those with solitary lesions. The EASL guideline on the management of benign liver tumours suggests treatment of these patients on the basis of the size of largest nodule as the risk of complications is not related to the number of HCA [3-11]. However, this might be challenging if there are multiple HCAs more than 5 cm in size. With the availability of advanced imaging techniques and their increased use, liver lesions, including multiple adenomas, seem to be diagnosed more often. The management of these lesions may be a challenge for physicians as the guidelines may not always be applicable.

We studied which patients are at risk for multiple HCAs and whether patient and lesion characteristics between single or multiple HCAs differ. Furthermore, we investigated whether the presentation of single or multiple adenomas may lead to different management strategies.

PATIENTS AND METHODS

The study protocol was in agreement with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local Institutional Review Board and Ethical Committee from the Erasmus Medical Center University. Informed consent was waived.

All patients who were diagnosed with HCA in our tertiary referral centre for focal liver lesions (the Erasmus Medical Center, Rotterdam) between 1999 and 2016 were included. With the availability of data on the diagnosis of all consecutive patients in this period, we selected those in whom the diagnosis had been confirmed on at least one MRI or, if indicated, by histopathological evaluation. The final diagnosis and management strategy had to be confirmed in a multidisciplinary hepatic tumour board committee.

From this database, we retrospectively collected baseline characteristics including sex, age and BMI from all patients. We derived the number (1 HCA, 2–9 HCA or >10 HCA), size and presence of bleeding from the radiological and pathological reports. Tumour size was defined as the diameter of the largest HCA on MRI in mm. Bleeding was defined using MRI criteria: on T1-weighting, a haematoma is hyperintense in the beginning, becoming more and more isointense in the chronic phase; on T2-weighting, a haematoma starts hyperintense and resolves in the chronic phase with zones of signal void (black) because of deposition of hemosiderine, mostly in the periphery.

Patients were subdivided into three groups: single HCA, multiple (2–9) HCAs [multiple adenoma (MA)] and more than 10 HCAs or liver adenomatosis (LA). Noninvasive MRI diagnosis of HCA was made on the basis of the typical features including results of using liver-specific contrast agents. HCA subtypes (H-HCA, I-HCA, β-HCA, β-IHCA and U-HCA) were based on immunohistochemistry as described by the Bordeaux-group [12] or on typical MRI features: H-HCA diffuse and homogenous fat signal, IHCA hyperintensity on T2-weighted images and T1-hyperintensity on the delayed phase or atoll sign on T2-weighted images. β-HCA and U-HCA have no validated specific sign [13] [14].

DATA ANALYSIS

All analyses were carried out using the statistical package for the social sciences (SPSS) (Released 2013, IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, New York, USA). Differences between groups were assessed using a one-way ANOVA for continuous variables or the χ^2-test for categorical variables. Statistical significance was considered at a P-value of less than 0.05.

RESULTS

Overall, 458 patients were included and 121 (26.4%) were found to have a single HCA, 235 (51.3%) had multiple HCAs and 102 (22.3%) had liver adenomatosis. Baseline characteristics are presented in Table 1. The median age at presentation was 39 (interquartile range: 15–78) years. Most patients were women (n=451, 98%), with 12 (2.6%) female patients having no history of oral contraceptive use. There were six male patients, all of whom were diagnosed with a single HCA. One was found to have an H-HCA, four were found to have an I-HCA and one had a U-HCA. The median follow-up period of all patients was 34 (interquartile range: 17–49) months. No malignant transformation of any HCA into a hepatocellular carcinoma was found in this period.

Table 1. Patient characteristics (N = 458)

	HCA (N= 121)	MA (N= 235)	LA (N= 102)	P-value
Age (years)[a]	38 (20–78)	38 (20–66)	39 (15–59)	0.527
Female[b]	115 (95)	234 (99.6)	102 (100)	0.002
BMI (kg/m^2)[a]	27.7 (17.0–41.0)	30.4 (18.3–62.1)	31.2 (20.3–47.4)	0.001
OC use[b]	116 (94)	233 (99)	97 (94)	0.005
Tumour size (mm)[a]	59 (9–177)	58 (9–200)	67 (12–200)	0.097
Tumour bleeding[b]	18 (15)	53 (23)	24 (24)	0.172

This table shows characteristics of patients with single hepatocellular adenoma, multiple hepatocellular adenomas and liver adenomatosis.
HCA, hepatocellular adenoma; LA, liver adenomatosis; MA, multiple adenomas; OC, oral contraceptive. [a]Data are presented as median with the range in parentheses.
[b]Data are presented as n (%).
P values below 0.05 were considered statistically significant.

Comparison between these three groups showed a significant difference in BMI (kg/m^2), with a median of 27.7 in patients with a single HCA, 30.4 in patients with MA and 31.2 in patients with LA (Fig. 1). Pairwise post-hoc analysis showed a significant difference in BMI between single HCA and MA and HCA and LA. No difference was observed between MA and LA. Female sex and the use of oral contraceptives were significantly different between groups. A pairwise post-hoc analysis showed a difference between single HCA and MA and single HCA and LA. Oral contraceptive (OC) use was significantly higher in MA compared with single HCA and LA. There was no difference in age or bleeding of adenomas between groups.

A total of 267 HCA were classified according to the Bordeaux-classification on the basis of MRI findings or pathology reports (Table 2). The percentage of H-HCA (17%) was significantly lower in the group with MA/LA compared with HCA (Fig. 2). Eight patients were found to have a β-catenin mutation on the basis of pathology. I-HCA

was the most common subgroup in single HCA as well as MA (63%). The median BMI in I-HCA was found to be 30.9 compared with a median BMI in H-HCA of 26.0 and 29.7 in U-HCA 29.7 in β-HCA. Additional analyses were carried out in patients in whom the largest lesion exceeded 50 mm as this specific group should be considered for resection or other curative treatment as described in the EASL Clinical Practice Guidelines on the management of benign liver tumours [3]. Larger lesions were found in 56 (46%) single HCAs, 109 (46%) MAs and 54 (52%) LAs. There were significant differences in intervention between the three groups (Table 3). More patients with a single HCA underwent resection if the lesion exceeded 50 mm compared with patients with larger lesions in MA or LA

Table 2. Bordeaux classification

Single HCA (N= 75)	MA/LA (N= 192)	P-value
H-HCA [n (%)] 22 (29)	33 (17)	0.023
I-HCA [n (%)] 44 (59)	122 (64)	0.485
β-HCA [n (%)] 1 (2)	7 (4)	0.449
U-HCA [n (%)] 7 (9)	28 (15)	0.315
I-HCA + β-HCA [n (%)] 1 (1)	2 (1)	1.000

DISCUSSION

In this study, we describe the largest series of patients with HCA, MA and LA with a follow-up of more than a decade. A review by Veteläinen et al. [8] described 94 patients from case reports and case series with LA. They reported abdominal ultrasound to be the initial imaging in all 94 patients, but confirmation of the diagnosis using highly advanced imaging modalities such as MRI, with or without contrast, or a contrast-enhanced ultrasonography was often missing. Currently, in our hospital, all patients with a suspected benign hepatic tumour will receive an MRI in at least four phases (precontrast, arterial, portal and delayed) after administration of an intravenous bolus nonliverspecific gadolinium chelate or a liver-specific contrast agent (Gadoxetate disodium, Primovist; Bayer Healthcare, Berlin, Germany or Gadobenate dimeglumine, Multihance; Bracco Imaging, Milan, Italy). Furthermore, patients are assessed by contrast-enhanced ultrasonography using a second generation contrast agent Sonovue (2.4–4.8ml, intravenous; Bracco Ltd., High Wycombe, UK). Both imaging methods provide additional information that improves differentiation of liver lesions [15] [16].

In our series, we did not find MA in male patients. All six male patients had a single HCA. No patients had a history of using anabolic steroids.

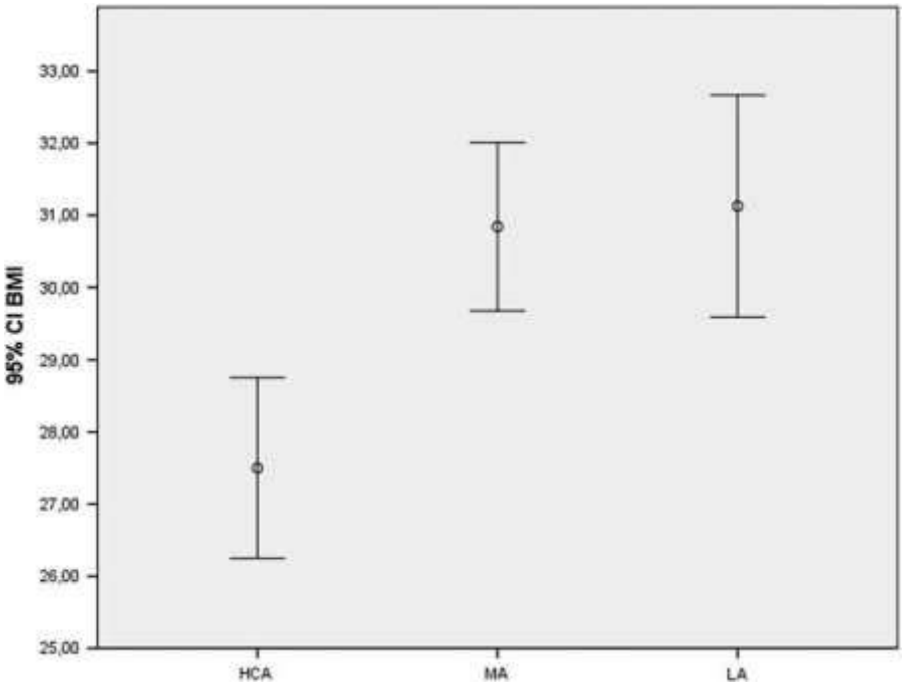

Fig. 1. BMI and number of adenomas. This figure shows BMI of patients with a single hepatocellular adenoma, multiple liver adenomas and liver adenomatosis.
CI, confidence interval; HCA, hepatocellular cellular adenoma; LA, liver adenomatosis; MA, multiple adenomas.
This table shows the Bordeaux classification the adenoma of patients with a liver adenomatosis, multiple liver adenomas and a single hepatocellular adenoma. β-HCA, hepatocellular cellular adenoma with mutations of the β-catenin gene; HCA, hepatocellular cellular adenoma; H-HCA, steatotic hepatocellular cellular adenoma; I-HCA, inflammatory hepatocellular cellular adenoma; LA, liver adenomatosis; MA, multiple adenomas; U-HCA, unclassified hepatocellular cellular adenoma without markers.

The aetiology and pathogenesis of HCA is unknown, although an association with the use of oestrogens was described in 1973 [17]. In the following years, many authors confirmed the hypothesis of an association between oestrogen-containing contraceptives and HCA [18-22]. Withdrawal of oral contraceptives in these patients will usually lead to regression of HCA [5]. However, we have yet to discover the physiological explanation for the association between oestrogen and HCA. The data on sex steroid receptors are rare, inconsistent and some of them used outdated techniques [23]. The largest study that used immunohistochemical analysis found an oestrogen and progesterone receptor in 26% of the HCA [24]. However, they did not draw any conclusions on the correlation between the number of HCA and the presence of the sex steroid receptors. New steroid hormone receptors have been identified in recent years, but have not yet been tested on HCA tissue [25-27].

Oestrogens are mostly known to be produced by the ovary. However, adipose tissue can contribute significantly towards the pool of oestrogens [25] [28]. Previous studies showed that obese patients have higher oestrogen levels compared with healthy individuals [28-29]. This could explain the relation between BMI and the number of HCA in this group of patients. In 2012, Rui et al. [29] carried out a study in which they found that high BMI had a significant positive association with the risk of liver tumours. Bioulac-Sage et al. [30] first suggested a connection between overweight and HCA. Bunchorntavakul et al. [31] found 23 cases of MA in obese patients and suggested a correlation between MA and obesity.

We describe a significant difference in BMI between single HCA, MA and LA. The median BMI is the highest in the group of patients with LA. We confirmed the suggested association between the number of HCA and BMI in a large group of patients. It has been suggested that HCA could decrease or disappear if patients lose weight [9]. The decrease could be attributed to a lower concentration of hormones because of weight loss [32].

Another explanation could be less inflammation because of weight loss as enhanced inflammation in the metabolic syndrome allows cell growth to develop HCA [30-31]. Currently, all patients with HCA are advised to stop the use of OC as well as lose weight. Therefore, it is not always clear whether the regression is caused by the withdrawal of OC or by the weight loss.

The Bordeaux subtype classification was introduced and included in our data. Subclassification of the largest HCA was performed in 267 patients. The incidence of the subgroup H-HCA has been reported previously to be 30–40% of all HCA [33]. Patients with H-HCA and thereby germline mutations of HNF1A are predisposed to develop LA [33]. However, in our cohort, only eight patients with LA were classified as H-HCA. In patients with I-HCA, obesity is a known risk factor. Furthermore, the presence of I-HCA is associated with MA as well [8] [30-31] [34-35]. I-HCA and a high BMI seemed to cause LA in our cohort as well. The BMI in the patients with I-HCA was significantly higher compared with the patients with H-HCA and LA.

Table 3. Management of patients with a single hepatocellular adenoma, multiple liver adenomas and liver adenomatosis, in which the largest lesion was at least 50 mm

Management	HCA (N= 56) [n (%)]	MA (N= 109) [n (%)]	LA (N= 54) [n (%)]
Conservative	18 (32)	64 (59)	36 (67)
Surgery	33 (59)	36 (32)	14 (26)
RFA	3 (5)	0 (0)	2 (4)
Embolization	2 (4)	8 (7)	0 (0)
Surgery and RFA	0 (0)	2 (2)	1 (2)
RFA and embolization and surgery	0 (0)	0 (0)	1 (2)

HCA, hepatocellular adenoma; LA, liver adenomatosis; MA, multiple adenoma; RFA, radiofrequency ablation. P< 0.001.

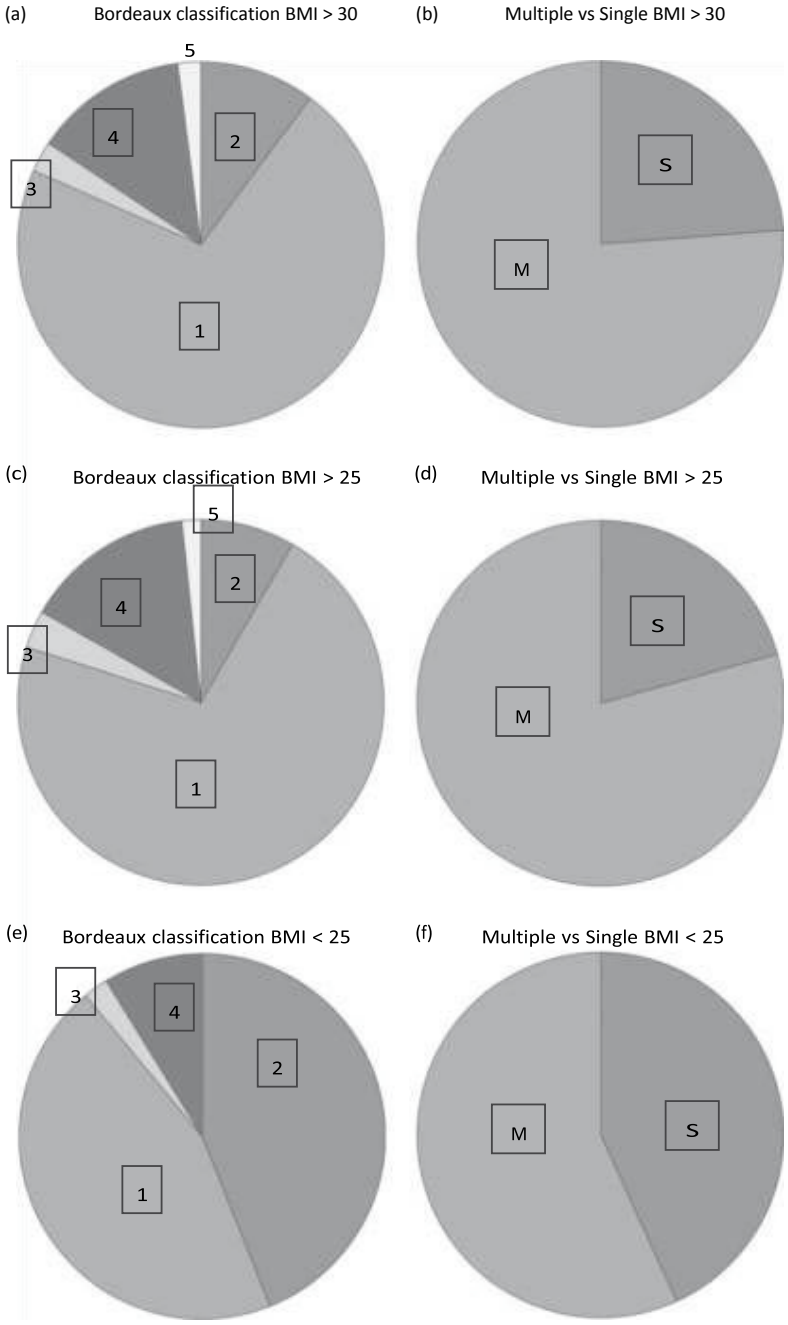

Fig. 2. Multiple and subtype distribution of HCA depending on BMI. a,c,e; 1 H-HCA; 2 I-HCA, 3 B-HCA; 4 U-HCA, IB-HCA (Inflammatory and B-cat positive HCA) b,d,f; S; single HCA, M: multiple HCA. HCA, hepatocellular cellular adenoma; β-HCA, hepatocellular cellular adenoma with mutations of the β-catenin gene; H-HCA, steatotic hepatocellular cellular adenoma; I-HCA, inflammatory hepatocellular cellular adenoma; U-HCA, inflammatory hepatocellular cellular adenoma.

In our cohort, the incidence of I-HCA is much higher compared with the distribution between the different subgroups described by the Bordeaux group [33]. This could be explained by the rapidly increasing incidence of obesity in women worldwide [36]. The increasing incidence of obesity could lead to a shift towards I-HCA, which will be observed more frequently. Furthermore, the prevalence of obesity in women is higher in the Netherlands (46.1%) compared with France (36.9%) [36].

We acknowledge that our study has a limitation. The final diagnoses were not all histologically proven. In those cases, combined imaging was used as the reference method for the final diagnosis, which was done after consensus in our multidisciplinary tumour board committee. In the early years, diagnoses of HCA have been differentiated from FNH with at least a conventional MRI. According to signal intensity and dynamic vascular patterns after an intravenous aspecific gadolinium injection, the different benign liver tumours are differentiated [13]. However, during the inclusion period of this study, specific hepatobiliary contrast agents were introduced and the differentiation is now more specific in challenging cases [37].

Biopsy is only approved in our hospital if there is doubt on the diagnosis or radiological examinations are not in agreement. However, MRI yields a highly accurate diagnosis, with a sensitivity of 91–100% and a specificity of 87–100% for differentiating HCA from FNH [38]. The Bordeaux subtype classification was performed on MRI in most patients; it should be noted that the MRI features of β-HCA are not completely defined [39]. Therefore, there could have been false negatives on MRI, possibly resulting in an underestimation of β-HCA.

Further research on the role of obesity in HCA and the effect of weight loss needs to be carried out. Because of the higher risk of surgery and the comorbidities of fatty liver, we suggest starting with weight reduction in all obese patients [3]. If follow-up indicates no decrease in the HCA, treatment should be decided depending on the anatomic location and the steatosis of the remaining liver tissue.

The management should be discussed by a multidisciplinary committee and strategies may be individualized.

CONCLUSION

Our series found a significantly higher BMI and frequency of inflammatory HCA in patients with multiple HCA compared with single HCA. As weight reduction could decrease the size of these HCA, this finding may help to personalize treatment, focusing on tailor-made lifestyle monitoring with OC cessation and body weight reduction in this specific subgroup.

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