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Assessment of hepatitis and fibrosis using Gd-EOB-DTPA MRI in dogs

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ABSTRACT

Background Gadoxetate sodium (Gd-EOB-DTPA) is taken into hepatocytes and excreted into the bile. Hepatocytes with reduced function or dysfunction due to hepatocellular carcinoma (HCC), hepatitis or hepatic fibrosis show impaired Gd-EOB-DTPA uptake. The purpose of the present retrospective case series was to assess the relationship between liver function and contrast enhancement using Gd-EOB-DTPA MRI.

Methods Sixteen dogs with a histopathological diagnosis of liver disease, including six with HCC, three with nodular hyperplasia, two with hepatocellular adenoma, two with liver fibrosis and three with hepatitis were included in the study along with three dogs with suspected liver disease but no histopathological diagnosis of liver disease. Relative signal intensities (RSI) of the common bile duct and gall bladder were calculated, and their relationship with the following serum biochemical parameters was assessed: total bilirubin, alanine transaminase, alkaline phosphatase and albumin (Alb). To assess anatomical liver function, relative contrast enhancement indices (RCEI) of the liver were calculated, and differences were assessed between normal and diseased liver.

Results RSI showed no significant differences between dogs without and with a histopathological diagnosis of liver disease (P=0.88) although they were significantly correlated with Alb (ρ=0.57, P=0.02) in dogs with a histopathological diagnosis of liver disease. RCEI was significantly higher in normal liver tissue than that in livers with hepatitis/fibrosis (P=0.048) and HCC (P=0.03) but not nodular hyperplasia/hepatocellular adenoma (P=0.51).

Conclusions Gd-EOB-DTPA MRI may be potentially useful in the assessment of anatomical liver function in dogs with liver disease.

INTRODUCTION

In humans, gadoxetate sodium (Gd-EOB-DTPA) is a hepatocyte-specific MRI contrast agent that shows extracellular distribution in the initial phase of contrast enhancement, followed by hepatocyte-specific uptake in the hepatobiliary phase.[1] The kidneys excrete approximately 50 per cent of Gd-EOB-DTPA, while the remaining 50 per cent is excreted into the bile.[2] Differential diagnosis of dysplastic nodules and hepatocellular carcinoma (HCC) can be based on MRI findings with or without uptake of Gd-EOB-DTPA.[3]

In humans, Gd-EOB-DTPA is taken into hepatocytes by the transporters OATP1B1 and OATP1B3, located on sinusoidal membrane, and subsequently excreted into the biliary system by multidrug resistance-associated protein (MRP2), without any metabolic change.[4] Hepatocytes with reduced function or dysfunction due to HCC, hepatitis or hepatic fibrosis show impaired Gd-EOB-DTPA uptake, which is mediated by organic-anion-transporting polypeptide (OATP). Therefore, liver contrast enhancement and excretion into the bile are reduced in the hepatocyte phase.[3 5–9]

In veterinary medicine, measurement of serum parameters and dynamic liver function tests are used to evaluate liver disease.[10] The serum parameters include alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALKP), bilirubin (Bil) and albumin (Alb).[11] ALT, AST and ALKP are markers of cellular turnover or damage.[11] Bil is influenced by hepatocyte function, intrahepatic cholestasis or extrahepatic bile duct obstruction.[11] Alb indicates protein production in the liver.[11] However, these serum parameters are not specific to liver disease,[11] and the most commonly used liver function test, the bile acid stimulation test,[10] is not sensitive enough for use in routine liver disease screening.[10] The indocyanine green (ICG) clearance test is used to assess liver function in dogs[10] but is not easily performed in the clinic, because it is complicated, requires ICG injection and does not provide anatomical detail.[7] In humans, ICG is a significant predictor of signal intensity in the bile duct during Gd-EOB-DTPA MRI.[6] In veterinary medicine, Gd-EOB-DTPA MRI is used to diagnose HCC[12] and has been proven safe for use in healthy dogs.[13] To the best of our knowledge, no veterinary studies have assessed the relationship between liver function and contrast enhancement by Gd-EOB-DTPA MRI.

The purpose of the present study was to assess the relationship between liver function

and contrast enhancement by Gd-EOB-DTPA MRI. Therefore, we evaluated Gd-EOB-DTPA excretion into bile of dogs without liver disease and dogs with liver disease and examined the relationship between this excretion and serum parameters of various liver enzymes. To assess anatomical liver function, we evaluated the relationship of liver contrast enhancement in the hepatobiliary phase between normal liver and liver lesions: hepatitis and fibrosis, nodular hyperplasia and hepatocellular adenoma, and HCC.

MATERIALS AND METHODS

The present study was a retrospective case series. The dogs with suspected liver lesions who had undergone MRI examination at our institution between 2016 and 2018 were eligible for inclusion in this study. In dogs with suspected liver lesions, dogs with potential liver disease were identified using our institutional medical database, and a total of 25 dogs were selected for further consideration. The following inclusion criteria were then applied: (1) histopathological diagnosis of liver disease, (2) use of Gd-EOB-DTPA, (3) measurement of selected serum biochemical parameters (total bilirubin (T-Bil), ALT, ALKP and Alb) before MRI. The exclusion criteria were as follows: bile duct obstruction, additional tumour, renal disease and intestinal disease.

Magnetic resonance imaging

MRI was performed using a 1.5 Tesla system (Brivo MR355; GE Healthcare Japan, Tokyo, Japan). All dogs underwent general anaesthesia, were positioned in the supine position and were ventilated during MRI examinations. Breath-hold was induced during image acquisition by a stop ventilator. To diagnose liver disease, conventional liver MRI was carried out using the following sequences: (1) axial T1-weighted images (T1WI) with a breath-hold in-phase, opposed-phase spoiled gradient echo (repetition time (TR): 280 ms, echo time (TE): 2.2/4.2 ms, flip angle (FA): 85°, field of view (FOV): 16–20 cm × 16–20 cm, bandwidth: 50 kHz, matrix size, 160×160; number of excitation (NEX): 1, slice thickness: 3 mm, interval: 0.6), and no parallel imaging (array spatial sensitivity encoding technique (ASSET)); (2) axial, fat-saturated, fast-recovery, fast-spin echo T2-weighted images with respiratory trigger (TR: 6000 ms, TE: 100 ms, FOV: 16–20 cm × 16–20 cm, bandwidth: 83.33 kHz, matrix size: 192×160, NEX: 6, slice thickness: 3 mm, interval: 0.6), with no ASSET; and (3) precontrast and postcontrast axial T1WI acquired using a breath-hold, fat-suppressed, three-dimensional, fast-spoiled/gradient-recalled echo sequence (liver acceleration volume acquisition) in the transverse plane (TR: 4.8 ms, TE: 2.3 ms, inversion time (TI), 8 ms, FA: 15°, FOV: 16–20 cm × 16–20 cm, bandwidth: 83.33 kHz, matrix size: 160×160, slab: 1, slice thickness: 3 mm), with no ASSET.

Each animal received 0.1 ml/kg (0.025 mmol/kg) of Gd-EOB-DTPA (Primovist Inj. Syringe; Bayer, Osaka, Japan), administered intravenously as a manual bolus, followed by 2 ml of saline flush. Postcontrast axial T1WIs were acquired 20 seconds (arterial phase), 60 seconds (portal phase), 180 seconds (late phase) and 20 minutes (hepatobiliary phase) after contrast medium injection. All images were evaluated on a workstation using commercially available DICOM image viewing software (OsiriX 6.5.2, 64 bit; Pixmeo, Bernex, Switzerland). The observers were aware of the final diagnoses at the time of MRI review, but they were blinded to serum biochemical parameters. To avoid potential bias, all images were assessed in random order in two different sessions, with at least a two-week interval between each session.

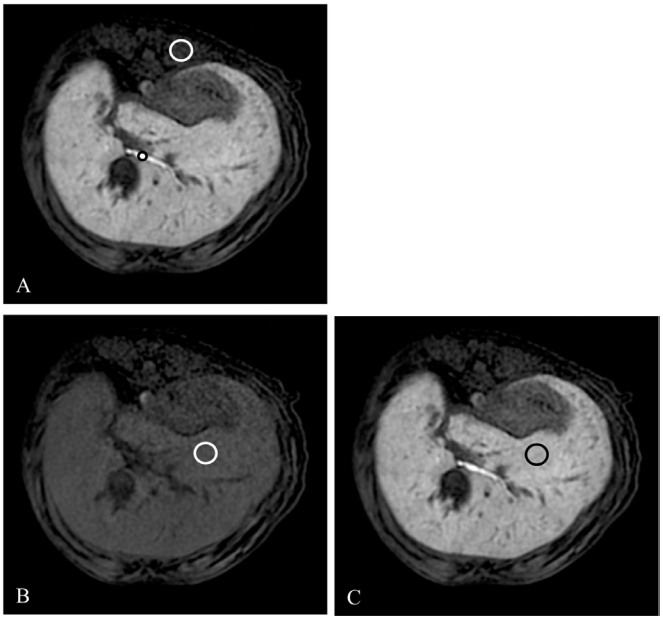

Figure 1 To calculate relative signal intensity (RSI), maximum signal intensities (SI) of the common bile duct (small circle) and mean SIs of the erector spinae muscle (big circle) were measured in the hepatobiliary phase (A). To calculate relative contrast enhancement indices of the liver, mean SIs of the liver parenchyma on precontrast were measured (B, circle), as were mean SIs of the liver parenchyma during the hepatobiliary phase (C, circle).

To assess Gd-EOB-DTPA excretion into bile, maximum signal intensities (SIs) of the common bile duct and gall bladder were measured during the hepatobiliary phase, according to previous studies.[6] Mean SI of the erector spinae muscle was measured using a region of interest (ROI) at the level of the porta hepatis. Relative SIs (RSI) of the common bile duct and gall bladder were calculated as follows: RSI=maximum SIbile duct/mean SImuscle (figure 1A).

To assess anatomical liver function of liver lesions, the SI of liver lesions in the hepatobiliary phase was measured using an ROI, as previously described.[14] Regions of interest were located deliberately to avoid necrosis, blood vessels, biliary structures or partial volume effects, although they were placed on histopathologically diagnosed areas, including normal liver, fibrosis, hepatitis, HCC, nodular hyperplasia and hepatocellular adenoma. Mean SI in the

liver was calculated during the hepatobiliary phase and used as the representative hepatic parenchyma SI. Relative contrast enhancement indices (RCEI) of the liver were calculated as follows: RCEI = (hepatobiliary phase SI − precontrast SI)/precontrast SI (figure 1B,C). The RSI and RCEI were measured three times in each case, and all measurements were recorded. Relative signal intensities and RCEI were measured repeatedly to determine consistency and reliability of the measurements.

Statistical analyses

Statistical data were analysed using R V.2.12.1 (R Development Core Team, 2010; R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0; available at: http://www.R-project.org/; accessed on 11 February 2011). Data normality was assessed using the Shapiro-Wilk test, which indicated that non-parametric testing was required. Results are reported in this study as median (minimum–maximum). The Mann-Whitney U test was used to test for a difference in RSI between dogs without and dogs with a histopathological diagnosis of liver disease. RCEI of normal and abnormal liver tissues were compared using the Kruskal-Wallis test. The Steel-Dwass test post hoc was performed to compare attenuation values. Spearman's rank correlation was performed to test the direction and strength of the relationship between RSI attenuation of dogs with a histopathological diagnosis of liver disease and other variables, namely T-Bil, ALT, ALKP and Alb concentrations. All Pvalues <0.05 were considered statistically significant. For Spearman's rank correlation, a coefficient value of <0.5, was regarded as low, 0.5–0.69 as moderate, 0.7–0.89 as high and 0.9–1.0 as very high.[15]

RESULTS

A total of 19 dogs were included in this study after excluding six dogs because they did not meet the all the inclusion criteria. There were 16 dogs with a histopathological diagnosis of liver disease included. The liver disease diagnoses were HCC (n=6), nodular hyperplasia (n=3), hepatocellular adenoma (n=2), liver fibrosis (n=2) and hepatitis (n=3). Some of the HCC (n=3; 50 per cent) and hepatitis (n=2; 67 per cent) cases were managed surgically. The periphery of the three surgically excised HCCs was histopathologically diagnosed as normal liver. Other liver diseases were sampled by ultrasound-guided tru-cut biopsy. In cases of surgically removed HCC (n=3), serum biochemical parameters (T-Bil, ALT, ALKP and Alb) were normal after surgery in all cases. The dogs consisted of neutered males (n=4), intact male (n=1), spayed females (n=9) and intact females (n=2). The median age of the dogs was 11 years (5–14 years). The breeds were Mixed (n=4), Dachshund (n=1), Yorkshire terrier (n=2), Pekingese (n=1), Chihuahua (n=3), Shiba (n=1), Beagle (n=1), Labrador retriever (n=1), Toy poodle (n=1), and Pomeranian (n=1). Three additional dogs without a histopathological diagnosis of liver disease were included in the study. These three dogs were referred due a suspected liver problem as blood tests had previously shown high concentrations of ALT; these dogs had been treated with intravenous fluid therapy or liver protection medicine such as glutathione and the concentrations of ALT went up and down before referral. One dog had suspected liver nodules by ultrasonography and was referred to our hospital to liver examination. At our hospital, the general condition of all three dogs was normal and haematological, and serum biochemical analyses were normal, and the ALT concentrations were also normal. MRI examinations were performed to exclude liver disease as having a normal ALT concentration does not rule out liver disease. These three dogs without a histopathological diagnosis of liver disease consisted of one intact male and two spayed females. The median age of the dogs was six years (4–12 years). The breeds were Cavalier King Charles Spaniel (n=1), West Highland White Terrier (n=1) and Dachshund (n=1).

Median RSI and serum parameters of various liver enzymes in the 16 dogs with liver disease were as follows: RSI: 7.78 (2.63–11.83); T-Bil: 0.5 mg/dl (0.1–7.8 mg/dl); ALT: 355 U/l (127–2555 U/l); ALKP: 951.5 U/l (54–3044 U/l); and Alb: 3.0 g/dl (2.1–3.8 g/dl). In the three dogs without a histopathological diagnosis of liver disease, the median RSI of the common bile duct was 8.37 (5.97–9.03). There was no significant difference in RSI between dogs without and dogs with a histopathological diagnosis of liver disease (P=0.88). Spearman's rank correlation analysis revealed that RSI of dogs with a histopathological diagnosis of liver disease was significantly correlated with Alb (ρ=0.57, P=0.02table 1, figure 2A,B).

To compare RCEI of normal versus abnormal liver tissue, the dogs were subdivided into four groups: (1) normal liver tissue meaning tissue from the dogs without a histopathological diagnosis of liver disease (n=3) and dogs where the periphery of excised HCCs was considered normal (n=3), (2) hepatitis (n=3) and fibrosis (n=2), (3) nodular hyperplasia (n=3) and hepatocellular adenoma (n=2) and (4) HCC (n=6). Normal liver RCEI showed significantly higher SI compared with those of hepatitis and fibrosis (P=0.048) and HCC (P=0.03) but was not different from nodular hyperplasia and hepatocellular adenoma (P=0.51, table 2 and figure 3).

Table 1 Spearman's rank correlation between attenuation of RSI in 16 dogs with a histopathological diagnosis of liver disease and other variables

Variables	Spearman's rank correlation coefficient (ρ)	P value
Total bilirubin	−0.41	0.1
Alanine transaminase	0.02	0.9
Alkaline phosphatase	0.08	0.8
Albumin	0.57	0.02

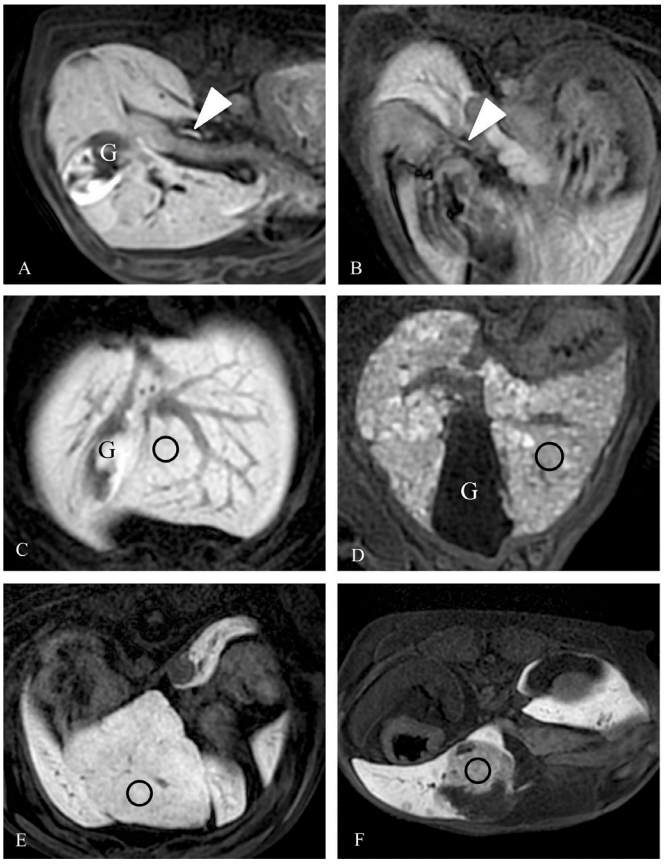

Figure 2 Representative figure of relative signal intensity (RSI) (A and B) and relative contrast enhancement indices of normal liver (C), fibrosis (D), hepatocellular adenoma (E) and hepatocellular carcinoma (F). High RSI (=8.37) (A) and low RSI (=4.67) (B). Arrow head: common bile duct. ROIs (circle) were placed to avoid necrosis, blood vessels, biliary structures or partial volume effects (C–F). G, gall bladder; ROI, region of interest.

DISCUSSION

Gd-EOB-DTPA is accumulated in hepatocytes at the hepatobiliary phase.[13] The uptake of Gd-EOB-DTPA by hepatocytes peaked at 10 minutes after administration of Gd-EOB-DTPA.[12] Another study described that SI of the hepatobiliary phase peaked at 26 minutes after administration of Gd-EOB-DTPA.[16] However, several reports showed that SI of the hepatobiliary phase reached the plateau at 20 minutes after administration of Gd-EOB-DTPA.[13 16 17] Therefore, we defined the hepatobiliary phase at 20 minutes after Gd-EOB-DTPA injection.

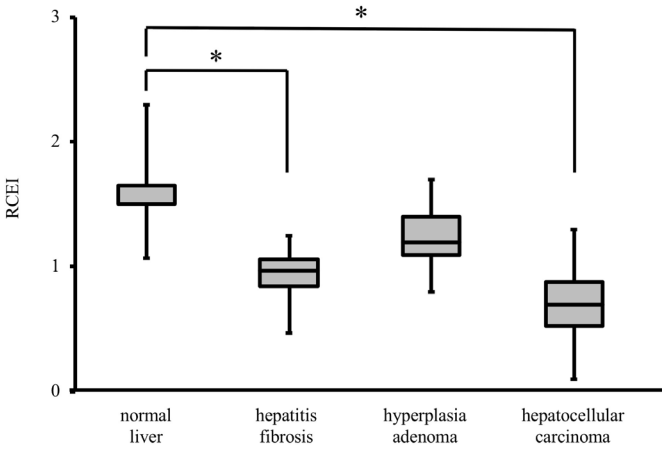

Figure 3 Relative contrast enhancement indices (RCEI) of normal and abnormal liver tissues. The distributions showed that normal liver tissue had significantly higher SI compared with tissues with hepatitis and fibrosis (P=0.048) and hepatocellular carcinoma (P=0.03) but not those tissues with nodular hyperplasia and hepatocellular adenoma (P=0.51). *P<0.05. SI, signal intensity.

We hypothesised that the median RSI of the common bile duct in the hepatobiliary phase following injection of Gd-EOB-DTPA would correlate with serum markers of hepatocellular function—Bil, Alb, ALT, AST and ALKP. This study showed that RSI in the hepatobiliary phase of dogs with liver disease was influenced by Alb. In humans, most patients with HCC have associated chronic liver disease, so impaired liver function renders liver resection unfeasible, resulting in a high risk of postoperative complications and death.[18] To assess function in the remaining liver of patients with HCC, hepatitis or fibrosis, the Alb–bilirubin (ALBI) score has recently been developed. It is a simple and objective scoring system for assessing the severity of liver function damage using only two indicators.[19 20] In humans, the ALBI score shows good correlation with the ICG clearance test.[21] The score is based on continuous variables calculated from serum Alb and T-Bil and is calculated as follows: ALBI = (log10 T-Bil [µmol/l]×0.66) + (Alb [g/l]×−0.085). The ALBI score is classified as grade 1 (−2.60 or less), grade 2 (−2.59 to −1.39) or grade 3 (greater than −1.39).[20] A higher grade

Table 2 Relative contrast enhancement indices (RCEI) of normal and abnormal liver tissues showing median, minimum (min) and maximum (max) values for signal intensity and a reference to a representative figure for each type of tissue

		RCEI		
Tissue types	**N**	**Median**	**Min–max**	**Representative figure**
Normal liver	3+3=6	1.50	1.07–2.30	2C
Hepatitis+fibrosis*	3+2=5	0.97	0.47–1.25	2D
Nodular hyperplasia+hepatocellular adenoma	3+2=5	1.20	0.80–1.70	2E
Hepatocellular carcinoma†	6	0.70	0.10–1.30	2F

*Different from normal liver tissue (P=0.048).
†Different from normal liver tissue (P=0.03).

indicates more severe liver function damage.[19 20] In the present study, we found that RSI was positively correlated with Alb in dogs. Hypoalbuminaemia indicates decreased protein production in liver.[11] As indicated by the above formula, ALBI score mainly depends on serum Alb.[19] Therefore, RSI may be influenced by liver function in dogs. Serum bile acids are used to assess hepatic function in dogs. Serum bile acid stimulation test is useful to assess hepatic function when serum liver enzyme activity is elevated; however, the results of the bile acid test are influenced by multiple factors including haemolysis lipaemia and ileal disease.[10] Unfortunately, we did not measure serum bile acids. Therefore, further study is needed to assess the relationship between the serum bile acids and RSI of the common bile duct in the hepatobiliary phase.

In the present study, RSI showed no significant difference between dogs without liver disease and dogs with liver disease. In humans, biliary excretion of Gd-EOB-DTPA in diffuse liver disease is decreased because of decreased capacity of uptake of Gd-EOB-DTPA.[22] Most patients with HCC have associated diffuse chronic liver disease.[18] However, in dogs, liver tumours including HCC, nodular hyperplasia and hepatocellular adenoma are not associated with diffuse chronic liver disease. Therefore, in livers without tumours, the uptake of Gd-EOB-DTPA by hepatocytes may not be affected. In the present study, focal liver tumours account for 11 of 16 (69 per cent). The frequency of focal liver tumours may influence the results of RSI. In humans, the severity of dysfunction, including fibrosis, is not uniform across the whole liver.[14] If liver function differs in each of the liver segments, measuring RSI alone may not assess regional liver function. In humans, RCEI can predict posthepatectomy liver failure.[14] Therefore, we calculated RCEI to assess regional hepatic function. RCEI have some advantages. In particular, fat deposition, iron deposition, perfusion effect from neighbouring major vessels and heartbeat do not affect the parameters.[23] In the hepatobiliary phase, as a result of hepatocyte uptake, normal liver parenchyma exhibit hepatocyte-selective enhancement, whereas chronic hepatic lesions such as hepatitis, fibrosis and cirrhosis, which lack normally functioning hepatocytes, do not exhibit hepatocyte-selective enhancement.[6–9] In humans, hepatitis is related to viral infection, leading to a chronic lesion and later fibrosis.[9] As hepatic fibrosis progresses, hepatocytes with reduced function or dysfunction display impaired Gd-EOB-DTPA uptake mediated via OATP.[24] Therefore, liver enhancement in the hepatocyte phase is reduced.[5 24]

In veterinary medicine, the ICG clearance test is used to assess liver function in dogs.[10] In humans, ICG is taken up by hepatocytes via OATP1B1 and excreted into the biliary system by MRP2, so the ICG clearance test provides information about the uptake and excretion functions of the liver.[25] ICG is a significant predictor of signal intensity in the bile duct during Gd-EOB-DTPA MRI,[6] although the ICG clearance test does not provide anatomical detail.[7]

In the present study, median RCEI in normal liver was significantly higher than that in hepatitis and fibrosis. In dogs, RCEI may be useful to assess regional hepatic function. In humans, abnormal livers show slow or absent regeneration and require a larger volume to maintain function.[14] By measuring RCEI, it is possible to assess remnant liver function after resection of a large tumour.

In the present study, RCEI of HCC was significantly lower compared with that of normal liver. HCC causes reduced function or dysfunction of hepatocytes, resulting in impaired Gd-EOB-DTPA uptake.[3 9] In study involving dogs, HCC and malignant nodules were hypointense under Gd-EOB-DTPA MRI during the hepatobiliary phase, compared with normal liver or benign lesion.[12 17] However, in the present study, RCEI of HCC showed no difference compared with that of benign tumour, including nodular hyperplasia and hepatocellular adenoma. In one study involving humans, the expression of OATP during the hepatocyte phase decreased with increasing HCC grade, corresponding to a decrease in Gd-EOB-DTPA enhancement of lesions.[3 12] Unfortunately, we did not assess HCC grade. Further study is needed to assess the relationship between HCC grade and RCEI.

The present study has some limitations. First, we assessed the relationship between serum parameters of liver enzymes and RSI. The present study indicates that RSI has potential to assess liver function in dogs. In dogs, the exact method of assessing liver function is the ICG clearance test. The exact mechanism of Gd-EOB-DTPA uptake and hepatobiliary excretion in dogs has not been confirmed. Further study may be required to assess the relationship between the ICG clearance test and Gd-EOB-DTPA MRI, including RSI and RCEI. Second, this study included a small number of dogs with liver disease. Further study is needed to assess the relationship between hepatic function and contrast enhancement by Gd-EOB-DTPA MRI, in a larger sample of dogs.

In conclusion, RSI in the hepatobiliary phase of dogs with liver disease was influenced by Alb. RCEI in the hepatobiliary phase in normal liver were higher than those in hepatitis and fibrosis. These findings indicate that Gd-EOB-DTPA MRI may be potentially useful in assessing anatomical liver function in dogs with liver disease.

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Contributors TT was the principal investigator and primary author of the manuscript. TT and HA conceived the idea of the study. HA supervised the surveillance components. TT, HN, KM, HY and L-SL validated, analyed and interpreted the data. TT prepared the initial draft, figures and table. All authors contributed to the writing and editing of the manuscript.

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Competing interests None declared.

Ethics approval The owners of clinical cases described in this study gave informed consent for the diagnostic procedures, treatment and use of clinical data, such as medical history, imaging studies and histopathological findings for research and publication purposes. Because all diagnostic studies and initiated treatments were

part of daily clinical activities, this study did not reach the threshold for submission to the local ethical and welfare committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Our data are not in a repository. Publishable contact detail is ORCID ID; 0000-0002-7911-913X.

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