Volumetric Assessment and Clinical Predictor of Cirrhotic Livers With Normal Liver Function Undergoing Hepatectomy

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Abstract

Aim: Indocyanine green retention rate at 15 minutes (ICGR15) is a frequently-used indicator of liver function. However, cirrhotic liver is sometimes observed intraoperatively despite a normal preoperative ICGR15 (≤10 %). Herein, we conducted clinical and volumetric assessments of cirrhotic livers with normal ICGR15.

Methods: Patients undergoing hepatectomy for hepatocellular carcinoma were divided into 3 groups: non-cirrhotic livers (Group A, n=112): cirrhotic livers with ICGR15 ≤10% (Group B, n=71): and cirrhotic livers with ICGR15 >10% (Group C, n=296). Background characteristics and surgical outcomes were compared between groups. Functional liver volume (FLV) was computed using total liver volume and signal intensity ratio. Liver parenchymal cell volume ratio was measured in non-cancerous tissue obtained from resected specimens. Univariate and multivariate analyses were performed to detect clinical characteristics correlating with cirrhotic liver pathology with normal ICGR15.

Results: There was no significant difference between groups in TLV. FLV was gradually reduced from Group A toward Group C. Liver parenchymal cell volume ratio was also gradually reduced from Group A toward Group C. Multivariate analysis revealed that platelet count (<12 x10^4/mm^3) (*P* = 0.001) and prothrombin time (<80 %) (*P* = 0.025) were significantly associated with cirrhotic liver pathology among patients with normal ICGR15.

Conclusion: Our results suggested that cirrhotic liver pathology despite normal liver function was characterized by slightly decreasing liver parenchyma as well as slight degree of fibrosis. Platelet count and PT% are useful for predicting liver cirrhosis with normal ICGR15.

Introduction

The indications for liver resection for hepatocellular carcinoma (HCC) is restricted not only by tumor extension but also by hepatic functional reserve. The Child-Pugh classification is the gold standard for evaluation of liver function worldwide.[1] However, because the Child-Pugh classification is not able to precisely predict postoperative liver failure in Child-Pugh Class A patients,[2, 3] Makuuchi's criteria, including indocyanine green retention rate at 15 minutes (ICGR15), has been increasingly employed.[4, 5] Some studies indicate that liver resection using this criteria can be performed with almost zero mortality.[4] As a result, ICGR15 is considered as a useful indicator for discriminating good and poor risk Child-Pugh Class A patients.[5] Therefore, in Japan and other Eastern countries, this criteria is utilized as the standard for HCC liver resections.[5]

Prior studies have shown that the average ICGR15 value in patients with liver cirrhosis (LC) is 20%.[6] However, some patients have LC despite ICGR15 values less than 10%, pointing towards appropriate hepatic functional reserve. In such cases, we are occasionally obliged to change operative plans due to concern for postoperative liver failure. Although a prior report showed that some patients with LC had

ICGR15 ≤10% (28.4%, 38/134),[7] it is still unclear how LC can be preoperatively predicted among HCC patients with ICGR15 ≤10%.

Functional liver volume (FLV), computed by signal intensity (SI) ratio from gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance image (MRI), can be used for quantitative assessment of liver functional reserve.[8] The result of Gd-EOB-DTPA-enhanced MRI is reported to be significantly correlated with ICGR15, as most Gd-EOB-DTPA uptake occurs via the same transporter as ICG.[8] Additionally, functional remnant liver assessment using enhanced MRI has been reported as useful for prediction of postoperative morbidity and as an operative indication for HCC in those with portal vein tumor thrombus. [9, 10] Although this evidence suggests that FLV is useful for preoperative liver functional assessment, the relationship between FLV and patients with LC and ICGR15≤10% is still unclear.

In the present study, we compared clinicopathological variables among three groups divided by pathological LC and ICGR15 value (>10/ ≤10, %). Additionally, FLV and liver parenchymal cell volume ratio among the groups were compared, and the reason for an ICGR15 value less than 10% in patients with LC was investigated. Lastly, we investigated clinical characteristics that were useful for predicting LC in patients with ICGR15 ≤10%.

Methods

Patients

We retrospectively reviewed the charts of 479 patients who underwent liver resection for HCC at the Second Department of Surgery, Dokkyo Medical University Hospital, between April 2000 and December 2015. The indications for liver resection and operative procedures were determined using Makuuchi's criteria.[5] Patients were divided into three groups using ICGR15 values and presence or absence of LC; Group A consisted of non-LC patients with ICGR15 ≤10%; Group B was LC patients with ICGR15 ≤10%; and Group C was LC patients with ICGR15 >10%.

Evaluation of the Value of Preoperative Computed Tomography for Diagnosing LC

To assess whether preoperative computed tomography (CT) is useful for predicting LC among HCC patients with ICGR15 ≤10%, we investigated the preoperative CT reports from radiologists at our hospital among HCC patients with ICGR15 ≤10%. CT findings of LC included an enlarged left lobe, atrophy of the right lobe, nodular liver contour, and splenomegaly.[11]

Diagnostic Criteria for Pathological LC

According to "The General Rules for the Clinical and Pathological Study of Primary Liver Cancer" (Liver Cancer Study Group of Japan, Third English Edition), LC (F4) was diagnosed when bridging fibrosis was observed surrounding the regenerative nodules throughout the entire liver parenchyma.[12] Patients with

pathological LC were included in our LC group and patients without LC were placed in our non-LC group. Group A included not only no liver fibrosis (F0) but also chronic hepatitis (F1, F2 and F3).

Calculation of Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4) Index

The aspartate aminotransferase-to-platelet ratio index (ARPI) was calculated as [actual serum aspartate aminotransferase (AST) level (IU/L)/ upper normal limit of serum AST level (30 IU/L)]/platelet counts (10^4/mm^3) × 100.[13] The fibrosis-4 (FIB-4) index was calculated as [serum AST level (IU/L) × age (yr)]/[platelet counts (10^4/mm^3)

$$\times\sqrt{\text{serum alanine aminotransferase (ALT) level (IU/L)}}\,].$$[14]

Cut-off Value of Clinical Characteristics

The cut-off values for clinical characteristics such as age, body mass index (BMI), AST, alanine aminotransferase (ALT), albumin, platelet count, prothrombin time (PT) %, total bilirubin, APRI, FIB-4 index, hyaluronic acid and type IV collagen 7S domain were determined using receiver operating characteristic (ROC) curve analyses for predicting LC in all 479 patients, with the exception of alpha-fetoprotein (AFP) and protein induced by Vitamin K antagonist II (PIVKA-II). The recommended cut-off values for these characteristics were determined using the most prominent point on the ROC curve (Youden index = maximum [sensitivity–(1 - specificity)]),[15] and we also calculated the area under the ROC (AUROC) curve.

Definition of Operative Complications

Post-operative complications after liver resections were classified according to the Clavien-Dindo grades.[16] Operative complications included bile leaks, gastrointestinal ulcers, ileus, postoperative bleeding, pleural effusion, ascites, bacterial infection, vascular diseases, liver failure and others.

Calculation of Total Liver Volume (TLV)

One-millimeter-thick CT images were transferred to a workstation (SYNAPSE VINCENT: FUJIFILM Medical Co., Ltd., Tokyo, Japan), which then automatically extracted liver parenchyma, portal vein, hepatic vein, and liver tumor characteristics using the region growing method. Additionally, this workstation automatically calculated total liver volume (TLV) (ml) using extracted three-dimensional liver images.

Calculation of Signal Intensity Ratio and Functional Liver Volume (FLV)

The average signal intensity (SI) in the regions of interest of the four liver segments (lateral, medial, anterior and posterior) and the back muscle on the 20 min post-contrast MRI image was computed using STELLAR (ASTROSTAGE Co., Tokyo, Japan). The SI ratio was calculated as follows: SI ratio = SI liver/ SI

muscle.[8] The SI liver was calculated as the average SI of four liver segments. The FLV was calculated as follows: Functional liver volume (FLV) = TLV x (SI ratio – 1) (ml).[8]

Calculation of Liver Parenchymal Cell Volume Ratio

Non-cancerous tissue was stained using hematoxylin and eosin. Five microscopic tissue images were randomly selected and photographed using light microscope with x40 magnification (Olympus Co., Tokyo, Japan). These images were transferred to Adobe Photoshop CC 2018 (Adobe Systems Inc., Los Angeles, USA). The liver parenchymal area in the images of each group was painted black using Adobe Photoshop (Figure 1). Liver parenchyma was defined as the complex of hepatocytes, sinusoids, and canaliculi. Non- parenchyma tissue was defined as fibrous tissues, bile ducts, lymph vessels, and/or blood vessels. The parenchymal cell volume ratio was calculated as follows: [black area divided by total area] x 100 (%). The average parenchymal cell volume ratio of the five images was available in this study.[17]

Statistical Analysis

Intergroup differences between groups were analyzed using the Chi-square, Kruskal-Wallis, and the Mann-Whitney *U* tests with Bonferroni correction, where appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated by univariate or multivariate analyses using logistic regression model. All statistical analyses were performed using IBM SPSS statistics version 25.0 software package for Windows (IBM Co., New York, NY, USA), and differences with a *P* value of <0.05 were considered statistically significant.

Results

Clinical Characteristics of the Three Groups Based on ICGR15 and Pathologically Proven LC

Table 1 shows the clinical characteristics of the 479 patients included in our cohort, divided into three groups. The Chi-squared and Kruskal-Wallis tests revealed significant intergroup differences in BMI (kg/m^2, $P = 0.040$), albumin (g/dL, $P < 0.001$), ALT (IU/L, $P = 0.016$), AST (IU/L, $P < 0.001$), ICGR15 value (%, $P < 0.001$), esophageal varix (no/yes, $P < 0.001$), platelet count ($x10^4/mm^3$, $P < 0.001$), PT% (%, $P < 0.001$), Child-Pugh classification (A/B, $P < 0.001$), HBs antigen (negative/positive, $P < 0.001$), HCV antibody (negative/positive, $P < 0.001$), APRI ($P < 0.001$), FIB-4 index ($P < 0.001$), hyaluronic acid (ng/mL, $P < 0.001$), type IV collagen 7S domain (ng/mL, $P < 0.001$), performance of anatomical resection (yes/no, $P < 0.001$) and major hepatectomy (yes/no, $P < 0.001$), operative complication (Clavien-Dindo grade 0-II/III-V, $P = 0.011$), tumor-node-metastasis (TNM) stage (I, II/III, IV, $P < 0.001$), postoperative hospital stay (day, $P < 0.001$), and degree of liver fibrosis (0–1/2–3/4, $P < 0.001$) .

Table 1
The clinical characteristics of three groups (A, B and C) divided by ICGR15 and pathologically proven liver cirrhosis

Variable	Group A (n = 112)	Group B (n = 71)	Group C (n = 296)	*P*-value
Age (yr)	68 (61–74)	67 (58–71)	66 (60–72)	0.605
Gender (male/female)	86/26	57/14	217/79	0.428
BMI (kg/m^2)	22.6 (20.6–24.7)	22.2 (19.7–25.1)	23.2 (20.5–26.1)	0.040
Albumin (g/dL)	3.8 (3.4–4.1)	3.6 (3.4–4.0)	3.3 (3.0–3.7)	< 0.001
ALT (IU/L)	33 (23 – 47)	31 (21–44)	34 (23–49)	0.016
AST (IU/L)	30 (19–43)	32 (24–42)	41 (31–59)	< 0.001
ICGR15 (%)	7 (5–9)	8 (6–9)	21 (16–31)	< 0.001
Esophageal varix (no/yes)	102/10	48/19	141/151	< 0.001
Platelet count (x10^4/mm^3)	18.5 (15.1–22.7)	12.5 (9.6–16.1)	10.6 (7.4–14.1)	< 0.001
PT% (%)	89 (81–95)	81 (76–89)	78 (70–85)	< 0.001
Total bilirubin (mg/dL)	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.7 (0.7–0.9)	0.503
Child-Pugh classification (A/B)	101/11	64/7	217/79	< 0.001
HBs antigen (negative/positive)	93/19	53/18	271/25	< 0.001
HCV antibody (negative/positive)	61/51	34/37	63/233	< 0.001
APRI	0.6 (0.4–0.8)	0.8 (0.6–1.4)	1.4 (0.8–2.1)	< 0.001
FIB-4 index	2.19 (1.63–2.80)	2.94 (2.07–4.28)	4.64 (3.01–6.72)	< 0.001
Hyaluronic acid (ng/mL)	69 (41–107)	108 (48 – 188)	237 (117 – 406)	< 0.001
Type IV collagen 7S domain (ng/mL)	5.1 (4.2–6.3)	5.9 (4.8–8.7)	7.5 (6.0–10.0)	< 0.001

Variable	Group A (n = 112)	Group B (n = 71)	Group C (n = 296)	*P*-value
Anatomical resection (no/yes)	22/90	18/53	174/122	< 0.001
Major hepatectomy (no/yes)	86/26	67/4	283/13	< 0.001
Operative bleeding (mL)	420 (210–772)	462 (201–789)	497 (254–955)	0.547
Operative complication (CD grade 0-II/III-V)	91/21	54/17	198/98	0.011
Operative time (min)	270 (220–360)	247 (200–337)	261 (205–342)	0.478
Surgery (open/laparoscopic)	110/2	67/4	292/4	0.074
TNM stage (I/II/III/IV)	41/24/45/2	36/21/11/3	67/108/90/31	< 0.001
Postoperative hospital stay (day)	14 (12–20)	19 (14–31)	23 (14–35)	< 0.001
Degree of liver fibrosis (0–1/2–3/4)	49/63/0	0/0/71	0/0/296	< 0.001

Chi-squared test, Median (IQR), Kruskal-Wallis test

AFP; alpha-fetoprotein, ALT; alanine aminotransferase,

APRI; Aspartate aminotransferase-to-platelet ratio index, AST; aspartate aminotransferase,

BMI; body mass index, CRP; C-reactive protein,

ICGR15; indocyanine green retention rate at 15 minutes,

PIVKA-II; protein induced by Vitamin K antagonist II, PT; prothrombin time,

TNM stage; Tumor-node-metastasis stage

In the comparison of clinical characteristics between the three groups, albumin, ALT, AST, total bilirubin, and Child-Pugh classification (A/B) of Group B were similar to those of Group A. On the other hand, PT% ($P = 0.001$), platelet count ($P < 0.001$), and postoperative hospital day ($P = 0.001$) of Group B were worse than those of Group A. In addition, these factors of Group C were significantly worse than those of Group B (PT%: P = 0.017, platelet count: P = 0.002, postoperative hospital stay: P = 0.007).

Postoperative Ascites of Patients in the Three Groups

Figure 2 shows the amount of postoperative ascites in the three groups (A, B and C). The Mann-Whitney U test revealed that the amount of ascites (mL) at postoperative day 4, day 7 and day 10 in patients of Group A was significantly smaller than that of the other two groups (Group A vs. Group B: $P = 0.006$ on day 4, $P < 0.001$ on day 7, and $P < 0.001$ on day 10; Group A vs. Group C: $P < 0.001$ on day 4, $P < 0.001$ on day 7, $P < 0.001$ on day 10).

Rate of LC and Change in Operation Plan Among Patients with ICGR15 ≤10%

Among 183 patients with ICGR15 ≤ 10% who underwent liver resection, 71 patients had pathologically proven LC. Additionally, operative plans were changed intraoperatively in 8 patients due to concerns for potential postoperative liver failure as follows: segmentectomy to partial liver resection in 4 patients, segmentectomy to subsegmentectomy in 2 patients, lobectomy to partial liver resection and subsegmentectomy to partial liver resection in one patient each. Among these 8 patients, 5 patients had postoperative complications: 2 patients developed pleural effusions, one patient developed ascites, one patient developed a bile leak, and one patient developed postoperative fevers. The median postoperative hospital day was 14 days (range 6 to 147 days).

Value of CT for Diagnosing LC in Patients with ICGR15 ≤10%

Using the available preoperative CT findings of 55 patients with both ICGR15 ≤ 10% and pathological LC, 24 patients (43.6%) were diagnosed as LC by radiologists. Among these 24 patients, 16 patients had nodular liver contour, 13 patients had splenomegaly, 10 patients had an enlarged left lobe, and 7 patients had atrophy of the right lobe.

Relationship between Enhanced MRI Imaging and Liver Volume in the Three Groups Divided by ICGR15 Value and Liver Cirrhosis

One-hundred and one patients had CT and MRI imaging available prior to surgery: 27 patients in Group A, 20 in Group B, and 54 in Group C. Figure 3 shows the relationship between enhanced MRI imaging and liver volume between the three groups. The median value of TLV in Group A, B and C was 1125 ml, 1146 ml and 1159 ml, respectively; the median value of FLV in Group A, B and C was 982 ml, 890 ml and 697 ml, respectively There was no significant difference in TLV among the three groups. FLV of Group C was significantly less than that of Group A and B (Group C vs Group A: $P < 0.001$, Group C vs. Group B: $P = 0.006$). Despite no significant difference in FLV between Groups A and B ($P = 0.282$), the median value of FLV in Group B was smaller than that in Group A (982 ml vs 890 ml).

Liver Parenchymal Cell Volume Ratio in the Three Groups Divided by ICGR15 Value and Liver Cirrhosis

Among the 101 patients with available MRI findings, sections of formalin-fixed paraffin-embedded non-tumor tissues were stained by hematoxylin and eosin. The median values of liver parenchymal cell volume ratio in Group A, B, and C was 88.7%, 84.3% and 79.7%, respectively. Mann-Whitney U-test showed a significant intergroup difference among the three groups (Group A vs. Group B: $P = 0.002$, Group A vs. Group C: $P < 0.001$, Group B vs. Group C, $P = 006$) (Fig. 4).

Uni- and Multi-variate Analyses to Detect Clinical Characteristics Correlating with LC in Patients with ICGR15 ≤10%

Table 2 shows uni- and multivariate analyses using liver fibrosis markers to identify useful predictors of LC in 183 patients with ICGR15 ≤ 10%. Univariate analysis revealed a significant association between LC and esophageal varix (yes/no), platelet count (< 12/≥12, $x10^4/mm^3$), PT% (< 80/≥80, %), APRI (> 0.8/ ≤0.8), FIB-4 index (> 2.6/≤2.6), hyaluronic acid (> 120/≤120, ng/mL), type IV collagen 7S domain (> 6.5/ ≤6.5, ng/mL) and AFP (> 8/≤8,ng/mL). Using these significant characteristics for diagnosis of LC, multivariate analysis revealed that platelet count (< 12/≥12, $x10^4/mm^3$) (OR, 5.012; 95% CI 1.116–13.08; *P* = 0.001) and PT% (< 80/≥80, %) (OR, 2.447; 95% CI 1.116–5.366; *P* = 0.025) were closely associated with LC. Sensitivity, specificity, and diagnostic accuracy of the combination of these two characteristics for diagnosing LC in patients with ICGR15 ≤ 10% were 69.0 %, 69.6 % and 69.3%, respectively.

Table 2
Univariate and multivariate analyses in relation to pathological liver cirrhosis among 183 patients with normal ICGR15 value (≤ 10%).

	Univariate analyses			Multivariate analyses		
Variable	*P*-value	OR	95% C.I.	*P*-value	OR	95% C.I.
Age (> 70/≤70, yr)	0.788	0.921	0.504–1.683			
Gender (male/female)	0.577	1.231	0.593–2.556			
BMI (< 22/≥22, kg/m^2)	0.781	1.088	0.600–1.973			
Albumin (< 3.7/≥3.7, g/dL)	0.115	1.620	0.890–2.951			
ALT (> 42/≤42, IU/L)	0.892	0.955	0.489–1.864			
AST (> 30/≤30, IU/L)	0.766	1.095	0.603–1.988			
Esophageal varix (yes/no)	0.001	3.998	1.727–9.254	0.569	1.352	0.478–3.827
Platelet count (< 12/≥12, x10^4/mm^3)	< 0.001	6.998	3.331–14.70	0.001	5.012	1.920–13.08
PT% (< 80/≥80, %)	0.006	2.520	1.301–4.879	0.025	2.447	1.116–5.366
Total bilirubin (> 0.6/≤0.6, mg/dL)	0.533	1.220	0.653–2.278			
Child-Pugh classification (B/A)	0.993	1.004	0.370–2.724			
HBs antigen (positive/negative)	0.171	1.662	0.803–3.441			
HCV antibody (positive/negative)	0.386	1.302	0.717–2.362			
APRI (> 0.8/≤0.8)	< 0.001	4.062	2.146–7.691	0.483	1.432	0.525–3.903
FIB-4 index (> 2.6/≤2.6)	< 0.001	3.676	1.966–6.874	0.898	0.934	0.329–2.655
Hyaluronic acid (> 120/≤120, ng/mL)	< 0.001	3.556	1.827–6.921	0.088	2.102	0.896–4.933

	Univariate analyses			Multivariate analyses		
Type IV collagen 7S domain (> 6.5/≤6.5, ng/mL)	0.013	2.293	1.193–4.408	0.894	1.057	0.471–2.370
AFP (> 8/≤8, ng/mL)	0.010	2.260	1.220–4.184	0.203	1.633	0.768–3.474

95% C.I.; 95% confidence interval, OR; odds ratio

AFP; a-fetoprotein, ALT; alanine aminotransferase,

APRI; Aspartate aminotransferase-to-platelet ratio index, AST; aspartate aminotransferase,

BMI; body mass index, ICGR15; indocyanine green retention rate at 15 minutes,

PT; prothrombin time

Discussion

Indocyanine green (ICG) is taken up by hepatocytes and ultimately excreted into the bile duct. The mechanism is as follows: intravenously administrated ICG passes through the portal vein and the sinusoid,[18] then, ICG is taken up by hepatocytes thought transporters including organic anion transporting polypeptide (OATP)1B1/3 and Na(+)-dependent taurocholate co-transporting polypeptide (NTCP) expressed on the sinusoidal membrane,[18] and lastly, ICG is excreted into bile via the multidrug resistance P-glycoprotein 2 trasnporter.[19]

The mechanism of elevated ICGR15 value is ascribed to decreased ICG transporters, malfunction of ICG transporters, or both. Kawasaki et al. reported that drug clearance per one hepatocyte was the same in normal and cirrhotic livers, regarded as the intact hepatocyte theory.[20] The reason for decreased drug clearance is that total hepatocyte count and liver parenchyma volume in LC are significantly less than in normal livers.[20] Hashimoto et al. revealed that liver parenchyma volume was significantly associated with ICGR15 value.[17] They concluded that liver dysfunction in LC is caused by the reduction of liver parenchymal cell volume ratio which is related to increased liver fibrosis.[17] This evidences indicates that the mechanism of elevating ICGR15 value in LC patients is decreasing ICG transporters of whole liver because of reduced liver parenchyma and increased liver fibrosis.

In addition, Chang et al. showed that FLV was strongly correlated with liver parenchyma volume.[8] Based on these findings, ICGR15 and FLV can represent liver parenchyma volume. Although our results showed no significant difference in FLV between Group A and Group B, Group B had significantly greater FLV in comparison with Group C ($P = 0.006$) (Fig. 3). Additionally, liver parenchymal cell volume ratio of Group B was significantly smaller than that of Group A ($P = 0.002$) (Fig. 4). These results indicate that Group B

would have mild liver fibrosis, which did not affect liver function, suggesting that liver parenchyma volume of Group B was similar to that of Group A despite an underlying cirrhotic liver.

Another possibility is that capillarization of sinusoidal vessels as well as the formation of portovenous shunt could be a reason for decreased ICG extraction and impaired ability to remove ICG.[21] ICG is almost completely bound to plasma protein, and therefore, its diffusion is greatly influenced by influenced by sinusoidal capillarization.

It is currently unknown whether there are any variables predicting LC in patients with ICGR15 ≤ 10%. Except for liver biopsy, non-invasive methods for diagnosing LC include CT imaging and liver fibrosis markers such as APRI, FIB-4 index, hyaluronic acid and type IV collagen 7S domain.[11, 22, 23] However, our results showed that the sensitivity of CT in diagnosing LC in patients with normal ICGR15 value was low (diagnosable rate: 43.6%, 24/55); therefore, there is a need for investigation of additional clinical characteristics capable of diagnosing LC, particular in patients with ICGR15 ≤ 10%. Multivariate analysis revealed that platelet count and PT% were significantly associated with LC in patients with ICGR15 ≤ 10% (Table 2). In addition to CT examination, the combination of platelet count (< 12 $x10^4/mm^3$) and PT% (< 80%) was a useful non-invasive marker of LC in patients with ICGR15 ≤ 10%.

In general, patients with LC, irrespective of ICGR15 value, have a higher degree of fibrosis than non-LC patients, leading to a higher frequency of postoperative complications including ascites, pleural effusion, and liver insufficieny.[24,25] Additionally, our results show that the postoperative hospital stay of Group B (median: 19 days) was longer than that of Group A (median: 14 days). However, the rate of operative complications, defined as Clavien-Dindo grade III-V, in Group A and B was similar (Group A 21/112 = 18.7% versus Group B 17/71 = 23.9%) (Table 1).

Because the amount of postoperative ascites was greater in Group B than that in Group A (Fig. 2), postoperative ascites was likely a reason for prolonged hospital stay in Group B compared to Group A. Our results revealed the significant intergroup difference in esophageal varix among the three groups (Table 1). Our findings may indicate that the reason for greater postoperative ascites in Group B compared to Group A is secondary to impaired collateral circulation around the liver and abdominal wall due to portal hypertension. Therefore, the significance of LC in patients with ICGR15 ≤ 10% is useful for estimating postoperative hospital stay.

Although patients in Group B are cirrhotic, it is still unclear why Group B had a degree of liver parenchyma similar to that of normal livers. According to the new Inuyama classification, step-by-step liver fibrosis progression such as bridging fibrosis, lobular distortion and regeneration nodules leads to LC in patients with chronic hepatitis.[14] This classification is not applicable to patients in Group B, because enhanced MRI revealed Group B had FLV similar to that of Group A in the present study (Fig. 2). These findings suggest that liver tissue of Group B patients likely does not follow step-by-step progression of liver fibrosis.

We acknowledge the limitations of our study. We did not routinely perform ^{99m}Tc-GSA SPECT scintigraphy before surgery, and thus we could not include the results of this examination in our present study. ^{99m}Tc-GSA SPECT scintigraphy is a well-known method for preoperative assessment of liver functional reserve.[26] Because ^{99m}Tc-GSA SPECT scintigraphy is affected neither by portal-systemic shunting nor jaundice, this imaging examination enables more accurate liver functional assessment in such conditions compared to the ICGR15 test.[27] Further study including ^{99m}Tc-GSA SPECT scintigraphy would be required.

In summary, volumetric assessment and pathological findings suggest that cirrhotic livers with normal liver function are characterized by slightly decreasing liver parenchyma as well as slight degree of liver fibrosis when compared to normal livers. Additionally, platelet count and PT% are useful for predicting LC in patients with ICGR15 ≤ 10%. Finally, the reason for an ICGR15 value ≤ 10% in patients with LC is that FLV of such patients is similar to that of patients with normal liver.

Abbreviations

ARPI: aspartate aminotransferase-to-platelet ratio index; FIB-4: fibrosis-4; FLV: functional liver volume; Gd-EOB-DTPA: Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; HCC: hepatocellular carcinoma; ICG: indocyanine green; ICGR15: indocyanine green retention rate at 15 min; SI: signal intensity; TLV; total liver volume.

Declarations

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We received no funding/grant support for this study.

Conflict of interest/ Competing interests

Authors declare no conflict of interests for this article.

Ethical approval

Our study was approved by the Institutional Review Board (provided ID number: R-8-14) on the basis of the Ethical Guidelines for Clinical Research of the Ministry of Health, Labor and Welfare in Japan prior to its initiation.

Consent to participate

We provided the enrolled patients with the opportunity to opt out on our website (www2.dokkyomed.ac.jp/dep-m/surg2/pg334.html).

Consent for publication

Not applicable.

Animal research

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

Clinical trials registration

Not applicable.

Authors' Contributions

Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and statistical analysis: T. S.; study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content: T. A.; study concept and design, and critical revision of the manuscript for important intellectual content: K. K.; acquisition of data: Y. N, K. H. P, T. M, T. S, Y. S, S. M, and Y. I; statistical analysis: M. I. All authors approved the final version of manuscript.

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Figures

Fig. 1.

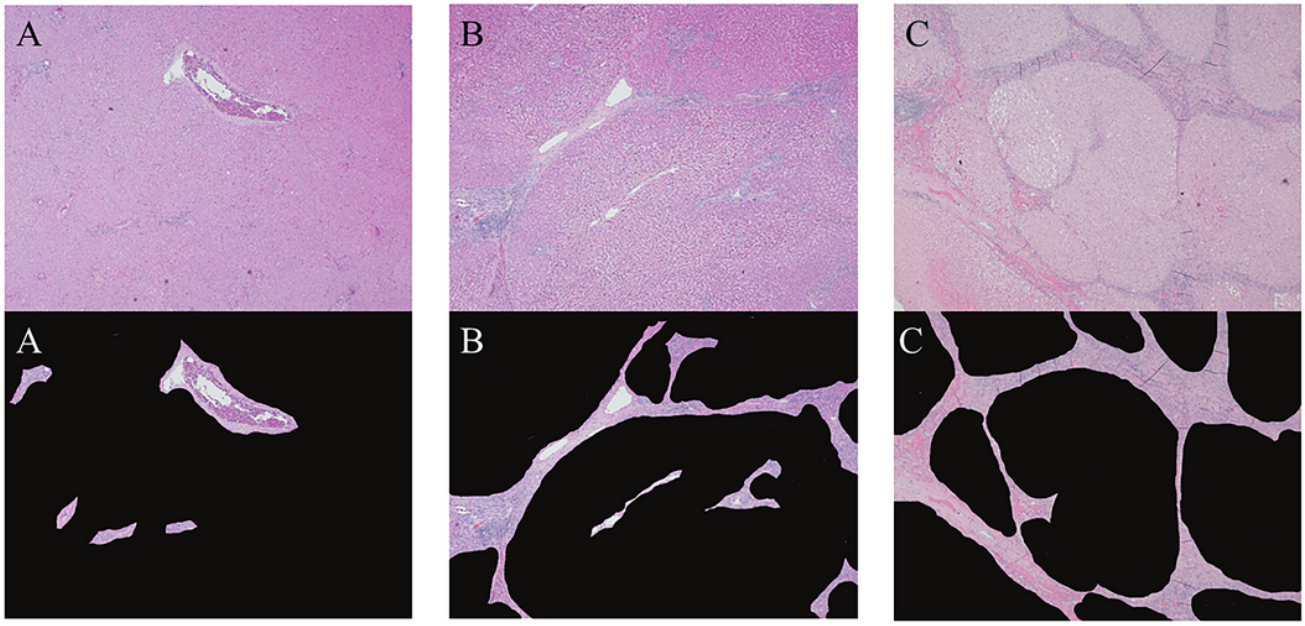
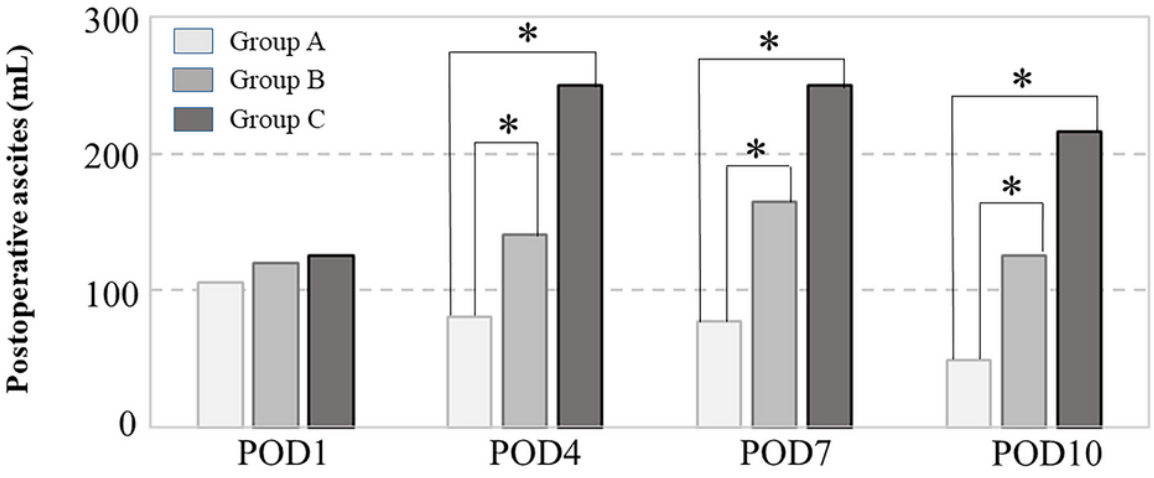


Figure 1

Microscopic image of liver parenchyma in the three groups (A, B and C) (hematoxylin and eosin, x40). Liver parenchyma of each image was painted black using Adobe Photoshop®.

Fig. 2.

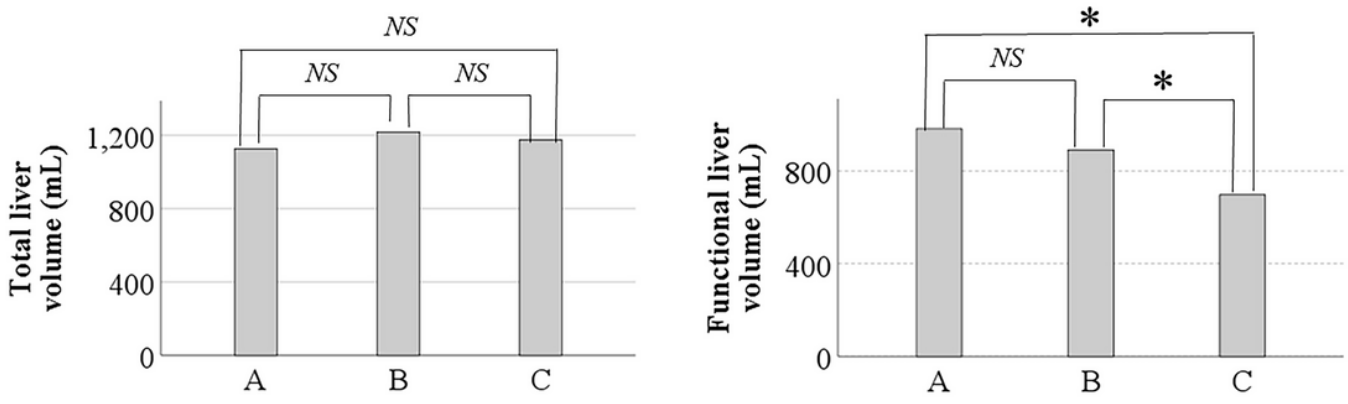


Data is expressed as the median. Mann-Whitney U test
*, statistically significant difference (P <0.0167)
POD; postoperative day

Figure 2

Postoperative ascites of patients in the three groups (A, B and C).

Fig. 3.



Data is expressed as the median. Mann-Whitney U test
*, statistically significant difference (P <0.0167); *NS*, not significant difference
FLV; functional liver volume, TLV; total liver volume

Figure 3

The relationship between enhanced MRI imaging and liver volume among the three groups (A, B and C) divided by ICGR15 value and liver cirrhosis.

Fig. 4.

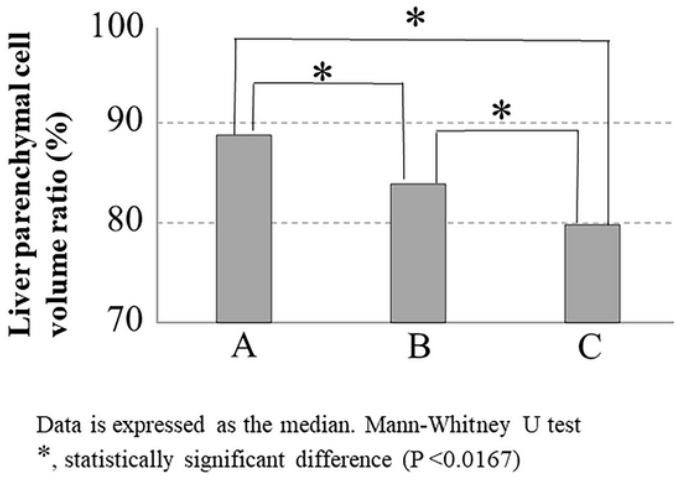


Figure 4

Liver parenchymal cell volume ratio of patients in the three groups (A, B and C).

Supplementary Files

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- GraphicalAbstract.png