

**Comparison between CT volumetry and extracellular
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hepatocellular carcinoma**

日本大学大学院医学研究科博士課程

内科系放射線診断学専攻

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修了年 2024 年

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Comparison between CT volumetry and extracellular volume fraction using liver dynamic CT for the predictive ability of liver fibrosis in patients with hepatocellular carcinoma

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Received: 23 February 2022 / Revised: 13 April 2022 / Accepted: 28 April 2022 / Published online: 20 May 2022
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Abstract

Objectives To compare the predictive ability of liver fibrosis (LF) by CT-volumetry (CTV) for liver and spleen and extracellular volume fraction (ECV) for liver in patients undergoing liver resection.

Methods We retrospectively analysed 90 consecutive patients who underwent CTV and ECV. Manually placed region-of-interest ECV (manual-ECV), rigid-registration ECV (rigid-ECV), and nonrigid-registration ECV (nonrigid-ECV) were calculated as $ECV(\%) = (1 - \text{haematocrit}) \times (\Delta HU_{\text{liver}} / \Delta HU_{\text{aorta}})$, where ΔHU = subtraction of unenhanced phase from equilibrium phase (240 s). Manual-ECV was compared with CTV for the estimation of LF. The total liver volume to body surface area (TLV/BSA), splenic volume to BSA (SV/BSA), ratio of TLV to SV (TLV/SV), ratio of right liver volume to SV (RV/SV), and liver segmental volume ratio (LSVR) were measured. ROC analyses were performed for ECV and CTV.

Results After excluding 10 patients, seventy-eight (97.5%) out of 80 patients had a Child-Pugh score of 5 points, and two (2.5%) patients had a Child-Pugh score of 6 points. AUC of ECV showed no significant difference among manual-ECV, rigid-ECV, and nonrigid-ECV. TLV/BSA, SV/BSA, TLV/SV, and RV/SV had a higher correlation with LF grades than manual-ECV. AUC of SV/BSA was significantly higher than that of manual-ECV in F0-1 vs F2-4 and F0-2 vs F3-4. AUC of SV/BSA (0.76–0.83) was higher than that of manual-ECV (0.61–0.75) for all LF grades, although manual-ECV could differentiate between F0-3 and F4 at high AUC (0.75).

Conclusions In patients undergoing liver resection, SV/BSA is a better method for estimating severe LF grades, although manual-ECV has the ability to estimate cirrhosis (\geq F4).

Key Points

- The splenic volume is a better method for estimating liver fibrosis grades.
- The extracellular volume fraction is also a candidate for the estimation of severe liver fibrosis.

Keywords ROC · Liver fibrosis · Computed tomography

Abbreviations

APRI	Aspartate aminotransferase-platelet ratio index
BSA	Body surface area
Cr	Creatinine

CTV	Computerised tomography volumetry
ECV	Extracellular volume fraction
FIB-4	Fibrosis index based on the four factors
Hct	Haematocrit
ICGR15	Indocyanine green retention rates at 15 minutes after injection
INR	International normalised ratio
LF	Liver fibrosis
LSVR	Liver segmental volume ratio, which is volume ratio of Couinaud segments I-III to segments IV-VIII
manual-ECV	ECV by manually placed region-of-interests
nonrigid-ECV	Nonrigid registration ECV
Plt	Platelet count

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rigid-ECV	Rigid registration ECV
RV/SV	Ratio of RV to SV
RV	Right liver volume
SV	Splenic volume
TLV/SV	Ratio of TLV to SV
TLV	Total liver volume

Introduction

Hepatic resection in the presence of cirrhosis is associated with serious postoperative complications [1, 2]. Liver biopsy is the standard method to evaluate liver fibrosis (LF), but it has limitations such as sampling error, invasiveness, and risk of complications [3, 4].

CT volumetry (CTV) [5, 6] and extracellular volume fraction (ECV) [7–9] are highly sensitive and specific tools for the diagnosis of LF.

In CTV analysis, the ratio of the total liver volume (TLV) to body surface area (BSA) (TLV/BSA) [10], ratio of splenic volume (SV) to BSA (SV/BSA) [6, 10, 11], ratio of TLV to SV (TLV/SV) [10], ratio of right liver to SV (RV/SV) [12], and the volume ratio of Couinaud segments I–III to segments IV–VIII (liver segment volume ratio: LSVR) [13, 14] are useful for evaluating LF grades.

ECV is an index calculated using haematocrit (Hct), non-contrast phase CT, and contrast equilibrium phase CT, and is useful for estimating the degree of LF [7, 8]. ECV requires the measurement of CT values by placing regions-of-interest (ROIs), which are set manually by an observer (manual-ECV). Rigid registration of ECV (rigid-ECV) refers to the alignment between objects with three-dimensional shapes and is performed only by rotation and translation. Nonrigid-registration of ECV (nonrigid-ECV) is a method of aligning objects by deforming them through affine transformation. In particular, ECV using nonrigid registration has attracted significant attention for liver stiffness measurement [7].

The study aimed to compare the ability to predict LF between CTV and ECV measured using liver dynamic CT. In addition, the manually placed ROI method and the nonrigid and rigid registrations were compared for the prediction of LF.

Materials and methods

Patients

This study was approved by the institutional review board (RK-20110-12). The requirement for informed consent was waived due to the retrospective nature of this study. Consecutive patients aged ≥ 20 years who were candidates for liver resection for liver tumour and had undergone

preoperative quadri-phase CT with equilibrium phase (240 s) were included. Patients who met the following criteria were excluded: (1) patients who had not undergone liver resection because of clinical or biochemical evidence of decompensated liver function (Child-Pugh classification C, ICG-R15 $\geq 35\%$, or serum total bilirubin level ≥ 2.0 mg/dL), tumour status, or portal hypertension (including the presence of high-risk esophageal varices); (2) patients who underwent quadri-phase CT > 4 weeks prior to liver resection; (3) huge liver masses larger than 500 mL. From February 2019 to April 2021, 90 consecutive patients underwent both CTV and ECV with liver dynamic CT. Patient characteristics, such as background liver disease, hepatic biochemical data, Child-Pugh score, and pathological fibrosis stage, were obtained from the electronic medical records.

Laboratory data

Blood test data (Hct, aspartate aminotransferase [AST], alanine aminotransferase [ALT], platelet count [Plt], international normalised ratio [INR], total bilirubin [T-Bil], albumin [Alb], creatinine [Cr], and indocyanine-green retention rate at 15min [ICGR15]) were obtained from the electronic medical records. The aspartate aminotransferase-platelet ratio index (APRI) and fibrosis-4 score (FIB-4) were computed as representative serum test-based fibrosis markers. APRI was calculated using the following formula [15, 16]: $(\text{AST [IU/L]} / \text{upper normal limit}) / \text{Plt} (10^9/\text{L}) \times 100$. FIB-4 was calculated as follows [16]: $(\text{age [years]} \times \text{AST [IU/L]} / (\text{Plt} [10^9/\text{L}] \times \text{ALT [IU/L]}^{1/2}))$. The model for end-stage liver disease (MELD) score was calculated using the following formula:

$$\text{MELD} = 3.8 \times \ln(\text{bilirubin [mg/dl]}) + 11.2 \times \ln(\text{INR}) + 9.6 \times \ln(\text{Cr [mg/dl]}) + 6.4 \times (\text{aetiology: 0, if cholestatic or alcoholic, 1 otherwise}) [17].$$

CT protocol

Quadri-phase dynamic liver CT was performed including the unenhanced, arterial (37 s) [18], portal (60 s), and equilibrium phases (240 s) after administering the contrast agent (350mg/mL, iomeprol; Iomeron® 350-syringe, Eisai, iodine content; 600mgI/kg). The contrast agent was intravenously injected at 3.0–3.5mL/s via an antecubital vein. The non-contrast and equilibrium phases measured ECV and CTV. The CT scanners of 16- or 320-CT (Aquilion16 or Aquilion ONE; Canon Medical Systems) and scanning parameters are shown in Table 1. A reconstruction slice thickness of 5mm was used for CTV and ECV. No difference in volume measurements was reported between 1 and 5 mm slices [19], but in this study, we used the more common 5 mm slice thickness.

Extracellular volume fraction analysis

Manual-ECV, rigid-ECV, and nonrigid-ECV were calculated as $ECV(\%) = (1 - Hct) \times (\Delta HU_{liver} / \Delta HU_{aorta})$, where ΔHU = subtraction of unenhanced phase from equilibrium phase (240 s) [7, 20]. Manual registration is a simple method in which the ROIs are placed on both the enhanced and unenhanced CT images by setting the same hepatic position (Fig. 1A, B). Rigid registration assumes that the organ is not deformed. It corrects for rotation and translation during the anatomical matching of the two datasets. This method is relatively easy to perform but has the disadvantage of introducing errors when the organ is deformed. Nonrigid registration is a function of deforming the liver to perform the registration, which minimises the deviation in the position caused by the breathing phase [21–24].

We investigated three registration methods to compare their superiority in estimating LF when measuring the ECV. The image analysis was performed by two radiologists with 6 and 3 years of experience in body CT. They were unaware of the liver biopsy results.

Subtracted images between the non-contrast and equilibrium phase CTs were used for rigid registration (Fig. 1C) and nonrigid registration (Fig. 1D). The semi-automatic process of generating subtraction images from the point of data loading required 90 s for rigid registration and 2 min for nonrigid registration.

Absolute enhancement (CT-value; HU) was defined as the difference between the unenhanced and equilibrium phase images. After training the ROI placement, two radiologists placed three ROIs on the images using copy and paste methods, excluding large intrahepatic vessels and liver tumours in the anterior and posterior segments of the right lobe and left lateral segment lobe. ROI was drawn to prevent a peripheral liver zone < 1 cm. Each radiologist placed the ROIs independently. Circle ROIs with a size of 10mm were used for the liver, 4mm in the axis for the portal vein, and 7mm for the abdominal aorta. ROIs were placed at the liver hilum level. The ΔHU_{aorta} and ΔHU_{portal} of each patient were

compared to ensure that the equilibrium phase was obtained properly. To ensure a sufficient equilibrium phase, patients with significant differences between ΔHU_{aorta} and $\Delta HU_{portal} > 10$ HU were excluded. Rigid and nonrigid registrations were performed using a viewer workstation (SYNAPSE VINCENT ® ver5.5, Fujifilm Medical).

CT volumetry analysis

TLV, SV, TLV/SV, RV/SV, and LSVR were measured using a viewer workstation (SYNAPSE VINCENT ® ver5.5, Fujifilm Medical). All CTV images were obtained by an abdominal radiologist with 6-years of experience with a reconstruction slice thickness of 5mm following the multiphasic liver CT protocol (Figs. 2 and 3). The measurement time for TLV and SV measurements was approximately 1min, and the segments were separated by 15 min. TLV did not include the volume of the hepatic tumours but included the volumes of the intrahepatic and intrasplenic vessels to ensure uniformity and reproducibility of the liver. TLV and SV were corrected by BSA (TLV/BSA, SV/BSA) [11, 25, 26]. BSA was calculated using Dubois' formula ($BSA [m^2] = 0.007184 \times \text{height [cm]}^{0.725} \times \text{weight [kg]}^{0.425}$) [11, 27].

Segmentation was performed using the falciform ligament as a landmark to separate liver segments II, III, and IV, based on the segmentation performed by Hunt et al [13]. The medial and lateral segments were separated using the central hepatic vein. The caudate lobe was separated by focusing on the difference in the contrast effect. The LSVR was then calculated by determining the ratio of segments I–III to segments IV–VIII [13] (Figs. 2B and 3B).

Pathology

The pathological evaluation was performed using surgically resected specimens. The pathological fibrosis stage was evaluated by two pathologists using the New Inuyama Classification [28]: F0, no fibrosis; F1, fibrous portal expansion; F2, bridging fibrosis; F3, bridging fibrosis with architectural distortion; F4, cirrhosis.

Statistical analysis

ROC analyses were performed for ECV and CTV. The correlation between the ECV results was analysed using Spearman's correlation coefficient. The intraclass-correlation-coefficients (ICCs) were used for interrater reliability, with an ICC of 0.40–0.59 defined as fair; 0.60–0.74 as good; and 0.75–1.00 as excellent. Friedman's method was used to determine whether there were significant differences between each ECV measurement method. The mean and standard deviation of CTV and ECV were calculated for each

Table 1 CT Parameters

	Aquilion ONE (n = 51)	Aquilion 16 (n = 29)
Tube voltage, (KVp)	120	120
Scan collimation (row × s)	320 × 0.5	16 × 1.0
Rotation (s)	0.5	0.5
Matrix	512 × 512	512 × 512
Pitch	0.828	0.938
Slice thickness (mm)	5	5
Reconstruction slice thickness (mm)	1	1

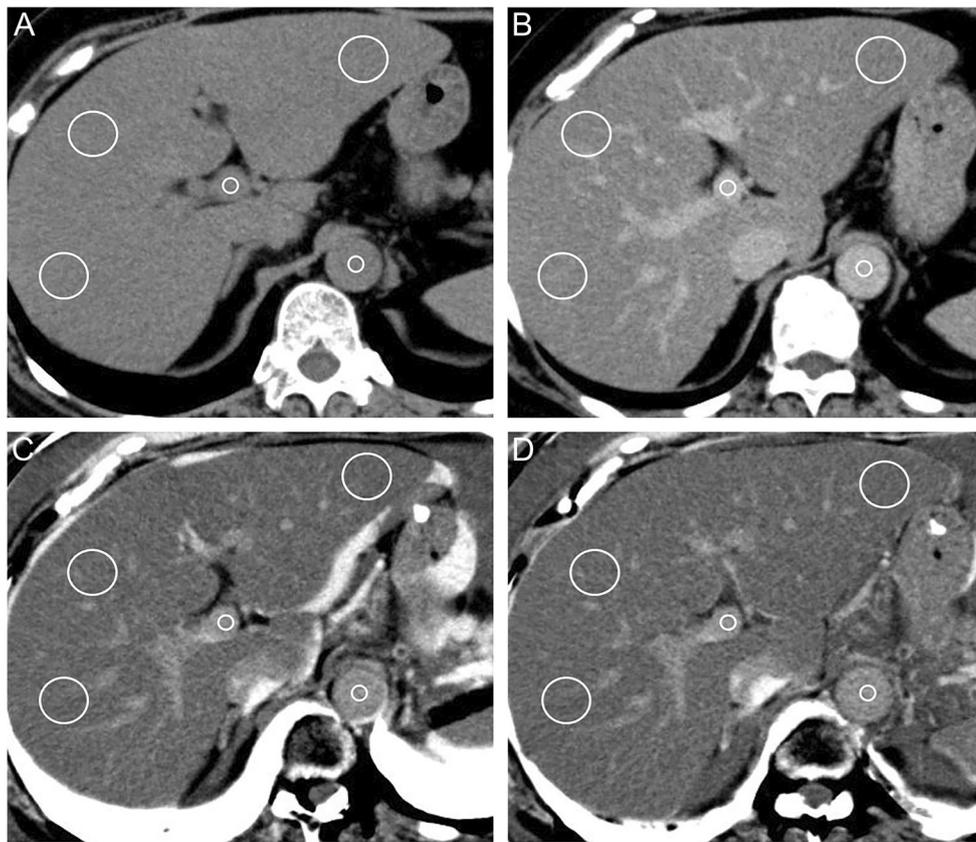


Fig 1 CT images of a 67-year-old woman with hepatocellular carcinoma, showing different inspiration levels for the unenhanced and equilibrium phase. **A** Manually measured methods on unenhanced phase image for three regions of the liver: the anterior segment of the right lobe (area 336 mm²), the posterior segment (area 336 mm²), and the lateral segment of the left lobe (area 336 mm²). The ROI of the abdominal aorta (area 61 mm²) and the portal vein (area 61 mm²) are placed. **B** Manually measured methods on equilibrium phase image for three regions of the liver: the anterior segment of the right lobe (area 336 mm²), the posterior segment (area 336 mm²), and the lateral segment of the left lobe (area 336 mm²). The ROI of the abdominal aorta (area 61 mm²) and the portal vein (area 61 mm²) are placed. **C** Subtraction image between the unenhanced and

equilibrium phase images using rigid registration for measuring three regions of the liver (anterior segment [area 336mm²], posterior segment [area 336mm²] of the right lobe, lateral segment [area 336mm²] of the left lobe). Anatomical misregistration was shown. The ROI of the abdominal aorta (area 61mm²) and the portal vein (area 61mm²) were placed. **D** Subtraction image between the unenhanced and equilibrium phase images using nonrigid registration for measuring three regions of the liver (anterior segment [area 336 mm²], posterior segment [area 336 mm²] of the right lobe, lateral segment [area 336 mm²] of the left lobe). Anatomical misregistration is shown. The ROI of the abdominal aorta (area 61 mm²) and the portal vein (area 61 mm²) are placed



Fig. 2. CT images of a 67-year-old woman with hepatocellular carcinoma, showing different inspiration levels for pre-contrast and equilibrium phase imaging. **A** Axial image of a TLV. After the raw data is manually sent to the workstation, the TLV is measured almost

automatically; the TLV contains blood vessels and fat. **B** Axial image of a segmented TLV. The falciform ligament and central hepatic vein are used as landmarks to separate II, III, and IV, medial and lateral, respectively. **C** Axial image of SV. In this workstation (ver5.5), SV is measured manually

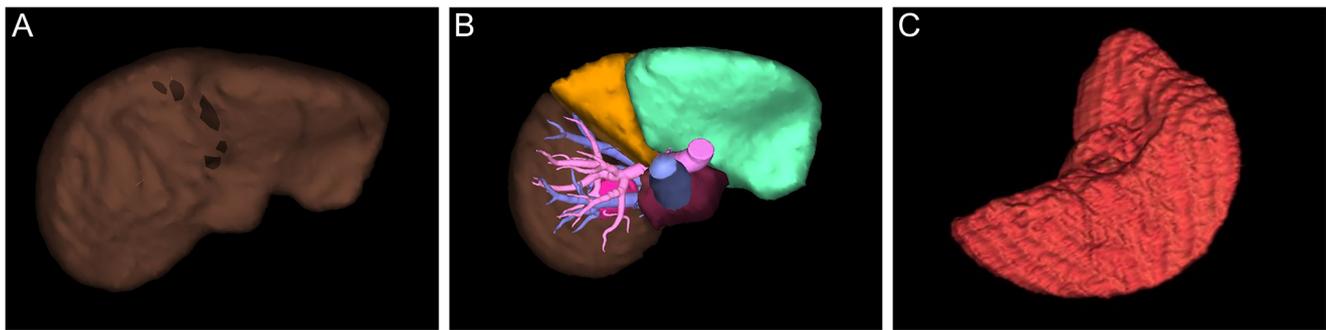


Fig. 3. CT Volumetry image (Volume Rendering) of a 67-year-old woman with hepatocellular carcinoma, showing different inspiration levels for pre-contrast and equilibrium phase imaging. **A** Three-dimensional reconstruction image of the whole liver. Inferior view. **B** Three-dimensional reconstruction image of the segmented liver. Inferior

view, Brown; right lobe (anterior and posterior segments) of the liver, Yellow; Medial segment of the left lobe, Green; Lateral segment of the left lobe. **C** Three-dimensional reconstruction image of the spleen. Inferior view

group. Spearman's correlation coefficient analysis was used to determine the correlation between the measured data (ECV and CTV) and LF grade. The Kruskal–Wallis test was used for ECV and CTV, followed by the Bonferroni correction. ROC analyses were performed for ECV and CTV. The highest AUCs by CTV and ECV were compared for the LF gradings. Delong test was used to compare the AUC values of ECV and CTV. SPSS Version-27.0 (IBM Corp.) was used for the analysis.

Results

Patients

The characteristics of 80 patients are shown in Table 2 after excluding ten patients (one patient with splenectomy, five post-hepatectomy patients, and four patients with huge liver masses [mean, 699.8mL; SD,136.5]) (Fig. 4). No one with more than 10 HU difference between $\Delta\text{HU}_{\text{aorta}}$ and $\Delta\text{HU}_{\text{portal}}$ was observed in this study. Hepatitis C virus (HCV) was the most common cause of liver disease (27.5%), followed by hepatitis B virus (HBV; 26.3%) and alcoholic cirrhosis (10.0%). Seventy-eight (97.5%) out of 80 patients showed a Child-Pugh score of 5 points, while two patients (2.5%) had a Child-Pugh score of 6 points. Thus, all patients were Child-Pugh A.

Extracellular volume fraction

The ICC between the two readers was considered fair for manual extracellular volume fraction (ECV) (0.69) and excellent for rigid-ECV (0.83) and nonrigid-ECV (0.83). The mean ECV values of F4 for manual-ECV, rigid-ECV, and nonrigid-ECV were higher than those of F0, 1, 2, and 3 (Table 3).

No significant difference (0.96, Friedman's test) was seen among manual-ECV, rigid-ECV, and nonrigid-ECV. There was a minimal correlation between ECV and LF stages (Table 3). The difference in AUC between manual-ECV, rigid-ECV, and nonrigid-ECV was about 0.01–0.02 with little difference (Table 4).

CT volumetry

The mean TLV/BSA of F4 and mean SV/BSA of F4 were higher than those of F0, 1, 2, and 3, and the mean TLV/SV of F4 and mean RV/SV of F4 were lower than those of F0, 1, 2, and 3 (Table 3). The mean LSVRs of F3 and 4 were higher than those of F0, 1, and 2 (Table 3).

TLV/BSA and SV/BSA increase as the exacerbation of LF. The hierarchisation for each stage of LF was clear in SV/BSA (Table 3). Spearman's correlation coefficient showed minimal correlation for TLV/BSA, moderate correlation for SV/BSA, moderate negative correlation TLV/SV, and RV/SV, and no meaningful correlation for LSVR.

AUCs of all parameters were the highest for F0-3 vs F4, and AUC of SV/BSA was the highest for all LF grades (AUC = 0.76–0.83) (Table 4). SV/BSA can accurately differentiate between all LF grades, although TLV/SV and RV/SV had relatively high accuracy for all LF grades (AUC = 0.74–0.81) (Table 4). AUC of SV/BSA showed the highest values to identify severe LF (\geq F3-4) or cirrhosis (\geq F4), because of 0.82 for severe LF and 0.83 for cirrhosis.

Comparison between ECV and CTV for estimation of liver fibrosis and cirrhosis

ECV and CTV were not significantly different in F0 vs F1, F1 vs F2, F2 vs F3, and F3 vs F4 (Fig. 5). There was a significant difference between F1 and F4 in all ECV measurement methods. SV/BSA and RV/SV were significantly different

Table 2 Patients characteristics

Sex, n (%)	
Male	53 (66.3%)
female	27 (33.7%)
Age (yr), mean (SD)	66.4 (10.6)
BMI (kg/m²), mean (SD)	23.0 (3.19)
BSA (m²), mean (SD)	1.64 (0.17)
Background liver disease, n (%)	
HBV	21 (26.3%)
HCV	22 (27.5%)
Alcoholic liver disease	8 (10.0%)
Others	29 (36.3%)
Child-Pugh score, n (%)	
5	78 (97.5%)
6	2 (2.5%)
7–15	0 (0%)
Pathological F grades, n (%)	
F0	10 (12.4%)
F1	19 (23.8%)
F2	19 (23.8%)
F3	16 (20.0%)
F4	16 (20.0%)
Laboratory data	
Hct (%), mean (SD)	40.8 (3.8)
AST (IU/L), mean (SD)	35.4 (22.4)
ALT (IU/L), mean (SD)	32.8 (29.0)
Plt (10 ⁹ /L), mean (SD)	188 (74.8)
INR, mean (SD)	1.03 (0.07)
T-bil (mg/dL), mean (SD)	0.72 (0.3)
Alb (g/dL), mean (SD)	4.4 (0.4)
Cr (mg/dL), mean (SD)	0.76 (0.2)
ICG-R15 (%), mean (SD)	11.7 (9.9)
ALBI, mean (SD)	−3.1 (0.3)
Grade 1*, n (%)	73 (91.3)
Grade 2a*, n (%)	7 (8.7)
Grade 2b*, n (%)	0 (0)
Grade 3*, n (%)	0 (0)
MELD, mean (SD)	2.28 (2.9)
APRI, mean (SD)	0.74 (0.59)
FIB-4, mean (SD)	2.77 (1.7)

Notes: *BMI*, body mass index; *BSA*, body surface area; *HBV*, hepatitis B virus infection; *HCV*, hepatitis C virus infection; *Hct*, haematocrit; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *Plt*, platelet; *INR*, international normalised ratio; *T-Bil*, total bilirubin; *Alb*, albumin; *Cr*, creatinine; *ICG-R15*, indocyanine green retention rates at 15 min after injection; *ALBI*, albumin-bilirubin grade; *MELD*, model for end-stage liver disease score; *APRI*, aspartate aminotransferase-platelet ratio index; *FIB-4*, fibrosis index based on the four factors

*; modified ALBI grade

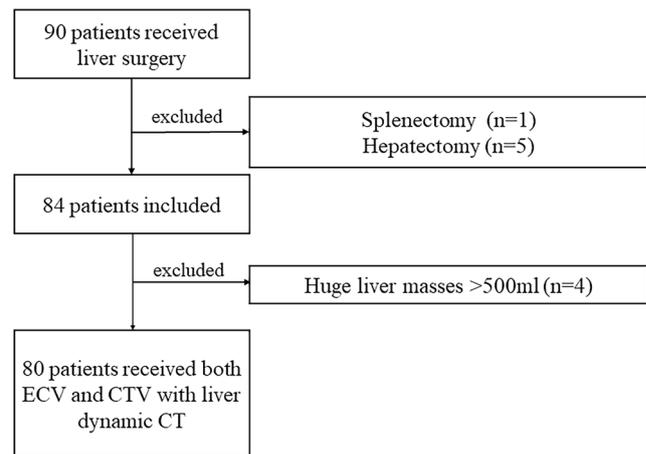


Fig. 4 Patient flowchart. Ninety patients underwent liver surgery. One patient with splenectomy, five patients with hepatectomy, and four patients with huge liver masses. All 80 patients received both extracellular volume fraction (ECV) and CT volumetry (CTV) with liver dynamic CT

in F0 vs F4, F1 vs F4, F1 vs F3, and F2 vs F4. TLV/SV was significantly different in F1 vs F3. There was no significant difference between TLV/BSA and LSVR.

Spearman's correlation coefficient analysis showed that the correlation between all ECV measurement methods and LF grades was minimal (Table 3).

AUC of SV/BSA (0.76–0.83), TLV/SV (0.74–0.77), RV/SV (0.75–0.83) was higher than any AUC of ECV (0.60–0.75) for all LF grades (Table 4). In particular, the AUC of SV/BSA was higher than other parameters in all LF grades. The next highest AUC was RV/SV for all LF grades. Since there is almost no difference in AUC between all methods of ECV measurement, and little difference in the correlation coefficient, manual-ECV, which can be measured most simply, was used for the Delong test.

AUC of SV/BSA was significantly higher than that of manual-ECV for significant LF (\geq F2) and severe LF (\geq F3–4). There was no significant difference in AUC between SV/BSA and manual-ECV for cirrhosis (\geq 4) (Table 5).

Discussion

This study is to search for the imaging parameters that can predict LF; in particular, SV/BSA is a better predictor of LF than manual-ECV. Splenic enlargement occurs because of portal hypertension and cirrhosis [29]. We believe that additional CTV, especially SV/BSA, facilitates superior estimation of LF and can contribute to safe operative management because liver stiffness is related to major complications after

Table 3 ECV and CT Volumetry for each liver fibrosis stage

	F0-1 (n = 29)	F2 (n = 19)	F3 (n = 16)	F4 (n = 16)	ρ	p value
ECV						
Manual-ECV	26.2 ± 4.8	27.3 ± 3.5	27.1 ± 4.4	31.8 ± 8.1	0.241	0.031
Rigid-ECV	26.2 ± 4.3	27.6 ± 3.5	26.3 ± 3.2	32.3 ± 6.8	0.254	0.023
Nonrigid-ECV	26.6 ± 4.1	27.3 ± 3.3	27.0 ± 4.1	31.8 ± 6.0	0.244	0.029
CT volumetry						
TLV/BSA (mL/m ²)	608.3 ± 120.2	609.3 ± 105.6	632.6 ± 143.7	734.0 ± 184.2	0.261	0.02
SV/BSA (mL/m ²)	68.5 ± 26.8	82.1 ± 29.0	114.4 ± 54.7	182.1 ± 117.7	0.546	< 0.001
TLV/SV	10.5 ± 5.3	8.1 ± 2.5	6.6 ± 3.1	5.4 ± 3.2	- 0.468	< 0.001
RV/SV	6.9 ± 3.3	5.5 ± 1.7	4.3 ± 2.2	3.1 ± 2.2	- 0.507	< 0.001
LSVR	0.3 ± 0.1	0.3 ± 0.1	0.4 ± 0.4	0.6 ± 0.5	0.18	0.11

Notes: Spearman’s correlation analysis was used to assess the correlation between each measurement and fibrosis stage. Data are presented as mean ± standard deviation. ρ, Spearman’s correlation coefficient. *ECV*, extracellular volume fraction; *manual-ECV*, ECV by manually placed region-of-interests; *rigid-ECV*, rigid registration ECV; *nonrigid-ECV*, nonrigid registration ECV; *TLV/BSA*, ratio of total liver volume to body surface area; *SV/BSA*, ratio of splenic volume to BSA; *TLV/SV*, ratio of TLV to SV; *RV*, right liver volume; *RV/SV*, ratio of RV to SV; *LSVR*, liver segmental volume ratio, which is volume ratio of Couinaud segments I–III to segments IV–VIII

liver resection [1, 2]. Furthermore, the probability of postoperative complications increases with increasing SV/BSA in patients with HCC [11]. Based on our results, SV/BSA may be a better predictor of postoperative complications than ECV. SV/BSA measurement can be acquired without using contrast

agents during routine preoperative CT, and the workstation enables semi-automatic and rapid reconstruction. Consequently, we recommend that all candidates for liver resection undergo measurement of SV/BSA to estimate LF. However, it must be noted that there are other causes of large SV besides cirrhosis (e.g., haematological diseases such as leukemia and infections).

Table 4 Differentiation of liver fibrosis by ROC analysis (AUC [95% CI])

	F0-1 vs F2 - 4	F0-2 vs F3 - 4	F0-3 vs F4
TLV/BSA	0.60 [0.48–0.73]	0.65 [0.52–0.80]	0.70 [0.54–0.87]
SV/BSA	0.76 [0.65–0.87]	0.82 [0.73–0.91]	0.83 [0.71–0.95]
TLV/SV	0.74 [0.63–0.85]	0.77 [0.66–0.89]	0.77 [0.63–0.92]
RV/SV	0.75 [0.64–0.86]	0.80 [0.70–0.90]	0.81 [0.67–0.95]
LSVR	0.59 [0.47–0.72]	0.64 [0.51–0.76]	0.63 [0.46–0.80]
Manual-ECV	0.61 [0.48–0.74]	0.62 [0.50–0.75]	0.75 [0.60–0.90]
rigid-ECV	0.63 [0.50–0.76]	0.61 [0.48–0.74]	0.76 [0.62–0.90]
Nonrigid-ECV	0.61 [0.48–0.74]	0.62 [0.49–0.75]	0.75 [0.60–0.90]

Notes: *ROC*, receiver operating characteristic; *AUC*, area under the ROC curve; *BSA*, body surface area; *TLV/BSA*, ratio of total liver volume to BSA; *SV/BSA*, ratio of splenic volume to BSA; *TLV/SV*, ratio of TLV to SV; *RV*, right liver volume; *RV/SV*, ratio of RV to SV; *LSVR*, liver segmental volume ratio, which is volume ratio of Couinaud segments I – III to segments IV – VIII; *ECV*, extracellular volume fraction; *manual-ECV*, ECV by manually placed region-of-interests; *rigid-ECV*, rigid registration ECV; *nonrigid-ECV*, nonrigid registration ECV

SV/BSA and RV/SV showed significant differences among the four factors and are considered the most useful among the methods measured in this study for the evaluation of LF. However, the AUC of CTV was the highest for SV/BSA in all LF grades. Therefore, it is possible to evaluate LF using only SV/BSA, which can be measured simply, without using other parameters.

As previously reported by Yoon et al [8] and Shinagawa et al [7], 180 or 240 s after contrast administration in the equilibrium phase were sufficient to estimate LF using the ECV method. However, the ECV in our study was not sufficient for estimating LF, although it showed the ability to estimate severe LF, such as F4 (AUC = 0.75–0.76).

The correlation coefficient of ECV was minimal, which was lower than that of the previous report [8]. Yoon et al stated that the ECV of Child A is significantly lower than that of Child B and Child C. All the patients in our study were Child A, which may have resulted in a lower correlation coefficient. There was no significant difference in the ability of either method to predict LF using the present measurement methods. However, the ICC of manual-ECV was fair (0.69), while those of rigid-ECV and nonrigid-ECV were good (0.83). Manual registration is prone to interobserver variability and errors [22]. This insufficient reproducibility of measurement of LF by manual-ECV may be a problem because different observers during follow-up

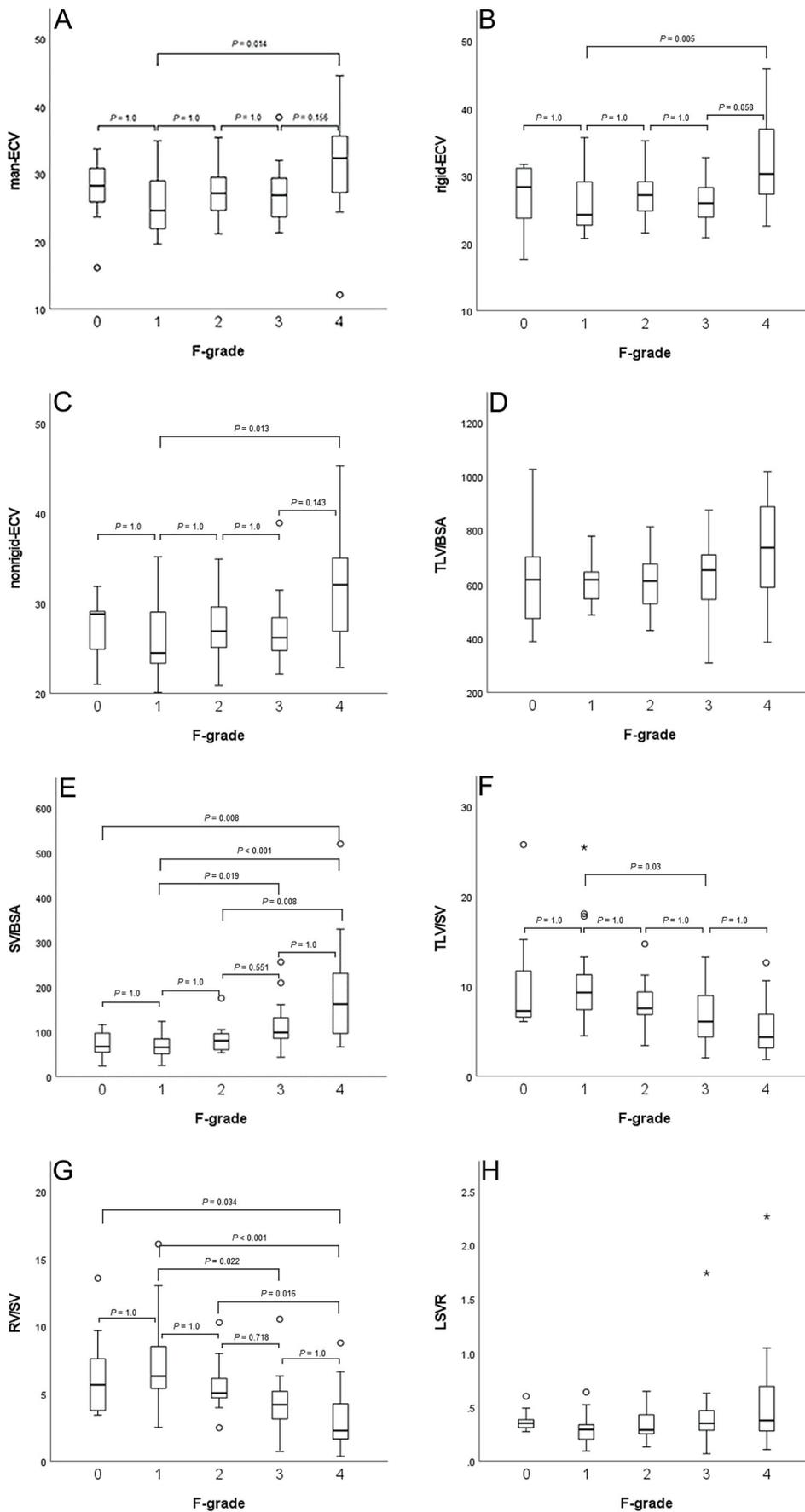


Fig. 5 **A** Graphs of manual ECV department on the LF stage. **B** Graphs of rigid ECV department on the LF stage. **C** Graphs of nonrigid ECV department on the LF stage. **D** Graphs of TLV/BSA department on the LF stage. **E** Graphs of SV/BSA department on the LF stage. **F** Graphs of TLV/SV department on the LF stage. **G** Graphs of RV/SV department on the LF stage. **H** Graphs of LSVR department on the LF stage. Graphs of extracellular volume fraction (ECV) and CT volumetry (CTV) in each liver fibrosis stage. F0 vs F1, F1 vs F2, F2 vs F3, and F3 vs F4 are not significantly different. There is a significant difference between F1 and F4 in all ECV measurement methods. The ratio of splenic volume to BSA (SV/BSA) and the ratio of right liver volume to SV (RV/SV) are significantly different in F0 vs F4, F1 vs F4, F1 vs F3, and F2 vs F4. The ratio of total liver volume to SV (TLV/SV) is significantly different in F1 vs F3. There is no significant difference between TLV/BSA and liver segmental volume ratio (LSVR)

may make measurements unreliable. However, AUCs of manual-ECV (0.61–0.75), rigid-ECV (0.63–0.76), and nonrigid-ECV (0.61–0.75) differed by 0.01–0.02 for all LF grades. However, manual-ECV is easily generated because no liver alignment using a workstation is required. Manual-ECV with three ROIs was predictive for LF as rigid-ECV and nonrigid-ECV in our study; thus, manual-ECV may be sufficient to estimate LF.

Table 5 Comparison Between SV/BSA and manual-ECV

Variable	SV/BSA	Manual-ECV
F0-1 vs F2-4		
Optimal cutoff value	86.37	26
Sensitivity [%]	0.67	0.69
Specificity [%]	0.79	0.52
AUC (95%CI)	0.76 (0.65–0.87)	0.61 (0.48–0.74)
<i>p</i> value	0.045	
F0-2 vs F3-4		
Optimal cutoff value	99.2	31.4
Sensitivity [%]	0.63	0.38
Specificity [%]	0.88	0.88
AUC (95%CI)	0.82 (0.73–0.91)	0.62 (0.49–0.75)
<i>p</i> value	0.006	
F0-3 vs F4		
Optimal cutoff value	105.6	32.1
Sensitivity [%]	0.75	0.56
Specificity [%]	0.86	0.89
AUC (95%CI)	0.83 (0.71–0.95)	0.75 (0.59–0.90)
<i>p</i> value	0.41	

Notes: SV, splenic volume; BSA, body surface area; SV/BSA, ratio of SV to BSA; ECV, extracellular volume fraction; manual-ECV, ECV by manually placed region-of-interests; AUC, area under the ROC curve. AUCs are shown along with 95% confidence intervals. The AUC, optimal cutoff value, sensitivity, and specificity of SV/BSA and manual-ECV for identifying fibrosis stages were calculated. SV/BSA and manual-ECV were compared using the Delong test, respectively

Shinagawa et al proposed that ECV obtained using equilibrium phase delay (240 s) could be a reliable biomarker of LF, although their study did not include the estimation of fibrosis factor by ROC analysis [7]. However, AUC value of ECV to estimate LF was not high (0.61–0.64) for significant LF (\geq F2-4), and severe LF (\geq F3-4) in our study, although AUC for more than F4 was relatively high (0.75–0.76). The reason for the different results is unknown, but the possible inclusion of specific groups of patients and the unreliable pathological assessment of LF by liver biopsy may be responsible. However, our staging of LF was performed by pathology of the resected liver specimens, and we believe that the staging was more reliable.

Pickhardt et al [5] and Hunt et al [13] stated that regional changes in LSVR correlate with the degree of LF, although TLV is a very poor predictor of underlying LF. In comparison, our results showed that the AUC value of LSVR to estimate LF was not high compared to those of TLV/BSA and SV/BSA. The mean LSVR of the cirrhotic liver was 0.55 in the study by Hunt et al [13], but it was 0.6 for F4 in our study. Similarly, the mean LSVR of the normal liver was 0.27, while our result was 0.4 (Table 3). AUC value of TLV/BSA was 0.74–0.77, which was more effective in estimating LF than LSVR (0.59–0.63). TLVs decrease with the progression of fibrosis and/or portal hypertension [10, 30]; however, in the results of this study, TLVs in patients with F4 were larger than those in patients with lower LF grade, which may have resulted in higher AUCs. This may be due to our study that included patients with Child-Pugh scores of 5–6. Furthermore, the diseases of the previous studies were different from ours; they had many patients with alcoholic liver disease (45 of 108, 41.7%), chronic hepatitis C (32 of 108, 29.6%), and non-alcoholic fatty liver disease (NAFLD) (16 of 108, 14.8%). In comparison, in our study, the candidates for surgical liver resection were patients with HBV (22 of 80, 27.5%) and HCV (21 of 80, 26.3%). Thus, the possible inclusion of specific groups of patients may be the cause of the difference.

Our study has several limitations. First, our study included a small number of patients. Further studies with a larger number of patients are recommended to confirm our results. Second, the equilibrium phase of ECV was 4min, as clinical CT examinations should be performed in a short time. Bandula et al measured the ECV using an equilibrium phase of 30min; therefore, 4 min may be insufficient [20].

The prediction of LF by ECV should be investigated at 5 or 10 min.

In conclusion, the diagnostic performance of CTV was superior to that of ECV in surgical patients without severe liver dysfunction. In particular, SV/BSA was found to be a better method for estimating LF, although ECV showed the ability to estimate cirrhosis ($>$ F4).

Acknowledgements The authors would like to acknowledge all of the patients for their willingness to participate in the study.

Funding The authors state that this work has not received any funding.

Declarations

Guarantor The scientific guarantor of this publication is Masahiro Okada.

Ethical approval Institutional Review Board approval was obtained.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was not required for this study because of the retrospective nature of this study.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Methodology

- retrospective
- observational
- performed at one institution

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Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Comparison between CT volumetry and extracellular
volume fraction using liver dynamic CT for the
predictive ability of liver fibrosis in patients with
hepatocellular carcinoma**

(要約)

日本大学大学院医学研究科博士課程

内科系放射線診断学専攻

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修了年 2024 年

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【研究の背景】

肝硬変や重度の肝線維化がある患者に肝切除を行う場合、深刻な術後合併症を伴う可能性が高くなる [1, 2]。術前に肝線維化を知ることによって術後合併症のリスクを推測し、有効な対策をとることができるため、術前の肝線維化の予測は重要である。

肝生検は肝線維化を評価する標準的な方法であるが、サンプリングエラー、侵襲性、合併症のリスクなどの限界がある [3, 4]。非侵襲的な検査として MR エラストグラフィ (Magnetic resonance elastography; MRE) が存在する。MRE は肝硬度測定において信頼性が高く、正確であると報告されているが [5, 6]、振動させる器具のような高価な追加装置が必要でありどの施設でも行える検査ではない。また超音波エラストグラフィも非侵襲的な肝線維化を評価する方法の一つである。音響的加圧による Virtual Touch Quantification (VTQ) や機械的加圧によるファイブロスキャンなど複数の方法が存在する。ファイブロスキャンは代表的な肝硬度測定方法の一つで、肝臓に剪断波を送り、振動を超音波で捕捉する装置である。検査時間も短く患者の負担もないが、肥満などで皮膚から肝臓まで 2.5 cm 以上離れている場合や腹水がある患者には利用できない。他の非侵襲的な肝線維化推定因子としてバイオマーカーや血液検査の組み合わせによる評価方法がよく知られている。しかし肝線維化のマーカーは全てが肝由来のみでない点、基礎疾患や個体差によって線維化と平行に上昇するとは限らないなど欠点も存在する。

低侵襲的かつどの施設でも簡易に行える肝線維化推定因子として、CT 容積分画 (CT volumetry; CTV) [7, 8] や細胞外容積分画 (extracellular volume fraction; ECV) [9-11] が注目されている。これらは通常、診療に必要な術前診断のために撮像された CT データを利用して解析可能である。

CTV では、体表面積 (Body surface area; BSA) に対する肝容積 (total liver volume; TLV) の比 (TLV/BSA) [12] (Fig. 2A, 3A)、BSA に対する脾容積 (splenic volume; SV) の比 (SV/BSA) [8, 12, 13] (Fig. 2C, 3C)、SV に対する TLV の比 (TLV/SV) [12]、SV に対する肝右葉容積 (right liver volume; RV) の比 (RV/SV) [14]、Couinaud 分類 S1-3 区域と S4-8 区域の容積比 (liver segment volume ratio; LSVR) [15, 16] (Fig. 2B, 3B) が、肝線維化の評価に有用であると報告されている。

ECV は、組織内の細胞外液腔の容積比のことである。平衡相において細胞外液性ヨード造影剤が細胞外液腔に均一に分布すると仮定した場合、非造影相と平衡相の肝実質の濃度変化を大動脈の濃度変化とヘマトクリットで補正することで算出される。細胞外液腔は細胞外血管外腔 (extravascular-extracellular space; EES) と血管内腔 (intravascular space; IVS) で構成されており、肝線維化は EES に生じる。このため細胞外液腔の容積比を計算すれば、EES における線維化などの病的プロセスを推定することが可能となる。ECV は肝臓の他、心臓や膵臓などでも線維化の指標として有用とされている。測定の際には観察者が手動で位置合わせを行う手動位置合わせ (manual-ECV)、回転と平行移動のみによって位置合わせを行う剛体位置合わせ (rigid-ECV)、アフィン変換 (画像の平行移動の他に、回転や拡大・縮小を行って座標を変換する方法) によって物体を変形させながら位置合わせを行う非剛体位置合わせ (nonrigid-ECV) などの方法があり、これらの手法により位置合わせをした後に関心領域

(Region of interest; ROI) で測定する方法が一般的である。特に非剛体位置合わせは位置ずれが少ないため造影前と造影後の画像の対応が正確であり ECV の測定に有用とされている [9]。

本研究では、肝ダイナミック造影 CT を用いて測定した CTV と ECV の肝線維化推定能を比較することを目的とした。さらに、manual-ECV、rigid-ECV、nonrigid-ECV の肝線維化の推定能についても比較した。

【研究方法】

患者

本研究は施設内審査委員会の承認を得た (RK-20110-12)。後ろ向き研究であり、インフォームドコンセントは免除された。

2019年2月から2021年4月に肝切除された20歳以上の患者のうち、術前に肝ダイナミック造影CTを撮像された患者を対象とした。肝ダイナミック造影CTの平衡相は造影剤投与後180秒よりも240秒の方が、細胞外液に存在する造影剤の分布が血管内と平衡状態に近くなるため、過去の報告を参照して、平衡相を造影後240秒に設定した[9]。

CTを撮像してから1か月以内に肝切除を受けた患者は90人いた。この中から、脾摘の既往のある患者、肝切除の既往のある患者、肝腫瘍の体積が500mlを超える患者を除外し、残りの患者についてECVとCTVを計測した。背景肝疾患、血液検査、Child-Pughスコア、病理学的肝線維化のステージなどの情報は電子カルテから入手した。

血液検査

Hct、aspartate aminotransferase [AST]、alanine aminotransferase [ALT]、血小板数[platelet count; Plt]、international normalised ratio [INR]、総ビリルビン[total bilirubin; T-Bil]、アルブミン[albumin; Alb]、クレアチニン[creatinine; Cr]、インドシアニンググリーン15分間保持率[indocyanine-green retention rate at 15min; ICGR15]などの血液検査を電子カルテから入手した。この他肝繊維化バイオマーカーとして実臨床で最も利用されているFibrinogen-4 (FIB-4) index [17]やAST/platelet ratio index (APRI) [18]も計算した。また肝予備能評価の指標であるAlbumin-

Bilirubin (ALBI) スコア [19]* (注釈 1)、慢性肝障害の予後予測因子である Model for end-stage liver disease (MELD) スコア [20] も併せて計算した。

CT プロトコル

造影剤 (350mgI/mL、イオメプロール ; イオメロン® 350 シリンジ、エーザイ、ヨウ素含量 ; 600mgI/kg) 投与後、非造影相、動脈相 (37 秒)、門脈相 (60 秒)、平衡相 (240 秒) を含む 4 相ダイナミック肝造影 CT を実施した [9, 21]。造影剤は 3.0-3.5mL/s の投与速度で肘正中静脈より静注した。非造影相と平衡相の画像データから ECV と CTV を測定した。装置は CT 検出器列が 16 列または 320 列の CT (Aquilion16 または Aquilion ONE ; とともにキヤノンメディカルシステムズ) で撮像し、CT 撮像パラメータはそれぞれ管電圧 120kVp、管球回転時間 0.5 秒、マトリックス 512×512、ピッチは 16 列が 0.938、320 列が 0.828 であった。CTV と ECV には再構成スライス厚 5mm を使用した。CT を用いた体積測定値は 1mm スライスと 5mm スライスで差はないと報告されているが [22]、本研究では診療 (読影) で用いられることが多い 5mm スライス厚を使用して CTV と ECV を計算した。

細胞外容積分画 (ECV)

ECV は、 $ECV(\%) = (1-Hct) \times (\Delta HU_{liver} / \Delta HU_{aorta})$ として算出した。 ΔHU は平衡相の CT 値から非造影相の CT 値を減算したものである [9, 23]。手動位置合わせは平衡相と非造影相の画像を手動で同じ肝の位置を設定し ROI を配置する方法である (Fig. 1A, B)。剛体位置合わせは 2 つの画像の解剖学的位置合わせの際に回転と平行移動のみによって補正する方法である (Fig. 1C)。この方法は比較的簡単に実行できるが、平衡相と非造影相で撮像したときに肝臓が

変形していないことを前提としているため、CT 検査での撮像における息止めの程度によって肝臓は容易に変形するため、ROI を置いている場所がずれて誤差が生じるという欠点がある。非剛体位置合わせは、肝臓を変形させて位置合わせを行う方法であり、息止めの程度が異なることによる位置のずれや肝変形を最小限に抑えることができる [24-26] (Fig. 1D)。本研究ではこれら 3 つの位置合わせの方法の優位性を比較した。画像解析は、肝生検の結果を盲検化した体幹部 CT の経験が 6 年と 3 年の 2 人の放射線診断医が行った。剛体位置合わせと非剛体位置合わせには、非造影 CT と平衡相 CT のサブトラクション画像（差し引き画像）を使用した。ROI の置き方のトレーニングを受けた 2 名の放射線診断医が独立してコピー&ペースト法を用いて同じサイズの ROI を画像上に 3 つ配置した。ROI の位置は大きな肝内血管や肝腫瘍は避け、肝辺縁から 1cm 以上離して基本的に肝門部レベルの肝内に配置した。肝実質は長径 10mm、門脈は長径 4mm、腹部大動脈は長径 7mm の円形 ROI を置いた。 $\Delta HU_{aorta} - \Delta HU_{portal} > 10$ HU の場合（すなわち大動脈の造影効果が門脈の造影効果よりも 10HU 高いという場合）は平衡相として不適切と判断し除外した。画像処理および ROI 測定はビューワーワークステーション（SYNAPSE VINCENT[®] ver5.5、富士フィルムメディカル）を用いて行った。

CT 容積分析 (CTV)

TLV、SV、TLV/SV、RV/SV、LSVR はビューワーワークステーション（SYNAPSE VINCENT[®] ver5.5、富士フィルムメディカル）を用いて測定した。CTV 画像は 6 年の経験を持つ放射線診断医が、肝ダイナミック CT プロトコルに従って再構成スライス厚 5mm を用いて作成した。TLV では全肝体積から腫瘍の体積を引いた。TLV や SV では肝や脾内の血管の体積は除外しなかった (Fig. 2, 3)。TLV

と SV は BSA で補正した (TLV/BSA、SV/BSA) [13, 27, 28]。BSA は Dubois の式 ($BSA [m^2] = 0.007184 \times \text{身長}[cm]^{0.725} \times \text{体重}[kg]^{0.425}$) を用いて算出した [13, 29]。LSVR は、S1-3 区域と S4-8 区域の比を求めることにより算出した [15]。

病理

病理学的評価は、外科的に切除した標本を用いて行った。病理学的線維化のステージは、新犬山分類を用いて 2 名の病理医により評価された。F0 は線維化なし、F1 は門脈域の線維性拡大、F2 は架橋性線維化、F3 はひずみを伴う架橋性線維化、F4 は肝硬変と分類した。

統計解析

ECV 測定の評価者間信頼性についてはクラス内相関係数 (intraclass correlation coefficients; ICC) を用いて評価した。3 つの位置合わせの方法の間に有意差があるかどうかを判定するために、Friedman 検定を用いた。各群について、CTV と ECV、血液検査バイオマーカーの平均値と標準偏差を算出し、Spearman の相関係数を用いて測定データ (ECV および CTV) と肝線維化ステージとの相関を求めた。ECV と CTV について Kruskal-Wallis 検定を用い、その後 Bonferroni 補正を行った。ECV と CTV のそれぞれの測定結果と血液検査バイオマーカーの相関解析および dot plot を作成した。ECV、CTV、血液検査バイオマーカーの各肝線維化ステージの AUC を計算した。また病因別の AUC も併せて計算した。肝線維化ステージを分別するために ECV と CTV それぞれ最も高い AUC を DeLong 検定を用いて比較した。解析には SPSS Version-27.0 (IBM Corp.) を用いた。

【結果】

患者

登録患者 90 例の中で 10 例（脾摘歴あり 1 例、肝切除歴あり 5 例、巨大肝腫瘍 4 例）が除外され、80 例が残った（Fig. 4）。 Δ HUaorta と Δ HUportal の差が 10HU 以上の症例はなかった。肝線維化の原因として最も多かったのは C 型肝炎ウイルス（hepatitis C virus; HCV）で 22 例（27.5%）、次いで B 型肝炎ウイルス（hepatitis B virus ; HBV）が 21 例（26.3%）、HCV+HBV が 1 例（1.3%）、alcoholic liver disease が 8 例（10.0%）、nonalcoholic fatty liver disease (NAFLD) が 5 例（6.3%、うち MAFLD 4 例）、nonalcoholic steatohepatitis (NASH) が 4 例（5.0%）、primary biliary cholangitis (PBC) が 2 例（2.5%）、その他が 17 例（21.3%）であった（Table 1）。APRI score の平均は 0.74 であった。また FIB-4 index は平均 2.77 であり、比較的高度な線維化が示唆された。80 例中 78 例（97.5%）が Child-Pugh スコア 5 点、2 例（2.5%）が Child-Pugh スコア 6 点であり、全例が Child-Pugh A であった。また modified ALBI grade は grade 1 が 73 人、grade 2a が 7 人、MELD スコアは平均 2.28 であった。これらの結果から肝予備能は全体的に良好であることが示唆された。

細胞外容積分画 (ECV)

2 人の読影者間の ICC は、manual-ECV では fair (0.69)、rigid-ECV では excellent (0.83)、non-rigid-ECV では excellent (0.83) であった。3 つの ECV 測定方法の平均 ECV 値は、F4 が F0-3 よりも高かった（Table 2）。

Friedman 検定の結果は 0.96 で 3 つの測定方法の間に有意差はなかった。Spearman の相関係数分析の結果では、ECV と肝線維化ステージの間には最小限

の相関しかなかった。3つの ECV 測定方法の AUC の差は約 0.01-0.02 で、ほとんど差がなかった (Table 3)。

CT 容積分析 (CTV)

F4 の平均 TLV/BSA と平均 SV/BSA は F0-1、2、3 より高く、F4 の平均 TLV/SV と平均 RV/SV は F0-1、2、3 より低かった (Table 2)。TLV/BSA と SV/BSA は肝線維化の増悪に比例して増加した。Spearman の相関係数は、TLV/BSA では最小の相関、SV/BSA では中程度の相関、TLV/SV および RV/SV では中程度の負の相関を示し、LSVR では意味のある相関は認められなかった。全ての CTV の AUC は F0-3 vs. F4 で最も高く、SV/BSA の AUC は全ての肝線維化ステージで最も高かった (AUC=0.76-0.83) (Table 3)。

肝線維化および肝硬変の推定における ECV と CTV の比較

F0 vs. F1、F1 vs. F2、F2 vs. F3、F3 vs. F4 では、ECV および CTV 全て有意差はなかった (Kruskal-Wallis 検定) (Fig. 5)。SV/BSA および RV/SV は、F0 vs. F4、F1 vs. F4、F1 vs. F3、F2 vs. F4 で有意差があった。SV/BSA、TLV/SV、RV/SV の AUC は、全ての肝線維化ステージにおいて ECV の AUC よりも高かった (Table 3)。特に、SV/BSA の AUC は、全ての肝線維化ステージにおいて全ての CTV、ECV、FIB-4 index や APRI score などの血液検査バイオマーカーの中で最も高かった。相関解析では SV/BSA が中程度の相関、RV/SV、TLV/BSA などが中程度の負の相関を示したのに対し、APRI score は弱い相関を示し、また FIB-4 index は有意な相関はなかった。ECV と CTV のそれぞれの測定結果と血液検査バイオマーカーの相関解析では有意な相関を示す結果は得られなかった (Fig. 6)。病因毎の AUC では HCV では F0-1 vs. F2-4 で

は RV/SV、F0-2 vs. F3-4 では LSVR、F0-3 vs. F4 では RV/SV が最も高かった (Table 4A)。HBV では F0-1 vs. F2-4 では RV/SV、F0-2 vs. F3-4 では RV/SV、F0-3 vs. F4 では TLV/BSA が最も高かった (Table 4B)。Alcoholic liver disease では F0-1 vs. F2-4 では FIB-4 index と APRI score、F0-2 vs. F3-4 と、F0-3 vs. F4 では SV/BSA が最も高かった (Table 4C)。NAFLD および NASH では F0-1 vs. F2-4 では APRI score、F0-2 vs. F3-4 では RV/SV、F0-3 vs. F4 では TLV/BSA が最も高かった (Table 4D)。Manual-ECV、rigid-ECV、nonrigid-ECV の AUC や相関係数にほぼ差がないため、最も簡便かつ迅速に測定できる manual-ECV の結果を DeLong 検定に用いた (Table 5)。

有意な肝線維化 ($\geq F2$) と重度の肝線維化 ($\geq F3-4$) では、SV/BSA の AUC が manual-ECV の AUC よりも有意に高かった。肝硬変 (F4) では SV/BSA と manual-ECV の AUC に有意差はなかった。

【考察】

本研究では ECV や CTV は肝線維化推定に有用であり、特に SV/BSA は manual-ECV よりも肝線維化の予測因子として優れていることが分かった。また ECV の AUC は FIB-4 index や APRI score と同程度であったのに対し、SV/BSA や TLV/SV、RV/SV の AUC や相関係数は FIB-4 index や APRI score より高かった。また F4 の症例 16 例中、SV/BSA が F4 推定のカットオフ値 (105.6 ml/m^2) 以上かつ FIB-4 index が 2.67 以下で APRI score が 1.0 未満の症例は 6 例あった。CTV の肝線維化推定能は血液検査バイオマーカーより優れている可能性が示された。脾腫は門脈圧亢進症や肝硬変のために起こる[30]。肝硬変は肝切除後の重大な合併症に関係するため、CTV の測定、特に SV/BSA は肝線維化推定を可能とすることで安全な手術管理に貢献できると考える[1, 2]。肝細胞癌患者では、SV/BSA が高くなるにつれて術後合併症の確率が高くなることが報告されているが[13]、今回の結果から SV/BSA は ECV よりも術後合併症の予測因子として優れている可能性がある。予後が悪い可能性があると判断された場合には、肝切除ではなく肝マイクロ波焼灼術や肝移植を選択することで 5 年生存率を改善できる可能性がある。SV/BSA 測定は、肝切除術前 CT で造影剤を使用せずとも取得でき、ワークステーションにより半自動的に迅速な（数分以内）計測が可能である。したがって、肝切除を希望する全ての患者に肝線維化を推定するために SV/BSA の測定を行うことを推奨する。まず術前 CT を撮像し、これを利用して手動/半自動的に脾臓の体積を計算し、体重と身長を用いて SV/BSA を計算する。そして SV/BSA の値によって肝線維化を推定する。このときカットオフ値を 86.4 ml/m^2 とすれば感度 67%、特異度 79% で F2 以上、 99.2 ml/m^2 とすれば感度 63%、特異度 88% で F3 以上、 105.6 ml/m^2 とすれば感度 75%、特異

度 86%で F4 と推定できる。しかし、肝硬変以外にも SV が大きくなる原因（白血病などの血液疾患、感染症など）があることに注意しなければならない。

以前 Yoon ら [10] や品川ら [9] の報告によると、ECV 法で肝線維化を推定する際、平衡相は造影剤投与後の 180 秒または 240 秒で十分であるとされる。しかし、今回の ECV 法では、F4 (AUC=0.75-0.76) のような極めて重度の肝線維化の推定は可能であったが、その他のグレードの肝線維化の推定には不十分であった。また ECV の相関係数は最小であり、以前の報告よりも低かった [10]。

Yoon らは、Child A の ECV は Child B および Child C の ECV より有意に低いと述べている [10]。今回は全症例が Child A であり、これが相関係数を低下させた原因の可能性がある。また manual-ECV の ICC は fair (0.69) であったが、rigid-ECV と nonrigid-ECV の ICC は good (0.83) であった。手動位置合わせは、観察者間のばらつきや誤差が生じやすいという問題点はあるものの、manual-ECV (0.61-0.75)、rigid-ECV (0.63-0.76)、nonrigid-ECV (0.61-0.75) の AUC は、全ての肝線維化ステージでほとんど差がなく、簡易さや所要時間を考慮すると手動位置合わせで十分かもしれない。

品川らは、ROC 解析による線維化因子の推定は行っていないものの、平衡相で造影後 240 秒を用いた ECV が信頼性の高い肝線維化のバイオマーカーになると提唱している [9]。今回の結果では、ECV の AUC は肝硬変 (F4) では 0.75-0.76 と比較的高かったものの、有意な肝線維化 (\geq F2-4) や重症の肝線維化 (\geq F3-4) では 0.61-0.64 と高くなく、また相関も最低限であり、総じて品川らの結果よりも肝線維化推定能が低かった。異なる結果が得られた理由は不明であるが、彼らの検討とは患者群が異なっている可能性や、彼らの検討では肝線維化の病理学的評価が肝生検や MRE でなされたことが原因である可能性

がある。我々が行った肝線維化の病期分類は切除肝標本を用いた病理検査であり、より信頼できるものであったと考えられる。

Pickhardt ら[7]と Hunt ら[15]は、LSVR の局所的変化は肝線維化の程度と相関するが、TLV は潜在的な肝線維化の予測因子としては非常に不十分であると述べている。これと比較して、我々の結果は、肝線維化を推定する LSVR の AUC 値は、TLV/BSA および SV/BSA の AUC 値と比較して高くなかった。Hunt らの研究では肝硬変肝の平均 LSVR は 0.55 であったが、我々の研究では F4 で 0.6 であった (Table 2)。同様に、正常肝の平均 LSVR は 0.27 であったが、我々の結果は 0.4 であった。TLV/SV*(注釈 2)の AUC 値は 0.74-0.77 であり、LSVR

(0.59-0.63) よりも肝線維化の推定に有効であった。TLV は F0-F3 では肝線維化や門脈圧亢進の進行に伴い増加するものの、肝硬変 (F4) ではより進行すると一般的に減少する[31]。これは代償性肝硬変から非代償性肝硬変へ移行することに起因する。しかし本研究では肝硬変 (F4) の患者の TLV は肝線維化グレードの低い患者の TLV よりも大きく、その結果 TLV/BSA の AUC が高くなった可能性がある。本研究では Child-Pugh スコアが 5~6 の患者を対象としたため、ほぼ全ての症例が代償性肝硬変であったことが原因かもしれない。さらに、先行研究ではアルコール性肝疾患 (108 例中 45 例、41.7%)、HCV (108 例中 32 例、29.6%)、非アルコール性脂肪性肝疾患 (non-alcoholic fatty liver disease; NAFLD) (108 例中 16 例、14.8%) の患者が多かった。これに対し、我々の研究では肝切除の対象は HCV *(注釈 3) (80 例中 22 例、27.5%) と HBV *(注釈 4) (80 例中 21 例、26.3%) が多かった。この患者群の違いが原因の可能性も考えられる。

病因毎の AUC では HCV では RV/SV や LSVR が高く (Table 4A)、HBV では RV/SV や TLV/BSA が高く (Table 4B)、alcoholic liver disease では FIB-4

index や APRI score、SV/BSA が高く (Table 4C)、NAFLD/NASH では APRI score や RV/SV、TLV/BSA などが高い肝線維化予測能を示しており (Table 4D)、必ずしも SV/BSA が最も高い肝線維化予測能を示すわけではなかった。しかしながら CTV の AUC は FIB-4 index や APRI score より高い場合が多く、病因毎でも CTV は血液バイオマーカーより優れた肝線維化推定能を有している可能性が示された。

本研究にはいくつかの限界がある。第一に、我々の研究は患者数が少なかった。本研究の結果を確認するためにより多くの患者を対象とした研究が望まれる。第2に臨床 CT 検査は短時間で行うべきものであるため、今回の研究では ECV の平衡相は4分とした。80 症例全例が ΔHU_{aorta} と ΔHU_{portal} の差が 10HU 未満であったため平衡相としては妥当と判断したものの、Bandula らは 30 分の平衡相を用いて ECV を測定しており、4分ではまだ不十分かもしれない [23]。平衡相として造影後 5分または 10分で ECV を測定するといった更なる検討が必要と考える。第3に、今回の症例は HBV の割合が多く、また HCV の割合が少なかった。このため選択にバイアスがかかり、SV/BSA に有利に働いた可能性がある。しかしながら病因毎でみると CTV の AUC は FIB-4 index や APRI score より高い場合が多く、CTV が血液検査バイオマーカーより優れた肝線維化推定能を有している可能性があることが分かった。今後更なる検討が必要と思われる。第4に、今回は ROI を 3か所に置き平均を用いて ECV を計算したが、線維化がびまん性かつ均一であることが前提となる。今回の症例群では肝実質は CT でみれば homogeneous であり切除部の肝実質と残肝の肝実質は同様のものと考えている。しかしながら、肝線維化の病理標本は本来摘出部の肝実質であり、限定的な線維化の評価には適さない可能性がある。摘出部により近い位置に ROI を置くことで ECV の結果がより良いものとなるかもしれない。第

5に、今回の研究では肝実質のROIのサイズは336 mm²に統一しているが、non-rigid処理を施すことで、サブトラクション画像上に置いたROIのサイズや形態は手動位置合わせで置いたROIとは厳密には異なると考えられる。しかし今回の結果ではmanual-ECVとnonrigid-ECVではAUCや相関に大きな差はなく、non-rigid処理によるサイズ変化がECVに及ぼす影響は少ないと思われる。

結論として、重篤な肝機能障害のない肝切除を受けた患者において、CTVの診断能はECVやFIB-4 index、APRI scoreなどの血液検査バイオマーカーよりも優れていた。特に、肝線維化の推定にはSV/BSAが優れていた。肝硬変

(F4) *(注釈5)の推定はECVでも同程度の推定能を有していた。Manual-ECV、rigid-ECV、nonrigid-ECVで肝線維化推定能に有意差はなかった。病歴毎で比較すると、CTVはFIB-4 indexやAPRI scoreよりもAUCが高い場合が多く、血液検査バイオマーカーよりも肝線維化予測に有用である可能性が示された。

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図

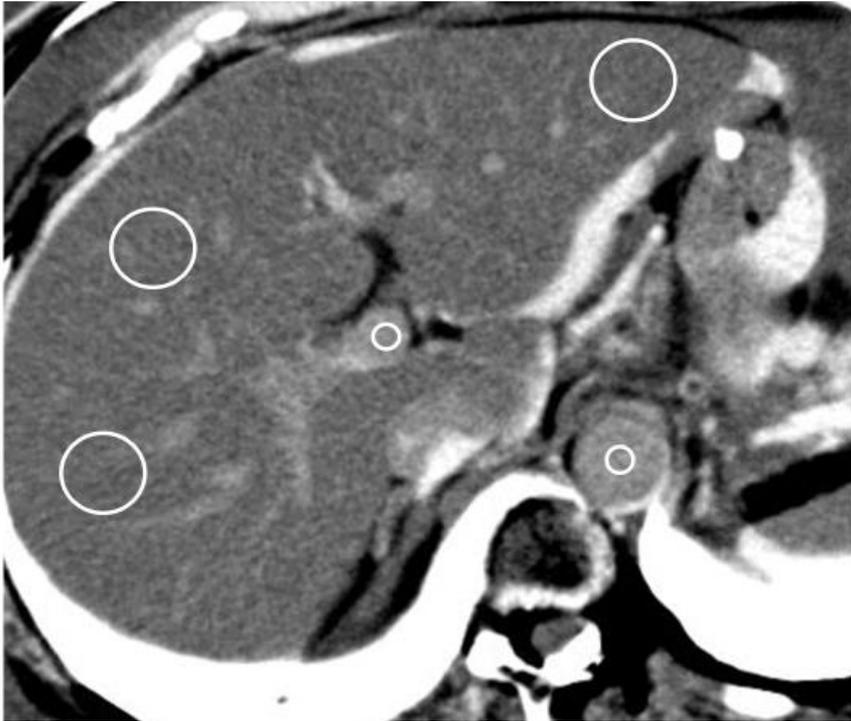
Figure 1. 肝細胞癌の 67 歳女性の CT 画像



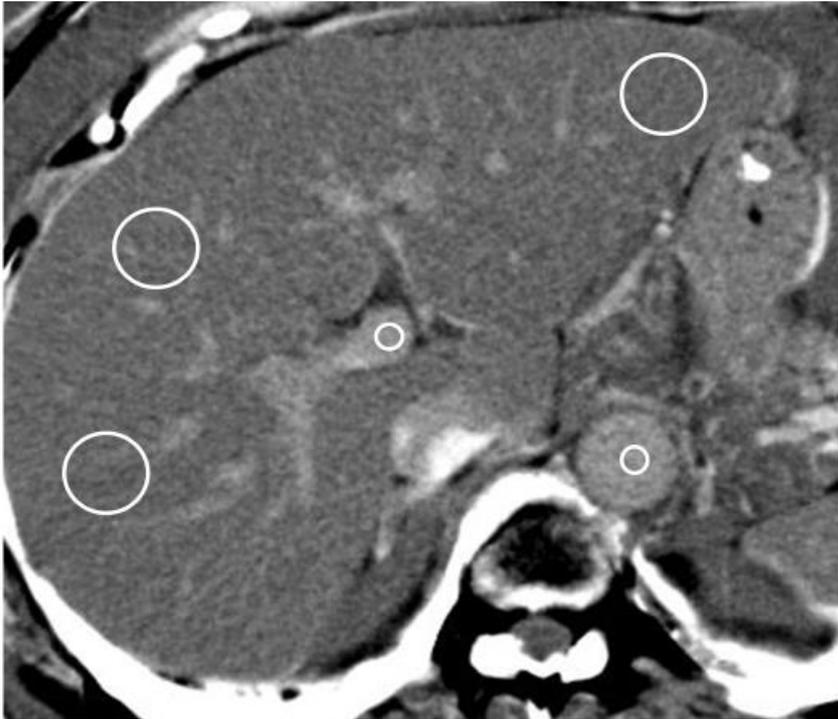
A). 非造影相において肝臓の 3 つの領域に ROI (右葉前区域[面積 336 mm^2]、右葉後区域[面積 336 mm^2]、左葉外側区域[面積 336 mm^2]) を置いた (手動位置合わせ)。腹部大動脈と門脈に ROI (面積 61 mm^2) を配置した。



B). 平衡相において肝臓の3つの領域にROI（右葉前区域[面積 336 mm²]、右葉後区域[面積 336 mm²]、左葉外側区域[面積 336 mm²]）を置いた（手動位置合わせ）。腹部大動脈と門脈にROI（面積 61 mm²）を配置した。



C). 剛体位置合わせを使用して非造影相と平衡相のサブトラクション画像を作成し、肝臓の3つの領域にROI（右葉前区域[面積 336 mm²]、右葉後区域[面積 336 mm²]、左葉外側区域[面積 336 mm²])を置いた。解剖学的な位置のずれがみられた。腹部大動脈と門脈にROI（面積 61 mm²）を配置した。

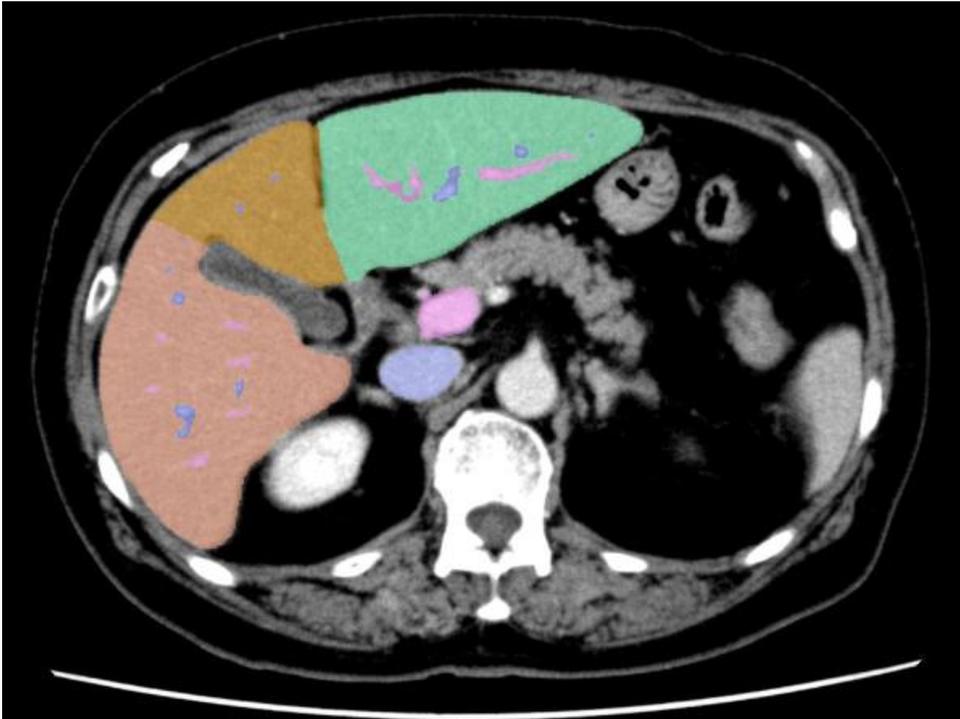


D). 非剛体位置合わせを使用して非造影相と平衡相のサブトラクション画像を作成し、肝臓の3つの領域にROI（右葉前区域[面積 336 mm²]、右葉後区域[面積 336 mm²]、左葉外側区域[面積 336 mm²])を置いた。解剖学的位置ずれはみられなかった*(注釈 6)。腹部大動脈と門脈にROI (面積 61 mm²)を配置した。

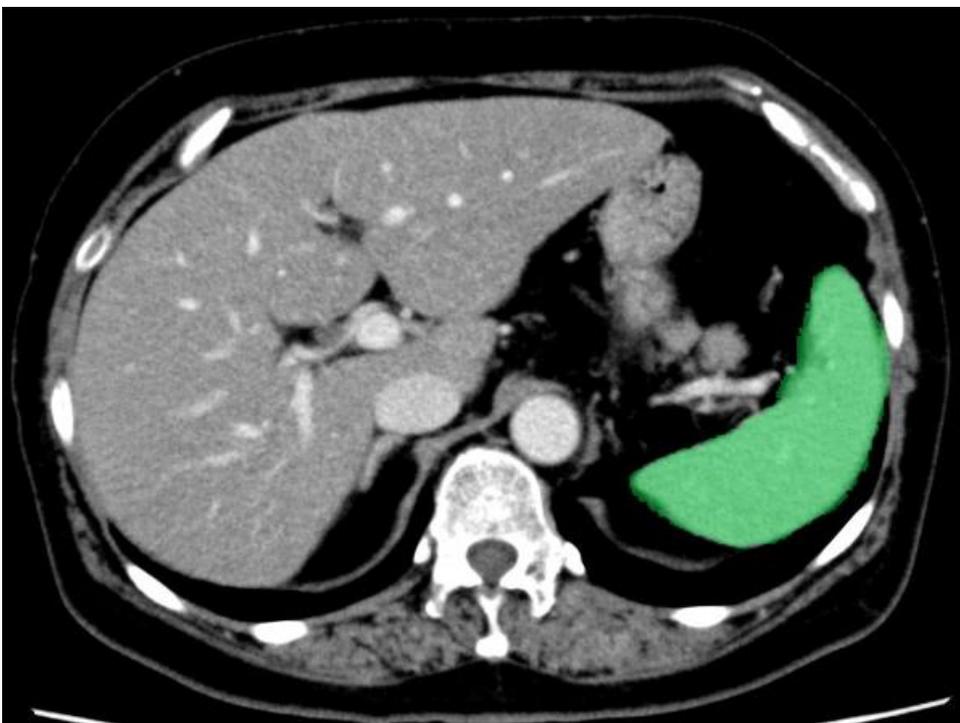
Figure 2. 肝細胞癌の 67 歳女性の CT 画像



A). TLV の軸位断像。生データを手動でワークステーションに送信後、TLV はほぼ自動的に測定された。TLV には血管と脂肪が含まれた。

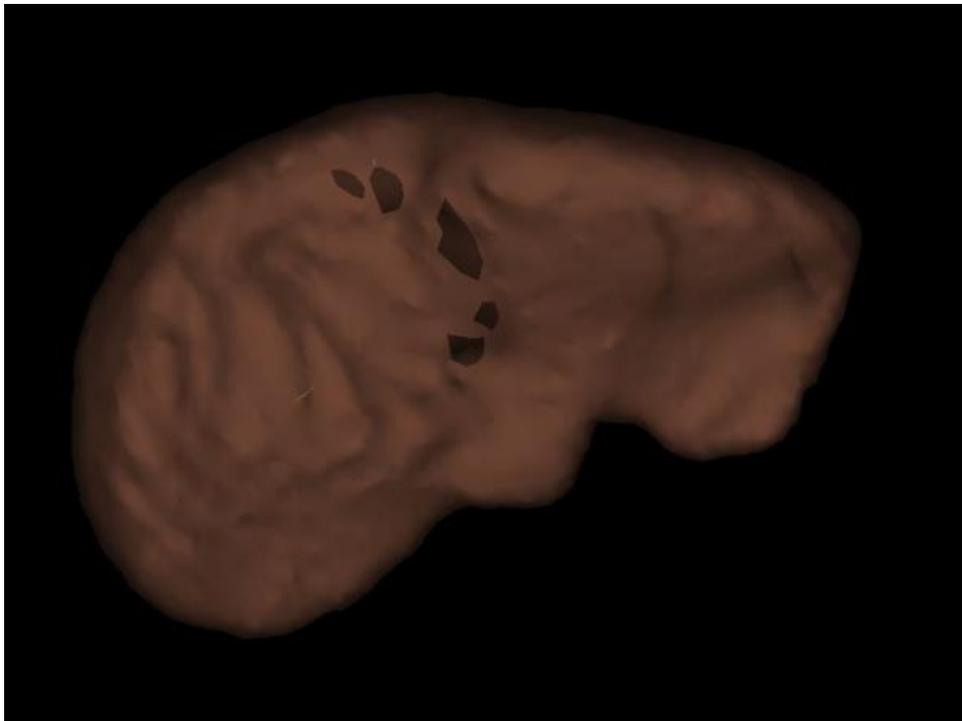


B). 分割された TLV の軸位断像。鎌状靭帯と中心肝静脈をランドマークとして、Ⅱ、Ⅲ、Ⅳの区域分けをした。

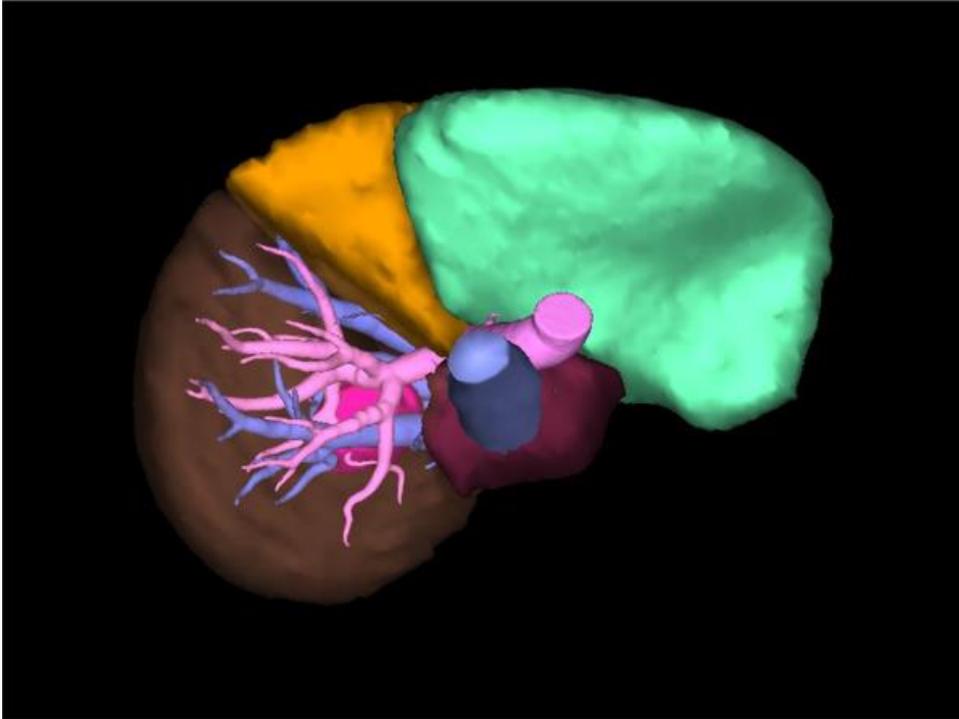


C). SV の軸位断像。SYNAPSE VINCENT[®] ver5.5 では、SV は手動で測定された。

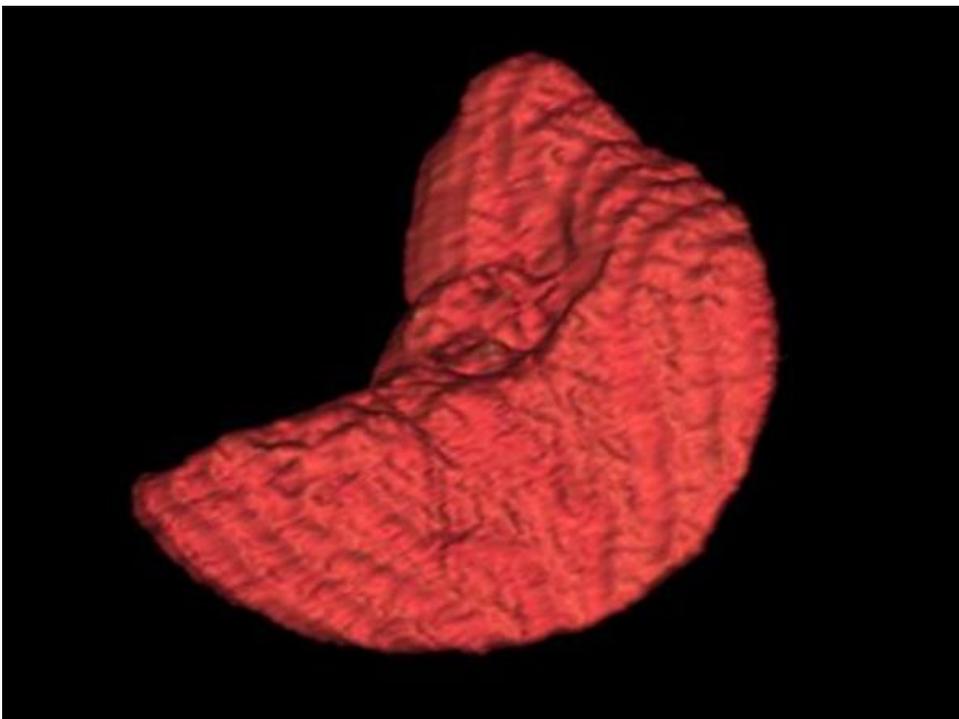
Figure 3. 肝細胞癌を有する 67 歳女性の CT 容積分析 (ボリュームレンダリング)



A). 肝臓全体の 3 次元再構成画像。下面図。

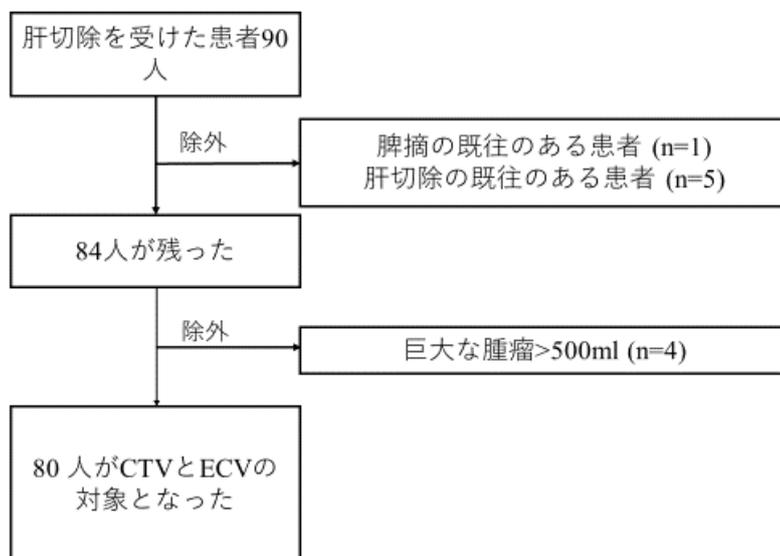


B). 区域分けした肝臓の3次元再構成画像。茶色が肝右葉（前区域および後区域）、黄色が肝左葉内側区域、緑色が肝左葉外側区域。



C). 脾臓の3次元再構成像。下面図。

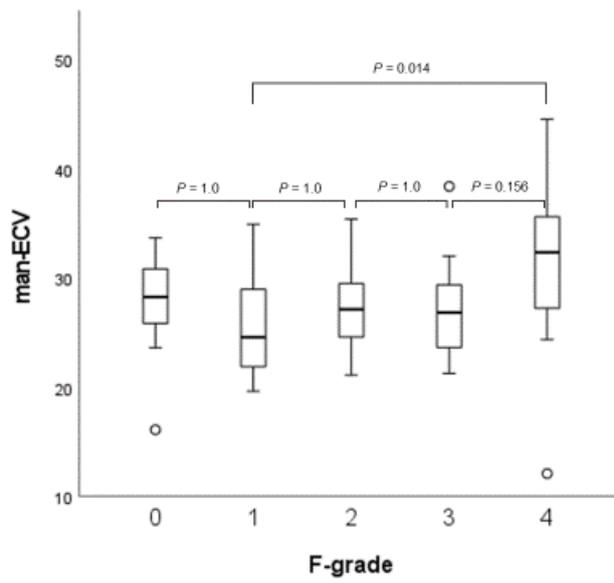
Figure 4. 患者のフローチャート



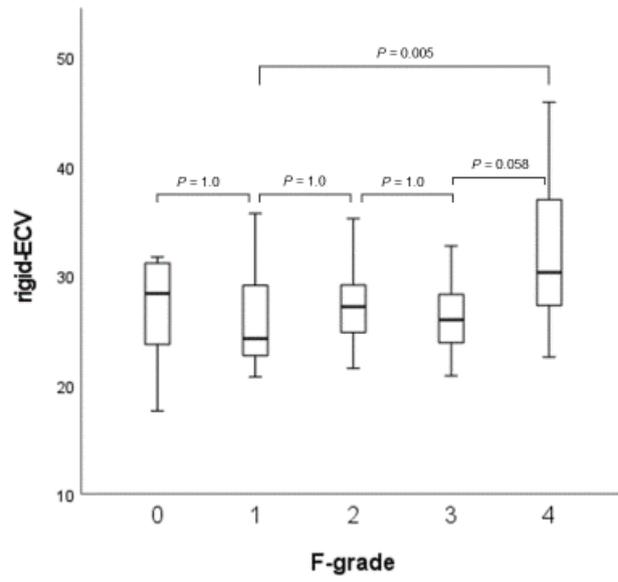
90人の患者が肝切除を受けた。脾摘の既往のある患者が1人、肝切除の既往のある患者が5人、巨大肝腫瘍がある患者が4人おり、これらは除外された。残った80人が肝ダイナミック造影CTで細胞外容積分画（ECV）とCT容積分画（CTV）の対象となった。

Figure 5. 各肝線維化ステージにおける細胞外容積率 (ECV) と CT 容積測定 (CTV) の箱ひげ図および Kruskal-Wallis 検定

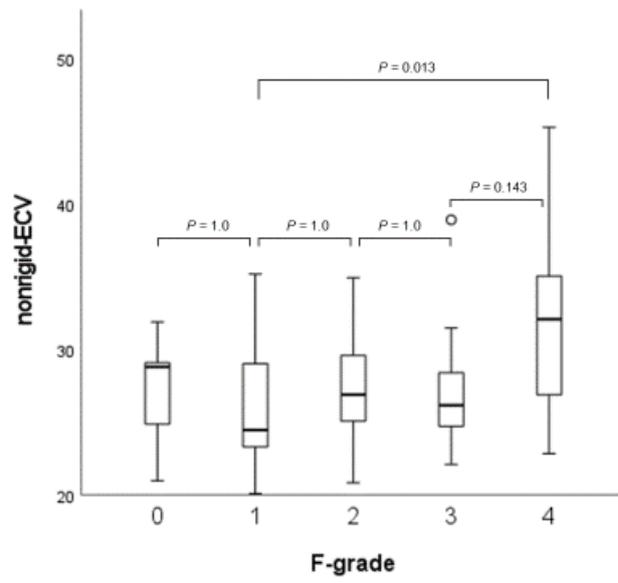
A



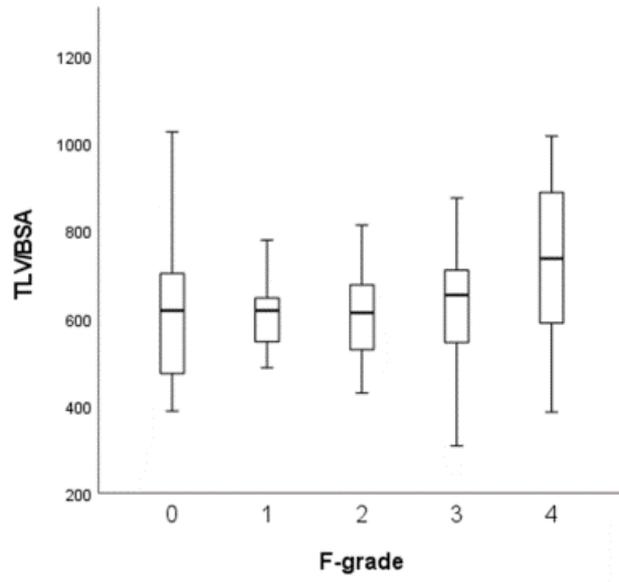
B



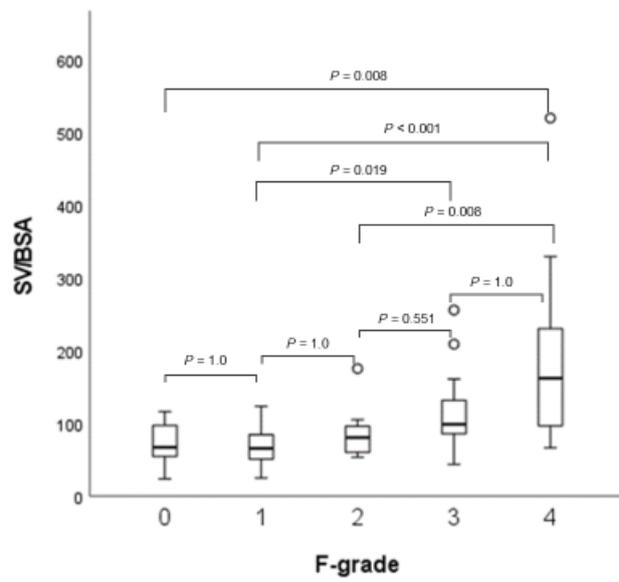
C



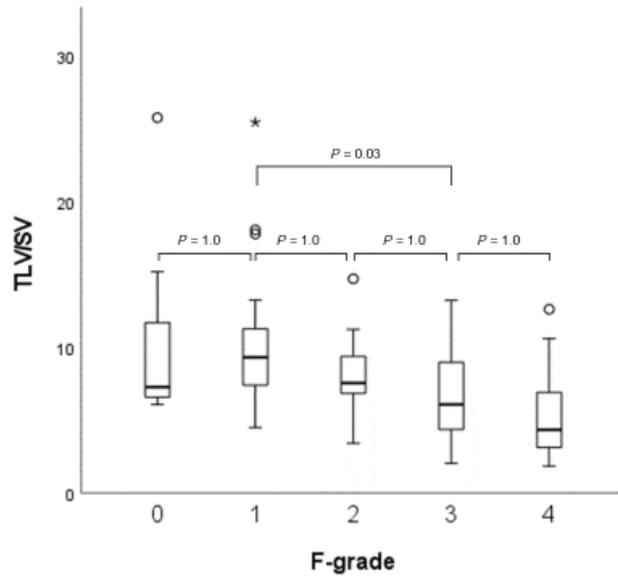
D



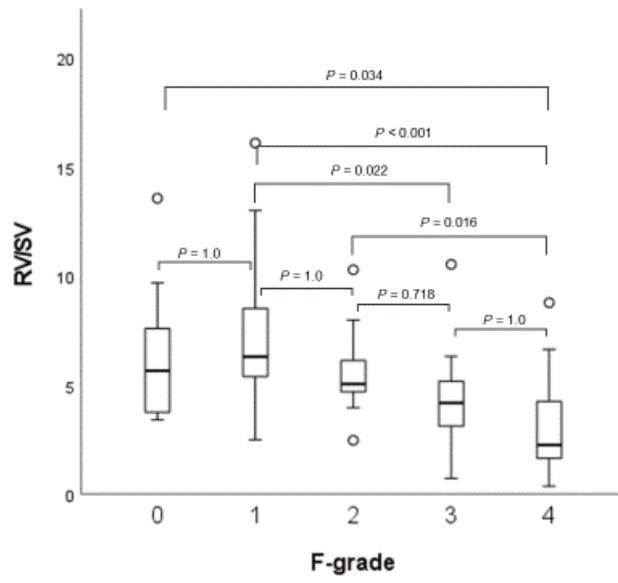
E



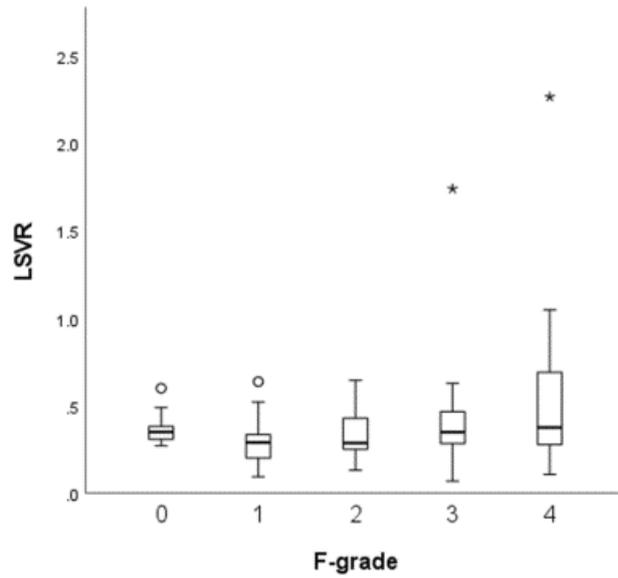
F



G



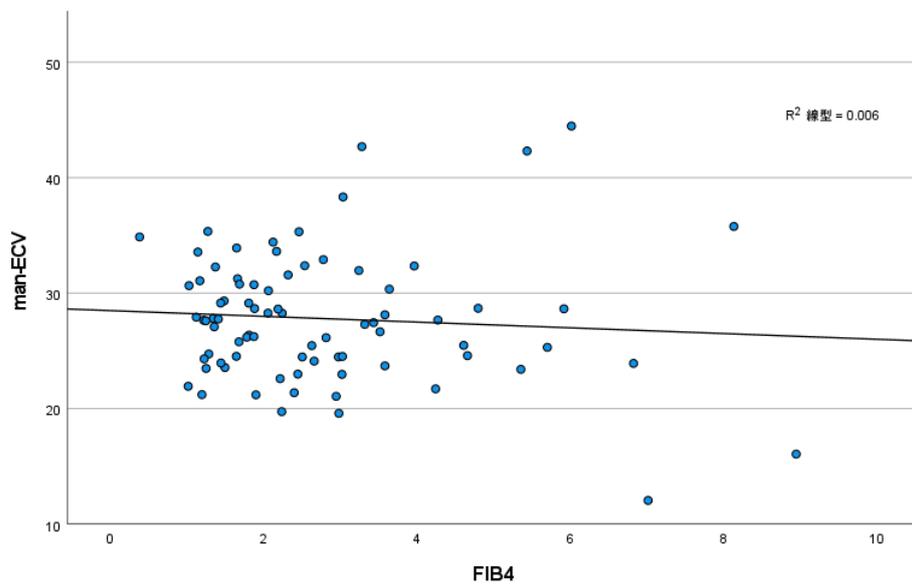
H



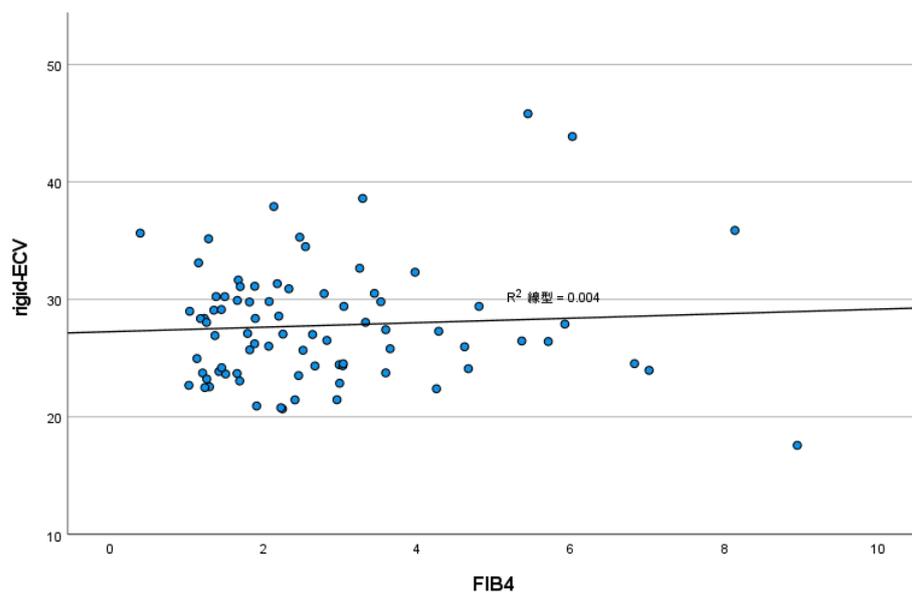
F0 vs. F1、F1 vs. F2、F2 vs. F3、F3 vs. F4 は全ての測定方法で有意差はなかった。全ての ECV において、F1 vs F4 に有意差があった。BSA に対する脾臓容積の比 (SV/BSA) および SV に対する肝右葉容積の比 (RV/SV) は、F0 vs. F4、F1 vs. F4、F1 vs. F3、F2 vs. F4 で有意差があった。SV に対する肝容積の比 (TLV/SV) は F1 と F3 で有意差があった。TLV/BSA および肝区域容積比 (LSVR) では有意差があるものはなかった。

Figure 6. 細胞外容積率 (ECV) および CT 容積測定 (CTV) の血液検査バイオマーカーとの相関および dot plot

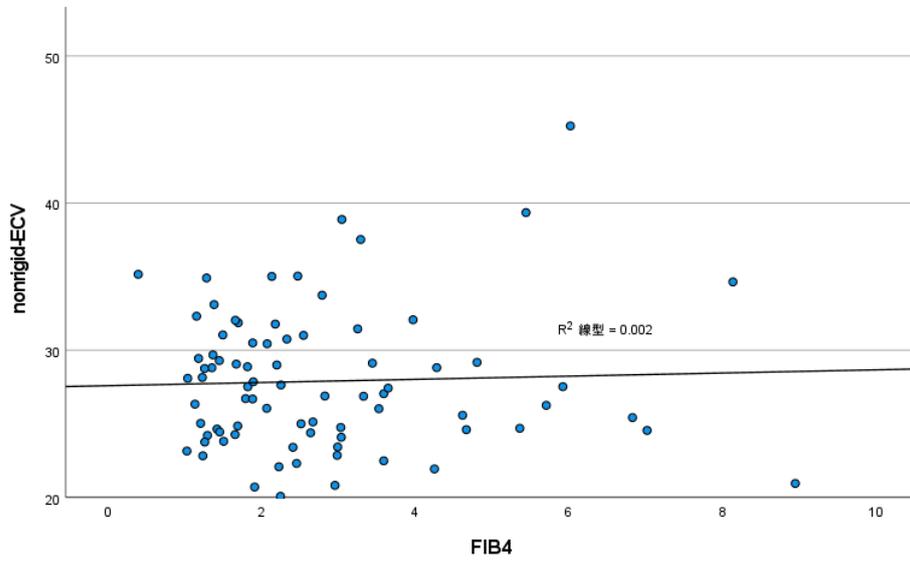
A



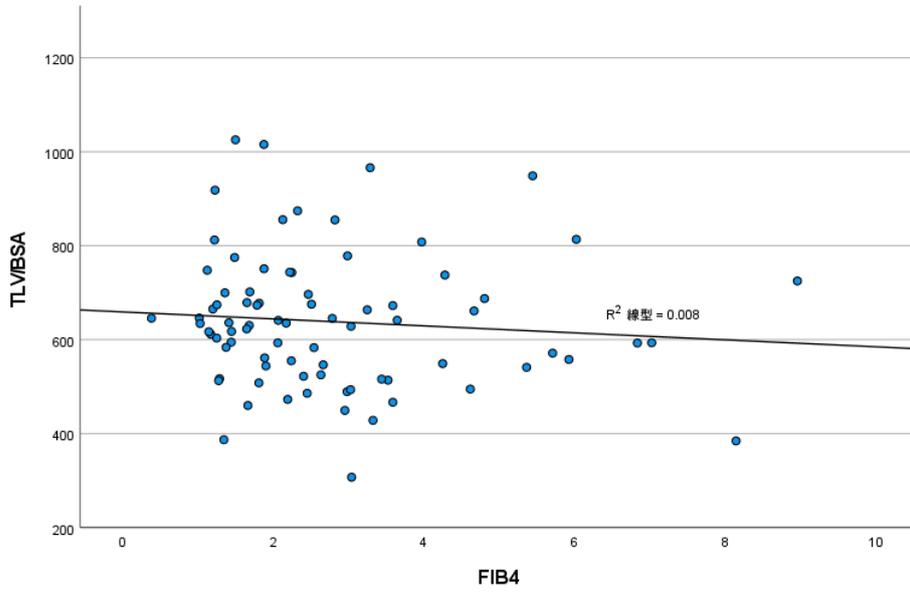
B



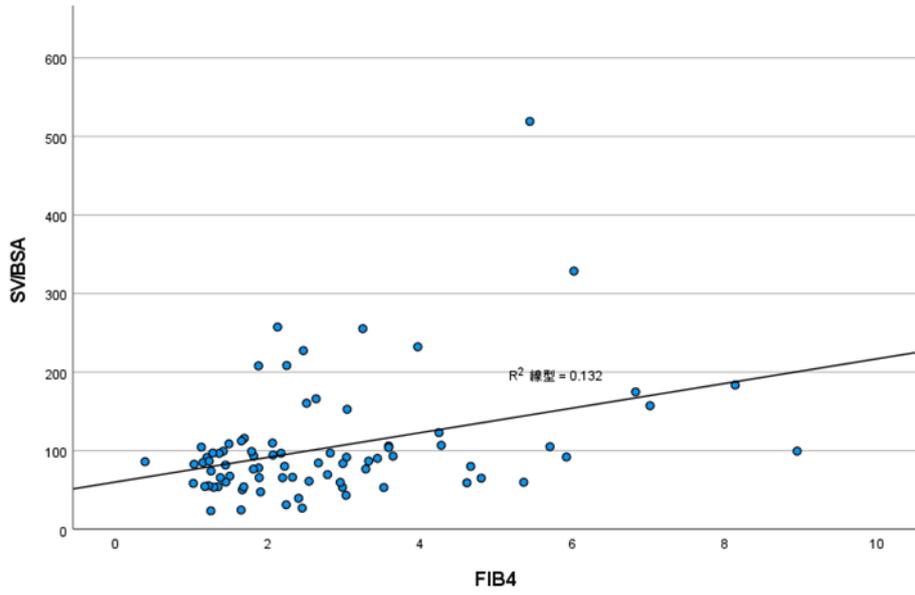
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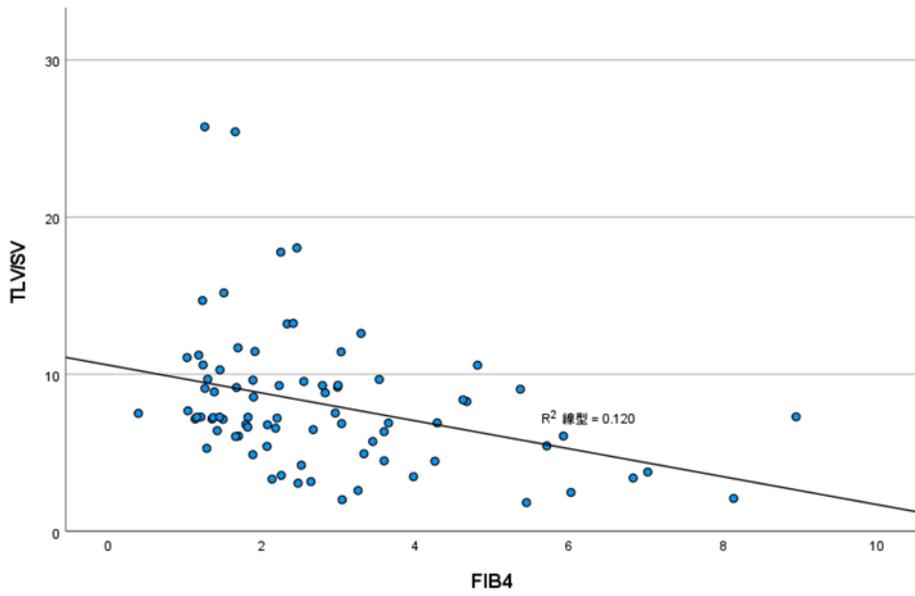
D



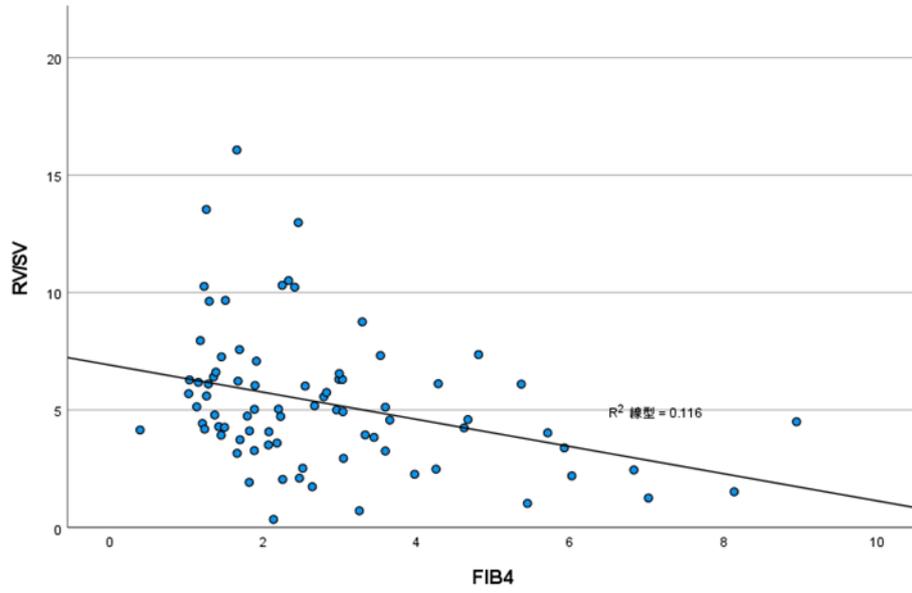
E



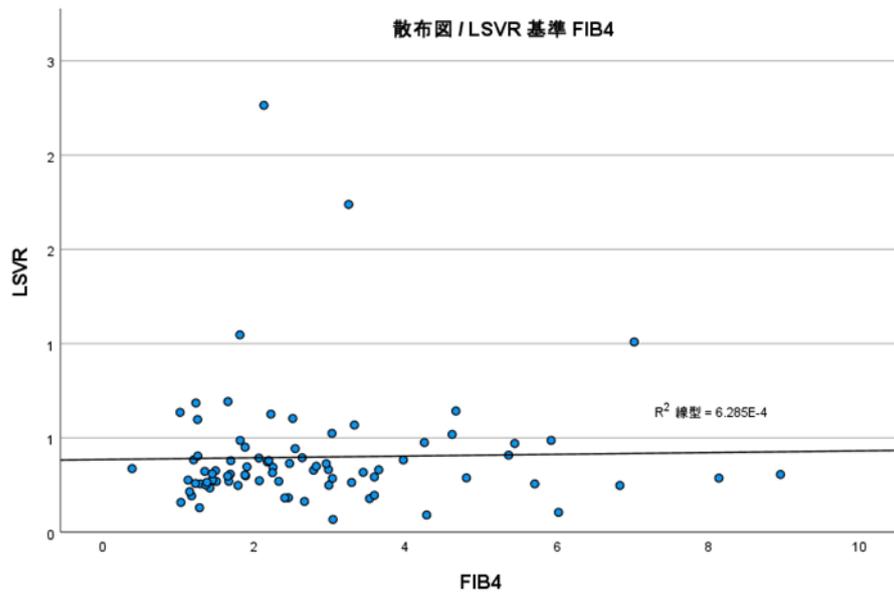
F



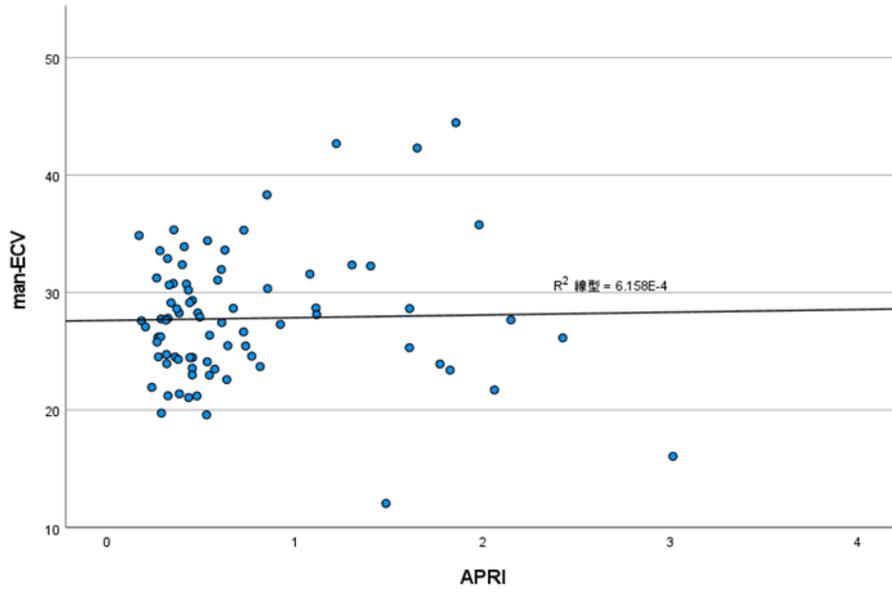
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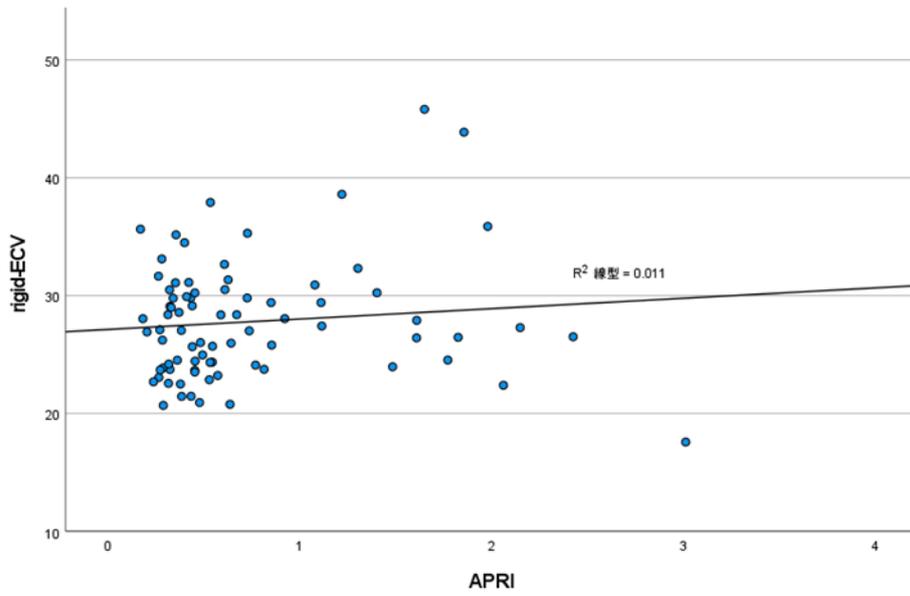
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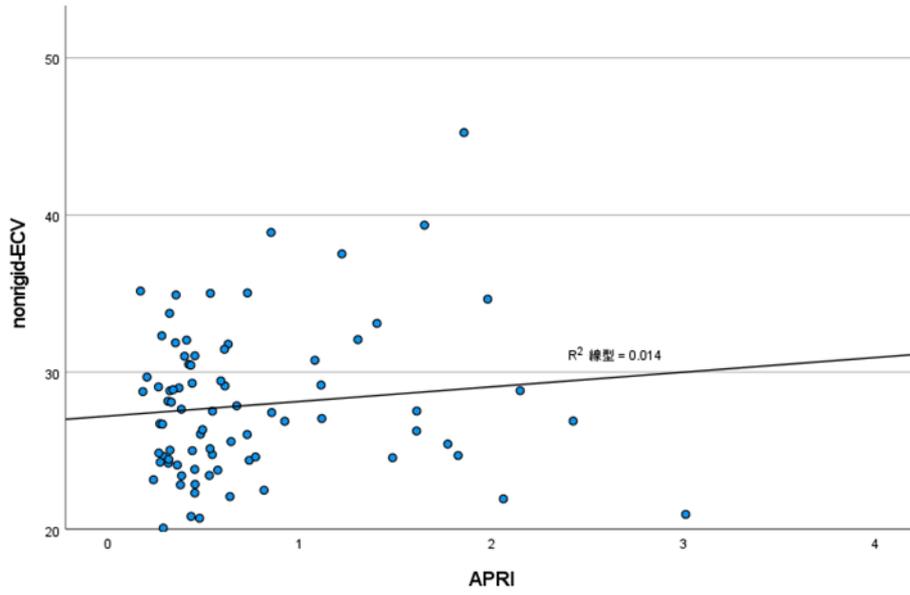
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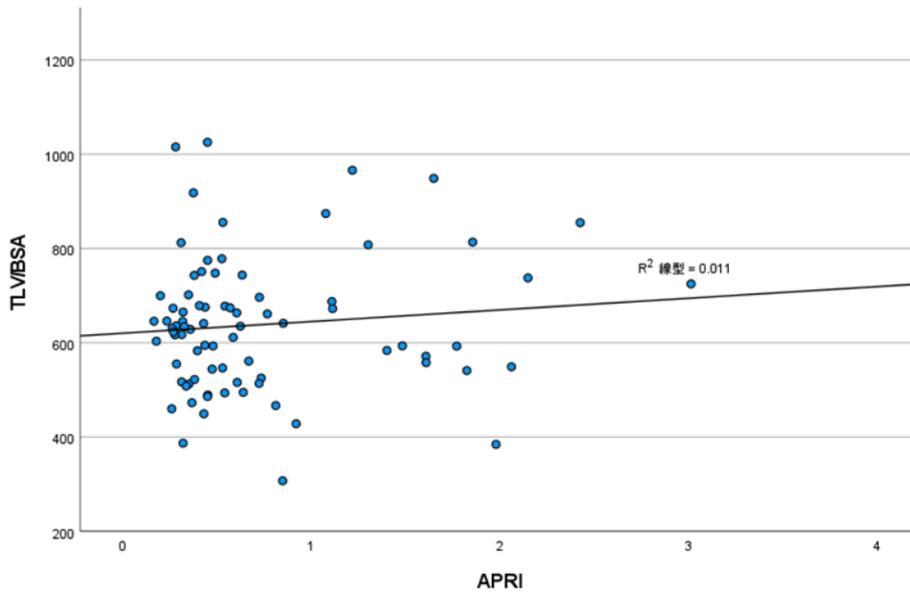
J



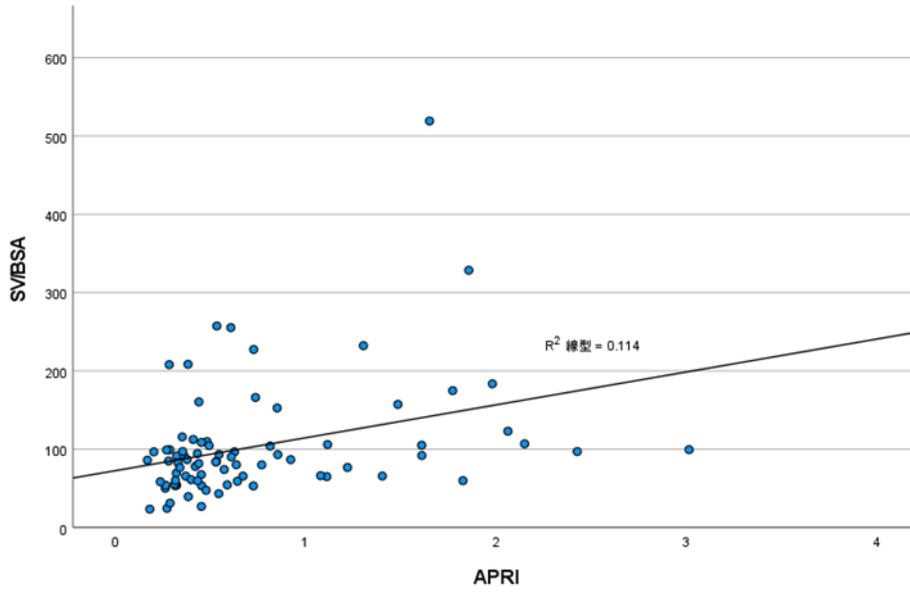
K



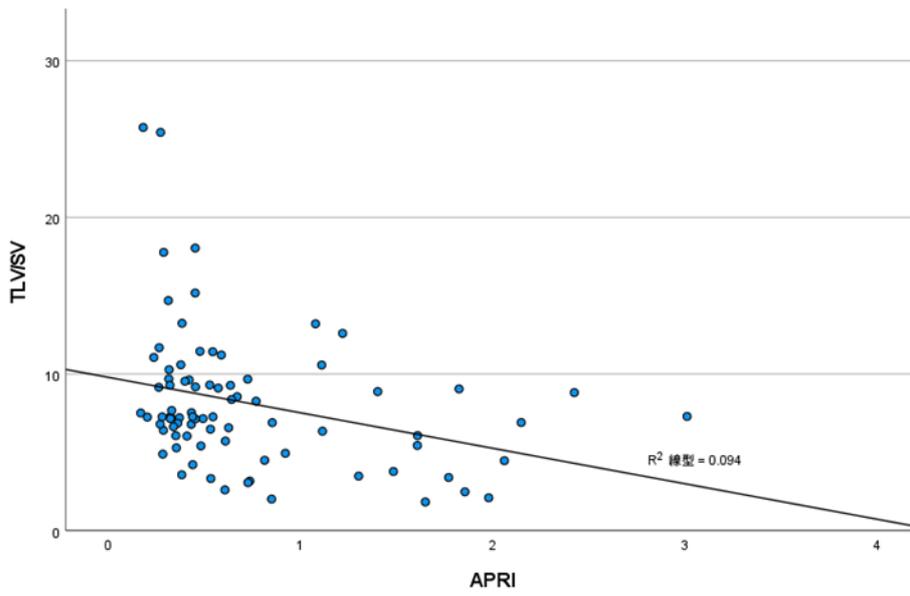
L



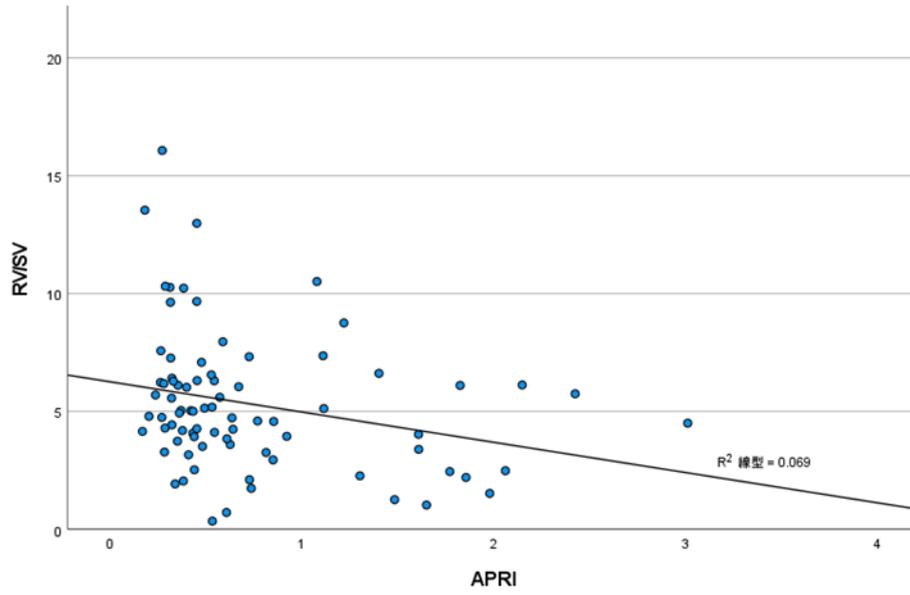
M



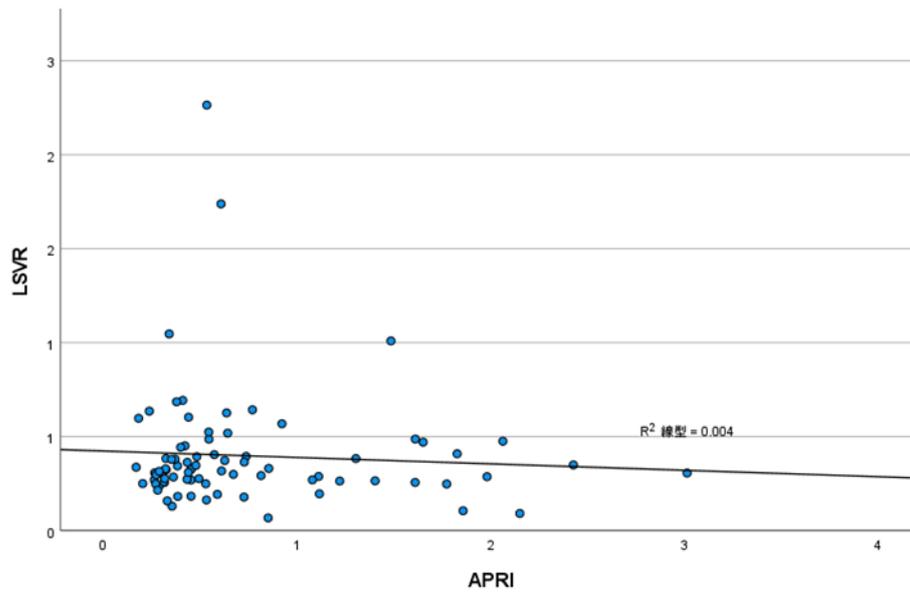
N



0



P



細胞外容積率 (ECV) と CT 容積測定 (CTV) のそれぞれの測定結果と血液検査バイオマーカーの相関解析および dot plot を示す。有意な相関を示す結果は得られなかった。

表

Table 1

患者背景

患者背景	
性別, n (%)	
男性	53 (66.3%)
女性	27 (33.7%)
Age (yr), mean (SD)年齢、平均 (標準偏差)	66.4 (10.6)
BMI (kg/m²), 平均 (標準偏差)	23.0 (3.19)
BSA (m²), 平均 (標準偏差)	1.64 (0.17)
背景疾患, n (%)	
HBV	21 (26.3%)
HCV	22 (27.5%)
HCV+HBV	1 (1.3%)
Alcoholic liver disease	8 (10.0%)
NAFLD	5 (6.3%)
(うち 4 例が MAFLD)	
NASH	4 (5.0%)
PBC	2 (2.5%)
Others	17 (21.3%)
Child-Pugh スコア, n (%)	
5	78 (97.5%)
6	2 (2.5%)
7-15	0 (0%)
病理学的肝線維化ステージ, n (%)	
F0	10 (12.4%)
F1	19 (23.8%)
F2	19 (23.8%)
F3	16 (20.0%)
F4	16 (20.0%)
血液検査	
Hct (%), 平均 (標準偏差)	40.8 (3.8)
AST (IU/L), 平均 (標準偏差)	35.4 (22.4)
ALT (IU/L), 平均 (標準偏差)	32.8 (29.0)
Plt (10 ⁹ /L), 平均 (標準偏差)	188 (74.8)
INR, 平均 (標準偏差)	1.03 (0.07)
T-bil (mg/dL), 平均 (標準偏差)	0.72 (0.3)

Alb (g/dL), 平均 (標準偏差)	4.4 (0.4)
Cr (mg/dL), 平均 (標準偏差)	0.76 (0.2)
ICG-R15 (%),平均 (標準偏差)	11.7 (9.9)
ALBI, 平均 (標準偏差)	-3.1 (0.3)
grade 1*, n (%)	73 (91.3)
grade 2a*, n (%)	7 (8.7)
grade 2b*, n (%)	0 (0)
grade 3*, n (%)	0 (0)
MELD, 平均 (標準偏差)	2.28 (2.9)
APRI score, 平均 (標準偏差)	0.74 (0.59)
FIB-4 index, 平均 (標準偏差)	2.77 (1.7)

注: BMI, body mass index; BSA, body surface area; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; Hct, hematocrit; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Plt, platelet; INR, international normalized ratio; T-Bil, total bilirubin; Alb, albumin; Cr, creatinine; ICG-R15, indocyanine green retention rates at 15 minutes after injection; ALBI, albumin-bilirubin grade; MELD, model for end-stage liver disease score; APRI score, aspartate aminotransferase-platelet ratio index, FIB-4 index, fibrosis index based on the four factors.

*; modified ALBI grade.

Table 2 肝線維化ステージの ECV、CTV、血液バイオマーカー

	F0-1 (n=29)	F2 (n=19)	F3 (n=16)	F4 (n=16)	ρ	<i>P</i> value
ECV						
manual-ECV	26.2±4.8	27.3±3.5	27.1±4.4	31.8±8.1	0.241	0.031
rigid-ECV	26.2±4.3	27.6±3.5	26.3±3.2	32.3±6.8	0.254	0.023
nonrigid-ECV	26.6±4.1	27.3±3.3	27.0±4.1	31.8±6.0	0.244	0.029
CTV						
TLV/BSA (ml/m ²)	608.3±120.2	609.3±105.6	632.6±143.7	734.0±184.2	0.261	0.02
SV/BSA (ml/m ²)	68.5±26.8	82.1±29.0	114.4±54.7	182.1±117.7	0.546	<0.001
TLV/SV	10.5±5.3	8.1±2.5	6.6±3.1	5.4±3.2	-0.468	<0.001
RV/SV	6.9±3.3	5.5±1.7	4.3±2.2	3.1±2.2	-0.507	<0.001
LSVR	0.3±0.1	0.3±0.1	0.4±0.4	0.6±0.5	0.18	0.11
血液バイオマーカー						
Fib-4 index	2.5±1.8	2.7±1.6	2.7±1.1	3.4±2.2	0.19	0.001
APRI score	0.6±0.7	0.6±0.5	0.8±0.5	1.0±0.6	0.36	0.09

注: Spearman's correlation analysis was used to assess the correlation between each measurement and fibrosis stage. Data are presented as mean \pm standard deviation. ρ , Spearman's correlation coefficient. ECV, extracellular volume fraction; manual-ECV, ECV by manually placed region-of-interests; rigid-ECV, rigid registration ECV; nonrigid-ECV, nonrigid registration ECV; TLV/BSA, ratio of total liver volume to body surface area; SV/BSA, ratio of splenic volume to BSA; TLV/SV, ratio of TLV to SV; RV, right liver volume; RV/SV, ratio of RV to SV; LSVR, liver segmental volume ratio, which is volume ratio of Couinaud segments I-III to segments IV-VIII; FIB-4 index, fibrosis index based on the four factors; APRI score, aspartate aminotransferase-platelet ratio index.

Table 3 ROC 解析による肝線維化の鑑別(AUC [95% 信頼区間])

	F0-1 vs F2-4	F0-2 vs F3-4	F0-3 vs F4
TLV/BSA	0.60 [0.48-0.73]	0.65 [0.52-0.80]	0.70 [0.54-0.87]
SV/BSA	0.76 [0.65-0.87]	0.82 [0.73-0.91]	0.83 [0.71-0.95]
TLV/SV	0.74 [0.63-0.85]	0.77 [0.66-0.89]	0.77 [0.63-0.92]
RV/SV	0.75 [0.64-0.86]	0.80 [0.70-0.90]	0.81 [0.67-0.95]
LSVR	0.59 [0.47-0.72]	0.64 [0.51-0.76]	0.63 [0.46-0.80]
manual-ECV	0.61 [0.48-0.74]	0.62 [0.50-0.75]	0.75 [0.60-0.90]
rigid-ECV	0.63 [0.50-0.76]	0.61 [0.48-0.74]	0.76 [0.62-0.90]
nonrigid-ECV	0.61 [0.48-0.74]	0.62 [0.49-0.75]	0.75 [0.60-0.90]
FIB-4 index	0.64 [0.47-0.74]	0.61 [0.49-0.74]	0.60 [0.44-0.76]
APRI score	0.69 [0.55-0.82]	0.70 [0.58-0.82]	0.68 [0.54-0.83]

注: ROC, receiver operating characteristic; AUC, area under the ROC curve; BSA, body surface area; TLV/BSA, ratio of total liver volume to BSA; SV/BSA, ratio of splenic volume to BSA; TLV/SV, ratio of TLV to SV; RV, right liver volume; RV/SV, ratio of RV to SV; LSVR, liver segmental volume ratio, which is volume ratio of Couinaud segments I-III to segments IV-VIII; ECV, extracellular volume fraction; manual-ECV, ECV by manually placed region-of-interests; rigid-ECV, rigid registration ECV; nonrigid-ECV, nonrigid registration ECV; FIB-4 index, fibrosis index based on the four factors; APRI score, aspartate aminotransferase-platelet ratio index.

Table 4A**HCV ROC 解析による肝線維化の鑑別 (AUC [95% CI])**

	F0-1 vs F2-4	F0-2 vs F3-4	F0-3 vs F4
TLV/BSA	0.56 [0.31-0.82]	0.67 [0.43-0.91]	0.54 [0.23-0.85]
SV/BSA	0.75 [0.50-1.00]	0.75 [0.55-0.95]	0.81 [0.58-1.00]
TLV/SV	0.74 [0.63-0.85]	0.77 [0.66-0.88]	0.77 [0.63-0.92]
RV/SV	0.84 [0.67-1.00]	0.81 [0.60-1.00]	0.91 [0.75-1.00]
LSVR	0.82 [0.63-1.00]	0.83 [0.64-1.00]	0.82 [0.55-1.00]
manual-ECV	0.71 [0.45-0.96]	0.76 [0.54-0.98]	0.69 [0.36-1.00]
rigid-ECV	0.72 [0.46-0.98]	0.73 [0.51-0.95]	0.72 [0.40-1.00]
nonrigid-ECV	0.64 [0.35-0.92]	0.76 [0.55-0.96]	0.71 [0.42-0.99]
FIB-4 index	0.51 [0.22-0.79]	0.58 [0.34-0.83]	0.66 [0.37-0.95]
APRI score	0.49 [0.20-0.79]	0.70 [0.47-0.93]	0.65 [0.37-0.92]

Table 4B**HBV ROC 解析による肝線維化の鑑別 (AUC [95% CI])**

	F0-1 vs F2-4	F0-2 vs F3-4	F0-3 vs F4
TLV/BSA	0.72 [0.47-0.97]	0.70 [0.47-0.93]	1.00 [1.00-1.00]
SV/BSA	0.85 [0.67-1.00]	0.88 [0.71-1.00]	0.87 [0.69-1.00]
TLV/SV	0.76 [0.54-0.99]	0.81 [0.60-1.00]	0.66 [0.34-0.98]
RV/SV	0.88 [0.71-1.00]	0.93 [0.82-1.00]	0.87 [0.70-1.00]
LSVR	0.65 [0.41-0.90]	0.70 [0.46-0.93]	0.84 [0.65-1.00]
manual-ECV	0.56 [0.24-0.88]	0.52 [0.26-0.78]	0.69 [0.41-0.97]
rigid-ECV	0.59 [0.28-0.90]	0.54 [0.28-0.79]	0.69 [0.31-1.00]
nonrigid-ECV	0.59 [0.28-0.90]	0.54 [0.28-0.79]	0.69 [0.31-1.00]
FIB-4 index	0.63 [0.39-0.87]	0.67 [0.44-0.91]	0.46 [0.12-0.79]
APRI score	0.90 [0.75-1.00]	0.71 [0.48-0.94]	0.51 [0.21-0.82]

Table 4C**Alcoholic liver disease****ROC 解析による肝線維化の鑑別 (AUC [95% CI])**

	F0-1 vs F2-4	F0-2 vs F3-4	F0-3 vs F4
TLV/BSA	0.60 [0.48-0.73]	0.65 [0.52-0.78]	0.70 [0.54-0.87]
SV/BSA	0.76 [0.65-0.87]	0.82 [0.72-0.91]	0.83 [0.71-0.95]
TLV/SV	0.74 [0.63-0.85]	0.77 [0.66-0.88]	0.77 [0.63-0.92]
RV/SV	0.75 [0.63-0.86]	0.80 [0.70-0.90]	0.81 [0.67-0.95]
LSVR	0.59 [0.46-0.71]	0.64 [0.51-0.76]	0.63 [0.46-0.79]
manual-ECV	0.61 [0.48-0.74]	0.62 [0.49-0.75]	0.75 [0.59-0.90]
rigid-ECV	0.63 [0.50-0.76]	0.61 [0.48-0.74]	0.76 [0.62-0.90]
nonrigid-ECV	0.61 [0.48-0.74]	0.62 [0.49-0.75]	0.75 [0.60-0.90]
FIB-4 index	0.80 [0.43-1.00]	0.56 [0.10-1.00]	0.67 [0.27-1.00]
APRI score	0.80 [0.43-1.00]	0.56 [0.10-1.00]	0.60 [0.19-1.00]

Table 4D**NAFLD/NASH ROC 解析による肝線維化の鑑別 (AUC [95% CI])**

	F0-1 vs F2-4	F0-2 vs F3-4	F0-3 vs F4
TLV/BSA	0.72 [0.47-0.97]	0.70 [0.47-0.93]	1.00 [1.00-1.00]
SV/BSA	0.85 [0.67-1.00]	0.88 [0.71-1.00]	0.87 [0.69-1.00]
TLV/SV	0.76 [0.54-0.99]	0.81 [0.60-1.00]	0.66 [0.34-0.98]
RV/SV	0.88 [0.71-1.00]	0.93 [0.82-1.00]	0.87 [0.70-1.00]
LSVR	0.65 [0.41-0.90]	0.70 [0.46-0.93]	0.84 [0.65-1.00]
manual-ECV	0.56 [0.24-0.88]	0.52 [0.26-0.78]	0.69 [0.41-0.97]
rigid-ECV	0.59 [0.28-0.90]	0.54 [0.28-0.79]	0.69 [0.31-1.00]
nonrigid-ECV	0.56 [0.22-0.90]	0.57 [0.31-0.83]	0.71 [0.38-1.00]
FIB-4 index	0.63 [0.39-0.87]	0.67 [0.44-0.91]	0.46 [0.12-0.79]
APRI score	0.90 [0.75-1.00]	0.71 [0.48-0.94]	0.51 [0.21-0.82]

注: ROC, receiver operating characteristic; AUC, area under the ROC curve; BSA, body surface area; TLV/BSA, ratio of total liver volume to BSA; SV/BSA, ratio of splenic volume to BSA; TLV/SV, ratio of TLV to SV; RV, right liver volume; RV/SV, ratio of RV to SV; LSVR, liver segmental volume ratio, which is volume ratio of Couinaud segments I-III to segments IV-VIII; ECV, extracellular volume fraction; manual-ECV, ECV by manually placed region-of-interests; rigid-ECV, rigid registration ECV; nonrigid-ECV, nonrigid registration ECV; FIB-4 index, fibrosis index based on the four factors; APRI score, aspartate aminotransferase-platelet ratio index.

Table 5 SV/BSA と manual-ECV の比較

Variable	SV/BSA	manual-ECV
F0-1 vs F2-4		
カットオフ値	86.37	26
感度[%]	0.67	0.69
特異度[%]	0.79	0.52
AUC (95%信頼区間)	0.76 (0.65-0.87)	0.61 (0.48-0.74)
<i>P</i> 値		0.045
F0-2 vs F3-4		
カットオフ値	99.2	31.4
感度[%]	0.63	0.38
特異度[%]	0.88	0.88
AUC (95%信頼区間)	0.82 (0.73-0.91)	0.62 (0.49-0.75)
<i>P</i> 値		0.006
F0-3 vs F4		
カットオフ値	105.6	32.1
感度[%]	0.75	0.56
特異度[%]	0.86	0.89
AUC (95%信頼区間)	0.83 (0.71-0.95)	0.75 (0.59-0.90)
<i>P</i> 値		0.41

注: SV, splenic volume; BSA, body surface area; SV/BSA, ratio of SV to BSA; ECV, extracellular volume fraction; manual-ECV, ECV by manually placed region-of-interests; AUC, area under the ROC curve.

AUCは95%信頼区間とともに示されている。肝線維化ステージを同定するためのSV/BSAおよびmanual-ECVのAUC、カットオフ値、感度、特異度を算出した。SV/BSAとmanual-ECVはそれぞれDeLong検定を用いて比較した。

有意な肝線維化(≥F2)と重度の肝線維化(≥F3-4)では、SV/BSAのAUCがmanual-ECVのAUCよりも有意に高かった。肝硬変(F4)ではSV/BSAとmanual-ECVのAUCに有意差はなかった。

注釈 1 : Albumin-Bilirubin (ALBI) スコアの記載が英語本文中に記載されていなかったため追記した。同部位の誤植の訂正を European radiology 誌に報告した。

注釈 2 : 英語本文中の同部位の誤植の訂正を European radiology 誌に報告した。 “AUG value of TLV/BSA was 0.74-0.77” → “AUG value of TLV/SV was 0.74-0.77”

注釈 3、4 : 英語本文中の同部位の誤植の訂正を European radiology 誌に報告した。 “the candidates for surgical liver resection were patients with HBV (22 of 80, 27.5%) and HCV (21 of 80, 26.3%)” → “the candidates for surgical liver resection were patients with HCV (22 of 80, 27.5%) and HBV (21 of 80, 26.3%)”

注釈 5 : 同部位の英語本文中の Conclusion の記載を (>F4)→(F4)に訂正するよう European radiology 誌に報告した。

注釈 6 : 英語本文中の同部位の誤植の訂正を European radiology 誌に報告した。 “Anatomical misregistration is shown” → “Anatomical misregistration was not shown”

またこの次の文の誤植箇所も訂正を European radiology 誌に報告した。 “The ROI of the abdominal aorta (area 61 mm²) and the portal vein (area 61 mm²) are placed” → “The ROI of the abdominal aorta (area 61 mm²) and the portal vein (area 61 mm²) were placed”