Original Article

Correlation between liver volume and liver weight in a cohort with chronic liver disease: a semiautomated CT-volumetry study

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Background: To estimate the optimal density coefficient for conversion of liver volume into liver weight in patients with chronic liver disease based on semiautomated CT-liver volumetry data and the histologic Ishak score of explanted liver.

Methods: A total of 114 patients (39 female; age, 46±20 years) with chronic liver diseases who underwent liver transplantation between January 2010 and September 2020 were identified over a patient chart search at our institution and subsequently analyzed in retrospect. All patients had contrast-enhanced CT-examinations (mean, 24 days) to liver transplantation. Liver volume was calculated by a semiautomated software and results compared with the liver weight registered by the pathologist. Each explanted liver was histologically scored into six classes according to the Ishak classification where the categories were subgrouped based on recommendation of the pathologists into the following categories 0–3, 4–5 and 6.

Results: Mean liver volume was 1,870±1,195, 1,162±679 and 1,278±510 mL for the categories 0–3, 4–5 and 6, respectively. Mean liver weight was 1,624±999, 1,082±669 and 1,346±559 g for the categories 0–3, 4–5 and 6, respectively. A coefficient of 0.92±0.22, 0.98±0.28 and 1.06±0.20 g/mL was found at best for conversion of liver volume into liver weight in these subgroups. Differences between Ishak-subgroups proved significant (0.002). In 4 patients with cystic liver disease, density coefficients varied significantly and were found generally lower compared to the other liver disorders.

Conclusions: Our results yielded significant differences between the density coefficients calculated along with the Ishak score and also for the subgroup with cystic liver disease.

Keywords: Liver volume; *syngo*-via liver analysis; liver transplantation

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Introduction

Accurate quantification of the liver volume and weight is a prerequisite for liver resection and transplantation (1-3), for avoiding metabolic mismatches between donor and recipient which may result in "small-for-size syndrome" or "large-for-size syndrome" and ultimately in an increased risk of graft rejection (4). In the past, surrogate variables to determine metabolic mismatches, such as the donor height to recipient height ratio (5) as well as formulas calculating the liver weight based on age, gender and body weight (6) led to controversial results. For this reason, preoperative CT-volumetry is frequently performed in clinical practice (7). Besides manual, time-consuming techniques, semiautomated reliable volume assessment techniques have emerged which are based on complex segmentation, organ surface, and structure (e.g., vessel) recognition algorithms (8-10). The most accurate method for liver volume quantification is ex-vivo by measuring either the displaced water volume of the explanted organ or by weighting e.g., the liver (11,12). However, a metabolic mismatch can also be caused by an excessive weight difference (3), which can be attributed to the varying liver consistency among patients mainly due to the underlying disorder and its grade (13-15). These coefficient factors have been evaluated in different clinical settings both in patients with normal livers as well as in such with chronic liver diseases (16,17). Most of them, however, have been calculated globally for all liver disorders without any further differentiation of disease stage, cause, etc. (16,18).

Hence, the intention of this study was to assess the optimal coefficient factors for conversion of liver volume into liver weight and vice versa differentiating between stages of liver diseases with distinct histologic features.

Methods

Patient characteristics

This retrospective data evaluation was approved by the institutional review board which was assigned the approval number 841/2020BO2. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Verbal and written informed consent was waived due to the retrospective nature of the study.

A total of 550 Patients underwent liver transplantation between January 2010 and September 2020 at University Hospital of Tübingen. A total of 300 patients were excluded from the study due to the missing cross-sectional CT-imaging. Finally, 114 patients who had comparable CT-scan image data [thin-slice (1 mm or less), contrast-enhanced studies] were included (*Figure 1*).

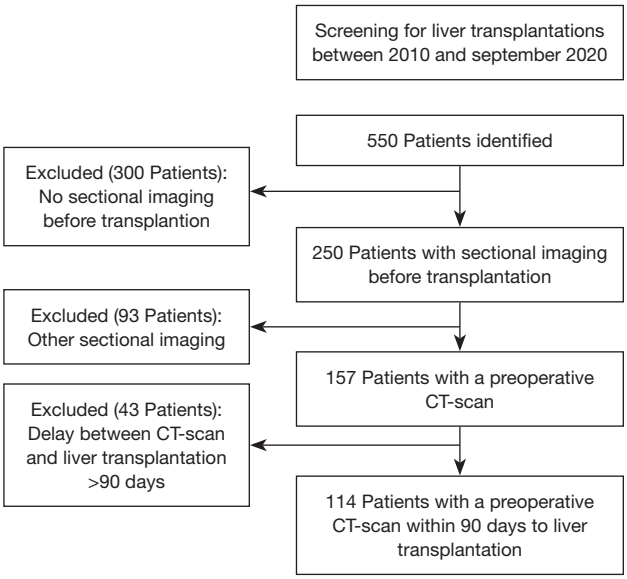

Figure 1 Study population.

CT-examinational protocol

CT-examinations were all performed on a multi-slice CT-scanner (Siemens Definition 16/AS+/Flash and/or Force, Forchheim, Germany). Only comparable CT-examinations including a portal venous phase were considered. The delay between injection of the contrast agent and the scan was about 65 seconds. The time interval between CT-imaging and liver explantation was mean, 24±26 days (range, 0–90 days).

CT-imaging data analysis

All image data were transferred to the *syngo*.via server (VB 30) for post-processing with a dedicated liver analysis application (*syngo*.CT Liver Analysis). Due to the poor differences of about 1–2 mL in total liver volume between inclusion of liver vessels of 3 or 15 mm, we opted for the widest range of vessel inclusion (15 mm).

Automated liver measurements

The main steps in the calculation of automated liver volumes are shown by the chart below (*Figure 2*).

For pose detection the marginal space learning (MSL)

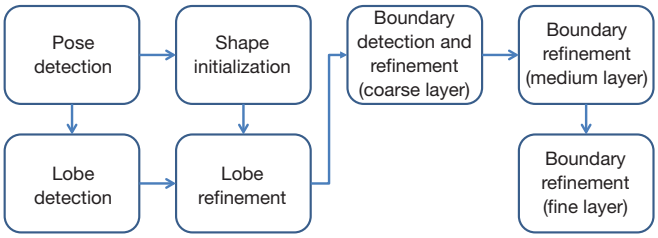

Figure 2 Flowchart and components of the liver segmentation system.

was applied whereas for learning the marginal probabilities [i.e. Pr(p|vol), Pr(θ|p, vol), and Pr(s|θ, p, vol)], the probabilistic boosting tree (PBT) was used.

For boundary detection we learned Pr(bdry|q, voll) using PBT and steerable features and in addition, the spherical coordinates of mesh points were included as features. The heterogeneity of texture pattern along liver boundaries imposed the use of patch-dependent boundary classifiers. To this end, we decomposed a liver surface to five patches: liver-lung, liver-heart, liver-kidney, liver-tissue, and liver-misc.

In about 10% of cases, an incorrect segmentation was followed by manual adjustment by an experienced radiologist (H.M.) with 30 years' experience in liver imaging.

Histopathology and surgery

Classification of the liver parenchyma depending on the degree of fibrosis was performed by the ISHAK-classification (19). Moreover, the Model for end-stage liver disease (MELD) score was calculated by incorporation of the 3 variables: total bilirubin, creatinine, and INR (20). Liver weight was calculated on exsanguinated and already formalin fixed liver grafts.

Liver explantation or hemi-hepatectomy was performed according to generally used technical requirements.

The surgical procedure in the particular case of the 4 patients presenting with polycystic liver disease was performed as follows: sharp severing of the ligamentum teres, falciformis, triangularis right and left as well as the omentum minus with subsequent mobilization of the left and right lobes of the liver; cutting of the cystic duct and the cystic artery. Isolation of the hepatic artery dextra and sinistra and cutting of the same below the hilar plate and free preparation of the same up to the level of the bifurcation of the hepatic artery communis with the gastroduodenal artery; dissection of the portal vein from periportal lymphatic tissue; dissection of the retrohepatic inferior caval vein from the retroperitoneum.

Statistical analysis

All nominal scaled variables were given as mean ± standard deviation. We calculated the density of the explanted livers by dividing their histopathological measured weight by their calculated volume (g/mL). We separated the livers into three independent groups depending on their histopathological proven degree of fibrosis (21). After verification of non-Gaussian distribution of every parameter by the Shapiro-Wilk test, we opted for a non-parametric test (Kruskal-Wallis-H test or Mann-Whitney-U test) to analyze differences between the independent samples. Post-hoc and Dunn-Bonferroni tests were used to differentiate the groups. A Pearson-test was used for the correlation between weight and measured liver volume. Regression analysis was diagrammed on a scatterplot. With regards to potential errors with respect to liver density due to differences caused by embedded HCC in patients who were screened for HCC we separately calculated the total tumor volume using the formula for spheric volume: $V = \frac{4}{3} \times \pi \times r^3$ and expressed it as ratio to the entire liver volume.

All statistical analyses and graphics were performed by using SPSS version 27.0 (IBM, Stanford). A two tailed P value of less than 0.05 was considered to indicate statistical significance.

Results

Characteristics

In total we included 114 patients who had a CT-scan previous to their liver transplantation. About 90 (78.9%) patients suffered from pathologies resulting in liver cirrhosis (see *Table 1*). Median MELD scores did not differ

Table 1 Patient characteristics

Characteristics	Data, n=114
Age (years)	46±20
Sex	
Male	75 (65.8%)
Female	39 (34.2%)
Liver transplantation	
Full liver transplantation	97 (85.1%)
Left split liver transplantation	9 (7.9%)
Right split liver transplantation	8 (7.0%)
Initial pathology	
Toxic (alcohol)	35 (30.7%)
Infectious (viral)	41 (35.9%)
Metabolic disorders	4 (3.5%)
Chronic stasis (cor pulmonale)	1 (0.9%)
Cryptogenic	9 (7.9%)
Primary tumor	3 (2.6%)
Secondary tumor	8 (7.0%)
Other causes	13 (11.4%)

statistically significantly among the different cirrhosis inducing etiologies (toxic, infectious, metabolic, chronic or cryptogenic) ranging between 19 and 21 (P>0.05). A total of 32 patients presented with subsequent hepatocellular carcinoma. Of them, 26 were initially inside Milan whereas 6 were outside Milan criteria. These 6 patients were successfully down staged by means of transarterial hepatic chemoembolization (TACE). The HCC-to-liver volume ratios ranged between 1.6% for cases inside Milan and 3.4% in patients classified out of Milan.

Polycystic liver analysis

The 4 patients suffering from polycystic liver disorder were analyzed separately due to the particular consistency of these livers (see *Table 2* and *Figure 3*). Their ages ranged between 55 and 62 years. All of them were female.

Density depending on ISHAK-Scores

Patients with an Ishak-stage of 6 had a significant higher liver parenchyma density (1.06±0.20 g/mL) compared to those with Ishak-stage of 0–3 (0.92±0.22) and 4–5 (0.98±0.28) (see *Table 3*).

All three subgroups showed an excellent Pearson correlation (P<0.000). Linear regression analysis is displayed in the scatterplots (*Figure 4*), demonstrating a higher gradient with increasing ISHAK-Score (ISHAK 0–3: 0.77, ISHAK 4–5: 0.87, ISHAK 6: 0.97).

Thirty-five patients suffered from liver fibrosis secondary to toxic mechanisms (alcoholism, drug abuse). Forty-one patients had liver fibrosis secondary to infectious diseases (viral genesis in all of the cases). Patients with liver fibrosis

Table 2 Polycystic liver analysis

Patient	Liver volume (mL)	Histopathological weight (g)	Density (g/mL)
1	2,931	2,664	0.91
2	5,397	4,573	0.85
3	5,318	3,975	0.75
4	5,862	4,279	0.73

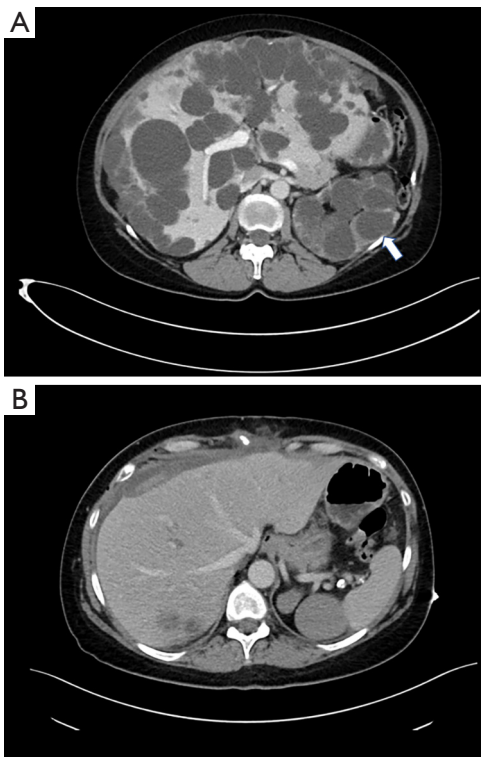

Figure 3 A 55-year-old patient with polycystic liver and kidney (white arrow) disease (A) before and (B) after liver transplantation.

Table 3 Density depending on ISHAK-stages

Variable	ISHAK 0-3 (n=32)	ISHAK 4-5 (n=18)	ISHAK 6 (n=60)	P value
Volume (mL)	1,870±1,195	1,162±679	1,278±510	0.010*
Weight (g)	1,624±999	1,082±669	1,346±559	0.048*
Density (g/mL)	0.92±0.22	0.98±0.28	1.06±0.20	0.002*
Delay between CT-scan and transplantation (days)	17±20	40±33	23±25	0.051*

*Kruskal-Wallis H-test.

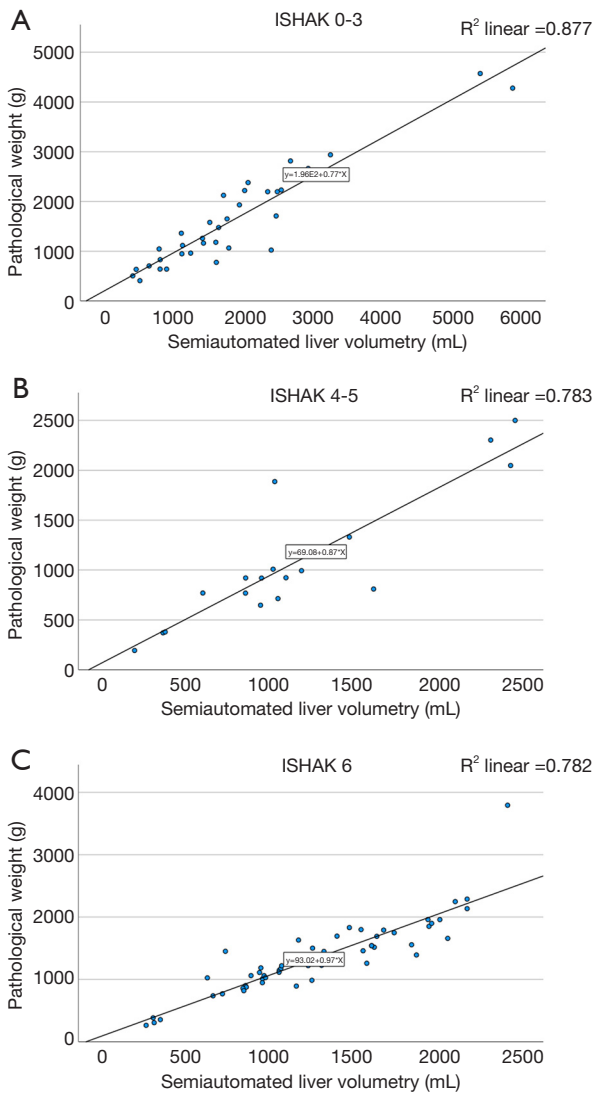

Figure 4 Linear regression analysis depending on ISHAK-Score.

induced by toxic mechanisms had significant higher liver parenchyma density compared to those with inflammatory liver pathology (P<0.05) (see *Table 4*).

Discussion

The intention of this study was to find out if the coefficients used for conversion of *ex vivo* measured liver weight into *in vivo* liver volume and vice versa significantly differ throughout the pathologic liver fibrosis classes defined by the Ishak classification. Expectedly, our results show a clear trend towards higher liver parenchymal density (coefficient factor) with increasing Ishak stage, reaching statistical significance in each class of our cohort, as well as additionally for the subgroup of patients with cystic liver disease which were analyzed separately.

Of note, liver weights were calculated in explanted livers which were exsanguinated, already formalin fixed so that these results are not perfectly comparable with *in-vivo* measurements, hence applicable only in this given clinical setting. However, the role of conversion coefficients is relevant, e.g., for concluding about the initial organ volume.

The risk of transplant rejection in the case of a liver that is too large or too small should not be underestimated. Therefore, several more or less promising attempts have been made to estimate the metabolic differences between recipient and donor as far as possible before transplantation e.g., graft weight to recipient weight ratio (22) or donor height to recipient height ratio (5), always with the final intention of reducing the rate of "small-for-size syndrome" or "large-for-size syndrome" (4,23). Previous reports using freehand computed tomographic volume quantification for assessment of the total liver volume have compared their

Table 4 Density depending on underlying causes of chronic liver disease

Variable	Toxic (n=35)	Infectious (n=41)	P value
Volume (mL)	1,290±496	1,349±519	0.393*
Weight (g)	1,365±494	1,280±469	0.518*
Density (g/mL)	1.08±0.26	0.97±0.18	0.025*
Delay between CT-Scan and transplantation (days)	26±28	23±26	0.851*

*Mann-Whitney-U-test.

results with the weights of explanted organs in cirrhotic patients and found the liver density to be about 1.1 kg/L (24). In this paper, the authors used by comparison with our study three-phase CECT-image data, thick-slices, excluding the main hepatic vessels from the final liver volume quantification. The exclusion of the larger liver vessels might explain to some extent the slight difference in liver density compared to our data. Satou *et al*. have shown that after back-table surgery has been completed, the weight of the explanted liver drops by up to 10% which would largely explain these differences (25). In normal livers, the specific gravity of a cirrhotic liver was demonstrated to be significantly lower (1 mg/L) (16). In a study conducted by Goumard *et al*. the coefficient factor for assessment of liver density was found in a similar range as in our study (26). The authors indicated that liver density and liver volume are changing with advancing cirrhosis and that differences in liver density compared with those of patients with e.g., NASH proved significant, the latter proving significantly lower which can be easily explained by fat deposition which exhibits lower density. Liver volume assessment was performed manually in their study by excluding the large central hepatic vessels. Yoneyama *et al*. found the liver density of cirrhotic livers to be also within similar ranges (mean, 1 g/1 mL) showing, however, significantly lower values (0.85 kg/L) in non-cirrhotic patients (16). Interestingly, Sonnemans *et al*. found higher density values in normal livers (1.13 g/mL) compared to our cirrhotic patients, demonstrating concomitantly, that these values significantly declined in patients with other pathologies like fatty liver and in particular in such with cardiovascular problems and secondary hepatic stasis causing changes in the liver parenchymal consistency by increased blood content (18). Hence, the linear relationship between liver volume and liver density as described by Van Thiel *et al.* could be reproduced in most studies including ours (11). Nevertheless, differences in the calculation of liver density may occur and are related either to technical issues (accuracy of liver volumetry, examinational protocol), hepatic particularities (unusual form, surface, collateral vessels, gallbladder, the presence of hepatic tumors, cysts, attached ligaments) or to surgical causes like intraoperative drainage of liquids from the liver. In our study, automated volumetry results were additionally controlled by a senior radiologist who in case of mismeasurement manually corrected the volumetric assessment. Moreover, we analyzed in our study also differences in liver volume and density between toxic and infectious chronic liver diseases which, however, proved insignificant. Hence, the assumption was that if the quantified liver volume would be the standard of reference and the exsanguinated explanted livers would all be weighted in a standardized fashion and the degree of liver fibrosis scored according to the Ishak classification, then the liver densities (coefficient factors) could be accurately assessed.

To our knowledge, this study is the first to report about differences in liver density throughout different stages of chronic liver disease as assessed histologically based on the Ishak stage as well as to address the expected conversion coefficient in case of *ex vivo* exsanguinated livers.

Our study has some limitations. First, the different underlying diseases and their stages made the cohort heterogeneous in these terms. However, this reflects the everyday situation where every patient is finally particular in these terms. Second, individual factors with potential impact on the volume quantification like the hydration grade, postoperative liver fixation with formalin, cardio-circulatory status, or accompanying disorders like steatosis have not been additionally considered in this study. Third, the semiautomated liver volumetry is not a gold-standard, but supplemented by the expertise of a senior radiologist supervising the results should be a guarantor for accurate measurements. Fourth, in case of polycystic livers, technical particularities like difficulties in the organ mobilization, intra-operative need for cyst transection due to adhesions could affect the entire liver volume measurements. This, however, was not the case in our series. Fifth, some patients

also had hepatocellular carcinomas diagnosed in the pre-operative setting. The HCC-to-liver volume ratios proved very low in both patient subgroups (inside and outside Milan criteria), so that the potential impact of the differences in the density of tumor to liver are not expected to affect the final results.

In conclusion, our results yielded significant differences between the density coefficients calculated along with the Ishak stage and also for the subgroup with cystic liver disease in exsanguinated explanted livers. This helps to reduce weight mismatches preoperatively and ultimately possibly minimize graft rejections.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/qims-21-299). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective data evaluation was approved by the institutional review board which was assigned the approval number 841/2020BO2. Verbal and written informed consent was waived due to the retrospective nature of the study.

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