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RESEARCH

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Assessment of hepatic steatosis of potential living donor before liver transplantation using liver/spleen CT attenuation ratio compared to liver biopsy

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Abstract

Background Hepatic steatosis has become a major worldwide health problem, so assessment of hepatic steatosis in potential living donors is crucial prior to liver transplantation. Until now liver biopsy (LB) is considered the gold standard for diagnosing steatosis before transplantation, however steatosis assessment using imaging modalities, such as computerized tomography (CT), would be better for the donor, due its non-invasiveness. This study aimed to assess the efficacy of CT as a semiquantitaive tool for liver steatosis assessment in liver donors in comparison to liver biopsy results.

Methods This cross-sectional study was carried out on 53 potential liver graft donors. All patients were subjected to non-contrast CT of the abdomen, tru-cut liver biopsy, and histopathological evaluation. The CT liver attenuation (CTL), the hepatic/splenic CT attenuation ratio (CTL/S) and difference between hepatic attenuation value and splenic attenuation values (CTL–S) were determined as well as the correlations of these indices and the findings of Liver biopsy (LB) were compared.

Results According to the hepatosteatosis grades in the pathology results, the patients were divided into two groups: group A: 38 patients with grade 0 hepatosteatosis and group B: 15 patients with grade 1 and 2 hepatosteatosis. CTL, CTL–S, CTL/S, ratio of mean right hepatic lobe and splenic attenuation (RT/S) and ratio of mean left hepatic lobe and splenic attenuation (LT/S) were found to be effective in the diagnosis of hepatosteatosis grades at cutoff values ≤ 55.4, ≤ 8.7, ≤ 1.17, ≤ 1.1548 and ≤ 1.2971 with 80%, 80%, 73.3%, 86.7% and 86.7% sensitivity and 71.1%, 56.8%, 73.7% 71.1% and 50.0% specificity respectively. Also, CTL/S was found to be very effective in the diagnosis of grade II hepatosteatosis at cutoff values ≤ 0.9 with 100% sensitivity and 100% specificity. There was significant negative correlations between the CT indexes and degree of hepatosteatosis.

Conclusions Compared to biopsy results, CT noninvasive indices strongly predicted the presence of hepatosteatosis, which can help in avoiding the necessity for this invasive technique.

Keywords Hepatic steatosis, Liver transplantation, CT Indices, Liver biopsy

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Background

Globally, fatty liver disease, especially liver steatosis, is a serious health issue. In liver transplantation, macrovesicular steatosis in donor livers is a major cause of graft failure and, is still challenging to diagnose [1].

Steatosis and donor age are two of the many characteristics in donors that affect graft function after transplantation, and they are both regarded as being the most crucial [2]. The presence of significant steatosis is linked to the development of early allograft dysfunction or primary non-function [3]. Although steatosis can regress within weeks after liver transplantation, the severe ischemia/reperfusion injury impaired immediate post-transplant regenerative capacity of fatty grafts [4].

The standard method for assessing hepatic steatosis is still liver biopsy [5]. For macro-vesicular steatosis, there appears to be satisfactory agreement between local pathologists' frozen section analysis and expert pathologists' permanent section appraisal, which is close to or above 70.25%. In a recent study, the intraobserver agreement was very high for the assessment of steatosis [6].

A better way to assess steatosis before organ transplantation would be a non-invasive imaging technique. Ultrasound (US) has an acceptable level of sensitivity but does not provide reproducible quantitative information. Its main weakness is its operator dependency. Most centers allow the use of US as a screening tool for steatosis detection during procurement [7].

Also, for diagnosis of hepatic steatosis, proton magnetic resonance spectroscopy and magnetic resonance imaging (MRI) are imaging techniques that give the best results with respect to sensitivity and specificity. However, their complexity does not allow their use in routine organ procurement [8].

Non-enhanced CT is much more common examination than MR and can provide high performance in qualitative diagnosis of hepatic steatosis, particularly for macrovesicular steatosis up to 30% [9]. Hounsfield units (HU) are an objective unit of measurement for X-ray attenuation provided by CT imaging. A healthy liver attenuation value ranges from 50 to 57 HU, which is approximately 10 HU higher than the attenuation value of a healthy spleen [10]. Therefore, using CT in assessment of graft steatosis generally considers a measurement of the difference, or the ratio of attenuation values, between the spleen and liver because an attenuation value of the liver less than 40 HU or 10 HU smaller than that of the spleen indicated the presence of steatosis [11].

The aim of this work was to assess the efficacy of the usage of CT for semiquantitative assessment of hepatic steatosis in living donor liver transplant compared to biopsy results.

Methods

This cross-sectional study was carried out on 53 potential liver graft donors aged from 20 to 50 years old, both sexes, who were potential candidates for liver donation and underwent liver biopsy in the preparation journey for transplantation.

The study was done after approval from the Ethical Committee of National Liver Institute, Menoufia University (approval code: 00515/2023). An informed written consent was obtained from all participants.

Exclusion criteria were previous chronic hepatic disease and potential donors who are unfit for donation.

All patients were subjected to: full history taking [previous morbidities, surgeries, drug intake and habits], clinical examination, laboratory investigations [complete blood count (CBC), bleeding profile, liver function tests, and hepatitis markers], non-contrast CT of the abdomen, Tru-cut liver biopsy, and histopathological evaluation.

By using multi-detector CT (Somatom biograph 128; Siemens Healthineers, Erlangen, Germany) CT images were taken of all donors. CT was performed first without contrast using fixed parameters for all patients with 120 kV, 200 mAs and 1 mm slice thickness. Then post IV contrast phases were taken and used for vascular reconstruction and surgical planning.

From the non-contrast CT images, the attenuation values of the liver and spleen using the mean Hounsfield units (HU) of regions of interest (ROIs) for all cases were conducted and calculated by a single same radiologist having more than 8 year experience at diagnostic and interventional radiology department, National liver institute, Menoufia university. He reviewed the CT images without knowing the pathology results to ensure the credibility. Then, the attenuation results were reviewed and agreed unanimously by the authors.

Hepatic attenuation was calculated by the mean of dividing the liver into right and left lobes then a circular region of interest (ROI) 1.5 cm in diameter was located in each segment of each.

lobe of total 8 ROIs in both lobes, the mean attenuation value of each lobe was then calculated separately and finally the mean total liver attenuation value was calculated. **Splenic attenuation** was also calculated by placing four ROIs of 1.5 cm diameter on different segments of the spleen avoiding the hilum and capsule then the mean attenuation value was calculated. Then the difference between the liver and splenic attenuation values was calculated (CT L-S), and the liver to spleen attenuation ration (CT L/S), in addition to mean right hepatic lobe attenuation to the splenic (RT/S), as well as the left hepatic lobe attenuation to the splenic attenuation ratio (LT/S). (Figs. 1, 2 and 3).

Tru-cut liver biopsy

The biopsy was done under local anesthesia (1% lidocaine) and using ultrasound guidance, a semi-automated 16G tru-cut needle was advanced through an intercostal

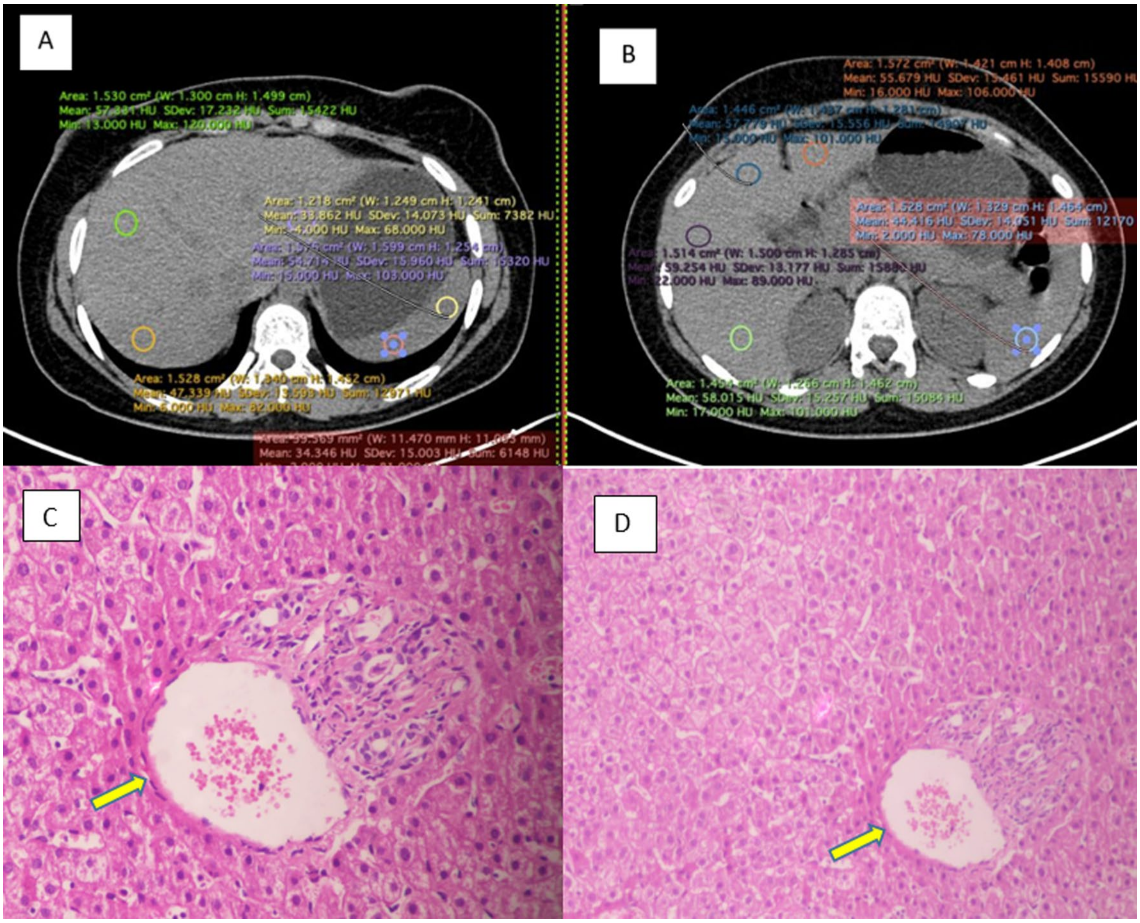

Fig. 1 **A** and **B** Axial non-contrast CT images of a 27-year-old female potential liver donor at the level of the liver and spleen showing regions of interests (ROIs) of fixed diameter put on each hepatic segment and on different levels of the spleen. The mean hepatic attenuation value (CTL) was 54.3HU, the mean splenic attenuation value (CTS) was 35.6HU, and the CT L/S ratio was 1.56. **C** and **D** 20× and 10× microscopic pictures of the hepatic core of the patient showing normal hepatocyte distribution and portal tract (yellow arrows) with no steatosis (0%) denoting grade 0. Therefore she was accepted for donation

space into the hepatic parenchyma and a single core or two were taken by the team of interventional radiology in National liver institute, Menoufia university, then the biopsy cores were sent to the pathology department for analysis.

Histopathological evaluation

All the samples were examined by a single expert pathologist at pathology department, National liver institute, Menoufia University, who has more than 10 year experience in the hepatic pathology field. He read the samples also without knowing the results of CT indices. Biopsy materials were fixed in 10% formalin and embedded in paraffin. The cross-sections were stained with hematoxylin and eosin, Masson's trichrome, Perls' Prussian blue and orcein stains. The samples were accepted as sufficient for examination if they were larger than 1 cm in length and contained more than 10 portal areas. Macrovesicular hepatosteatosis was graded according to the percentage and divided into three groups as follows: grade 0 (0–5%), grade 1 (6–20%), or grade 2 (> 20%). (Figs. 1, 2 and 3) Fibrosis was examined also with the use of Masson's trichrome stain.

The primary outcome was the diagnostic accuracy of CT indices in diagnosis of hepatosteatosis. The secondary outcomes were measurements agreement of CT indices with liver biopsy.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's *t*-test. Qualitative variables were presented as frequency

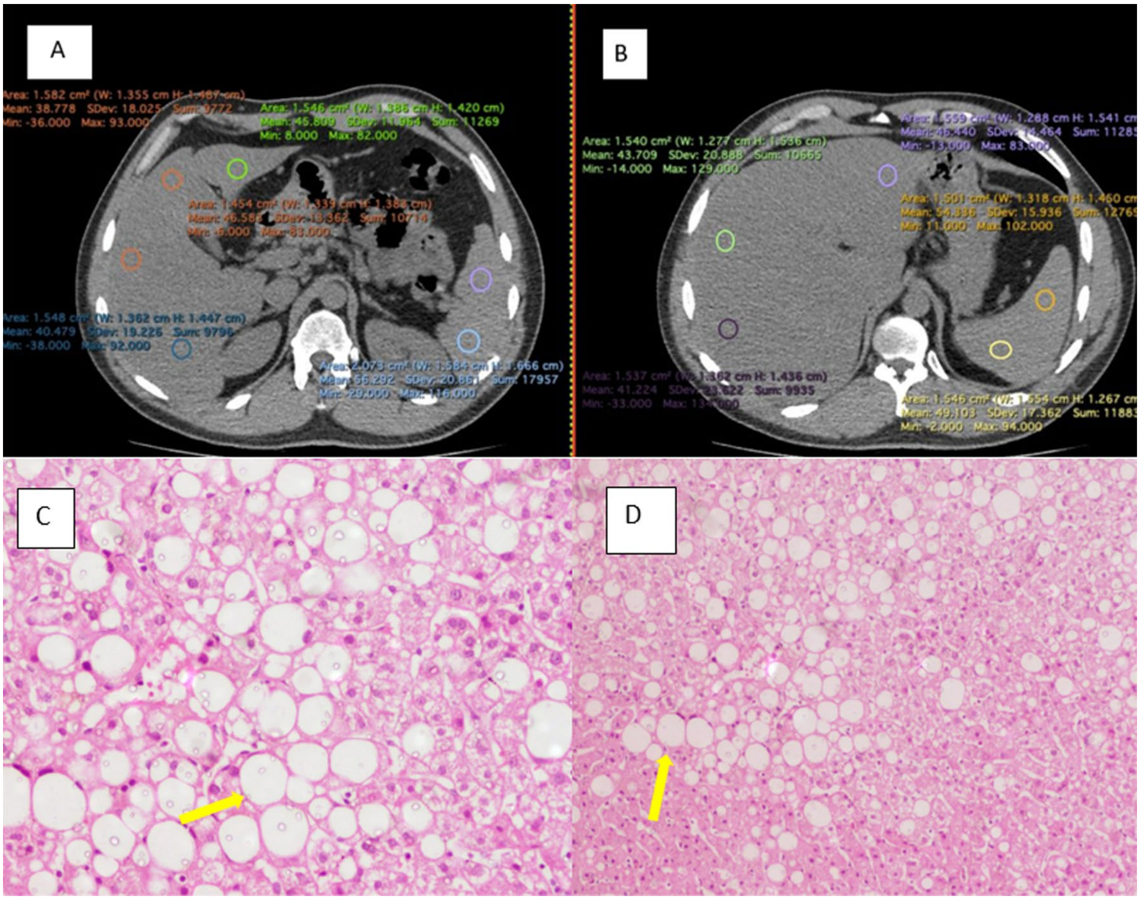

Fig. 2 **A** and **B** Axial non-contrast CT images of a 21-year-old male potential liver donor at the level of the liver and spleen showing regions of interests (ROIs) of fixed diameter put on each hepatic segment and on different levels of the spleen. The mean hepatic attenuation value (CTL) was 44.9 HU, the mean splenic attenuation value (CTS) was 53.2 HU, and the CT L/S ratio was 0.8. **C** and **D** 20× and 10× microscopic pictures of the hepatic core of the patient showing more than 25% steatosis of the hepatocytes with large fat droplets displacing the nucleus to the periphery (Yellow arrows), indicating grade II steatosis. Therefore he was refused for donation

and percentage (%) and were analyzed utilizing the Chi-square test. A two tailed *P* value < 0.05 was considered statistically significant.

Correlations among CT indices [i.e., CTL, CTL–S, CTL/S] and degree of hepatosteatosis were evaluated using the Pearson correlation coefficient.

Results

In this study, 67 patients were assessed for eligibility, 9 patients did not meet the criteria and 5 patients refused to participate in the study. The remaining 53 patients, of both sexes and aged between 20 and 50 years old, were allocated according to the hepatosteatosis grade in the pathology results into two groups: group A: 38 patients with grade 0 hepatosteatosis and group B: 15 patients with grade 1 and 2 hepatosteatosis. All allocated patients were followed-up and analyzed statistically. (Fig. 4).

There was insignificant difference between group A and B regarding demographic and laboratory data. Table 1

Regarding CT indices, CTL, CTL-S, CTL/S, RT/S, LT/S, Mean right lobe attenuation and Mean left lobe attenuation were significantly increased in group A than group B. However, CTS was insignificantly different between both groups. Table 2

The three indices (CTL, CTL–S, and CTL/S) were found to be effective in the differentiating of hepatosteatosis grades ($p < 0.001$). CTL, CTL–S, and CTL/S cutoff values were ≤ 55.4, ≤ 8.7, and ≤ 1.17, respectively; sensitivity and specificity results were 80%, 71.1% and 80%, and 65.8% and 73.3%; 73.7 and the area under the curve values were 0.817, 0.788, and 0.783, respectively. Table 3.

CTL/S cut-off value of ≤ 0.9 can effectively diagnose grade II hepatosteatosis ($p < 0.001$). Table 4.

There was significant negative correlation between the CT indices [i.e., CTL (r: − 0.610; $p < 0.001$), CTL–S (r: − 0.561; $p < 0.001$), CTL/S (r: − 0.528; $p < 0.001$] and degree of hepatosteatosis. Table 5

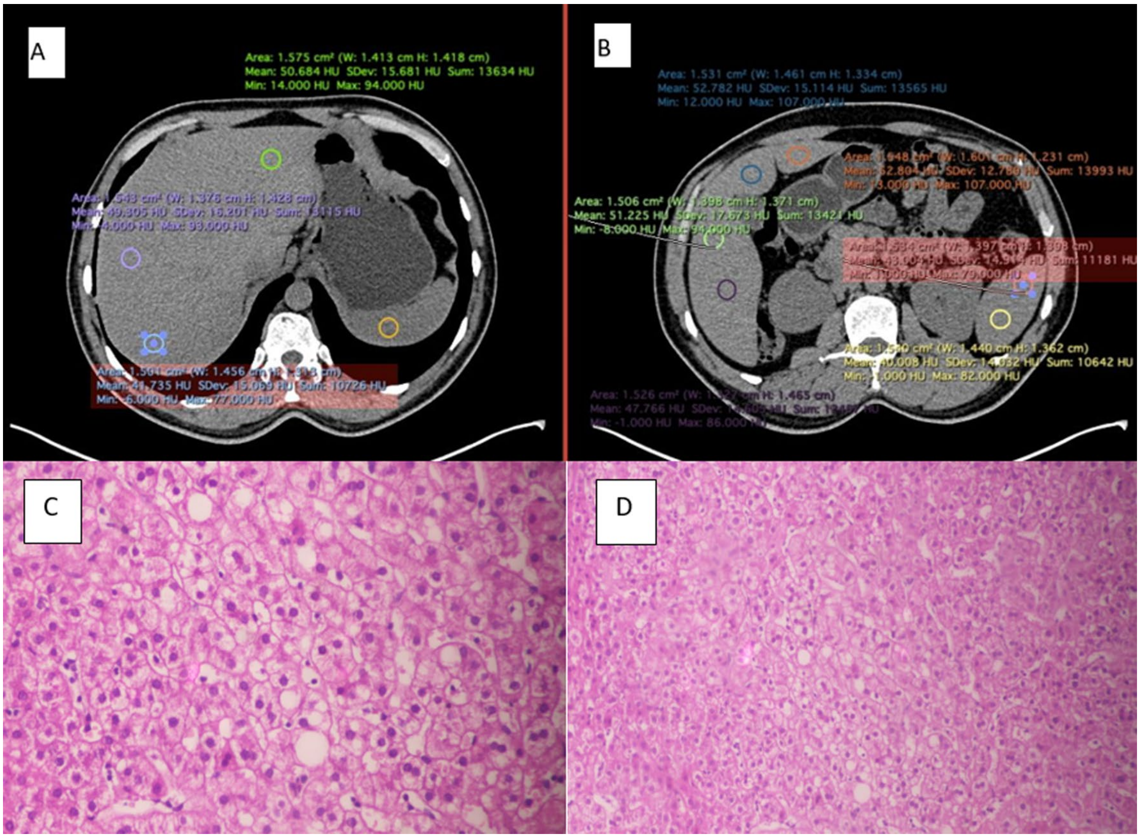

Fig. 3 **A** and **B** Axial non-contrast CT images of a 25-year-old male potential liver donor at the level of the liver and spleen showing regions of interests (ROIs) of fixed diameter put on each hepatic segment and on different levels of the spleen. The mean hepatic attenuation value (CTL) was 46.5 HU, the mean splenic attenuation value (CTS) was 41.8 HU, and the CT L/S ratio was 1.1. **C** and **D** 20× and 10× microscopic pictures of his hepatic core biopsy showing 10% steatosis of the hepatocytes denoting grade I. Therefore he was accepted for donation

Discussion

Living donor liver transplantation (LDLT) allows healthy donors to provide a partial liver graft to compatible patients who have hepatocellular carcinoma or end-stage liver disease [12]. The donor may experience severe morbidity and mortality as a result of either a partial right or left hemi-hepatectomy for donation. To ensure safe, successful graft procurement, and successful LDLT for the recipients, the selection of suitable living liver donors is very important [13]. Therefore, an accurate quantitative assessment of hepatic steatosis in donors is very essential [14].

The most common diffuse liver disease that prevent an apparently healthy patient from being a donor is fatty liver [15]. As significant liver steatosis may worsen ischemia reperfusion damage and increase the incidence of graft primary non-function [16]. Some institutions prefer more conservative cutoffs despite the fact that 30% steatosis has been considered an acceptable upper barrier for living donors [17].

The most reliable way to diagnose and monitor the majority of liver disorders is still liver biopsy [18]. Since it is an invasive procedure, the complications observed during and after the procedure may be serious enough to threaten the life of the involved patients [19]. Many methods have been suggested as alternatives to liver biopsy, with CT being the most prominent option among them and the preferred method due to its wide availability. CTL, CTL/S, and CTL-S considered the most frequently used indices in the evaluation of hepatosteatosis. If the CTL and CTS values are low, this indicates hepatosteatosis [20].

In our study, we aimed to assess the efficacy of the usage of CT for semiquantitative assessment of hepatic steatosis in living donor liver transplant compared to biopsy results.

We classified the patients according to the hepatosteatosis grade in the pathology results into two groups: group A: 38 patients with grade 0 hepatosteatosis and group B: 15 patients with grade 1 and 2 hepatosteatosis.

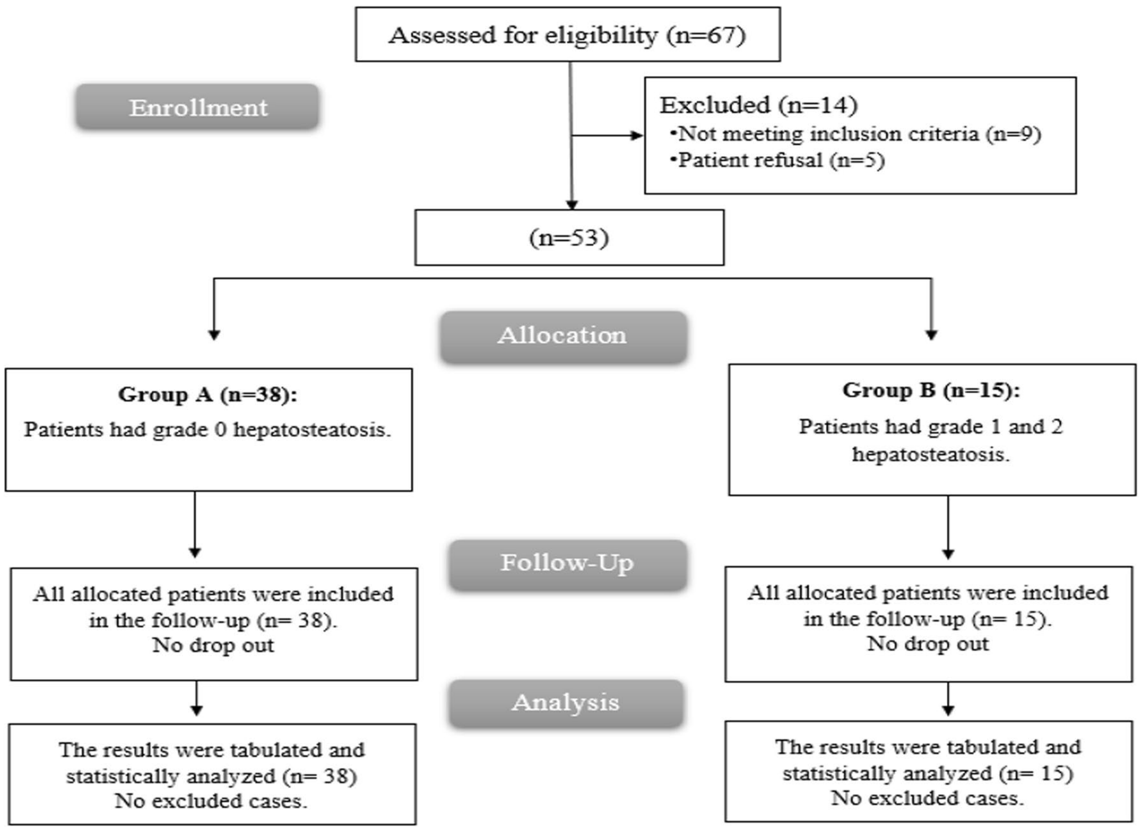

Fig. 4 The study flow chart

Table 1 Demographic and laboratory data of the studied patients

	Group A ($n=38$)	Group B ($n=15$)	*P* value
Age (years)	25.26 ± 3.39	26.80 ± 4.71	0.191
BMI (kg/m^2)	23.618 ± 4.162	24.433 ± 2.998	0.494
ALT (IU/L)	20.61 ± 5.19	39 ± 16.34	0.000*
AST (IU/)	15.32 ± 3.19	23.33 ± 4.12	0.000*

Data are presented as mean ± SD. *BMI* Body mass index, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase

*Significant. $P < 0.05$

Table 2 CT indices of the studied groups

	Group A ($n=38$)	Group B ($n=15$)	*P* value
CTL	57.04 ± 4.48	50.02 ± 6.77	0.000*
CTS	45.4 ± 4.22	44.88 ± 4.7	0.697
CTL-S	11.64 ± 5.51	5.14 ± 6.04	0.000*
CTL/S	1.27 ± .15	1.11 ± .15	0.001*
RT/S	1.24 ± .15	1.09 ± .13	0.001*
LT/S	1.29 ± .16	1.15 ± .15	0.004*
M. right lobe attenuation	55.78 ± 4.78	48.67 ± 6.92	0.000*
M. left lobe attenuation	58.39 ± 4.62	51.41 ± 6.89	0.000*

Data are presented as mean ± SD. *CTL* Liver attenuation, *CTL_S* Difference between liver and spleen attenuation, *CTL/S* Ratio of hepatic attenuation to splenic attenuation, *CTS* Splenic attenuation, *RT/S* Ratio of right hepatic attenuation to splenic attenuation, *LT/S* Ratio of left hepatic attenuation to splenic attenuation

Our study was performed on 53 living donors of both sex, the mean age was 25.26 ± 3.39 years in group A and 26.80 ± 4.71 years in group B, unlike Swelam et al. 2020 [22] who performed their study on 639 brain dead donors with median age 58 years, but similar to Gencdal et al. 2020 [24], who performed a similar study on 60 living donors with mean age 32.4 ± 7.7 years.

The mean BMI in our study was 23.618 ± 4.162 in group A and 24.433 ± 2.998 in group B which was like Gencdal et al. 2020 [24] whose patients had a mean BMI 26 ± 3.

In our study, the efficacy of all three non-contrast CT indices (CTL, CTL/S, and CTL-S) were higher for assessing hepatic steatosis degree at cutoff values of 55.4, 1.1 and 8.7, the sensitivity values were 80%, 80%

Table 3 Role of CT indices in diagnosis of hepatosteatosis

	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	*P* value
CTL	≤ 55.4	80	71.1	52.2	90	0.817	< 0.001 *
CTL-S	≤ 8.7	80	65.8	48	89.3	0.788	< 0.001 *
CTL/S	≤ 1.17	73.3	73.7	52.4	87.5	0.783	< 0.001 *
RT/S	≤ 1.1548	86.7	71.1	54.2	93.1	0.786	< 0.001 *
LT/S	≤ 1.2971	86.7	50.0	40.6	90.5	0.726	< 0.001 *

PPV Positive predictive value, *NPV* Negative predictive value, *AUC* Area under the curve, *CTL* Liver attenuation, *CTL_S* Difference between liver and spleen attenuation, *CTL/S* Ratio of hepatic attenuation to splenic attenuation, *RT/S* Ratio of right hepatic attenuation to splenic attenuation, *LT/S* Ratio of left hepatic attenuation to splenic attenuation

Table 4 Role of CTL/S in diagnosis of grade II hepatosteatosis

	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	*P* value
CTL/S	≤ 0.9	100	100	100	100	1.000	< 0.001 *

PPV Positive predictive value, *NPV* Negative predictive value, *AUC* Area under the curve, *CTL/S* Ratio of hepatic attenuation to splenic attenuation

Table 5 Role of CT indices in diagnosis of hepatosteatosis

	Hepatosteatosis	
	R	*P*
CTL	− .610	< 0.001*
CTL-S	− .561	< 0.001*
CTL/S	− .528	< 0.001*

* Significant as *P* value ≤ 0.05. *r* Pearson correlation. *Statistically significant at *P* ≤ 0.05, *CTL* liver attenuation, *CTL_S* Difference between liver and spleen attenuation, *CTL/S* Ratio of hepatic attenuation to splenic attenuation

and 71.1% and the specificity values were 65.8%, 73.7%, and 73.4%, respectively, while AUC values for these cutoff levels were 0.817, 0.783, and 0.788 respectively.

This was similar to Park et al. 2006 [9], who investigated also the diagnostic accuracy of unenhanced CT hepatic attenuation value, liver-to-spleen attenuation ratio, and the difference of liver and spleen attenuation value for the diagnosis of macrovesicular steatosis of 30% or higher; they observed the highest specificity (100%) for 42 HU, 0.8 and -9 HU, respectively, with no diagnostic superiority among them. While Kodama et al. 2007, evaluated hepatic measurement only and comparison of liver attenuation with spleen on both unenhanced and portal phase contrast-enhanced CT images. They found that association of all measurements with pathologic fat content is statistically significant [21]. Moreover, Gencdal et al. 2020 [24] found that CTL, CTL/S, and CTL-S cutoff values of 48.3, 1.06, and 3.2, respectively and according to these cut off values, the sensitivity values were 64.7%, 64.7%, and 88.3% and the specificity values were 86%, 86%, and 64.7%, respectively, while AUC values for these cut off levels were found to be 0.81, 0.79, and 0.80, respectively.

Our study also showed that macrosteatosis ≥ 25% could be predicted by using CT L/S ratio with cut off value 0.9, which came in agreement with a study done by Swelam et al. 2020 [22] who could find that hepatic macrosteatosis ≥ 30% could be predicted with CT L/S ratio cut off value of 0.77. Also, Rogier et al. 2015, used liver-to-spleen attenuation ratio, and showed that a ratio of 0.9 discriminated 30% or more hepatic steatosis with a sensitivity of 79% and a specificity of 97% [1].

In line with our results, Park et al. 2006 [9] reported as well that the CTL/S sensitivity and specificity as 91% and 97%, respectively, by establishing the cutoff value of CTL/S as 0.9 in serious hepatosteatosis.

However these cutoff values seem to be close to each other, the small differences in between them could be due to variations in the vendors of CT scanner used and also the parameters used in each study.

The good selection of the potential liver donors through a multidisciplinary team specialized in liver transplantation is mandatory in our center, to exclude any patients who may have any suspected liver diseases or co-morbidities that can affect the liver. Since the attenuation value of the liver can be affected by factors other than fat contents, such as iron deposition and inflammation, these patients are not even undergo the CT examinations or liver biopsy for the donation purpose.

Limitations and recommendations of the study

Although we found a good performance of CT L/S ratio as a predictor of hepatic steatosis, our study was limited by the small sample number ($n = 53$), because this was a one center study and also because our center was restricted to living donor liver transplantation (LD-LT) only. However, our results came in agreement with a cohort study done by Rogier et al. 2015 which confirmed that the CT L/S attenuation ratio cut off value of 0.9 was associated with significant macrosteatosis on 109 donors after brain death [1].

In addition to the small sample number as mentioned before, also the number of patients with macrosteatosis more than 25% remained limited, due to good selection of the potential donors by the hepatologists and transplantation team in our institute as the candidates with high body mass index are discarded early from the transplantation procedure.

Despite using low radiation dose and despite the fact that all donors undergo CT scan for the preparation of donation, CT radiation exposure may be considered a limitation especially if repeated examinations were needed. For this reason more researches are needed to validate the use of ultrasound and MRI as efficient tools in quantitative hepatic steatosis assessment.

In addition, because we found high correlation between the CT attenuation indices and the liver biopsy results, we recommend further multi-center studies that allow large scale researches to support our results and hypothesis.

Finally, it should be taken into consideration that, from the results of intersegmental variation of L/S ratio, it is likely that fat deposition is heterogeneous throughout the liver. Because a single biopsy specimen shows the grade of hepatic steatosis only at the area where it was taken, multiple needle biopsies would be necessary to accurately evaluate steatotic changes in the whole liver. On the other hand, evaluation of hepatic steatosis using CT attenuation values enables the assessment of fatty changes in each part of the liver. To simultaneously express a representative value of fatty changes of the whole liver as well as to estimate the risks of both the graft and the remnant liver.

Conclusions

Our study indicated that L/S ratio on non-contrast CT can be clinically used as a noninvasive method to correctly evaluate hepatic steatosis. This method is actually feasible because CT examination has been routinely done in donor preoperative evaluation for the assessment of liver anatomy and graft size and the calculation of L/S ratio is not time consuming. By employing this modality, preoperative liver biopsy could be replaced for most donors at our institution. However, when other pathologies of the liver is suspected, e.g. granulomatous or other forms of hepatitis, biopsy should be considered.

Abbreviations

CT	Computed tomography
LB	Liver biopsy
MRI	Magnetic resonance imaging
CT L–S	Difference between liver and splenic attenuation values
CT L/S	Liver to spleen attenuation ration
CT RT/S	Right hepatic lobe attenuation to the splenic
CT LT/S	Left hepatic lobe attenuation to the splenic attenuation ratio
HU	Hounsfield units
CBC	Complete blood count
ROIs	Regions of interest
LDLT	Living donor liver transplantation
NAFLD	Nonalcoholic fatty liver disease
SD	Standard deviation

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None to be declared.

Author contributions
EMK, NAA and MMH conceived and supervised the study; HMA and MIG were responsible for data collection. HMA and AME analysed and interpreted the data. All authors provided comments on the manuscript at various stages of development. All authors read and approved the final manuscript.

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Availability of data and materials
Data and material are available on a reasonable request from the author.

Declarations

Ethics approval and consent to participate
The study was done after approval from the Ethical Committee of National Liver Institute, Menoufia University, and it was started at 2018 till March 2023. An informed written consent was obtained from the participants. Approval code: (00515/2023).

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

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