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Role of Measurement of Hepatic Hemodynamics by Triphasic CT in the Evaluation of Patients with Liver Cirrhosis

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Abstract

Background: Liver biopsy has been the main method for diagnosis, but it is an invasive method, with many complications, so a non-invasive method is needed to assess the severity of liver cirrhosis.

Aim of Study: To assess the severity of liver cirrhosis by measurement of hepatic blood flow using triphasic CT.

Patients and Methods: Our case control, single centre study involved 30 patients with chronic diffuse parenchymatous liver disease (which were further divided into Child-Pugh A, B, and C subgroups) and 30 healthy volunteers. All cases underwent supervision of their medical history, clinical examination, liver function tests, and triphasic CT scan. Measurement of contrast enhancement fraction (CEF) as a parameter of hepatic blood flow was calculated using triphasic CT, assessment of ROI (region of interest) in HU for the hepatic parenchyma in both arterial and venous phases were done. The contrast enhancement (CEF) was obtained by dividing the contrast concentration in the hepatic arterial phase by that in the portal venous phase using ROI measurement in HU. CEF values and the ROI measurements from the study and control groups were compared.

Results: The differences in the ROI measurements were statistically significant between the subgroups with multiple comparisons, except between the control and the Child-Pugh (A) group. The ROI measurement in the portal phase was higher than that measured in the hepatic arterial phase in both the study and control groups. There was a decrease in ROI measurement in both the arterial and portal phases with increase of the Child-Pugh grade; more evident in the portal phase. The value of CEF in the control group was 0.74. The CEF values increased with increasing Child-Pugh grades in the study group. There were noticeable differences for CEF between Child-Pugh A and B groups, Child-Pugh A and C groups and Child-Pugh B and C groups. The CEF increased as liver function (Child-Pugh grade) deteriorated in the study group.

Conclusion: Measurement of hepatic blood flow and CEF by using triphasic CT can be used to evaluate the liver hemodynamics and severity of liver cirrhosis.

Key Words: *Liver cirrhosis - Triphasic CT - Contrast enhancement fraction.*

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Introduction

LIVER cirrhosis causes portal hypertension due to mainly parenchymal necrosis, then connective tissue deposition, nodular regeneration of hepatocyte, resulting in distortion of the hepatic architecture and normal liver blood flow hemodynamics, causing decreased portal flow to the liver and increased arterial flow. Liver cirrhosis causes abnormal permeability of the sinusoid causing abnormal arterioportal communications. In advanced cirrhosis, the hepatic artery becomes enlarged and tortuous and in severe cirrhosis, portal vein thrombosis is frequently seen **[1,2]**.

The very first "World Health Organization (WHO) study of liver disease, total deaths worldwide from cirrhosis and liver cancer rose by fifty million per year over two decades". Liver cancer was the main cause of the increase in the number of annual chronic liver disease deaths which rose by 1.25 to 1.75 million from 1990 to 2010. In 2010, hepatitis B virus was associated with 45% of liver cancer and 30% of cirrhosis deaths; hepatitis C caused about 25% of liver cancer and cirrhosis deaths **[3]**. In West Africa, Hepatitis B is highly endemic in with a prevalence of 8%. In addition, 2% of the population in the region are chronically infected with hepatitis C **[4-6]**. Chronic liver disease reduces quality of life, regardless the type of disease. Old age and increased severity were associated with poorer quality of life **[7]**.

The most common noninvasive methods used for diagnosing liver cirrhosis are CT, Ultrasonography (US), and MRI. Cross-sectional imaging evaluate the liver hemodynamics providing additional vital data in the diagnosis of diffuse liver diseases **[8]**.

Ultrasound & Doppler US are not helpful in detecting the degree of fibrosis. Contrast-enhanced US has been reported helpful in grading the severity

of fibrosis in patients with hepatitis C, but it requires more validation. CT can display signs of fibrosis including abnormal morphology as left lobe hypertrophy, nodular edge, and regenerating nodules that appear of low density in CT [9].

The liver blood supply consists of two parts making helical computed tomography (CT) a profoundly appropriate method for liver imaging. Spiral CT allows a solitary breath-hold image acquisition clear of motion artifacts, makes evaluation of the liver at different phases possible. The hepatic arterial and portal circulations have several communications. If vascular compromise happens, changes in the blood flow volume and direction occurs in individual vessels. These abnormalities can be recognized with spiral CT as transient hepatic parenchymal enhancement (THPE) that displays the affected site as an area of high attenuation in arterial phase and returns to normal in portal phase due to decreased portal venous flow and resulting in an arterioportal shunt (APS) [10].

With advances in knowledge; the contrast enhancement fraction (CEF) can be calculated using triphasic CT and could be used as a new parameter to observe liver hemodynamics [11].

Liver biopsy has been the main method for diagnosis of liver fibrosis and cirrhosis, but it is an invasive method, with many complications, so a non-invasive method is needed to assess the severity of liver cirrhosis.

So our study aimed to assess the severity of liver cirrhosis by measurement of hepatic blood flow using triphasic CT.

Patients and Methods

Study population:

Our prospective, single center, case control study approved by the local institutional ethics committee; written informed consent was obtained from all patients. The study involved 60 subjects (divided into 30 patients with chronic diffuse parenchymatous liver disease and 30 healthy volunteers of matches ages and sex), there were 37 males, and 23 females. Patients displayed mean age of (59.3±7.26) in the control group, and (59.7±9.3) in the study group with age range of 28-82 years old. All patients were referred from Gastrointestinal department to MRI Unit at Radiodiagnosis department, Suez Canal University Hospital over a period of one year from February 2018 to January 2019.

All cases underwent supervision of their medical history, clinical examination, laboratory confirmation of chronic diffuse liver disease (Albumin, Prothrombin time, Total bilirubin, ALT, AST, GGT, Aspartate aminotransferase), and triphasic CT.

The inclusion criteria for case group involved (a) Patients with liver cirrhosis confirmed by clinical history, laboratory, ultrasound or MRI, the severity of cirrhosis was evaluated using the Child-Pugh classification. (b) Age >18 years, (c) Creatinine clearance >30ml/min/1.73m^2. The inclusion criteria for the control group were as follows: (a) Normal liver function and haemodynamics, (b) No prior liver disease (such as hepatitis B or C), (c) No evidence of portal vein thrombosis.

The exclusion criteria included; (a) Patients with known allergic reaction to contrast, (b) Creatinine clearance less than 30ml/min/1.73m^2, (c) pregnant women, (d) patients in the pediatric age group (<18 years).

Imaging technique:

All the studied patients were subjected to Triphasic CT using 16-slice Toshiba Aquilion CT scanner.

Patient preparation:

Patients were kept fasting for at least 6 hours. Intravenous access (with 18 G cannula) through antecubital vein was done.

Imaging technique:

A CT scan of the liver was obtained without IV. contrast medium injection during a breath hold at the end of expiration. The scan coverage was from the diaphragmatic dome to the lower poles of both kidneys. The acquisition was done in shallow and slow breathing. CT examination of the total liver volume was acquired after intravenous injection of nonionic contrast Opitray (Ioversol): 1.5ml/Kg with overall dose from 80-100ml at 3ml/s using a automatic injector.

Liver was scanned in arterial phase (scanning delay, 20-25 seconds), portal phase (scanning delay, 45-60 seconds), and equilibrium (scanning delay, 2-5 minutes) phases. All the CT examinations were performed with the following parameters: Detector collimation: 0.625-1.250mm; Matrix: 512x512; Reconstruction intervals: 3.75-5.00mm; Scan time: 50s; Gantry rotation time: 0.4s; Tube voltage: 80-100kV; Tube current: 150-300mAs/Auto mAs.

Image analysis:

A circular region of interest (ROI) of approximately 200mm^2 was placed on four areas of the

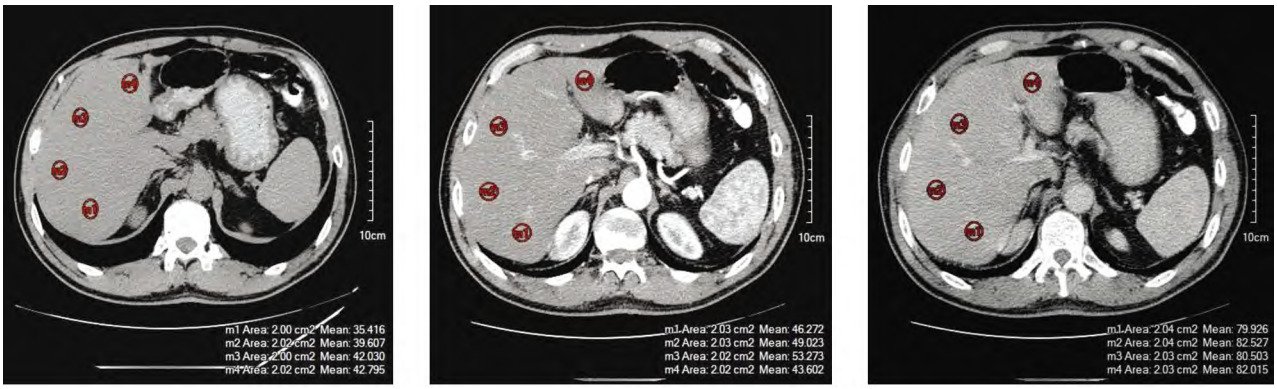
liver parenchyma: Right posterior, right anterior, left medial, and left lateral segments, with caution avoiding the large vessels in the hepatic arterial phase (HAP) and portal venous phase (PVP), to measure the attenuation of the area selected in pre-contrast arterial and porto-venous phases, Figs. (1,2).

Then the contrast concentration was calculated by dividing the contrast concentration in the hepatic arterial phase by that in the portal venous phase using ROI measurement in HU. The CEF was calculated using the following formula **[10]**:

CEF = Contrast concentration (HAP)/
Contrast concentration (PVP).

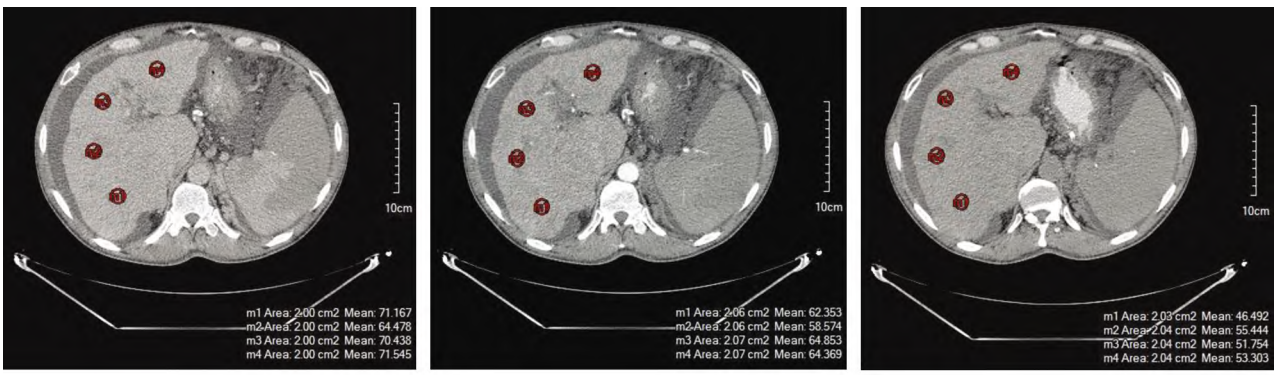
Statistical analysis:

Data collected was coded analyzed using Microsoft Excel software in the form of: Serial ID, age, sex. Data was then import into SPSS (Statistical Package for Social Sciences) software program version 13.0 for analysis. According to the type of data, the following tests were used to test differences for significance; Chi square, *t*-test, and one-way ANOVA with least significance difference. Chi square test and non parametric tests used to compare categorical variables. p-value was set at <0.05 for significant results. Data was presented in the form of table presentation.



(A) (B) (C)

Fig. (1): Triphasic CT of the liver in normal volunteer aged 45 years old. (A) Pre-contrast. (B) Arterial phase. (C) Porto-venous phase. A circular region of interest (ROI) with an area of approximately 200mm ^{2} was placed on the right posterior, right anterior, left medial, and left lateral liver segments on the slice with the largest liver parenchyma, avoiding the large vessels. The ROI was placed on a similar area and location in the different phases. The calculated CEF=0.74.



(A) (B) (C)

Fig. (2): Triphasic CT of the liver in a 51 years old male patient with liver cirrhosis (Child-Pugh grade C), displayed irregular nodular hepatic contour, enlarged caudate lobe, attenuated hepatic veins, portal venous thrombosis and ascites. (A) Precontrast. (B) Arterial phase. (C) Porto-venous phase. There is increase in ROI measurement in the arterial and portal phases compared to the pre-contrast phase. The ROI measurement in the portal phase was lower than the arterial phase indicating slow drainage of the contrast media from the liver parenchyma due to portal out- flow obstruction which has an impact on liver function by decreasing portal perfusion. The calculated CEF was increased= 1. 1.

Results

A total of eligible 30 chronic liver disease patients with similar normal control ones with a total of 60 patients were subjected for this work. 37 of them were males, while 23 patients were females & patients were found in age group between 28 to 82 years old with a mean age (59.3±7.26) in the control group, and (59.7 ±9.3) in the study group.

Of the 30 patients in the study group with chronic liver disease 20 patients had ascites and 10 patients did not. And only 7 patients had hepatic encephalopathy out of the 30 chronic liver disease patients.

In all the 30 chronic liver disease patients, there were an abnormal liver function laboratory results including: Albumin, Prothrombin time, Total bilirubin, ALT, AST, Aspartate aminotransferase, GGT. While the control cases had normal liver function. All the 30 subjects in the study group were Hepatitis C virus positive, while in the control group were free.

The total subjects in our study were divided according to lab results and clinical data into a control group 30 subjects (50%) and a study group 30 subjects (50%). The 30 subjects in the study group were subdivided in our study according to lab results and clinical data into child Pugh class (A) 10 subjects (33.3%), child Pugh class (B) 11 subjects (36.7%), and child Pugh class (C) 9 subjects (30.0%).

The ROI measurement in HU in all liver segments in different groups are listed in (Table 1). The ROI measurement in the porto-venous phase was higher than the arterial phase in both the study and control groups.

Table (1): ROI (region of interest) measurement in Hounsfield unit (HU) of different groups measured in ALL Liver segments at each phase.

	ROI measurement- All segments			
	Control Group	Child-Pugh A	Child-Pugh B	Child-Pugh C
CT phase:				
Pre-contrast:				
Mean ± SD	49.6±4.3	45.5± 13.4	45.9±5.2	44.5±6.3
Range	35-61	11-72	36-56	31-55
Arterial phase:				
Mean ± SD	57.8±4.9	49.1±9.6	52.9±7.5	48.9±8.7*
Range	44-70	22-62	40-74	26-64
Portal phase:				
Mean ± SD	77.7± 10.7	75.0± 12.4	67.1± 10.6*	57.2±8.1 *
Range	55-115	50-105	51-94	41-74

*Significant difference versus control group.

In the arterial phase, the ROI measurement of the control group was slightly higher than that of the study group but there were no significant difference". However, the ROI measurement in the portal phase of the study subgroups was significantly lower than the portal venous phase in the control group (Table 2).

Table (2): ROI (region of interest) measurement in Hounsfield unit (HU) of different groups in arterial phase.

	ROI measurement-arterial phase			
	Rt post. segment	Rt ant. Segment	Lt med. Segment	Lt lat. Segment
Group:				
Control	55.8±4.5	58.4±4.7	58.3±4.8	58.5±5.2
Child-Pugh A	47.9±8.6	48.0± 11.2	49.0±9.6	51.5± 10.1
Child-Pugh B	51.2±5.5	53.3±8.3	53.7±7.4	53.6±9.1
Child-Pugh C	47.1±9.4	46.9±9.5	51.9±6.9	50.0±9.0

There was significant difference between the ROI measurement in the portal phase of the Child-Pugh (C) and the control group, with almost no difference between the control group and Child-Pugh (A). There was statistical difference between HU in the control group and Child-Pugh (B), Child-Pugh (A) and (B), Child-Pugh (A) and (C), Child-Pugh (B) and (C) (Table 3). With increase in the Child-Pugh grade there was a decrease in ROI measurement in both the arterial and portal phases but more marked in the portal phase.

Table (3): ROI (region of interest) measurement in Hounsfield unit (HU) of different groups in portal phase.

	ROI measurement-portal phase			
	Rt post. segment	Rt ant. Segment	Lt med. Segment	Lt lat. Segment
Group:				
Control	75.9± 10.3	78.2± 11.1	79.2±9.8	77.6± 11.8
Child-Pugh A	75.9± 13.8	72.5± 12.5	75.3± 12.3	76.4± 12.7
Child-Pugh B	66.5± 11.4	66.2±9.6*	67.8± 11.1 *	67.8± 11.8*
Child-Pugh C	58.6±7.8*	51.4±6.8*	60.1 ±9.1 *	58.7±6.6*

*Significant difference versus control group.

The value of CEF in subject with normal liver function in the control group was 0.74. The CEF values increased with increasing Child-Pugh grades in the study group. There were noticeable differences for CEF between Child-Pugh A and B groups, Child-Pugh A and C groups and Child-Pugh B and C groups. The CEF increased as liver function (Child-Pugh grade) deteriorated in the study group (Table 4)".

Table (4): The ROI measurement in the arterial and portal phases and CEF (contrast enhancement fraction) for the study and control groups.

Group	ROI-arterial	ROI-portal	CEF
Control	57.8±4.9	77.7±10.7	0.74±0.45
Child-Pugh A	49.1±9.6	75.0±12.4	0.65±0.77
Child-Pugh B	52.9±7.5	67.1±10.6	0.79±0.70
Child-Pugh C	48.9±8.7	57.2±8.1	0.85±1.07

Discussion

Liver biopsy has been the main method for diagnosis, but it is an invasive method, with many risks as: Sampling error, serious complications, and even death. The accuracy of liver biopsy has been questioned because of these risks that may lead to over- or under staging of fibrosis. Therefore, an accurate noninvasive method is needed to measure the degree of hepatic cirrhosis [1].

In our study, we used triphasic CT to detect the severity of hepatic cirrhosis by quantitatively measuring hepatic tissue blood flow. The main point of this study was to compare the hepatic parenchymal enhancement obtained in triphasic CT imaging of cirrhotic patients to that of the control group with normal liver function, and to evaluate the possibility of estimating the liver haemodynamics of cirrhotic patients using ROI measurement in HU and calculated CEF.

In our study, there was a significant decrease in ROI measurement in the portal phase in Child-Pugh (C) patients as compared to the control group in all liver segments and this is due to the presence of portal hypertension and possible decrease in parenchymal portal venous flow resulting in decreased blood flow and consequently decreased contrast perfusion throughout the liver.

Cirrhotic nodules or fibrotic scars obliterate hepatic vascular space and thus raising resistance to portal flow [12]. This resulted in decreased perfusion of contrast throughout the liver parenchyma and subsequently decreased ROI measurement in the portal phase as compared to the control group".

However, in the arterial phase, there was a slight decrease in ROI measurement in Child-Pugh (C) as compared to the control group probably due to increased arterial flow pressure cirrhotic patients due to the hyperdynamic circulation that occurs with portal hypertension as proved in previous literature. Therefore, the ROI measurement in the arterial phase was not affected as the ROI measurement in the portal venous phase. The hyperdynamic circulation resulted in a minimal decrease in the ROI measurement in the hepatic arterial phase.

For the different Child-Pugh grades, our study demonstrated that ROI measurement decreased as liver function (Child-Pugh grade) deteriorated in the study group, which may be a result of the increased arterial supply and decreased portal supply of the liver parenchyma in advanced liver cirrhosis [1]. ROI measurement could be a successful predictive indicator for liver haemodynamics of cirrhosis patients as a quantitative method because it reflects changes in haemodynamics and correlates with Child-Pugh grade.

The timing of the arterial and portal phases is a crucial factor in this study to ensure accurate and consistent results. If the arterial phase acquisition begins too early, the ROI measurement of the liver parenchyma measured would be lower owing to insufficient hepatic arterial infusion. However, if the acquisition begins too late, ROI measured would probably be higher owing to the participating portal venous infusion and the same happens in the portal phase. In addition, the ROI measurement could be affected by factors, as the dose, concentration, and injection rate of contrast material.

The CEF reflects the ratio of the hepatic arterial flow to that of the total hepatic flow based on the contrast concentration in the liver parenchyma. The CEF values increased with increasing Child-Pugh grades in the study group. There were noticeable differences for CEF between Child-Pugh (A) and (B) groups, Child-Pugh (A) and (C) groups, and Child-Pugh (B) and (C) groups.

Our study matches with a study done by Zhao et al., that the iodine content (contrast enhancement in our study) measured with triphasic CT in the arterial phase is proportional to the arterial blood flow, and the porto-venous phase is mainly proportional to the whole liver blood flow. Theoretically, the CEF would then reflect the ratio of the hepatic arterial blood flow to that of the total liver flow [11]. There was a difference in CEF between the control and study groups, and between the subgroups in the study group. The ROI measurement showed that the portal phase was higher than that in the arterial phase in both the study and control groups. The CEF values increased with increasing Child-Pugh grades in the study group.

In our study, the ROI measurement of hepatic parenchyma was found to be higher in the portal

phase and lower in the arterial phase for patients in the study group than in the control group, resulting in an elevated CEF for cirrhotic patients. This value was significantly lower than that for patients with normal liver functions.

The increase of CEF of liver parenchyma with increased Child-Pugh grade may be explained by the increased portal pressure and decreased hepatic excretory function in these cases. Also, collagen deposition and increased hepatic vein wedge pressure causing more retention of contrast in the liver parenchyma. Accordingly, CEF could be a successful predictive indicator for liver haemodynamics of cirrhosis patients when used as a quantitative parameter because it reflects changes in haemodynamics and correlates with Child-Pugh grade.

Our study agree with Tripodi et al., **[13]**, that liver cirrhosis increases portal flow resistance and slowing-down the blood out-flow, this favors PV thrombosis and have an impact on liver function by decreasing portal perfusion. This decrease in out-flow of blood caused increase in ROI measurement of the portal phase as compared to the arterial phase.

Our study had some limitations as; firstly: Even though our study showed that the numerical value of ROI measurement in HU of the hepatic parenchyma attenuation, the exact correlation and the consistency between the ROI measurements and the HPI (hepatic perfusion index) is still unknown and should be further studied. Secondly: More studies with correlation to perfusion CT parameters as (hepatic perfusion flow, hepatic perfusion volume MTT (mean transition time) and permeability surface) can be done and reflect the liver haemodynamics more accurately from different views.

In conclusions:

The ROI measurement of liver parenchyma attenuation in Triphasic CT and calculation of contrast enhancement fraction (CEF) can be used to quantify liver fibrosis as a promising technique, and aid in the staging of hepatic cirrhosis; with many advantages, as follows: Non-invasive technique, no anesthetic risk, can be used if liver biopsy is contraindicated, palatable by patients, can be used to evaluate the treatment response, and quantify hemodynamic changes in liver cirrhosis.

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تقييم مدى دقة التصوير المقطعى ثلاثى المراحل فى تقييم ديناميكية الدورة الدموية فى تليف الكبد

بعد تليف وتشمع الكبد من اهم المشاكل الصحية التي تسبب فى الاختلال الوظيفى للكبد . إن المرضى المصابين بفيروسى الكبد ب،سي عرضة لخطر كبير متمثل فى نشوء تليف وتشمع الكبد مما يؤدى الي مرحلة متأخرة من أمراض الكبد وزيادة ضغط الدم فى الوريد البابى و سرطان الكبد.

إن قياس درجة تليف الكبد عن طريق قياس انتشار الصبغة بوحدات هاوسنفيلد لانسجة الكبد فى المرحلة الشريانى الكبدية و المرحلة الوريدية فى الكبد في الاشعة المقطعية الروتينية من الممكن استخدامها لتقييم الدودة الدموية و درجة تليف الكبد فى مرضى التليف الكبدى وتعتبر وسيلة تشخيصية غير تداخليه. وايضاً لمتابعة تأثير العلاج بمضادات الفيروسات ومضادات التليف والمساعدة فى أخذ القرارات اليومية فى الممارسات الإكلينيكية.

تهدف الدراسة إلى تقييم ديناميكية الدودة الدموية في تليف الكبد باستخدام الاشعة المقطعية ثلاثية المراحل لزيادة الحساسية والخصوصية التي يمكن بها تحديد أمراض الكبد. قياس انتشار الصبغة بوحدات هاوسنفيلد لانسجة الكبد في المرحلة الشريانى الكبدية والمرحلة الوريدية في الكبد في الاشعة المقطعية الروتينية والتي يمكن استخدامها لتقييم الدودة الدموية فى مرضى التليف الكبدى.

تشمل الدراسة علي فحص ٦٠ مريض فوق ١٨ سنة (ثلاثون مريض بتليف الكبد وثلاثون بدون إمراض فى الكبد (وسوف يتم لكل مريض الاتي: أخذ التاريخ الطبى ومراجعة الفحوصات المعملية أو تحاليل عينات كبد سابقة ووظائف الكلى وتصوير الكبد بالاشعة المقطعية ثلاثية المراحل.

وجد انه التصوير المقطعى ثلاثى المراحل له حساسية عالية فى تقييم ديناميكية الدودة الدموية فى تليف الكبد ويمكن استخدامه كفحص روتينى خالى من اضرار العينة الضارة فى تشخيص ومتابعة المرضى الذين يعانو من تليف الكبد وايضا يمكن الاعتماد عليه كوسيلة لمتابعة التليف بعد واثناء علاجه عن طريق قياس انتشار الصبغة بوحدات هاوسنفيلد.