[11C]Choline as a Novel PET/CT Biomarker of Liver Cirrhosis: A Prospective Pilot Study

Hanna Bernstine, Rachel Gingold-Belfer, David Groshar, Meital Nidam, Eli Rosenbaum, Nidal Issa, Doron Boltin, Boris Sapoznikov, Idan Goren, Assaf Issacchar, Michal Cohen Naftali, Avraham Weiss and Hemda Schmilovitz-Weiss

1 Sackler School of Medicine, Tel Aviv University, Tel Aviv 6997801, Israel
2 Department of Nuclear Medicine, Rabin Medical Center, Beilinson Hospital, Petach Tikva 4920235, Israel
3 Department of Gastroenterology, Rabin Medical Center, Beilinson Hospital, Petach Tikva 4920235, Israel
4 Uro-Oncology Unit, Davidoff Cancer Center, Beilinson Hospital, Petach Tikva 4920235, Israel
5 Department of Surgery B, Rabin Medical Center, Beilinson Hospital, Petach Tikva 4920235, Israel
6 The Service for Liver Diseases, Rabin Medical Center, Hasharon Hospital, Petach Tikva 49372, Israel
7 National Liver Institute, Rabin Medical Center, Beilinson Hospital, Petach Tikva 4920235, Israel
8 Geriatric Department, Rabin Medical Center, Beilinson Hospital, Petach Tikva 4920235, Israel

Both authors contributed equally to the study as first author

Corresponding author: Hemda Schmilovitz-Weiss, The Service for Liver Diseases, Rabin Medical Center, Hasharon Hospital, Petach Tikva 49372, Israel, Tel: +972-3-9372509; Fax: +972-3-9372644; E-mail: hemdaw@clalit.org.il

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Introduction

Choline is a quaternary ammonium base serving as an essential nutrient in all mammalian cell membranes, including hepatocytes. Its metabolism is cell- and tissue-specific [1,2]. Choline can either be phosphorylated and used to make phospholipid or oxidized and used as a donor of methyl groups [3]. Phosphatidylcholine is the most abundant phospholipid in hepatocytes [4]. There is growing evidence that choline plays a role in hepatic mitochondrial impairment, oxidative stress and DNA methylation levels of genes involved in lipid metabolism. The aim of this study was to compare findings between patients with liver cirrhosis and subjects with a normal liver on a [11C]choline PET/CT.

Methods: This prospective pilot study was conducted between the years 2012-2016. The cohort included 14 patients with prostate cancer (reference group) and 11 patients with cirrhosis attending a tertiary medical center. Demographic, clinical and laboratory data were obtained from the medical files. All participants underwent a dynamic [11C]choline PET/CT (Discovery ST, GE Medical Systems, Milwaukee WI). We compared the maximal standard uptake values (SUVmax) and the area under the curve (AUC) at 1110 seconds in both groups.

Results: The mean age of the cirrhosis group (63.4% men) was 68.4 ± 10.7 and the control group, 69.7 ± 7.3 years. The mean SUVmax was significantly higher in the cirrhosis group than in the controls (right lobe, 10.06 ± 12 vs. 6.3 ± 1.6, P=0.011; left lobe, 8.6 ± 11.6 vs. 5.4 ± 0.9, P=0.024; spleen 17.99 ± 27.8 vs. 13.4 ± 2.6, P=0.027; kidney, 35.9 ± 59.5 vs. 19.3 ± 4.8, P=0.025). The corresponding AUC values at 1110 seconds was significantly distinguished between the groups (right lobe, 13538 ± 20020 vs. 8427.3 ± 1557.9, P=0.026; left lobe 12304 ± 18871 vs. 6878.9 ± 1294.3, P=0.02; spleen, 12875 ± 17930 vs. 8263.9 ± 1279.2, P=0.023; kidney, 24623 ± 36025 vs. 13667 ± 3873.9, P=0.032).

No correlations were found between the clinical characteristics and the imaging-derived parameters in the patients with cirrhosis.

Conclusions: Our findings suggest a role for [11C]choline PET/CT as a noninvasive biomarker of cirrhosis. Further larger-scale studies are needed to confirm these observations.

Abstract

Aim: Choline plays a role in hepatic mitochondrial impairment, oxidative stress and DNA methylation levels of genes involved in lipid metabolism. The aim of this study was to compare findings between patients with liver cirrhosis and subjects with a normal liver on a [11C]choline PET/CT.

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No correlations were found between the clinical characteristics and the imaging-derived parameters in the patients with cirrhosis.

Conclusions: Our findings suggest a role for [11C]choline PET/CT as a noninvasive biomarker of cirrhosis. Further larger-scale studies are needed to confirm these observations.
liver fibrosis and portal hypertension is a validated tool for the diagnosing and follow-up of patients. The incorporation of spleen stiffness measurements in non-invasive algorithms using validated software and improved measuring scales, might enhance the non-invasive diagnosis of portal hypertension in the near future [8].

A PET/CT with $^{[11]}$C-choline is increasingly being used to evaluate recurrence and metastasis of prostate cancer [9,10]. Based on clinical observations, we hypothesized that the molecular imaging of choline phospholipid metabolism might serve as a useful means of evaluating the entire liver parenchymal function and integrity. The aim of the present study was to compare tracer uptake of a $^{[11]}$C-choline PET/CT scan between patients with cirrhosis and subjects with a normal liver.

**Methods**

**Study design**

This prospective pilot study was conducted between January 2012 and December 2016 as a collaborative effort of the Uro-Oncology Unit of the Davidoff Center Treatment and Research Center at Beilinson Hospital, the Department of Nuclear Medicine, the Liver Clinic of Hasharon Hospital and the National Liver Institute of Beilinson Hospital, all affiliated with the Rabin Medical Center. The protocol of the study adhered to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Committee. All participants provided written informed consent. In order to set reference values for imaging derived parameters of the $^{[11]}$C-choline PET/CT, a pre-pilot study was conducted (approval no. 0275-12). When the reference values were established, patients with liver cirrhosis were recruited (approval no. 0052-14) (Table 1).

The cohort included 14 patients with prostate cancer and a normal liver (control group) and 11 aged matched patients with hepatitis C virus (HCV) cirrhosis. The control group underwent a $^{[11]}$C-choline PET/CT as part of the oncological surveillance protocol for prostate cancer to identify distant metastases or tumor recurrence. Control patients were evaluated for liver abnormalities by abdominal ultrasound or CT. Screening blood tests including serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γ-glutamyltransferase (GGT), bilirubin, albumin, international normalized ratio (INR), hemoglobin concentration, white blood cell and platelet count. We included only those with no evidence of any liver disease: HCV, hepatitis B virus (HBV), human immunodeficiency virus (HIV), autoimmune liver disease, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), metabolic or alcoholic liver disease. The maximal standard uptake values (SUVmax) and the area under the receiver operating curve (AUC) at 1110 seconds of the control group, served as the reference values for assessment of the cirrhosis group.

<table>
<thead>
<tr>
<th>Characteristic (mean ± SD)</th>
<th>Normal liver controls (n=14)</th>
<th>Patients with cirrhosis (n=11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.7 ± 7.3</td>
<td>68.4 ± 10.7</td>
<td>0.45</td>
</tr>
<tr>
<td>Men (%)</td>
<td>100</td>
<td>63.4</td>
<td>0.55</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>23.7 ± 13.6</td>
<td>44.9 ± 28.9</td>
<td>0.013</td>
</tr>
<tr>
<td>Albumin (gr/dL)</td>
<td>4.2 ± 0.2</td>
<td>4 ± 0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.6 ± 0.3</td>
<td>0.98 ± 0.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Hemoglobin (gr/dL)</td>
<td>13.36 ± 1.2</td>
<td>13.43 ± 2</td>
<td>0.05</td>
</tr>
<tr>
<td>Platelets (K/µL)</td>
<td>223 ± 56.6</td>
<td>140.6 ± 62.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Leukocytes (K/µL)</td>
<td>10.05 ± 10.8</td>
<td>5.36 ± 1.06</td>
<td>0.1</td>
</tr>
<tr>
<td>INR</td>
<td>0.96 ± 0.08</td>
<td>1.17 ± 0.15</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Table 1: Clinical and laboratory characteristics of study group (n=25).*

The study group comprised patients with HCV cirrhosis (Tables 2a and 2b), regularly followed at the Liver Clinic, Hasharon Hospital or the National Liver Institute, Beilinson Hospital. Included were only patients with genotype 1B HCV and no evidence of other liver disease: HBV, HIV, autoimmune liver disease, PBC, PSC, metabolic or alcoholic liver disease. Although fatty infiltration of the liver may accompany a chronic HCV infection [11], to ensure homogeneity of the cirrhosis group, we also excluded patients with findings of fatty infiltration of the liver on ultrasound or CT. The diagnosis of liver cirrhosis was established by the Fibroscan, Fibrotest or a liver biopsy [8,12,13]. The extent of liver disease was assessed with the Model for End-Stage Liver Disease (MELD) [14].

The medical files of the patients were reviewed for demographic parameters, clinical, laboratory and pathology data and findings on other imaging modalities.

$^{[11]}$C-Choline PET/CT imaging protocol

A PET/CT was performed at the Department of Nuclear Medicine, Beilinson Hospital. Patients were asked to fast 4 hours prior to the test. All images were obtained using an integrated 8-slice PET/CT scanner (Discovery ST, GE Medical Systems, Milwaukee WI). A low-dose static CT acquisition (30 mA) was performed following an injection of 20-30 mCi (900-1125 MBq) $^{[11]}$C-choline for attenuation correction in the subsequent dynamic PET acquisition. The CT scan was preceded by a scout view of the upper abdomen centered on the liver to set PET coverage to a single bed position centered on the liver (15.3 cm coverage). $^{[11]}$C-choline was injected as a rapid bolus, flushed with 50 cc saline 0.9%, at a rate of 5.0 mL/sec using an automatic power injector (Dual-shot, Nemoto, Japan) [15].
Table 2a: Clinical characteristics of patients with cirrhosis (n=11).

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Ascites</th>
<th>Splenomegaly</th>
<th>Esophageal/gastric varices or portal gastropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>No</td>
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<tr>
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</tr>
<tr>
<td>9</td>
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<td>No</td>
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</tr>
<tr>
<td>10</td>
<td>No</td>
<td>Yes</td>
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</tr>
<tr>
<td>11</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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</tbody>
</table>

Table 2b: Laboratory features of patients with cirrhosis (n=11).

<table>
<thead>
<tr>
<th>Patient#</th>
<th>ALT (IU/L)</th>
<th>Total bilirubin (mg/dL)</th>
<th>Albumin (gr/dL)</th>
<th>Hemoglobin (gr/dL)</th>
<th>WBC count (K/µL)</th>
<th>Platelet count (K/µL)</th>
<th>INR</th>
<th>Cr (mg/dL)</th>
<th>MELD</th>
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<td>1</td>
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<td>0.6</td>
<td>4.5</td>
<td>13.3</td>
<td>7.3</td>
<td>252</td>
<td>1.08</td>
<td>1.07</td>
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<tr>
<td>2</td>
<td>66</td>
<td>1.1</td>
<td>3.9</td>
<td>14.5</td>
<td>4.6</td>
<td>246</td>
<td>0.95</td>
<td>0.79</td>
<td>7</td>
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<tr>
<td>3</td>
<td>89</td>
<td>0.8</td>
<td>4.3</td>
<td>14.9</td>
<td>5.8</td>
<td>112</td>
<td>1.1</td>
<td>0.93</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>0.4</td>
<td>4.3</td>
<td>16.4</td>
<td>5.7</td>
<td>94</td>
<td>0.87</td>
<td>0.67</td>
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<tr>
<td>5</td>
<td>43</td>
<td>1.4</td>
<td>3</td>
<td>10.8</td>
<td>4.8</td>
<td>90</td>
<td>1.2</td>
<td>0.73</td>
<td>10</td>
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<tr>
<td>6</td>
<td>93</td>
<td>1.2</td>
<td>4.1</td>
<td>16.5</td>
<td>6</td>
<td>184</td>
<td>1.2</td>
<td>0.83</td>
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<tr>
<td>7</td>
<td>52</td>
<td>1.9</td>
<td>3.1</td>
<td>10.9</td>
<td>6.2</td>
<td>72</td>
<td>1.2</td>
<td>0.97</td>
<td>11</td>
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<tr>
<td>8</td>
<td>37</td>
<td>1.3</td>
<td>3.4</td>
<td>11.7</td>
<td>3.3</td>
<td>90</td>
<td>1.09</td>
<td>0.6</td>
<td>8</td>
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<tr>
<td>9</td>
<td>19</td>
<td>0.72</td>
<td>4.3</td>
<td>14.3</td>
<td>5.5</td>
<td>134</td>
<td>1.4</td>
<td>0.82</td>
<td>10</td>
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<tr>
<td>10</td>
<td>13</td>
<td>0.9</td>
<td>4.5</td>
<td>12.9</td>
<td>5.4</td>
<td>112</td>
<td>1.02</td>
<td>1.03</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>14</td>
<td>0.5</td>
<td>4.7</td>
<td>11.6</td>
<td>4.4</td>
<td>161</td>
<td>1</td>
<td>0.86</td>
<td>6</td>
</tr>
</tbody>
</table>

The dynamic PET 2-D acquisition (matrix size 128 × 128; 3.27 slice thickness) consisted of 18 sequential frames, 10 seconds each, followed by 17 frames of 60 seconds each. A fused axial section at an anatomic level of the seventh segment of the liver, was chosen on the PET blood flow images and a 3-D volume of interest (VOI) measuring 2 cm³, was created.

Additional VOIs were outlined: 1 cm³ for sampling the abdominal aorta (for the Cp curve) and 1.5 cm³ for the left liver, spleen and left kidney. Time activity curves were generated from the activity of each VOI. Blood-flow parameters related to the first-pass delivery of choline were derived for each VOI, as follows: time to peak (TTP), AUC, at 1110 sec and hepatic perfusion index (HPI). The SUVmax was measured at peak intensity when tissue activity was maximal. The tracer accumulation was calculated using the AUC, derived from the time activity curve (TAC), which calculates the integral activity over time, 1110 seconds in our study. The tracer uptake was calculated using the K1 constant of the kinetic model (1 tissue compartment analysis) and a tracer clearance using the K2 constant of the kinetic model.

Statistical analysis

Continuous data are expressed as mean and standard deviation, categorical data are presented as frequency. Continuous data were analyzed with the independent t-test for parametric variables and the Mann-Whitney U test for nonparametric variables. Categorical data were analyzed by the Pearson’s chi-square test. The Pearson correlation coefficient was calculated to test correlations between the clinical data and the image-derived parametric data in the cirrhosis group. Analyses
were generated by the IBM SPSS, version 21. A P value of less than 0.05 was considered significant.

Results

Clinical characteristics

Most of the patients in the cirrhosis group were diagnosed by the Fibroscan (6/11, 55%), followed by the Fibrotest (27%) and ultrasound-guided liver biopsy (18%). The clinical characteristics of patients with prostate cancer and cirrhosis are summarized in Table 1. There was no significant difference between groups as to mean age. Males constituted all patients in the control group and 63.4% of the patients in the cirrhosis group. The cirrhosis patients had a significantly higher mean serum ALT level than the controls (44.9 ± 28.9 vs. 23.7 ± 13.6 IU/L, P=0.013) and a significantly lower mean serum albumin level (4.0 ± 0.6 vs. 4.2 ± 0.2 gr/dL, P=0.002).

Within the cirrhosis group, 5 patients exhibited clinical signs of portal hypertension: 4 with splenomegaly of whom 2 also had esophageal varices and 1 with portal gastropathy and esophageal varices. The MELD score ranged from 6 to 11. Three cirrhosis patients scored high on the MELD score (≥ 10) (Table 2a) with laboratory signs suggestive of hypersplenism (leukopenia and thrombocytopenia) (Table 2b).

[¹¹C]choline PET/CT scan

Data analysis yielded a significant between-group difference in two imaging parameters. Mean SUVmax was significantly higher in the cirrhosis patients than the controls, in the liver (right lobe, 10.06 ± 12 vs. 6.3 ± 1.6, P=0.011; left lobe, 8.6 ± 11.6 vs. 5.4 ± 0.9, P=0.024; spleen 17.99 ± 27.8 vs. 13.4 ± 2.6, P=0.027; kidney, 35.9 ± 59.5 vs. 19.3 ± 4.8, P=0.025) (Figure 1a-1d). The AUC significantly distinguished the two groups at 1110 seconds (Figure 2a-2d), in the liver (right lobe, 13538±20020 vs. 8427.3 ± 1557.9, P=0.026; left lobe, 12304 ± 18871 vs. 6878.9 ± 1294.3, P=0.024), spleen (12875 ± 17930 vs. 8263.9 ± 1279.2, P=0.023), and kidney (24623 ± 36025 vs. 13667 ± 3873.9, P=0.032). No correlations were found between the clinical data of the patients with cirrhosis and the imaging-derived parametric data.

Discussion

The present study of [¹¹C]choline PET/CT findings in patients with cirrhosis and controls with normal liver yielded significant differences in the bio distribution of the tracer. There was no significant difference in tracer uptake (K1) and clearance (K2) between patients with cirrhosis and controls.Apparently, in this study, the significant difference in the AUC between the two groups implies a difference in the perfusion/retention. The lack of correlation between the clinical data of the patients with cirrhosis and the imaging-derived parametric data might be explained by the small number of the participants in the study group, thus, the intragroup differences could not be captured.

The pathologic hallmark of cirrhosis is the development of excessive fibrous tissue (scarring) which replaces the normal parenchyma. Inflammation-induced damage to the hepatic parenchyma activates the stellate cells, the major cell type involved in liver fibrosis to increase the production of myofibroblasts, thereby obstructing hepatic blood flow [6]. Ultimately the bands of fibrous tissue (septa) separate the hepatocytes into nodules, defacing the entire liver architecture. The spleen becomes congested, thus, leading to hypersplenism and splenic retention of platelets. The resulting portal hypertension is responsible for the most severe complications of cirrhosis. As the disease process progresses in the cirrhotic liver, the perfusion pattern is altered.
portable hypertension is a validated tool for the diagnosis and follow-up of patients. Assessment of etiology specific cut-offs for ruling in and ruling out clinically significant portal hypertension is an unmet clinical need. The incorporation of spleen stiffness measurements in non-invasive algorithms using validated software and improved measuring scales, might enhance the non-invasive diagnosis of portal hypertension in the near future [8].

Figure 2: Area under the curve at 1110 seconds. (a) right liver lobe; (b) left liver lobe; (c) spleen; (d) kidney.

The novelty of $[^{11}C]\text{choline}$ PET/CT offers another non-invasive tool for assessing portal hypertension including both liver and spleen imaging. This is the first published study to date describing a higher concentration of $[^{11}C]\text{choline}$ in a cirrhotic liver compared to a normal liver. Following a thorough search in the literature, no information was found relating to choline metabolism in a cirrhotic liver. The liver is characterized by the highest choline, methyl folate, methionine, and S-adenosyl methionine of the body organs and it is where most methylation reactions occur [3-5]. Studies have shown that additional choline injected into the body is rapidly destroyed [16]. The only known mechanism for such destruction is the enzymatic system that oxidizes choline to betaine aldehyde and possibly further to betaine. The only known locations of this system are liver and kidney tissue.

Thus, in patients with cirrhosis, the extra choline may accumulate in the sick liver and the affected kidneys [17] since they are unable to effectively clear and metabolize it.

Another choline isotope, $^{18}$F fluorocholine, has been established as a radio-labeled tracer in detecting malignant lesions on a PET/CT, being an extremely versatile radiotracer for detecting proliferative or mitogenic activity [18]. Studies of PET/CT with $^{[18]F}\text{fluorocholine}$ in patients with liver cancer found that those with cirrhosis had, on average, lower levels of tracer uptake in the liver and tracer clearance than those without cirrhosis [19,20].

There might be several explanations for the discrepancy in the present study. The mechanism for the uptake and metabolism of $[^{11}C]\text{choline}$ in the liver may be different from $[^{18}F]\text{fluorocholine}$ in view of the fact that it is a different molecule. We could not find evidence for these assumptions in the literature. All our patients with HCV cirrhosis exhibited a fibrosis score of ≥ 4, reflecting some degree of portal hypertension. However, Kwee et al., studies [19,20], 73% of the patients with chronic liver disease exhibited a fibrosis score of only 0-2. Unlike our cohort, they showed various etiologies for the chronic liver disease, with differences in the $[^{18}F]\text{fluorocholine}$ uptake between patients with chronic HCV and chronic HBV disease [20]. Furthermore, it is noteworthy, that the aim of the $[^{18}F]\text{fluorocholine}$ studies were to evaluate the risk of the development of hepatocellular carcinoma in a diseased liver [19,20]. As such, all the patients revealed malignant transformation (HCC, cholangiocarcinoma and sarcoma), whereas, our patients with HCV cirrhosis, showed no evidence of hepatic neoplasic lesions. Thus, the hemodynamic pattern in their liver may have differed.

In the spleen, we also found that the mean SUVmax and AUC measurements were higher in the patients with cirrhosis than controls. This phenomenon has been described in the context of portal hypertension in older studies using technetium scintigraphy [21] wherein, total uptake in the spleen was significantly greater in patients with cirrhosis than in patients without. It should be pointed out, however, that these studies used a different tracer than $[^{11}C]\text{choline}$ and a different imaging modality. Talwalkar et al., [22] measured spleen stiffness using magnetic resonance elastography in patients with chronic liver disease of various causes and controls and noted significantly higher values in the study group.

Predictors of high spleen stiffness were splenomegaly, high spleen volume, and low platelet count. In our study, 4 patients with cirrhosis (36.4%) had splenomegaly, of whom 2 also had thombocytopenia, and another 5 (45.4%) thrombocytopenia alone (platelet count <150 K/µL). Thus, the majority of our study group had predictors of high spleen stiffness. The architectural and dynamic circulatory alterations that apparently take place in the spleen in the presence of chronic liver disease, including pulp hyperplasia, congestion from increased blood flow, and even fibrosis [22,23], might explain the slow clearance rate of $[^{11}C]\text{choline}$ from the spleen in our patients with cirrhosis relative to the controls.

The reason for the accumulation of $[^{11}C]\text{choline}$ in the kidneys of the patients with cirrhosis is less clear. As of today, there have been no other imaging studies that have investigated the bio-distribution of cholin in the kidneys of patients with cirrhosis. In patients with cirrhosis splanchic, vasodilatation causes systemic vascular vasoconstriction and activation of the renin-angiotensin aldosterone system. Splanchnic vasodilatation exacerbates hyperdynamic circulation which triggers increased hyperdynamic output followed by

a decrease in cardiac output [17]. All our patients had compensated cirrhosis at the time of the $^{11}$C-choline PET/CT and probably on the spectrum of evolving hyperdynamic circulation which might explain in part the high perfusion/retention of the tracer in those kidneys as expressed by higher AUC compared to the controls.

Serum creatinine levels in our patients with cirrhosis were within normal range, hence, no evidence of hepatorenal syndrome was found. Yet, patients with cirrhosis have lower muscle mass [24,25] thereby, the low or even normal serum creatinine levels might not accurately reflect kidney function in this setting. It is possible that the high mean SUVmax and AUC curve measurements suggest renal involvement due to early hemodynamic changes. Variable clinical presentations with different expressions of portal hypertension were observed amongst the patients with cirrhosis, with a similar severity of portal hypertension (MELD score 6-11). However, the small number of patients precluded statistical analysis of intra-group differences in imaging parameters. Nevertheless, the results of this pilot study point to a perfusion pattern change in the organs affected by portal hypertension: liver, spleen, and kidneys compared to a normal functioning liver.

Since the results of each scan are quantitated, $^{11}$C-choline PET/CT might serve as a useful bio-marker for assessing the severity of liver cirrhosis and for follow-up. As all our patients with cirrhosis showed a similar tracer perfusion pattern, probably due to the severity similarity of portal hypertension amongst them (MELD score 6-11), the intragroup differences could not be demonstrated. We believe that larger scale studies of patients in different stages of cirrhosis severity, utilizing a $^{11}$C-choline PET/CT, may find it sensitive enough to identify changes in the blood flow during the different stages of portal hypertension. This is important because the rate at which the cirrhotic liver deteriorates is individual and influenced by many parameters: HCV genotype [26], patient’s age [27], ethnicity, and gender, duration of infection [28], co-morbidities, i.e., metabolic syndrome, ethylism [29], HIV/HBV co-infections [30,31] and other genetic factors [32,33].

Another limitation of this study, in addition to the small number of patients, is the inability to compare our findings with the literature owing to the lack of similar studies using the same tracer. Furthermore, it should be noted that $^{11}$C-choline has a short half-life and is currently very costly, which might limit its routine clinical use.

## Conclusion

In conclusion, this pilot study revealed a persistent high concentration of $^{11}$C-choline in the liver, spleen, and kidneys in patients with cirrhosis compared to controls. This is the first time that this tracer has been used to evaluate patients with liver cirrhosis. Larger scale studies are needed to validate our results. $^{11}$C-choline PET/CT may serve as an effective noninvasive bio-marker for the assessment of overall liver and spleen in patients with cirrhosis.

## Acknowledgment

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## References


