are more commonly applied in clinical practice and in population-based studies [9–11]. Although CT is considered a reliable technique to assess steatosis, its use is limited because of radiation exposure. In addition, it is less sensitive than sonography and MRI [12]. The latter is also an accurate technique for the diagnosis and characterization of fatty liver, but it is expensive and poorly tolerated by some patients [13–16]. In contrast, sonography is cost effective and widely available, but it is limited by interobserver and intraobserver variability [17] and is not considered precise enough for the quantification of steatosis [18–22].

Moreover, the ability of these three techniques to detect steatosis in less than 15–30% of the hepatocytes is limited [10]. The aim of this study was to test whether sonography can serve as an objective tool for the quantification of hepatic steatosis by comparing sonography with histology.

OBJECTIVE. Quantification of liver steatosis is clinically relevant in various liver diseases but cannot be done by conventional sonography, which only provides a qualitative assessment with significant observer variability. The aim of this study was to assess sonography as an objective tool for the quantification of liver steatosis.

MATERIALS AND METHODS. Files of 111 patients with chronic liver disease who were referred for sonographically guided liver biopsy were collected. A hepatorenal sonographic index was calculated on the basis of the ratio between the echogenicity of the liver and that of the right kidney cortex using histogram echo intensity. Liver steatosis was graded by histology.

RESULTS. A significant correlation was found between histologic steatosis and the hepatorenal sonographic index ($r = 0.82, p < 0.001$). The validity of the hepatorenal sonographic index for the diagnosis of fatty liver was compared with liver biopsies with a steatosis level > 5%. The area under the receiver operating characteristic curve was 99.2% (95% CI, 98–100%). The optimal hepatorenal sonographic index cutoff point for the prediction of steatosis > 5% was 1.49, with sensitivity of 100% and specificity of 91%. The optimal hepatorenal sonographic index cutoff point for the prediction of steatosis ≥ 25% was 1.86, with sensitivity of 90% and specificity of 90%. The optimal hepatorenal sonographic index cutoff point for the prediction of steatosis ≥ 60% was 2.23, with sensitivity of 90% and specificity of 93%.

CONCLUSION. The hepatorenal sonographic index is a sensitive noninvasive method for steatosis quantification. It can diagnose small amounts of liver fat that would be missed by conventional sonography. It is reproducible and operator independent and can serve as an efficient tool to follow patients with steatosis and evaluate the efficacy of new treatment techniques.

Liver steatosis, defined as the accumulation of more than 5% fat in the liver, is the hallmark of most prevalent liver diseases, mainly alcoholic and nonalcoholic fatty liver disease. It is also highly prevalent in chronic hepatitis C virus (HCV) infection [1].

Steatosis exposes the liver to a range of inflammatory cytokines, which most likely play a major role in the development of steatohepatitis [2]. It also plays a major role in chronic HCV infection, where it is considered to be a risk factor for fibrosis severity and may reduce the viral response to therapy [3–6].

Liver biopsy is the reference standard for quantification of liver steatosis in nonalcoholic fatty liver disease [1, 7]. However, it is not routinely performed because it is an invasive procedure with a significant degree of sampling error [8]. Therefore, noninvasive methods such as CT, MRI, and sonography are more commonly applied in clinical practice and in population-based studies [9–11]. Although CT is considered a reliable technique to assess steatosis, its use is limited because of radiation exposure. In addition, it is less sensitive than sonography and MRI [12]. The latter is also an accurate technique for the diagnosis and characterization of fatty liver, but it is expensive and poorly tolerated by some patients [13–16]. In contrast, sonography is cost effective and widely available, but it is limited by interobserver and intraobserver variability [17] and is not considered precise enough for the quantification of steatosis [18–22].

Moreover, the ability of these three techniques to detect steatosis in less than 15–30% of the hepatocytes is limited [10]. The aim of this study was to test whether sonography can serve as an objective tool for the quantification of hepatic steatosis by comparing...
computerized liver echogenicity to that of the right kidney.

**Materials and Methods**

**Study Population**

Files of 111 consecutive patients referred for sonographically guided liver biopsy in the liver unit of the Tel Aviv Sourasky Medical Center were retrospectively collected between April 2005 and March 2006. The indications for liver biopsy included HCV infection, hepatitis B virus (HBV) infection, nonalcoholic fatty liver disease, and unexplained elevation of liver enzymes. HCV and HBV were diagnosed by serological tests. The diagnosis of nonalcoholic fatty liver disease was based on published criteria (the specific pattern of the liver on sonography, elevated serum transaminase levels, and exclusion of all other known liver diseases).

The study population was restricted to patients with diffuse homogeneous hypechochogenicity of the liver. Patients with heterogeneous geographical or focal steatosis or with focal lesions of the liver such as hemangioma and focal nodular hyperplasia (FNH), which can cause focal distortion of the liver echostucture, were excluded from the study, as were patients with ascites. Patients with a diseased or absent or ectopic right kidney were also excluded from the study. Informed consent to participate in the study was obtained from all subjects before the biopsy.

**Histologic Assessment**

All consenting patients underwent a simultaneous sonography and liver biopsy that was conducted by the same operator. Percutaneous sonographically guided liver biopsy was performed with a Tru-Cut needle (Baxter Healthcare) (16-gauge Klatskin needle). A liver specimen of 10 mm with at least nine portal tracts was considered adequate for evaluation. Liver biopsy specimens were fixed in formalin and embedded in paraffin. All biopsy specimens were examined by the same pathologist who was blinded to the hepatorenographic index results.

For patients with nonalcoholic fatty liver disease, the extent of liver steatosis and the degree of fibrosis and necroinflammatory activity were assessed histologically according to the Brunt [23, 24] criteria. Patients with HBV or HCV were assessed according to the Batts and Ludwig [25] criteria, and the amount of fatty infiltration was estimated by the pathologist on the whole sample and expressed as a percentage. The amount of liver steatosis was classified as follows: none (≤ 5%), mild (> 5% and ≤ 25%), and moderate to severe (≥ 25%) [26]. Furthermore, to diagnose massive fatty liver infiltration, we added another classification of massive steatosis (≥ 60%) [27].

**Sonography for Fat Quantification**

Each liver biopsy was performed under sonographic guidance using an EUB-8500 scanner (Hitachi Medical Systems) with a 3.5-MHz phased-array convex transducer. For each patient, the computer program presented a startup menu with measurement options that included a histogram of brightness levels—a graphic representation of echo intensity within a region of interest (ROI) on a B-mode sonogram. The ROI was determined by using the rectangle method (Fig. 1). In the liver the ROI corresponded to the site where the biopsy was performed, usually at the intercostal space in the mid or anterior axillary line (seventh or eighth intercostal space) in the superficial aspect of the liver. The ROI had to be as uniform as possible, excluding nonhepatic anatomic structures such as vessels or bile ducts. In the right kidney, the ROI was determined as the cortical area between the pyramids.

The area of the ROI in the liver was between 3.5 and 4 cm² in all patients. This area is large enough to calculate an average histogram value and small enough to avoid the inclusion of vessels or bile ducts in the specimen. Several ROI parameters were displayed including circumference and area, total brightness level, mean brightness level, SD, most frequent brightness level, and a histogram. Of all these parameters, we used only the mean brightness level for each organ (liver and right kidney) in this study.

Technically, the echo intensity can be influenced by many factors, particularly by gain intensity. To avoid confounding by factors that can modify the echo intensity and thus bias comparisons, the mean brightness levels of both the liver and the right kidney cortex were obtained on the same longitudinal sonographic plane. The ratio between the mean brightness level of the liver and the right kidney was calculated manually to determine the hepatorenographic index.

In each case, the calculation of the hepatorenographic index was repeated at least twice. When the difference was less than 0.20, the average was calculated. If there was a greater discrepancy, a third measure was performed and the average of the two closest measurements was used.

Hepatorenographic index reproducibility was evaluated on a sample of 20 hospital workers who underwent two repeat measures within 7–14 days. Sonography was performed by the same operator, who was unaware of the results of the first examination at the time of the second examination because the results were recorded and held by another individual. The results of the first and the second hepatorenographic indexes were highly correlated (r = 0.77, p < 0.001). The mean hepatorenographic index difference between the two examinations was 0.02 (± 0.15 SD), which was not significant in a paired test (p = 0.63). Applying the cutoff point of 1.49 for the diagnosis of steatosis yielded a κ of 0.86, which represents an excellent degree of agreement.

**Statistical Analysis**

All statistical analyses were performed using SPSS version 13.0 for Microsoft Windows (SPSS). Continuous variables are presented as means ± SD. Comparisons of continuous variables were performed with analysis of variance. The Bonferroni test was used for post hoc comparisons. Pearson’s or Spearman’s correlations were used for correlation between the sonographic index and histologic steatosis. For the assessment of hepatorenographic index reproducibility, within-subject variations were assessed using the Wilcoxon’s signed rank test (a nonparametric paired test).

To define the optimal hepatorenographic index cutoff point for the diagnosis and classification of fatty liver on the basis of liver biopsy, we applied a receiver operating characteristic (ROC) curve. Using that cutoff point, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the index were calculated. The kappa statistic was calculated. Values for p < 0.05 were considered statistically significant for all analyses.

**Results**

A total of 111 patients were included in the study (mean age, 44 ± 12 years; 54% men). The causes of their chronic liver diseases were HCV, 56; nonalcoholic fatty liver disease, 43; HBV, three; and abnormal liver enzymes, nine. The mean hepatorenographic index was 1.65 ± 0.75 (0.88–3.78).
The mean degree of steatosis was $18.7 \pm 28\%$ (0–80%). Sixty-six patients had no significant steatosis ($\leq 5\%$), 15 had mild ($> 5\%$ and $< 25\%$), and 30 had moderate to severe ($\geq 25\%$) steatosis. All grades of inflammation ($25\%$), 15 had mild ($> 5\%$ and $< 25\%$), and 30 had moderate to severe steatosis ($\geq 25\%$) steatosis. All grades of inflammation ($25\%$), 15 had mild ($> 5\%$ and $< 25\%$), and 30 had moderate to severe steatosis ($\geq 25\%$) steatosis.

The hepatorenal sonographic index provided a reliable quantification of steatosis compared with biopsy as the standard. The mean hepato-renal sonographic index ($r = 0.64$) for mild steatosis, and $2.59$ ($2.3–2.8$) for moderate to severe steatosis ($p < 0.001$ between all levels). Significant correlations were observed for every stage of fibrosis (Table 1) and in every grade of inflammation ($r = 0.8–0.9$, $p < 0.001$ for all). High correlation rates were found between the hepatorenal sonographic index and the amount of steatosis in HCV ($r = 0.68$) and nonalcoholic fatty liver disease ($r = 0.70$) ($p < 0.001$ for all cases).

**Hepatorenal Sonographic Index for Sonography of Liver Steatosis**

Further assessments of the capacity of the hepatorenal sonographic index to distinguish between different levels of steatosis were performed by comparing the index with histologic steatosis levels $\geq 25\%$ and $\geq 60\%$. The $A_z$ values (95% CI) were $96\%$ (93–99%) for steatosis $\geq 25\%$ and $95.7\%$ (92–99%) for steatosis $\geq 60\%$ (Fig. 4).

The optimal hepatorenal sonographic index cutoff point for the prediction of steatosis $\geq 25\%$ was 1.86, with sensitivity of 90% and specificity of 90%. The optimal hepatorenal sonographic index cutoff point for the prediction of steatosis $\geq 60\%$ was 2.23, with sensitivity of 90% and specificity of 93% (Table 2).

**Concordance Between Steatosis by Hepatorenal Sonographic Index and Biopsy**

The hepatorenal sonographic index was divided into categories in accordance with the optimal cutoff points determined from the ROC curves. These categories were compared with the steatosis categories and the kappa statistic was calculated. For three categories of steatosis ($\leq 5\%$, $> 5\%$ to $\leq 25\%$ steatosis, and $> 25\%$ steatosis) a $\kappa$ of 0.75 ±

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**TABLE 1: Correlation Between Hepatorenal Sonographic Index and Steatosis by Stage of Fibrosis**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Fibrosis</th>
<th>$r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0</td>
<td>0.64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>23</td>
<td>1</td>
<td>0.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>0.86</td>
<td>0.002</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>0.91</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>0.66</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Note—$r$ indicates Spearman’s correlation.

**TABLE 2: Validity of Hepatorenal Sonographic Index Compared with Percentage of Steatosis on Liver Biopsy**

<table>
<thead>
<tr>
<th>Steatosis (%)</th>
<th>Optimal Cutoff ($A_z$, 95% CI)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 5%$</td>
<td>($n = 45$)</td>
<td>1.49 (99.2, 98–100)</td>
<td>100 (45/45)</td>
<td>91 (60/66)</td>
<td>88 (45/51)</td>
</tr>
<tr>
<td>$&gt; 5%$ to $\leq 25%$</td>
<td>($n = 30$)</td>
<td>1.86 (96.0, 93–99)</td>
<td>90 (27/30)</td>
<td>90 (73/81)</td>
<td>77 (27/35)</td>
</tr>
<tr>
<td>$\geq 60%$</td>
<td>($n = 20$)</td>
<td>2.23 (95.7, 92–99)</td>
<td>90 (18/20)</td>
<td>93 (85/91)</td>
<td>75 (18/24)</td>
</tr>
<tr>
<td>$&gt; 25%$ steatosis</td>
<td>($n = 40$)</td>
<td>2.41 (96.7, 95–98)</td>
<td>90 (60/60)</td>
<td>91 (67/76)</td>
<td>78 (60/77)</td>
</tr>
</tbody>
</table>

Note—For sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), data in parentheses indicate number of patients. $A_z$ = area under the receiver operating characteristic curve.
0.05 was found (Table 3). Adding a fourth category of steatosis ≥ 60% yielded a κ of 0.68 ± 0.06 with discordance in one class of 0.153 (17/111), discordance in two classes 0.045 (5/111), and discordance in three classes 0 (0/111).

**Discussion**

Fatty liver is the most prevalent hepatic histopathologic finding in the Western population [28, 29]. Until recently, simple steatosis was regarded as a benign condition, but increasing evidence indicates that a fatty liver is more vulnerable to factors that lead to inflammation and fibrosis [30, 31]. The current theory regarding nonalcoholic fatty liver disease is the two-hit theory, which involves accumulation of fat in the liver (first hit) coupled with increased oxidative stress and reactive oxygen species (second hit) [2, 32, 33]. Because steatosis is the hallmark of nonalcoholic fatty liver disease, its assessment is important for both evaluation and treatment.

Steatosis is also a frequent histologic finding in patients with chronic HCV infection, occurring in approximately 50% of liver biopsy samples with a reported range of 30–70% [34]. Recent studies suggest a correlation between the degree of steatosis and liver fibrosis in hepatitis C [3, 4, 35–39]. Significant steatosis may also lower the sustained viral response rate to therapy [5, 6, 40]. Among patients suffering from coinfection with HCV and HIV, the fibrosis rate has been shown to increase in a linear fashion with the grade of steatosis [41, 42].

Significant liver steatosis can affect liver graft survival. If the degree of steatosis is more than 30%, there is a 25% chance of developing primary nonfunction. Thus, this degree of steatosis is a contraindication for transplantation [43]. Liver biopsy is the current reference standard for the quantification of steatosis in live liver donors. An accurate technique for the quantitative assessment of steatosis could spare healthy volunteers the need to undergo liver biopsy.

Although several imaging techniques can be used to assess liver steatosis, sonography is the most commonly applied and cost-effective. Sonographic findings of fatty liver include increased echogenicity of liver, blurring of vascular margins, and increased acoustic attenuation [44]. However, sonography is an operator-dependent technique and lacks the capacity for objectively quantifying liver steatosis.

This study presents an innovative method for the quantification of hepatic steatosis using a sonography-based index: the hepatorenal sonographic index. Using the hepatorenal sonographic index, we were able to identify the presence of minimal steatosis, as low as 5%. Thus, the known limitation of sonography to detect steatosis with high sensitivity only if it involves more than 30% of hepatocytes [10] is resolved by the hepatorenal sonographic index. Furthermore, the high correlation between the hepatorenal sonographic index and steatosis was independent of the cause and was seen at every level of inflammation and fibrosis.

The suggested hepatorenal sonographic index cut point of 1.49 yielded very high sensitivity (100%) and specificity (91%), enabling us to attain good PPV and NPV (88% and 100%, respectively) for the diagnosis of hepatic steatosis > 5% (Fig. 4 and Table 2). This high sensitivity rate could be attributed to the ability of the hepatorenal sonographic index to identify relatively low degrees of steatosis. In other studies, the sensitivity of sonography ranged from 60% to 94% and specificity from 84% to 95% [18–22, 30, 45, 46]. The sensitivity of sonography was reported to increase with the increasing degree of fatty infiltration. For example Ryan and colleagues [47] identified liver fat in only 55% of 11 patients with 10–19% steatosis. The sensitivity rose to 80% in the presence of steatosis of 30% or more.

All these previous studies dealt with the detection of steatosis rather than with the precise determination of hepatic fat content. The hepatorenal sonographic index also proved to be useful for predicting the degree of steatosis, with sensitivity of 90% and specificity of 90% for moderate to severe steatosis and sensitivity of 90% and specificity of 93% for severe steatosis (Table 2). The hepatorenal sonographic index is an objective, computerized calculated index, whereas the routine sonographic interpretation of steatosis is based on a subjective impression of a “bright liver echo” pattern. Thus, the interpretation is observer-driven with interobserver and intraobserver variance and limited reproducibility and comparability [10, 17]. As an objective quantitative tool, the hepatorenal sonographic index overcomes this major limitation and is ideal for patient follow-up and determination of the efficacy of treatment in liver diseases involving steatosis.

Few studies have addressed the role of sonography in the quantification of liver steatosis, and most of these lack complete histologic evaluation. Some of these studies were based on the visual assessment of hepatic

**TABLE 3: Concordance Between Steatosis Predicted by the Hepatorenal Sonographic Index and Predicted by Biopsy for the Three Categories**

<table>
<thead>
<tr>
<th>Hepatorenal Sonographic Index</th>
<th>Histologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis ≤ 5%</td>
<td>Steatosis &gt; 5 and ≤ 25%</td>
</tr>
<tr>
<td>&lt;1.49</td>
<td>60</td>
</tr>
<tr>
<td>≥1.49 and &lt;1.86</td>
<td>5</td>
</tr>
<tr>
<td>≥1.86</td>
<td>1</td>
</tr>
</tbody>
</table>

Note—Data are number of patients. Overall κ, 0.75 ± 0.05; discordance in one class 15 of 111, 14%; and discordance in two classes, one of 111, 1%.
echogenicity and thus were operator dependent. In addition, sonography failed to provide a precise determination of hepatic fat content [16].

In other studies, the capacity of sonography to quantify hepatic steatosis was assessed in an experimental setting with special software packages for textural analysis or by signal analysis applied to backscattered acoustic echoes [48–51]. The correlation between sonography and steatosis was inconsistent in the presence of fibrosis or inflammation [50].

Our study has some limitations. The hepatorenal sonographic index could not be measured in patients with disease in the right kidney, including structural disease or ectopic or absent right kidneys, or in patients with single or multiple focal abnormalities that distort liver architecture, especially in the right hepatic lobe (focal steatosis, giant or multiple hemangiomas, FNH).

Liver biopsy is considered the reference standard. However, it is an invasive procedure that can be performed only if clinically justified, so the resulting study population is selective. Nevertheless, this study population represents a variety of different liver diseases and also represents patients without steatosis or with varying degrees of steatosis. Moreover, there is no reason to believe that the correlation found in the current study between the hepatorenal sonographic index and steatosis by histology is affected by selection bias.

In conclusion, the use of the hepatorenal sonographic index facilitates quantification of liver steatosis, even in small degrees, and is not affected by fibrosis or steatohepatitis. It is reproducible and operator-independent and easily can be made available and applicable in routine clinical practice. The hepatorenal sonographic index is promising as an effective tool for the follow-up of patients with steatosis and for evaluation of the efficacy of new treatment techniques.

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