

# T1 relaxation time in the evaluation of liver fibrosis; with native MR relaxometry

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## ABSTRACT

**Objective:** Non-invasive methods have been investigated as an alternative to biopsy in assessing liver fibrosis. This study aimed to evaluate the relationship between liver T1 relaxation time and liver fibrosis as a non-invasive alternative method.

**Patients and Methods:** This study analyzed 1.5T magnetic resonance (MR) images of 86 patients retrospectively. The participants were divided into two groups: patients with chronic hepatitis and the control group. Native variable flip angle (VFA) T1 mapping technique was used to estimate liver T1 relaxation time. T1 mapping sequence, T2\* mapping sequence, and image analysis were performed. The liver size, the spleen size, the liver T1 relaxation time, and the liver T2\* relaxation time were recorded.

**Results:** The T1 relaxation time was  $758.4 \pm 121.1$  ms in the chronic hepatitis group and  $600.2 \pm 67$  ms in the control group. The T1 relaxation time of the patient group was significantly higher than that of the control group ( $p < 0.001$ ). The spleen size of the patient group was statistically significantly larger than the control group ( $p < 0.001$ ). There was a significant positive correlation between liver T1 relaxation time and Ishak score ( $r = 0.683$ ,  $p < 0.001$ ). Also, a significant positive correlation was observed between T1 relaxation time and histological activity index score ( $r = 0.542$ ,  $p < 0.001$ ).

**Conclusion:** A native T1 map is a non-invasive method that works as an alternative to biopsy in the follow-up and diagnosis of chronic hepatitis. Moreover, this method can be used to measure liver T1 relaxation time in patients with liver fibrosis.

**Keywords:** Fibrosis, Liver, MRI, Relaxometry, T1

## 1. INTRODUCTION

Hepatitis is an inflammation of the liver that develops due to many reasons. Chronic hepatitis is characterized by inflammation lasting for at least six months. The processes that cause morbidity and mortality in chronic hepatitis include liver fibrosis, cirrhosis, hepatocellular carcinoma, and portal hypertension [1]. Magnetic resonance imaging (MRI) is one of the most commonly used methods for liver imaging in clinical practice in both focal and diffuse liver diseases. Chronic hepatitis can be diagnosed by MRI findings such as nodularity in the liver parenchyma, irregular contours, heterogeneous parenchyma intensity, decreased liver size, increased spleen size, and increased portal vein calibration [2].

Liver fibrosis is an essential indicator of disease progression in patients with chronic hepatitis. Liver biopsy is an invasive

method that has been used to grade fibrosis. However, the biopsy may result in complications such as pain, bleeding, perforation, and other complications that may be developed during the surgical procedure [3]. The mortality rate of a liver biopsy ranges between 1/10000 and 17/10000 [4]. As a result, non-invasive methods that can be used as an alternative liver biopsy have been investigated. MRI can be used to make quantitative measurements of the liver parenchyma. Therefore, magnetic resonance (MR) relaxometry can be used to determine the T1 relaxation time of the liver parenchyma [5] and to assess fibrosis in patients with chronic hepatitis [6].

Magnetic resonance relaxometry sequences that allow quantitative evaluation of relaxation times have been developed for qualitative assessment with MRI [7]. MR relaxometry

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can review the quantitative information in diagnosing some heart, liver, brain, and skeletal system diseases and follow-up. In recent years, MRI sequences that display T1, T2, or T2\* relaxation times as parametric color maps, which can be used for quantitative evaluation of tissues via the direct region of interest (ROI) analysis on images, have been developed [8]. In addition, quantitative information about tissues can be obtained by measuring T1 relaxation time in milliseconds (ms) [9]. Furthermore, prolongation at the T1 relaxation time of the tissue indicates conditions characterized by irregular collagen deposition, such as fibrosis [10].

T1 relaxation time can be derived from contrast differences in color maps using the variable rotation angle (VFA) T1 mapping technique using two or more gradient-echo datasets obtained from different rotation angles [11]. The VFA T1 mapping method is frequently used in liver T1 mapping. Two different turning angles were used in a T1-weighted volumetric interpolated breath-hold examination (VIBE) sequence. Liver T1 relaxation time can be measured from pre- and post-contrast images on the 3-dimensional gradient-echo sequences [12]. As a result, T1 relaxation time can be used in ms as quantitative data to assess pathologies like liver fibrosis and predict liver function. Fibrosis, inflammation, and hepatosteatosis prolong the T1 relaxation time. However, since chronic hepatitis is associated with inflammation and fibrosis, the liver T1 relaxation time is predicted to be prolonged [13].

This study aims to determine the predictive value of T1 relaxation time as a non-invasive method that can be used as a biomarker of liver fibrosis in chronic hepatitis patients. In addition, it is investigated whether T1 relaxation time could be an alternative to biopsy in diagnosing and following liver fibrosis in chronic hepatitis patients. For this purpose, we compared liver T1 relaxation time in patients with chronic hepatitis and the control group using native liver T1 mapping. In addition, we evaluated the relationship between histopathological results and T1 relaxation time.

## 2. PATIENTS and METHODS

Upper abdomen MRI cases were investigated retrospectively in the Department of Radiology, Ankara Health Application and Research Center MRI unit using a 1.5 Tesla MRI device (Magnetom Aera, Siemens Healthcare GmbH, Erlangen, Germany) between April 2017 and December 2017. We performed liver native T1 mapping sequence in routine examination protocol.

A total of 86 cases were included in the study population. Patients with fatty liver and iron overload in both control and chronic hepatitis groups were excluded from the study. Patients with a liver fat fraction greater than 5% were excluded from the study. Therefore, all cases included in the groups had free fatty liver. Liver fat fractions were calculated using dual-echo T1 images obtained with a single excitation. Patients with iron overload were also excluded from the study because the calculation of liver fat fraction could be misinterpreted in the case of iron

overload. T2\* relaxation times were obtained by routine liver T2\* mapping in the protocol.

Our study consisted of two groups, the control, and the chronic hepatitis group. The data from each group were measured and compared as a mean. Patients in the control group have MR findings, clinical findings, and laboratory data inconsistent with chronic hepatitis and do not have a prior diagnosis of parenchymal liver disease. In addition, there were 44 patients in the control group. The second group was comprised of chronic hepatitis patients who had MRI findings, clinical findings, and pathological diagnoses consistent with chronic hepatitis. In addition, there were 42 patients in the chronic hepatitis group. In addition, 19 patients in the second group had liver biopsy results six months before and after the MRI. There were no biopsy results in 23 patients during this period. However, the clinical diagnosis, laboratory findings, and MRI findings all pointed to chronic hepatitis. All of the scans were done on a 1.5 Tesla MR scanner with a 32-channel superficial body coil and a phased array (Magnetom Aera, Siemens Healthcare GmbH, Erlangen, Germany).

### T1 Mapping Sequence

Parameters of T1 mapping sequence (without contrast agent) obtained using two different rotation angles in one breath attitude by VFA technique; TR: 4.76 ms, TE: 2.08 ms, 3.5 mm cross-sectional thickness, 2°-14.9° turning angles, FOV: 310x310 mm, voxel size: 1,6x1,6x3,5 mm<sup>3</sup>, bandwidth: 1955 Hz / pixel and matrix size: 96x77 mm.

### T2\* Mapping Sequence

T2\* mapping parameters obtained using multi-gradient echo sequence in single breath attitude; TR: 200 ms, TE: 0.93 to 14.24 ms in 12 different echo times (0.93+ (Nx1,11msn), 10 mm section thickness, 20° turning angle, FOV: 325x400 mm, voxel size: 3.1x3.1x10 mm<sup>3</sup>, bandwidth: 1953 Hz / pixel and matrix size 128x104 mm.

### Image Analysis

T1 and T2\* relaxation time were measured and averaged using a volumetric ROI of 1 cm<sup>3</sup> from all liver segments. Furthermore, in-phase liver and spleen intensity and out-phase liver and spleen intensity were measured with the help of ROI. The liver fat fraction was calculated using single excitation dual-echo T1 images. The liver and spleen sizes were measured, and values were recorded in the control and chronic hepatitis groups using conventional MR images.

### Statistical Analysis

IBM® SPSS® 23 program was used to analyze the data obtained in the study. Data were expressed as mean ± standard deviation (SD). Normality was tested using the Kolmogorov-Smirnov test. Student t-test or One-way ANOVA followed by post-hoc Fisher's LSD test were used to compare the data between the groups. Pearson correlation test was used to evaluate the correlation between the data. Comparisons were evaluated by ROC curve

analysis to determine cut-off values for T1 times.  $p < 0.05$  was accepted as statistically significant.

### 3. RESULTS

Our study had 86 participants, 42 of whom were in the control group and 44 in the chronic hepatitis group. The general population ranged in age from 16 to 78 years old, with a mean age of  $50.14 \pm 15.6$  years.

The control group consisted of 15 male and 29 female participants. The mean age of the control group was  $53.93 \pm 14.9$  years. The chronic hepatitis group comprised of 15 female and 27 male patients. The mean age of the patient group was  $46.52 \pm 15.7$  years.

T1 mapping images were analyzed in control and chronic hepatitis groups in each case. Fig 1 and Fig 2 show the T1 map image of one case each from the control and patient groups, respectively.

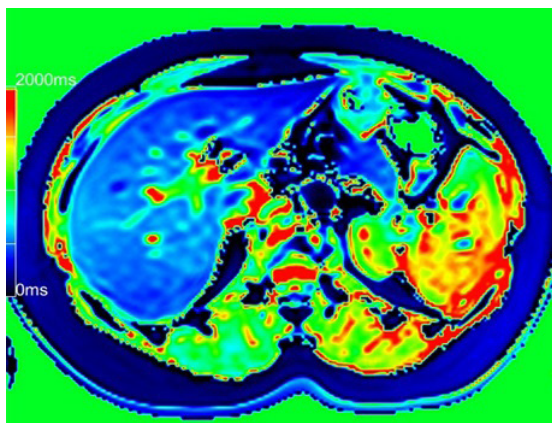


Figure 1. A 38 year-old woman with normal liver. T1 relaxation time of the liver was 642 ms.

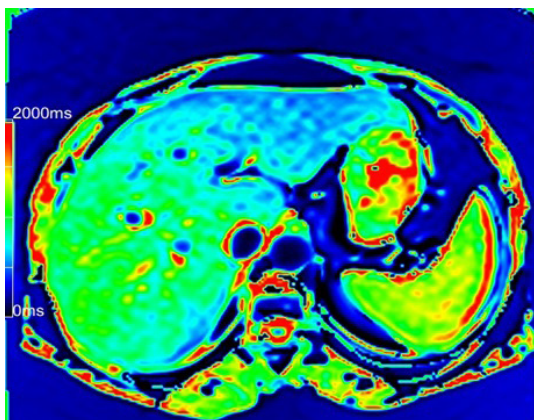


Figure 2. A 54 year-old man with chronic hepatitis. T1 relaxation time of the liver was 988 ms.

The mean liver size, mean spleen size, mean liver T1 time, and mean liver T2\* time was recorded in both control and chronic hepatitis groups. The mean liver T1 time, liver T2\* time, spleen size, and liver size were expressed in Table I.

Table I. Demographic and clinical data of study groups

	Control Group (n=44)	Chronic Hepatitis Group (n=42)	P value
Age	$53.93 \pm 14.9$	$46.52 \pm 15.7^*$	$< 0.05$
Liver size (mm)	$113.9 \pm 18.3$	$106 \pm 21.3$	$> 0.05$
Spleen size (mm)	$107.5 \pm 20.6$	$133.2 \pm 29.8^{**}$	$< 0.001$
Liver T1 time (ms)	$600.2 \pm 67$	$758.4 \pm 121.1^{**}$	$< 0.001$
Liver T2* time (ms)	$29 \pm 3.4$	$29.5 \pm 4.1$	$> 0.05$

Data are presented as mean  $\pm$  SD. (\*) Statistically significant compared to control group ( $p < 0.05$ ). (\*\*) Statistically significant compared to control group ( $p < 0.001$ ).

The mean liver sizes of the control and chronic hepatitis groups were  $113.9 \pm 18.3$  mm and  $106 \pm 21.3$  mm, respectively. The mean liver size of the control group was larger than that of the patient group. However, the difference between the groups was not statistically significant ( $p > 0.05$ ).

The mean spleen sizes of the control and chronic hepatitis groups were  $107.5 \pm 20.6$  mm and  $133.2 \pm 29.8$  mm, respectively. The results are expressed in Fig 3. There was a statistically significant difference in spleen sizes between the control and chronic hepatitis groups. The mean spleen sizes of the patient group were statistically significantly greater than the control group ( $p < 0.001$ ).

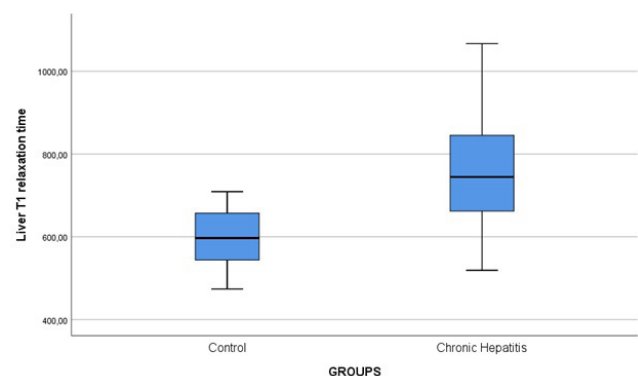


Figure 3. Liver T1 relaxation time of control group and chronic hepatitis group

The mean liver T1 relaxation time was  $600.2 \pm 67$  ms and  $758.4 \pm 121$  ms in the control and chronic hepatitis groups, respectively, as shown in Fig. 4. The T1 relaxation time of the patient group is statistically significantly higher than the control group ( $p < 0.001$ ).

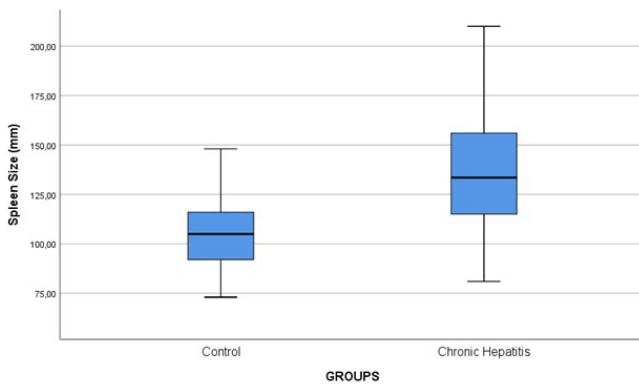


Figure 4. Spleen size of control group and chronic hepatitis group

The mean liver T2\* time of the control and chronic hepatitis groups were  $29 \pm 3.4$  and  $29.5 \pm 4.1$  ms, respectively, as expressed in Fig 5. The mean liver T2\* time was higher in the chronic hepatitis group than in the control group. However, there was no statistically significant difference between groups regarding liver T2\* time.

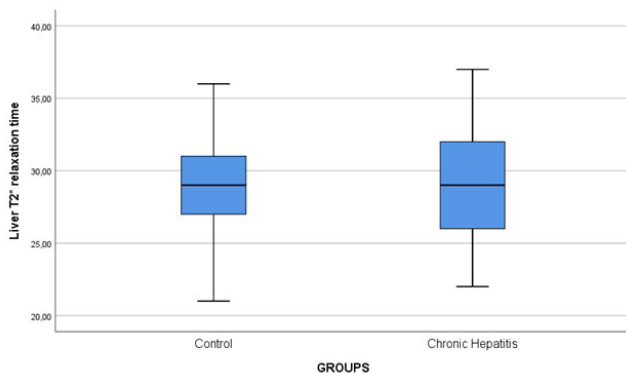


Figure 5. Liver T2\* relaxation time of control group and chronic hepatitis group

The correlation analysis was performed between age, mean liver size, mean spleen size, mean liver T1 time, and mean liver T2\* time. Correlation analysis revealed a statistically significant positive correlation between liver T1 time and spleen size ( $r=0.447$ ,  $p<0.001$ ). However, no statistically significant correlation was observed between age and any parameters, including mean liver size, mean spleen size, mean liver T1 time, and mean liver T2\* time.

The correlation analysis was conducted on 19 chronic hepatitis cases with liver biopsy results. A positive and significant correlation was found between liver T1 relaxation time and ISHAK score ( $r=0.683$ ,  $p<0.001$ ). Moreover, a positive and significant correlation between liver T1 relaxation time and histological activity index score was also observed ( $r=0.542$ ,  $p<0.001$ )

ROC analysis was performed to evaluate the predictive value of T1 relaxation time. The results of ROC analysis indicated that liver T1 relaxation time was statistically significant in differentiating the control group from the chronic hepatitis group ( $AUC= 0.877 \pm 0.037$ ;  $p <0.001$ ) (Fig. 6). The sensitivity and specificity of liver T1 relaxation time for predicting chronic hepatitis were calculated at different cut-off values. The cut-off value of 661 ms for the liver T1 relaxation time resulted in 76.2% sensitivity and 79.5% specificity. The cut-off value of 678.5 ms for the liver T1 relaxation time resulted in 71.4% sensitivity and 88.6% specificity.

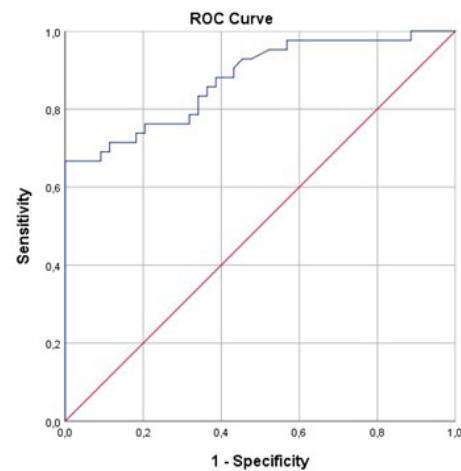


Figure 6. ROC analysis of liver T1 relaxation time

#### 4. DISCUSSION

The most important recent advances in MRI tissue quantification include T1, T2, and T2\* mapping. Tissue quantification can be performed using the native T1 mapping method without contrast material. T1 relaxation time can reveal important and crucial details about the characteristics of the tissue [14]. T1 relaxation time is known to be elongated by fibrosis, while T2\* relaxation time is shortened by iron accumulation [15]. However, recent studies have also shown that fatty liver patients have longer T1 relaxation time [16].

The degree of fibrosis plays a vital role in the treatment plan in patients with the chronic liver parenchymal disease. Several studies reported that non-invasive methods could be used to evaluate liver fibrosis, including MR elastography, diffusion-weighted imaging, MR spectroscopy, MR perfusion, diffusion tensor imaging, and double-contrast MRI. Venkatesh et al., found a strong correlation between MR-elastography-measured liver stiffness and fibrosis stage ( $r=0.945$ ,  $p<0.0001$ ) [17]. Huwart et al., reported that the degree of fibrosis (low, moderate, and high) was correlated with liver stiffness, and there were statistically significant differences between the groups ( $p<0.05$ ) [18].

T1 and T2\* relaxation times vary depending on magnetic field strength and device. Cassinotta et al., reported that the liver

T1 time of healthy cases was  $500 \pm 79$  ms tested using 1.5 Tesla MRI [19]. De Bazelaire et al., measured  $586 \pm 39$  ms [20], and Henninger et al.,  $592 \pm 11$  ms in the study with 1.5 Tesla MRI [9]. Our study measured the T1 and T2\* times of the liver parenchyma in chronic hepatitis and control groups. The mean liver T1 time was  $758.4 \pm 121$  ms in the chronic hepatitis group and  $600.2 \pm 67$  ms in the control group. This finding was similar to those of previous studies reported.

In our study, the mean liver T1 time was  $758.4 \pm 121$  ms in the chronic hepatitis group and  $600.2 \pm 67$  ms in the control group. The difference was statistically significant ( $p < 0.05$ ). In the literature, similar findings were reported. Cassinotto et al., reported a statistically significant difference between the control and cirrhosis groups regarding T1 relaxation time, and the liver T1 relaxation time in cirrhosis patients was  $690 \pm 147$  ms. In addition, they used native T1 mapping to investigate liver fibrosis and found that the Child-Pugh degree correlated with liver T1 relaxation time in cirrhosis patients [19]. Banerjee et al., in their native T1 mapping study, found a strong correlation between liver fibrosis and T1 relaxation time ( $r = 0.68$ ,  $p < 0.0001$ ) [21].

In studies conducted using hepatocyte-specific agents, comparing T1 map measurements obtained pre- and post-contrast can provide information about liver function and predict hepatocyte damage in chronic liver parenchymal disease. Haimerl et al., reported no statistically significant difference between the cirrhosis patients and the control group in terms of precontrast T1 time. However, there were statistically significant differences between the groups in terms of post-contrast T1 time and T1 time reduction rate ( $p < 0.05$ ) [22]. In our study, T1 mapping was not performed after applying the contrast material. The results were evaluated with native T1 mapping, and we obtained similar findings to the literature. However, in our study, we could not assess the liver functions of the participants due to the lack of information about the post-contrast T1 relaxation time and the reduction rate of T1 relaxation time.

In the study population, the lowest liver T2\* time was 21 ms, and the highest liver T2\* time was 37 ms. Chandarana et al., stated that a liver T2\* time less than 14 ms indicates hepatic iron accumulation with a 100% sensitivity and 97.3% specificity [23]. In our study, the lowest liver T2\* time was 21 ms, and the highest was 37 ms. Thus, our participants had no iron accumulation based on these results. In the literature, studies reporting normal liver T2\* time in normal cases were similar to our research. Anderson et al., measured mean liver T2\* time as  $33 \pm 7$  ms [24], and Pepe et al., measured it as  $25.6 \pm 3.4$  ms [25] in normal cases.

Despite all these data, our study has some limitations. The first limitation is that the liver biopsy results were unavailable for most cases. Therefore, without biopsy results, we could not make a clear histological definition of the liver parenchyma of the control and the chronic hepatitis group. In addition, the lack of biopsy results prevented us from evaluating the relationship between T1 relaxation time and fibrosis stage in patients with chronic hepatitis. The second limitation is the sample size of our study groups. Therefore, our results cannot be generalized to the general population. Finally, since the T1 relaxation time of the

liver can increase due to inflammation, it was impossible to state whether the increase in T1 times in the study population was due to fibrosis. There is a need for studies with a larger sample size with patients with a diagnosis proven by liver biopsy. For all these reasons, new studies should be conducted with a more significant number of cases who underwent a liver biopsy to support the data obtained from our research.

In conclusion, our study found the mean liver T1 relaxation time was longer in chronic hepatitis. In addition, T1 relaxation time and fibrosis grade were found to be correlated. In the literature, only a few studies evaluated liver T1 time in patients with chronic hepatitis. The previous studies supported our findings. Therefore, our study results will contribute meaningful data to the literature. However, there is a need for comparative studies with larger samples and longer terms to suggest the native T1 mapping method as a non-invasive alternative to biopsy in examining liver tissue.

### Compliance with Ethical Standards

**Ethical Approval:** This retrospective investigation was authorized by The Human Research Ethics Council of Ankara Training and Research Hospital, Ankara, Turkey (11.07.2018/525).

Informed consent was obtained from the patients before the MRI examination.

**Financial Support:** No special funding was obtained.

**Conflict of Interest Statement:** There is no conflict of interest.

**Authors' Contributions:** PNK: Conceptualization, HY: Methodology, FS: Software, FS, HY: Validation, FS, HY, EE and PNK: Investigation, FS: Writing – Original Draft, HY, EE: Writing - Review and Editing, HY: Supervision. All authors approved the final version of the manuscript.

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