Disease duration and Medsger's severity score are associated with significant liver fibrosis in patients with systemic sclerosis

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ABSTRACT

Objective. *We investigated the prevalence and predictors of significant liver fibrosis in patients with systemic sclerosis (SSc) who had no evidences of liver diseases due to viral infection, drug, and heavy alcohol consumption.*

Methods. *A total of 44 SSc patients were recruited. In addition to the clinical and laboratory data, the 2013 College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria score, modified Rodnan skin score (mRSS), and Medsger's severity score (MSS) were analysed. Liver stiffness (LS) was measured using transient elastography to assess the degree of liver fibrosis and 7.4 kPa was adopted as the cut-off value for significant liver fibrosis.*

Results. *The median age of patients (38 women) was 54 years and the median disease duration was 41.0 months. The median LS value was 4.6 kPa. The median mRSS and MSS were 7.0 and 5.0, respectively. Six (13.6%) patients had significant liver fibrosis. Disease duration (standardised β=0.375, p=0.018) and MSS (standardised β=0.398, p=0.047) significantly correlated with LS values. In multivariate analysis, disease duration ≥63 months (odds ratio (OR) 19.166, 95% confidence interval 1.090, 336.962, p=0.043) and MSS ≥7 (OR 19.796, 95% confidence interval 1.439, 272.252, p=0.026) independently predicted the presence of significant liver fibrosis.*

Conclusion. *The prevalence of significant liver fibrosis was relatively high (13.6%) and its independent predictors were disease duration and MSS.*

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterised by progressive and irreversible fibrosis of the skin and internal organs that can reduce the quality of life and shorten life expectancy (1). The lung is the internal organ that is the most commonly affected by the progressive fibrosis of SSc (2). As for liver, the main causes of biochemical liver abnormalities in SSc patients are viral hepatitis, drug and heavy alcohol consumption (3). On the other hand, SSc-related liver abnormalities include primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in SSc patients to some extent. Especially, antibodies related to primary biliary cirrhosis, anti-mitochondrial antibody (AMA), have been reported in up to 20% of SSc patients (3-6). However, given that histological changes occur in up to 9% of SSc patients on autopsy (7), liver involvement may have been underestimated by previous clinical studies due to the difficulty of detecting liver-related symptoms in contrast to lung and heart involvement.

During SSc pathogenesis, tissue damage caused by autoantibodies, toxins, and infections activates both innate and adaptive immune cells to secret pro-inflammatory and pro-fibrotic cytokines and growth factors. Inflammation and autoreactive immunity can, in turn, induce fibroblast activation and myofibroblast differentiation, leading to increased extracellular matrix accumulation and collagen cross-linking (1, 8). A similar pathophysiology has been proposed for liver fibrosis in SSc; autoreactive immune processes can account for hepatocellular damages, stellate cell activation, and myofibroblast expansion, resulting in the accumulation of collagen or glycoproteins in the liver (1, 6). Given this immunological similarity, liver fibrosis may occur in a considerable number of SSc patients in a higher proportion than previously reported (3). Therefore, evaluating the presence of liver fibrosis and assessing

its severity is important in SSc patients. Recent trials have assessed the severity of liver fibrosis in SSc patients using non-invasive tools that confer acceptable accuracy, and are approved for use in patients with chronic liver diseases; for examples, the enhanced liver fibrosis (ELF) test assessing indirect serum concentration of extracellular matrix constituents, and transient elastography (TE; FibroScan®, EchoSens, Paris, France) performance (9, 10). However, previous studies have not assessed significant liver fibrosis specifically in the context of SSc, while controlling for the influence of viral hepatitis, drug and heavy alcohol consumption. Therefore, we herein used TE to investigate the prevalence of significant liver fibrosis, and assessed its independent predictors in SSc patients exhibiting no signs of liver disease due to viral infection, drug, and heavy alcohol consumption, and with normal liver function and structures (11, 12). In addition, the newly developed 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc using the initial medical information at diagnosis, were applied to our participants, all of whom had been previously classified as SSc using the 1980 ACR criteria to achieve subject homogeneity and minimise the influence of confounding factors (13, 14).

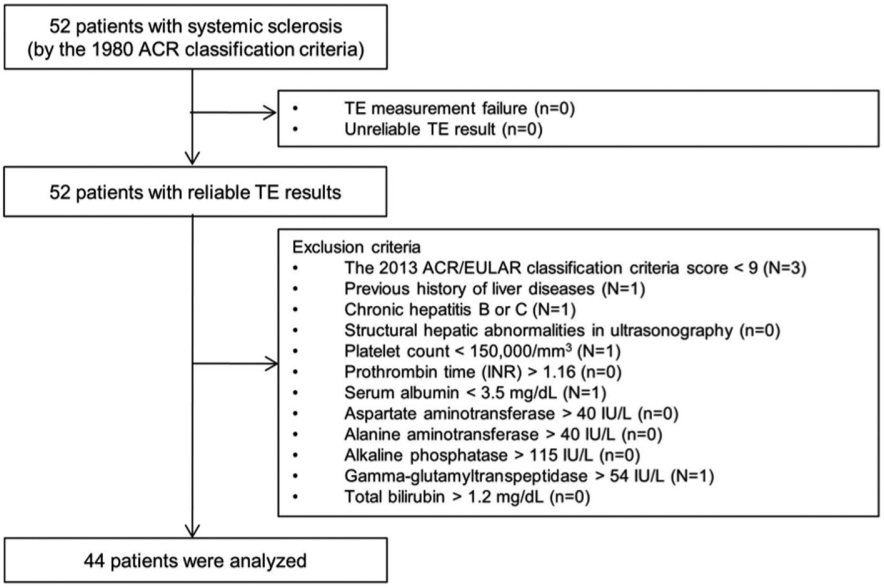

Fig. 1. Selection of the study population.
TE: transient elastography; INR: international normalised ratio.

Patients and methods

Patients

We consecutively enrolled 52 SSc patients, who fulfilled the 1980 ACR classification criteria for SSc, at Severance Hospital, Yonsei University College of Medicine, and who agreed to participate in this study, between April 2014 and December 2014 (13). The exclusion criteria were as follows: (i) failure to obtain a valid TE measurement (valid shot = 0) or unreliable liver stiffness (LS) values (indicated by an interquartile range/median value >0.3, <10 valid shots, or a shot success rate <60%); (ii) failure to meet the 2013 ACR/EULAR classification criteria for SSc using the initial medical information at diagnosis (14); (iii) evidence of chronic liver disease including chronic hepatitis B and C; (iv) hepatic structural abnormalities on ultrasonography; (v) drug-induced hepatitis or alcoholism; (vi) abnormal liver laboratory test results for at least two consecutive time-points (11, 12); and (vii) delayed laboratory test results after TE and ultrasonography (>3 days) (11). Based on these exclusion criteria, 8 patients were excluded (Fig. 1); therefore, 44 SSc patients were included in the final analysis. This study was approved by the Institutional Review Board of Severance Hospital (4-2014-1079). Informed consent was obtained from all of the patients.

Clinical data, laboratory findings and medications

We collected baseline information on age, sex, body mass index, metabolic syndrome and SSc subtype and duration, which was defined as the period between SSc symptom onset and TE measurement. We applied the newly developed and recommended 2013 ACR/EULAR classification criteria for SSc to all of the screened patients that were previously classified using the 1980 ACR criteria using the initial medical information at diagnosis. We devised a short clinical research form including all variables of the 2013 ACR/EULAR classification criteria, except anti-RNA polymerase III antibody which is not routinely available in our institute (14). Two rheumatologists performed physical examinations, collected blood samples for laboratory tests, and completed the clinical research forms. Normal range of liver-related laboratory test results was determined using the reference ranges for each type of analysis (11). Skin thickness was evaluated using modified Rodnan skin score (mRSS) with SSc severity assessed by Medsger's severity score (MSS) (15, 16). Medications including D-penicillamine, aspirin, calcium channel blocker, angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, glucocorticoid and azathioprine were also recorded.

TE and ultrasonography

A single, experienced independent physician, blinded to patients' clinical data, performed TE to assess LS and controlled attenuation parameter (CAP) values. TE was performed on the right lobe of the liver through the intercostal spaces with patients in the dorsal decubitus position with the right arm maximally abducted (17). LS values are expressed as kilopascals (kPa). The interquartile range (IQR) was defined as an index of the intrinsic variability of LS corresponding to the LS value containing 50% of the valid measurements between the 25th and 75th percentiles. The median value of successful meas-

urements was used to represent the LS value of a given patient; only LS values with ≥10 valid shots, an IQR/median value ratio (IQR/M) <0.3, and a success rate ≥60% were considered reliable. Any LS value not satisfying the above conditions was considered unreliable and excluded from the analysis (18). Ultrasonic attenuation was used to measure the degree of hepatic steatosis with a novel proprietary algorithm (CAP); the ultrasonic attenuation coefficient represents an estimate of total ultrasonic attenuation (go-and-return path) at 3.5 MHz, expressed in dB/m. CAP is evaluated using identical radio-frequency data and is calculated only when the LS measurement is valid for the same signals, ensuring that liver ultrasonic attenuation data are obtained simultaneously and in the same volume of liver parenchyma as the LS measurement (19). The final CAP value was denoted by the median of all of the individual CAP values. To index variability, the ratio between IQR and median CAP values (IQR/Mcap) was calculated. Ultrasonography was also performed in addition to TE to exclude patients exhibiting structural abnormalities in the liver.

Statistical analyses

All of the analyses were conducted using the SPSS package for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). The frequencies of non-continuous variables and continuous variables were expressed as percentages and median (IQR) values, respectively. Univariate analysis of the correlation between continuous variables and LS values was performed using linear regression. A cut-off LS value of 7.4 kPa was used to indicate the presence of significant liver fibrosis. This value was selected based on a large-scale meta-analysis and a previous Korean study (20, 21). Group differences were assessed using the chi-square test, and with Fisher's exact test for categorical data, and the Mann-Whitney U-test was used for continuous variables. Odds ratio (OR) for significant variables in univariate analyses were derived using multivariate logistic regression. Optimal cut-off for variables with statistical significance and clinical relevance in multivariate binary regression informed by the LS value (7.4 kPa), disease duration (63 months), mRSS (12) and MSS (7), were extrapolated by calculating the area under the receiver operator characteristic curve (AUROC) and selected among those with the high sensitivity and specificity and medical implications. For all statistical evaluations, *p*-values <0.05 were considered to indicate statistical significance.

Table I. Baseline characteristics of the study population (n=44).

	Values	
Demographic variables		
Age (years)	54.0	(26.0-79.0)
Female gender	38	(86.4)
Body mass index (kg/m^2)	22.0	(16.0-28.8)
Metabolic syndrome	3	(6.8)
Disease subset (diffuse)	13	(29.5)
Disease duration (months)	41.0	(2.0-96.0)
Laboratory variables		
C-reactive protein (mg/L)	1.1	(0.3-7.6)
Erythrocyte sedimentation rate (mm/hr)	30.0	(2.0-40.0)
White blood cell (/mm^3)	6,905.0	(3,850-14,450)
Haemoglobin (g/dL)	13.5	(11.1-17.1)
Platelet count (x1,000/mm^3)	252.0	(154.0-356.0)
Prothrombin time (INR)	0.9	(0.8-1.1)
Calcium (mg/dL)	9.0	(7.9-10.1)
Inorganic phosphorus (mg/dL)	3.9	(3.2-5.0)
Glucose (mg/dL)	94.0	(70.0-148.0)
Blood urea nitrogen (mg/dL)	12.9	(7.0-25.7)
Creatinine (mg/dL)	0.7	(0.5-1.2)
Uric acid (mg/dL)	4.6	(3.1-7.0)
Total cholesterol (mg/dL)	182.0	(126.0-302.0)
Total protein (mg/dL)	7.2	(4.7-8.6)
Serum albumin (mg/dL)	4.1	(3.6-4.6)
Alkaline phosphatase (IU/L)	65.5	(35.0-111.0)
Aspartate aminotransferase (IU/L)	19.0	(12.0-39.0)
Alanine aminotransferase (IU/L)	17.0	(6.0-38.0)
Total bilirubin (mg/dL)	0.5	(0.2-1.1)
Gamma-glutamyltranspeptidase (IU/L)	19.5	(7.0-51.0)
Triglyceride (mg/dL)	109.5	(51.0-391.0)
High-density cholesterol (mg/dL)	48.0	(27.0-84.0)
Low-density cholesterol (mg/dL)	108.6	(25.6-183.4)
Liver stiffness measurement by transient elastography		
Liver stiffness		
Liver stiffness measurement value (kPa)	4.6	(2.9-27.0)
Interquartile range/median value (%)	13.0	(7.0-27.0)
Success rate (%)	100.0	(70.0-100.0)
Liver steatosis		
Controlled attenuation parameter (dB/m)	230.0	(148.0-328.0)
Interquartile range/ median value (%)	13.0	(3.0-36.0)

Values are expressed as median (range) or n (%).
INR: international normalised ratio; kPa: kilopascal.

Results

Participants' baseline characteristics and clinical features related to SSc

Participants' baseline characteristics are listed in Table I. The median age of 44 patients (38 women) was 54 years. The median body mass index was 22.0 kg/m^2 and 3 patients (6.8%) had metabolic syndrome. The median disease duration was 41.0 months and 13 patients (29.5%) were classified as diffuse-type SSc. Liver-related laboratory test results were within the normal reference range. The median values of LS and CAP were 4.6 kPa and 230.0 dB/m, respectively. Clinical features associated with SSc are summarised in Table II. Raynaud's phenomenon (100%) was the most frequently observed manifestation, followed by abnormal nailfold capillaries (97.7%) and sclerodactyly (75.0%). Anti-Scl 70, anti-centromere and antinuclear antibody (centromere type) were de-

Table II. Clinical features associated with systemic sclerosis of the study population (n=44).

	Values
The 2013 ACR/EULAR classification criteria score at diagnosis	14.5 (9.0-26.0)
Clinical manifestations at diagnosis	
Raynaud's phenomenon	44 (100)
Scleroderma (proximal)	20 (45.5)
Puffy finger	18 (40.9)
Sclerodactyly	33 (75.0)
Digital tip ulcer	11 (25.0)
Fingertip pitting scar	11 (25.0)
Telangiectasia	4 (9.1)
Abnormal nailfold capillaries	43 (97.7)
Pulmonary arterial hypertension	1 (2.3)
Interstitial lung disease	21 (47.7)
Renal crisis	0 (0)
Autoantibodies at diagnosis	
Antinuclear antibody (centromere)	13 (29.5)
Anti-centromere	15 (34.1)
Anti-Scl-70	18 (40.9)
Modified Rodnan skin score	7.0 (0-17.0)
Medsger's severity score	5.0 (1.0-9.0)
General	0 (0-2.0)
Peripheral vascular	1.0 (1.0-3.0)
Skin	1.0 (0-2.0)
Joint/tendon	1.0 (0-2.0)
Muscle	0 (0-1.0)
Gastrointestinal tract	0 (0-1.0)
Lung	0 (0-1.0)
Heart	0 (0-1.0)
Kidney	0 (0)

Values are expressed as median (range) or n (%).

tected in 18 (40.9%), 15 (34.1%) and 13 (29.5%) patients, respectively. The median SSc criteria score was 14.5 and the median mRSS and MSS were 7.0 and 5.0, respectively. Glucocorticoid was the most frequently administered medication (23 patients), followed by D-penicillamine (14 patients).

Correlation between LS values and other variables

On univariate analysis, disease duration (r=0.433), prothrombin time (r=0.328), SSc criteria score at diagnosis (r=0.430), mRSS (r=0.359), and MSS (r=0.442) were significantly correlated with LS values in SSc patients (all $p<0.05$; Table III). Of these, only disease duration (standardised $\beta=0.375$, $p=0.018$) and MSS (standardised $\beta=0.398$, $p=0.047$) were independently associated with LS values in multivariate analysis (Table III).

Comparison between patients with and without significant liver fibrosis

Six patients (13.6%) were characterised by significant liver fibrosis (≥7.4 kPa). Patients with significant liver fibrosis exhibited diffuse-type SSc more frequently and a longer disease duration

Table III. Linear regression analysis between liver stiffness values and other clinical variables.

Variables	Univariate				Multivariate		
	Regression Coefficient (Crude B)	Correlation Coefficient (R=β)	95% CI	*p*-value	Standardised β	95% CI	*p*-value
Demographic variables							
Age (years)	0.079	0.250	-0.016, 0.175	0.102			
Body mass index (kg/m^2)	0.046	0.034	-0.375, 0.467	0.826			
Disease duration (months)	0.066	0.433	0.023, 0.108	0.003	0.375	0.010, 0.104	**0.018**
Laboratory variables							
White blood cell (/mm^3)	-0.219	-0.112	-0.823, 0.385	0.468			
Hemoglobin (g/dL)	0.734	0.197	-0.406, 1.874	0.201			
Platelet count (x1,000/mm^3)	-0.014	-0.194	-0.037, 0.008	0.208			
Prothrombin time (INR)	19.473	0.328	2.011, 36.935	0.030	0.260	-0.554, 31.452	0.058
Creatinine (mg/dL)	1.491	0.049	-7.929, 10.911	0.751			
Serum albumin (mg/dL)	-3.013	-0.179	-8.158, 2.133	0.244			
Alkaline phosphatase (IU/L)	0.057	0.290	-0.002, 0.115	0.056			
Aspartate aminotransferase (IU/L)	0.169	0.267	-0.021, 0.359	0.080			
Alanine aminotransferase (IU/L)	0.094	0.218	-0.037, 0.225	0.156			
Total bilirubin (mg/dL)	2.767	0.135	-3.577, 9.111	0.384			
Gamma-glutamyltranspeptidase (IU/L)	0.076	0.253	-0.015, 0.167	0.097			
The 2013 ACR/EULAR classification criteria score at diagnosis	0.289	0.430	0.100, 0.477	0.004	-0.119	-0.379, 0.219	0.592
Modified Rodnan skin score	0.313	0.359	0.059, 0.566	0.017	0.054	-0.286, 0.380	0.777
Medsger's severity score	0.950	0.442	0.349, 1.551	0.003	0.398	0.014, 1.698	**0.047**

CI: confidence interval; INR: international normalised ratio.

Table IV. Comparison of clinical and laboratory variables between patients with and without significant liver fibrosis (≥7.4 kPa).

Variables	Patients without significant liver fibrosis (<7.4 kPa, n=38, 86.4%)	Patients with significant liver fibrosis (≥7.4 kPa, n=6, 13.6%)	*p*-value
Demographic variables			
Age (years)	53.0 (26.0-79.0)	60.5 (40.0-79.0)	0.240
Female gender	33 (86.8)	5 (83.3)	0.816
Body mass index (kg/m^2)	21.9 (16.0-28.8)	23.7 (20.7-28.8)	0.293
Metabolic syndrome (n, (%))	3 (7.9)	0 (0)	0.476
Disease subset (diffuse) (n, (%))	9 (23.7)	4 (66.7)	**0.032**
Disease duration (months)	33.5 (0-96.0)	79.5 (62.0-95.0)	**0.013**
Disease duration ≥ 63 months (n, (%))	7 (18.4)	5 (83.3)	**0.001**
Laboratory variables			
White blood cell (/mm^3)	6,965.0 (3,850.0-14,450.0)	5,765.0 (4,850.0-8,740.0)	0.272
Haemoglobin (g/dL)	13.5 (11.1-17.1)	13.6 (11.1-15.0)	0.886
Platelet count (x1,000/mm^3)	257.5 (154.0-355.0)	226.0 (155.0-356.0)	0.700
Prothrombin time (INR)	0.9 (0.8-1.1)	1.0 (0.9-1.11)	0.051,
Creatinine (mg/dL)	0.7 (0.5-1.2)	0.7 (0.5-0.7)	0.458
Serum albumin (mg/dL)	4.2 (3.6-4.6)	4.1 (3.7-4.4)	0.319
Alkaline phosphatase (IU/L)	65.5 (35.0-111.0)	73.0 (48.0-108.0)	0.527
Aspartate aminotransferase (IU/L)	18.0 (12.0-39.0)	30.0 (15.0-39.0)	0.095
Alanine aminotransferase (IU/L)	15.0 (6.0-38.0)	32.0 (10.0-38.0)	0.134
Total bilirubin (mg/dL)	0.5 (0.2-1.1)	0.6 (0.4-0.8)	0.731
Gamma-glutamyltranspeptidase (IU/L)	19.5 (7.0-51.0)	19.5 (12.0-49.0)	0.985
Autoantibodies at diagnosis (n, (%))			
Antinuclear antibody (centromere)	13 (34.2)	0 (0)	0.088
Anti-centromere	15 (40.0)	0 (0)	0.058
Anti-Scl 70	12 (31.6)	6 (100)	**0.002**
Liver stiffness measurement by transient elastography			
Liver steatosis			
Controlled attenuation parameter (dB/m)	227.5 (148.0-328.0)	254.0 (211.0-289.0)	0.130
Interquartile range/median value (%)	13.0 (3.0-29.0)	12.5 (9.0-36.0)	0.485
The 2013 ACR/EULAR classification criteria score at diagnosis	13.5 (9.0-26.0)	26.0 (23.0-26.0)	**<0.001**
Modified Rodnan skin score	6.0 (0-17.0)	12.5 (9.0-14.0)	**0.013**
Modified Rodnan skin score ≥12 (n, (%))	9 (23.7)	4 (66.7)	**0.032**
Medsger's severity score	4.0 (1.0-8.0)	7.5 (6.0-9.0)	**0.001**
Medsger's severity score ≥7 (n, (%))	4 (10.5)	4 (66.7)	**0.001**
Medications ever used (n, (%)			
D-penicillamine	13 (34.2)	1 (16.7)	0.391
Aspirin	5 (13.2)	1 (16.7)	0.816
Calcium channel blocker*	11 (29.0)	2 (33.3)	0.827
ACEI or ARB**	4 (10.5)	1 (16.7)	0.660
Glucorcorticoid***	20 (52.6)	3 (50.0)	0.905
Azathioprine	2 (5.3)	3 (50.0)	**0.001**

Values are expressed as median (range) or n (%). INR: international normalised ratio; kPa: kilopascal.

than those without (66.7% *vs*. 23.7%, *p*=0.032, and 33.5 *vs*. 79.5 months, *p*=0.013, respectively). Furthermore, when we divided patients according to the cut-off of disease duration, more patients with significant liver fibrosis belonged to disease duration ≥63 months group than those without (83.3% *vs*. 18.4%, *p*=0.001). Using the medical information at diagnosis of SSc, higher detection frequency of anti-Scl 70 and SSc criteria score were shown in patients with significant liver fibrosis than those without (100% *vs*. 31.6%, *p*=0.002 and 26.0 *vs*. 13.5, *p*<0.001, respectively) (Table IV).

Patients with significant liver fibrosis were also showed significantly high mRSS and MSS, compared to those without (12.5 *vs*. 6.0, *p*=0.013, and 7.5 *vs*. 4.0, *p*=0.001, respectively). When we divided patients according to the cut-off of mRSS and MSS, more patients with significant liver fibrosis were found to have mRSS ≥12 and MSS ≥7 than those without (66.7% *vs*. 23.7%, *p*=0.032 and 66.7% *vs*. 10.5%, *p*=0.001, respectively). However, there was no significant difference in items of mRSS regarding abdominal skin thickness, which might be considered a confounding factor for the results of TE and ultrasonography. The frequency of administration of azathioprine significantly differed between patients with and without significant liver fibrosis (50.0% *vs*. 5.3%, *p*=0.001), but the number of patients receiving it was insufficiently large to be included in analyses (Table IV).

Independent predictors of significant liver fibrosis

Since anti-Scl 70 and the 2013 ACR/EULAR classification criteria score were used for the reclassification of the subjects and they were investigated using the initial medical information,

we did not include these variables in multivariate analysis despite statistical significance. By contrast, the disease subset is relatively unchangeable variable and might have higher burden of systemic fibrotic progression, so we included it in multivariate analysis. In multivariate analysis, disease duration ≥63 months (odds ratio (OR) 19.166, 95% confidence interval 1.090, 336.962, p=0.043) and MSS ≥7 (OR 19.796, 95% confidence interval 1.439, 272.252, p=0.026) independently predicted the presence of significant liver fibrosis (Table V).

Table V. Independent predictors of significant liver fibrosis ((≥7.4 kPa) in patients with systemic sclerosis during follow-up period.

Variables	Odd Ratio	95% Confidence Interval	p-value
Not considering azathioprine			
Disease subset (diffuse)	5.208	0.009, 3,056.937	0.612
Disease duration ≥ 63 months	19.166	1.090, 336.962	**0.043**
Modified Rodnan skin score ≥12	0.263	0.000, 162.881	0.684
Medsger's severity score ≥7	19.796	1.439, 272.252	**0.026**

kPa: kilopascal.

Discussion

This study has a clinical meaning to assess the prevalence and predictors of significant liver fibrosis using TE in SSc patients exhibiting no signs of liver disease due to viral infection, drug, and heavy alcohol consumption, and with normal liver function and structures (11, 12). Finally, we found that the prevalence of significant liver fibrosis was relatively high (13.6%) and its independent predictors were disease duration and MSS.

In real clinical settings, when SSc patients show no evidence of liver diseases or abnormality in liver laboratory tests, the possibility of fibrosis progression is typically ignored. Therefore, we investigated the prevalence of significant liver fibrosis in such patients, of whom 13.6% (6 of 44) were positive for significant liver fibrosis, a significantly higher rate compared to previous studies (1–9%) (4, 6, 7). Prevalence may have been even higher, if we had not excluded patients with viral hepatitis or drug or heavy alcohol consumption. When we reanalysed the data to include five patients with chronic liver disease or abnormal liver-related laboratory results, 16.3% (8 of 49) exhibited LS value over 7.4 kPa. These data indicate that prevalence of significant liver fibrosis may have been underestimated by previous studies assessing liver fibrosis using ultrasonography or other conventional liver function tests (8, 9). Furthermore, it appears that liver fibrosis in SSc patients can markedly progress in the absence of clinical symptoms. Because it can detect liver fibrosis in SSc patients with an acceptable accuracy, TE could be used to diagnose fibrosis at an earlier stage, thereby preventing further liver damage commensurate with the prescription of non-hepatotoxic drugs or dosage adjustment.

We first investigated the association between the 2013 ACR/EULAR classification criteria for SSc score at diagnosis and LS values; SSc criteria score was positively correlated with the severity of liver fibrosis in univariate, but not in multivariate analyses. The future studies using larger samples will elucidate whether SSc criteria score might represent a useful predictor of significant liver fibrosis during the diagnosis of SSc. In our study, only disease duration and MSS were independently correlated with the severity of liver fibrosis; disease duration might reflect the overall progression of SSc, during which fibrotic burden in the liver can increase (similarly to the lung) (22), whereas MSS contains more items pertaining to a larger range of internal organs, compared to more-recent classification system, and therefore may represent a more comprehensive determinant of significant liver fibrosis (14, 16). Diffuse type, disease duration, mRSS and MSS significantly differed between patients with and without significant liver fibrosis (Table IV). And, in multivariate analysis, we found that disease duration ≥ 63 months and MSS ≥ 7 could independently predict the presence of significant liver fibrosis with significance (OR 19.166, p=0.043, and OR 19.796, p=0.026, respectively), while diffuse type and mRSS reflecting the diffuse skin thickness had no statistical significance (Table V). However, these data require further validation due to our relatively small sample size. Primary biliary cirrhosis is one of major concerns regarding liver involvement of SSc. Previous studies reported primary biliary cirrhosis in up to 2% SSc patients and furthermore, its related antibody, AMA, in up to 20% patients. In our study, we performed AMA only in 6 patients who had significant liver fibrosis and we found no AMA detected in them. This result might be due to the limited enrolment of SSc patients who had never had evidence of chronic liver disease including chronic hepatitis B and C, hepatic structural abnormalities on ultrasonography, drug-induced hepatitis or alcoholism, and abnormal liver laboratory test results.

In Abignano *et al*., ELF test was selected as a substitute for liver biopsy to assess overall fibrotic activity in SSc patients (9). Numerous serological markers, including those measured by ELF test, have been proposed to assess liver fibrosis severity (23). However, a major limitation of these serum biomarkers is their lack of liver- or other organ-specificity; furthermore, they may be affected by changes in their clearance and excretion. Indeed, hyaluronate can increase in the post-prandial state (24). In addition to the questionable reproducibility of measurement derived from serum biomarkers (25), the inter-laboratory reproducibility of ELF scores remains to be validated. In contrast, TE exhibits high inter- and intra-observer variability (18). Furthermore, TE uses the physical properties of liver texture by calculating the velocity of ultrasonic propagation and is therefore completely liver-specific (18). Because the links between liver fibrosis and the overall fibrotic activity of SSc and which one is better in predicting long-term prognosis

between liver-specific TE or no liver-specific ELF, but potentially reflecting the overall fibrotic activity have not been validated, future studies are required to resolve these issues.

Our study had several limitations. First, we did not perform histological analysis on fibrotic changes in the liver, which could have validated the accuracy of TE for the diagnosis of significant liver fibrosis in SSc patients. However, obtaining liver sample for SSc patients, in the absence of evidence of liver disease, was unfeasible. Second, we could not establish an association between LS values and degree of lung involvement of SSc due to the small number of subjects exhibiting lung involvement. Because lung involvement of SSc is one of important complications, further studies are required to confirm the role of TE in the assessment of lung involvement. Third, we could not obtain serial LS values. The principal advantage of TE is its non-invasiveness during repeated examinations; if TE can be used as a dynamic tool to monitor changes in the degree of significant liver fibrosis, serial LS measurement might enable physicians to modify treatment strategies and forecast long-term prognoses for SSc patients. Finally, future studies are warranted to compare the diagnostic accuracy and efficiency of currently available non-invasive tools including TE and ELF test. In conclusion, we herein report a relatively high prevalence of significant liver fibrosis in SSc patients (13.6%). Furthermore, disease duration ≥63 months and MSS ≥7 increased the risk of significant liver fibrosis. Therefore, in addition to skin thickness and SSc involvement of internal organs other than the liver, the presence of significant liver fibrosis should also be assessed using TE, even when there is no specific evidence of liver disease and liver-related laboratory results are normal.

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